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Editorial

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Editorial

The Unmet Need of Stroke Prevention in Atrial Fibrillation in the Far East and South East Asia

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Abstract

The prevalence of atrial fibrillation (AF) is high in both community- and hospital-based studies in the Far East and South East Asia. Hypertension is the most common risk factor, but coronary heart disease and diabetes mellitus are other important co-morbidities in these countries. Anticoagulant therapy use was low, being 0.5%–28% in Malaysia, Singapore, and China. The reported rate of stroke related to AF was 13.0%–15.4% based on community studies in those countries and was 3.1%–24.2% of stroke rate in hospital-based cohorts. Better assessment of thromboembolic and bleeding risks is important. International guidelines now recommend the use of the CHA_2DS_2-VASc score to identify the "truly low-risk" AF patients, who do not need antithrombotic therapy, whilst those with ≥ 1 stroke risk factors can be offered oral anticoagulation. Aspirin is ineffective and may not be any safer than oral anticoagulants, especially in the elderly. It is anticipated that the availability of the new oral anticoagulant drugs would improve our efforts for stroke prevention in the Far East and South East Asia, especially where anticoagulation monitoring for warfarin is suboptimal.

Keywords: *anticoagulation, atrial fibrillaton, burden, Far East, stroke*

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. Stroke and systemic thromboembolism are its major complications, resulting in substantial morbidity and mortality. The management of AF has evolved greatly in the past few years, and the burden of AF and the need of stroke prevention strategies have been well documented in North America and Europe (1). However, the burden of AF in the Far East and South East Asia is also great, necessitating improvement of thromboprophylaxis strategies in these countries.

A systematic review of the global burden of AF, with particular focus on non-European and non-American countries, has recently been published (2). The prevalence of AF in community-based studies ranges from 0.1%–2.8% in Far East, with various studies reporting 0.8%–2.8% in China, 0.6%–1.6% in Japan, 0.4%–2.2% in Thailand, 1.4% in Singapore, and 0.1% in India (2). In hospital-based studies, the prevalence of AF was (unsurprisingly) higher, ranging from 2.8%–14% (2). Amongst hospital admissions, the prevalence of AF was 2.8% in Malaysia, 7.9% in China, and 12%–14% in Japan (Table 1) (2).

In keeping with epidemiological data from white populations, increasing age could subsequently increase the prevalence and incidence of AF in the Far East and South East Asia. Overall 57%–98% of patients with AF

Table 1: Prevalence and incidence of atrial fibrillation in Far East

Area	Study date	Design/patients	Prevalence/Incidence
Community-based studies			
China	2003	Prospective, cross-sectional N = 29 079 Age ≥ 30 years	Overall: 0.77% Male: 0.91% Female: 0.63%
	2004	Prospective, random cluster sampling N = 18 615 Age ≥ 35 years	Overall: 1.04% Male: 1.09% Female: 1.00%
	2003–2006	Prospective, cross-sectional N = 19 964 Age ≥ 50 years	Overall: 0.80% Male: 1.15% Female: 0.66%
	2009	Prospective N = 30 000 Mean age: 50.5 (30.5) years	Overall: 2.83% Male: 5.66% Female: 2.87%
Japan	1963–1966 1972–1975 1984–1987	Prospective, cross-sectional N = 8539 Age: 40–69 years	Male: 1.1%, Female: 0.6% (1963 = 43) Male: 1.1%, Female: 0.6% (1972 = 75) Male: 1.7%, Female: 0.6% (1984 = 98)
	1980	Retrospective review of prospective national survey N = 9 483 Age ≥ 30 years	Overall: 0.64% Male: 0.65% Female: 0.62%
	1996–1998	Prospective cohort N = 235 818 Age ≥ 20 years	Overall: 0.7%
	1980, 1990, 2000	Retrospective analysis of prospective national surveys N = 23 713 Age ≥ 30 years	Male: 1.0% Female: 0.6%
	1998–2000	Prospective, cross-sectional N = 1 098 Age: 25–83 years	11 / 1098 (Lone AF or atrial flutter)
	2002–2004	Prospective N = 26 472 Age ≥ 18 years	Overall: 1.56% Male: 3.29% Female: 0.64%
	2003	Retrospective N = 630 138 Age ≥ 40 years	Male: 1.35% Female: 0.43%
	2005–2007	Multi-center, prospective N = 2 242 Age: 20–90 years	14.3%

Area	Study date	Design/patients	Prevalence/Incidence
Community-based studies			
	2006	Prospective N = 41 436 Age ≥ 40 years	Overall: 1.6% Male: 2.4% Female: 1.2%
Singapore	2008	Prospective N = 1 839 Age ≥ 55 years	Overall: 1.4% Male: 2.6% Female: 0.6%
South Korea	2000	Prospective N = 14 540 Age: 40–92 years	Overall: 0.7% Male: 1.2% Female: 0.4%
Taiwan	1990–2000, with follow-up 9 years	Prospective N = 3 580 Age ≥ 35 years	Overall: 1.07% Male: 1.4% Female: 0.7%
Thailand	1991	Prospective N = 8 791 Age ≥ 30 years	Overall: 0.39% Male: 0.39% Female: 0.38%
	2002	Prospective N = 963 Age ≥ 60 years	Overall: 2.2% Male: 1.8% Female: 2.3%
Hospital-based studies			
China	1999–2001	Retrospective N = 9 297 Age: 18–99 years	Incidence: 7.9% per year
Japan	1995	Prospective N = 19 825 Mean age: 63 (13) years	Overall: 14% Male: 17% Female: 10%
	2004–2008	Prospective N = 4 719 Mean age: 53.8 (15.3) years	Overall: 12.2%
Malaysia	2000	Prospective N = 1 435	Overall: 2.8% Male: 21 Female: 19
Taiwan	1997–2002	Retrospective N = 162 340	Overall incidence: Annual mean 127 per 100 000 Male: 137 per 100 000 Female: 116 per 100 000

Abbreviation : AF = atrial fibrilation.
[a] Source: Lip GY, et al. *Chest*. 2012.

were aged 60 years or older in most studies (2). Men were more likely to develop AF than women, with 4.4%–7.9% in men and 2.2%–6.4% in men among patients aged over 80 years in the studies (2). 40% of patients with AF had hypertension in Malaysia, compared to 51.4%–56.3% in China, 24.4%–57.7% in Japan, and 73.1% in Singapore (2). 45% of patients had coronary heart disease in Malaysia (2). Valvular heart disease was also reported as a common comorbidity in Chinese and Japanese cohorts with AF (Table 2).

Suboptimal stroke prevention is fairly common in the Far East and South East Asia. The rate of anticoagulation use is low and aspirin is still commonly used in many Far East countries. Indeed, oral anticoagulation use ranges between 0.5%–28% in Malaysia, Singapore, and China (Table 3). In Malaysia, for example, the rate

Table 2: Risk factors for AF/AF comorbidities in Far East

Area	Age	Gender	Hypertension	CHD
China	Age ≥ 60: 72.8% Age ≥ 70: 31.4%	Male: 40.9%–54.9%	51.4%–56.3%	13.0%–34.8% (MI 8.3%)
Japan	Age ≥ 80: 3.0%–37%	Male: 50.2%–68.8%	24.4%–57.7%	9.3%–16.8% (MI 3.5%)
Singapore	**	Male: 73.1%	73.1%	**
South Korea	Age ≥ 65: 56.6%	Male: 71.7%	27.4%	**
Taiwan	Age ≥ 75: 23.7%	Male: 63.2%	52.6%–56.8%	38.6%
Malaysia	**	**	40%	45%
Area	**Diabetes**	**CHF**	**Previous stroke/TE**	
China	4.1%–23.6%	7.7%–3.9%	13.4%	
Japan	10.4%–20%	21.8%–22.7%	**	
Singapore	**	15.4%	15.4%	
South Korea	3.8%	**	**	
Taiwan	**	32.7%	15% (TE)	
Malaysia	**	**	**	

Abbreviations: AF = Atrial fibrillation, CHD = Coronary artery disease, CHF = Congestive heart failure, MI = Myocardial infarction, TE = Thromboembolism.
[a] Lip GY, et al. *Chest*. 2012. ** No available data.

of warfarin usage was 20%. The proportion of patients receiving antiplatelet therapy was 18%–58%, although there was significant variability. Of concern, 22%–47% patients with AF did not receive any antithrombotic drugs. In one Chinese retrospectively hospital-based study, for example, no antithrombotic therapy was evident in 35.5%. The rate of stroke related to AF was similar in community-based cohort (5 studies), which was 13.0%–15.4% in China, Japan, and Singapore (2). The stroke rate was 3.1%–24.2% in hospital-based cohorts (8 studies) (2) (Table 3).

Are things better elsewhere? Perhaps not. Indeed, 53% patients were treated with oral anticoagulants in 1996–1997 in North America and 64.8% in the Euro Heart survey (4,5). The annual rate of ischemic stroke or systemic embolism was 1.27% in patients on warfarin (4). The Swedish nationwide AF cohort study in 2005–2008 showed that only 40% patients with AF were on warfarin (6); of note, the 3-year incidence of ischemic stroke decreased from 8.7% for patients with AF in 1987–1991 to 6.6% in 2002–2006 in Sweden (7).

The management focus, at least until recently was the identification of "high risk" patients who would be candidates for an inconvenient anticoagulant drug, warfarin. Thus, warfarin use was suboptimal in the Far East and South East Asia, especially where anticoagulation monitoring infrastructures may be less evident. However, the requirements for regular monitoring, the various food or drug interactions still make warfarin a rather inconvenient drug, even in Western countries with excellent anticoagulation clinics (e.g., Sweden).

How can things change? The focus has recently shifted towards identification of "truly low risk" patients who do not need any antithrombotic therapy, whilst those with 1 or more stroke risk factors can be offered effective stroke prevention, which is oral anticoagulation–whether will well-managed warfarin or 1 of the new oral anticoagulants (e.g., dabigatran, rivaroxaban) that overcome the many limitations of warfarin (8,10–13).

Until recently the $CHADS_2$ score (Cardiac Failure, Hypertension, Age, Diabetes, and Stroke [double]) was the most widely recommended and used risk stratification scheme. The limitations of the $CHADS_2$ score have been recognized (14,15). Based on a nationwide cohort study, for example, those with a $CHADS_2$

Table 3: Antithrombotic treatment and stroke/TE among patients with AF in Far East

Area	Study date	Design/patients (N)	Antithrombotic therapy	Prevalence/Incidence for stroke/TE
China	2003–2004	Community-based Prospective N = 18 615–2 979 Age ≥ 30 years	Warfarin: 0.5%–2.7% ASA: 28.4%–37.9%	Stroke: 13.0%–13.4%
	1999–2002	Hospital-based Retrospective N = 3 425–9 297	Warfarin: 6.6%–9.1% ASA: 56%–57.9% No-ATT: 35.5%	Stroke: 17.5%–24.2%
Japan	2005–2007	Community-based Prospective N = 2 242 Age: 20–90 years	Warfarin: 70.1% ASA: 31.0% Ticlopidine: 4.1%	Stroke: 14.3%
	1991–2008	Hospital-based Prospective/ Retrospective N = 1 810–19 825	Warfarin: 9.3%–57% ASA: 18%–28.5% Ticlopidine: 7.5%–7.9%	Cerebral infarction: 3.1% Ischemic events: 4.6% (1.7 years follow-up) Embolic events: 8.6% (4.6 years follow-up)
Singapore	2008	Community-based Prospective N = 1 839 Age ≥ 55	Warfarin: 3/26	Stroke: 15.4%
South Korea	2000	Community-based Prospective N = 14 540 Age: 40–92 years		Stroke: 2.8%
Taiwan	1990–2009	Community-based Prospective/ Retrospective N= 3 580–39 541 Age ≥ 35 years Mean age: 70.1 (12.1) years	Warfarin: 21.1% ASA: 46.7% Ticlopidine/clopidogrel: 5.4%	Stroke incidence: 37.7 per 1000 person-years Prevalence previous TE: 15.0%
	1997–2002	Hospital-based Prospective/ Retrospective N = 4 435–162 340	Warfarin: 28.3% ASA: 37.9% Any ATT: 62.0%	Stroke: 15.2% Male: 12.1%–15.2% Female: 14.7%–17.6%
Malaysia*	2000-2003	Hospital-based Prospective N = 1 435	Warfarin: 20%	

ASA = Aspirin, ATT = Antithrombotic therapy, TE = Thromboembolism, TIA = Transient ischemic attack.
[a] Source: Lip GY, et al. *Chest*. 2012.

score = 0 were not truly "low risk", with one-year event rates ranging from 0.84 (CHA_2DS_2-VASc score = 0) to 3.2 (CHA_2DS_2-VASc score = 3) (9).

In 2010, the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 years [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65–74 years, sex category [female]) was recommended for the assessment of risk of thromboembolism in patients with AF. Various validation studies have shown that the CHA_2DS_2-VASc score can better identify truly low risk AF patients, who are unlikely to benefit from antithrombotic therapy (8,16).

Table 4: Stroke and bleeding risk score

$CHADS_2$	Stroke rate (%/year)	CHA_2DS_2-VASc	Stroke rate (%/year)	HAS-BLED	Points awarded
0	1.9	0	0	H	1
1	2.8	1	1.3	A	1 or 2
2	4.0	2	2.2	S	1
3	5.9	3	3.2	B	1
4	8.5	4	4.0	L	1
5	12.5	5	6.7	E	1
6	18.2	6	9.8	D	1 or 2
		7	9.6		
		8	6.7		

$CHADS_2$ and CHA_2DS_2-VASc score: Low risk = 0, Intermediate = 1, High risk = ≥ 2. HAS-BLED score: Low risk = 0–1, Intermediate risk = 2, High risk = ≥ 3. Abbreviations: $CHADS_2$ = Cardiac failure, hypertension, age, diabetes, and stroke (doubled), CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥ 75 years (doubled), diabetes mellitus, stroke (doubled), vascular disease, age 65–74 years, sex category (female), HAS-BLED = Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly.

Bleeding risk needs to be balanced against stroke and systemic embolism risk when making decisions for thromboprophylaxis. The HAS-BLED (Hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score has been proposed to use in conjunction with CHA_2DS_2-VASc, with which clinicians might make a simple and informed judgment to the benefits and risks of anticoagulation (Table 4). A high HAS-BLED score is not a means to stop oral anticoagulation, as such patients have an even greater net clinical benefit (17).

In conclusion, the importance of oral anticoagulation in the management of AF has been beyond any doubt documented. With the exception of real low risk patients (CHA_2DS_2-VASc = 0), every patient with AF will benefit from oral anticoagulation. This rule seems to apply irrespective of age, gender, or ethnicity. It is crucial to fill the gap between clinical trial and clinical practice in the management of AF. The simplicity and efficacy of risk stratification tools and the advantages of new oral anticoagulants are expected to significantly contribute to the improvement of our practice. With respect to the AF population in the Far East and South East Asia, the limited data have showed that the rates of AF-related stroke are high, representing a great healthcare burden. Things can only improve.

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Leptospira proliferate in fresh water, damp soil, vegetation, and mud. The occurrence of flooding after heavy rainfall facilitates the spread of the organism because, as water saturates the environment, *Leptospira* present in soil pass directly into surface waters.

Sir Roy Calne – Living Fields
Oil on board

"The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated" – Plato.

Original Article

Rapid Diagnosis of Leptospirosis by Multiplex PCR

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Abstract

***Background*: Traditionally, the most common diagnostic approach used for diagnosing leptospirosis was the demonstration of immune-seroconversion in acute and convalescent patient serum samples. Recently, a variety of molecular techniques, including conventional and real-time polymerase chain reaction (PCR), have been developed for the specific detection of pathogenic bacteria from the genus *Leptospira*. PCR is a sensitive, specific, and rapid technique that has been successfully used to detect several microorganisms; including those of clinical significance.**

***Methods:* In this study, we developed a multiplex PCR (mPCR) assay for detecting *Leptospira's* DNA. The mPCR assay detects both the 16S rRNA gene and the major outer membrane lipoprotein gene, which is known as *LipL*32. Representative serovars were tested from 10 species of *Leptospira* and 23 other species of bacteria.**

***Results:* A positive result was obtained from all leptospiral serovars. The amplification sensitivity for the multiplex assay was 21.8 pg and 1×10^3 leptospires/ml. This mPCR assay has the potential to facilitate a rapid and sensitive diagnosis for acute leptospirosis.**

***Conclusion:* The mPCR assay developed in this study can be used for the early detection of leptospirosis. The *LipL*32 gene could also serve as another target to aid in the efficient detection of leptospiral infection because using 2 sets of primers in mPCR increases the sensitivity and specificity of the test.**

Keywords: *16S rRNA, leptospirosis, LipL32, mPCR, nucleic acid amplification test*

Introduction

Leptospirosis is one of the most common zoonoses in the world. Recently, leptospirosis has been recognised as a re-emerging infectious disease among animals and humans (1–3). Although leptospirosis is distributed worldwide (4), it is most common in temperate and tropical climates. However, leptospirosis has the potential to become even more prevalent with the anticipated rise in global temperature (2,5,6). It was reported that the whole region of Southeast Asia is an endemic area for leptospirosis (7), including Malaysia as several outbreaks have been recorded. An outbreak of acute febrile illness was reported among the athletes participating in the Eco-Challenge located in Sabah, and the Segama River was found to be the primary source of infection (8). Furthermore, 46 cases were identified in an outbreak in Kampung, Kebatu, Beaufort, Sabah that was associated with swimming in a creek near an oil palm plantation (9) and a few outbreaks involving individuals (10). Lastly, there was a report of a sudden outbreak of acute febrile illness following the heavy rain and floods in the southern state of Johor (11,12).

Leptospirosis is caused by pathogenic bacteria from the genus *Leptospira*, which is a spirochete of the family Leptospiraceae and the order Spirochatales. Approximately 10 million people are affected by leptospirosis throughout the year with a 5%–25% fatality rate (5). However, with early detection and treatment, leptospirosis is a treatable disease. Nevertheless, early detection and treatment depends on

epidemiological factors, symptoms and laboratory tests. A large array of tests for this disease have been described, including microscopic demonstration, molecular diagnosis, isolation and identification of leptospires, as well as serological diagnosis, such as the microscopic agglutination test (MAT) (3). There are several limitations to MAT, including the false-negative results obtained early in the course of the disease, the cross-reactivity excluding the ability to distinguish between serovars, the highly labour-intensive and time-consuming nature of the technique, and the requirement of a large panel of live leptospires (1). Thus, MAT is a complex test to control, perform, and interpret.

Enzyme-linked immunosorbent assay (ELISA) and micro-capsular agglutination test (MCAT) are serological tests that reduce the false-positives associated with vaccinal responses and provide earlier detection. In Australia, it was found that the IgM ELISA test could exhibit notably high sensitivity (100%) for the detection of acute leptospirosis (13). However, the same commercial assay demonstrated poor diagnostic accuracy (sensitivity of 60.9% and specificity of 65.6%) using admission serum in Laos (14). Bacterial culture, MAT, and ELISA can be applied in well-equipped laboratories by trained staff. However, few diagnostic facilities have the capacity and expertise to perform these tests for leptospirosis.

PCR has been used to detect leptospiral DNA in samples obtained from animals (15,16) and human (17–22). In this study, we have developed an mPCR amplification with 2 sets of primers, which will aid in the specific and sensitive detection of *Leptospira* species. The mPCR targets the well-known 16s rRNA gene (17), and a newly designed primer that targets the *LipL*32 gene. The *LipL*32 gene is a major outer-membrane lipoprotein from the genus *Leptospira*. Furthermore, the *LipL*32 gene is an important virulence factor confined to pathogenic strains of all *Leptospira* species. The mPCR could be used as an alternative to the traditional diagnostic methods, such as leptospiral isolation and the MAT serological assay.

Materials and Methods

Organisms and growth conditions

Leptospiral serovars were obtained from Universiti Putra Malaysia, Selangor. *Leptospira* were grown in Ellinghausen, McCullough, Johnson, and Harris (EMJH) medium (Becton-Dickinson Biosciences, Detroit, US) at 28 °C and were periodically subcultured in fresh medium. Commonly encountered commensal and pathogenic bacteria cultures from our own stock culture were used as controls.

Genomic DNA isolation and purification

Using an in-house genomic extraction protocol, DNA extraction was carried out on the cell pellets of leptospiral and bacterial cultures. Briefly, 1.5 mL of culture isolate was centrifuged at 13 000 g for 5 minutes to obtain approximately 0.1 µg of pellet. A solution of 200 µL of 20% sucrose, 50 mM Tris-HCl, 1% SDS, 0.2 N NaOH, 25 mM EDTA, and 0.1 M NaCl was added and the mixture was inverted gently. The mixture was subsequently incubated at room temperature for 5 minutes. For protein precipitation, 200 µL of 3 M NaOAc (pH 5.2) was added and the mixture was gently inverted. The mixture was subsequently spun down at 13 000 g for 5 minutes at 4 °C to separate the supernatant containing the DNA. The clear supernatant was subsequently placed into a fresh tube and 600 µL of ice-cold 95% ethanol was added to precipitate the genomic DNA. The mixture was incubated in liquid nitrogen for 15 minutes and spun down at 13 000 g for 15 minutes at 4 °C to pellet the DNA. Next, the pellet was washed with 1 mL of 80% ethanol, air-dried, and resuspended in 50 µL of sterile distilled water. The concentration of the DNA extract was measured using a spectrophotometer and stored at –20 °C.

Primers design and PCR amplification

Oligonucleotide sequences of Lep F, Lep R, Lau01, and Lau02 used for the mPCR amplification of the *Leptospira* species are listed in Table 1. Lep F and Lep R primer (17) amplified a 330 bp sequence from the 16S rRNA gene. The Lau01 and Lau02 primer pair was designed by aligning the *LipL*32 gene (accession number: NC 005823) using the ClustalW programme (EMBL, UK) (23), and primers were selected using the Primer3 programme (Whitehead, US) (24). Lau01 and Lau02 primer pair amplifies a 660 bp sequence of the *LipL*32 gene. The specificity of the primers was bioinformatically verified using the Primer-Blast programme (NCBI, MD).

The final optimised conditions for the mPCR were as follows: PCR was performed with the 1X Colorless GoTaq® Flexi Buffer (Promega, US), 200 µM (each) deoxynucleoside triphosphates, 1.5 mM $MgCl_2$, 1U of GoTaq® Flexi DNA Polymerase (Promega, US), 5 µM of Lau primers, and 10 µM of Lep primers in

Table 1: Primers for the mPCR amplification of *Leptospira* species

Oligonucleotide sequence 5'-3'	Length (bp)	Amplicon size (bp)	Ref.
Lep F: GGCGGCGCGTCTTAAACATG	20	330	17
Lep R: TCCCCCCATTGAGCAAGATT	20	330	17
Lau01: ACTCTTTGCAAGCATTACCGC	21	660	This study
Lau02: AGCAGACCAACAGATGCAACG	21	660	This study

a total 20 µL reaction volume. Amplification was performed in a thermocycler (Bio-Rad, US) with initial denaturation at 94 °C for 3 minutes followed by 29 cycles of denaturation at 94 °C for 30 seconds, primer annealing at 58 °C for 30 seconds, and DNA extension at 72 °C for 40 seconds before the final extension step at 72 °C for 5 minutes to complete synthesis of all strands.

Detection of amplified DNAs

PCR products were analysed by gel electrophoresis. Next, 10 µL with 2 µL of gel loading buffer of each sample was loaded onto a 1.2% electrophoresis-grade agarose gel (Bio-Rad, California, US) and run in 1X TAE buffer at 100 V for 45 minutes. Gels were stained with ethidium bromide and visualised using a UV transilluminator (UVP Inc., CA).

Detection limits and specificity of primers

The detection limits and sensitivity of the mPCR was determined using a serial dilution of leptospiral DNA mix and by urine-spiking experiments. *L. interrogans* serovar Icterohaemorrhagiae was used for the spiking of urine sample. Leptospiral cell concentration was measured by spectrophotometry at an optical density (OD) of 0.14 at 420 nm (approximately 5×10^8 cells/ml) (33). Next, 400 µl of the cultured *Leptospira* in liquid EMJH (number of cells as 2×10^8 cells) was added to 1.6 ml of urine from a healthy human (final concentration of cells is 1×10^8 cells). A 10-fold serial dilution was subsequently prepared by diluting the spiked urine sample with urine of a healthy human. Next, 1 ml of each dilution was used for DNA extraction. Leptospires in each 1 ml dilution were concentrated by centrifugation at 13 000 g for 15 minutes and washed once with 1 ml PBS. Next, 500 µL of chelex slurry (10% 200–400 mesh) (Bio-RAD, US) was added and the solution was vortexed for 15 seconds and quickly spun for 1 minute. The samples were subsequently incubated in a 100 °C water bath for 20 minutes. The samples were vortexed for 15 seconds and spun at 13 000 g for 20 minutes to ensure that all contents were in the bottom of the microcentrifuge tube. Lastly, 5 µL of the supernatant was used for the mPCR.

The specificity of the primers was evaluated with 9 serogroups identified in Malaysia and 23 strains of commensal and pathogenic bacteria (non-*Leptospira*) commonly encountered in clinical specimens.

Results

Optimisation of mPCR amplification

Because primer-dimers and other nonspecific products may interfere with the specific products of mPCR, the reaction often requires extensive optimisation. Amplification specificity is also influenced by other factors, such as the $MgCl_2$ concentration in the PCR buffers and primer concentration. We split our mPCR optimisation strategy into 3 main steps: annealing temperature, amount of primers used, and concentrations of $MgCl_2$ in the PCR reaction. We began the optimisation strategy by performing the mPCR in standard 20 µL reactions (consisting of 200 mM dNTP, 1.5 mM $MgCl_2$, 10 pmole each of primers, 1X PCR buffer, 1 unit Taq polymerase, and 218 ng of template DNA from a mixture of leptospiral genomic DNA).

Optimisation of annealing temperature

The annealing temperature in a PCR usually depends directly on the length and composition of the primer(s). In our mPCR, we chose to detect 2 targets: 16S rRNA and the leptospiral *LipL32* gene. For the 16S rRNA target, we took advantage of previously reported primers (17). Concerning the *LipL32* gene, we extracted the sequence from genebank and designed new primers. Recently, the *LipL32* gene has been suggested to be a target for nested and real-time PCR (25–27).

We first optimised the multiplex PCR amplification conditions using both the primer sets of Lep-F-Lep-R and Lau01-Lau02 with the genomic DNA mixture from the extracted DNA.

A gradient PCR was carried out to determine the best annealing temperature using a BioRAD MyCycler Thermocycler. Figure 1a shows the result of the gradient PCR at an annealing temperature of 50 °C–60 °C. The annealing temperature of 58 °C was chosen as the optimal annealing temperature for the mPCR.

Optimisation of primer concentration

The quantity of DNA primer(s) supplied to the PCR may influence the results of the mPCR. Extremely high or low primer amounts should be avoided because high primer concentrations may inhibit the multiplex reaction, whereas low amounts may not be sufficient. In order to amplify all of the specific PCR products with equal efficiency, the concentrations of the individual primer pairs were optimised. Figure 1c shows that the best combinations of primers were 5 µM and 10 µM for Lau01-Lau02 and Lep-F-Lep-R primers, respectively.

Optimisation of $MgCl_2$ concentration

Finally, optimisation was carried out to determine the best amount of $MgCl_2$ to be added to each reaction. The optimal $MgCl_2$ concentration yields maximal amplification of a specific target with minimal non-specific products and primer-dimer formation. In order to find the optimal amount, $MgCl_2$ concentration was varied between 1.5 mM–4.0 mM. As shown in Figure 1b, 1.5 mM of $MgCl_2$ was selected as the optimal concentration.

Detection limits of mPCR

The sensitivity and detection level of the mPCR was determined using a serial dilution of genomic DNA mix from leptospiral strains and by urine-spiking. The PCR was performed using the optimised conditions, as mentioned previously. The lowest limit of detection using genomic DNA of *Leptospira* in this assay was found to be 21.8 pg, as shown in Figure 2. However, the sensitivity of the test using urine samples spiked with serial dilutions of a pure culture of leptospires was 1×10^3 cells/ml urine (Figure 3).

Specificity of multiplex PCR

10 leptospiral serovars representative of different serogroups commonly isolated in Malaysia were analysed to determine the specificity of the mPCR. Our results showed that each strain produced a positive signal for both targeted genes (a 330 bp band and a 660 bp band) (Figure 4). The specificity of the oligonucleotide primer sets were also tested against a number of commensal and

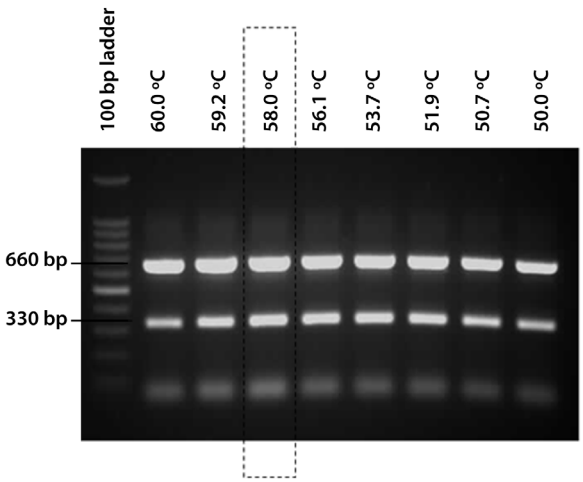

Figure 1a: The optimisation of the reaction's annealing temperature. The optimum annealing temperature was 58.0 °C.

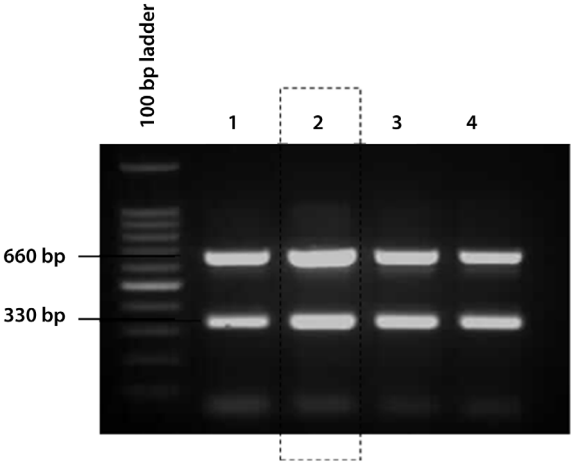

Figure 1c: The optimisation of the primer concentration. The optimal ratio of primers was 5 µM of Lau primers and 10 µM of Lep primers. Lane 1: Lau 10 µM and Lep 10 µM, Lane 2: Lau 5 µM and Lep 10 µM Lane 3: Lau 5 µM and Lep 15 µM, Lane 4: Lau 5 µM and Lep 20 µM.

pathogenic bacteria (*Yersinia enterocolitica, Methicillin Resistance Staphylococcus aureus, Psuedomonas aeruginosa, Enterococcus* species, *Burkholderia pseudomallei, Shigella flexneri, Enteropathogenic Escherichia coli polyval, Shigella boydii, Staphylococcus aureus, Salmonella paratyphi B, Corynebacterium diphtheria, Shigella dysenteriae, Bacillus subtilis, Morganella morganii, Enteropathogenic Escherichia coli, Staphylococcus saprophyticus, Diphteroid, Vibrio cholera, Providencia stuarti, Trepanoma pallidum, Flovobacterium* species, *Shigella sonnei,* and *Klebsiella* species) commonly encountered in clinical specimens. All of the non-*Leptospira* bacteria commonly encountered in clinical specimens were negative with both of the primer sets used in the multiplex PCR (results not shown).

Discussion

Detection of the pathogenic *Leptospira* species is important for the early diagnosis of leptospirosis because it provides unequivocal evidence of active infection. However, the application of this strategy was hampered by the limitation of conventional methods. As a result, clinical diagnosis is often based on serological tests, despite the fact that antibodies begin to appear 8–10 days after the onset of the illness.

The use of PCR is now gaining popularity for the diagnosis of fastidious organisms,

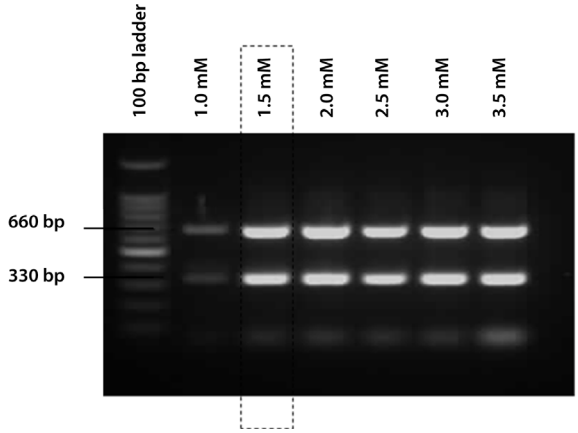

Figure 1b: The optimisation of the $MgCl_2$ concentration. The optimal amount of $MgCl_2$ was 1.5 mM.

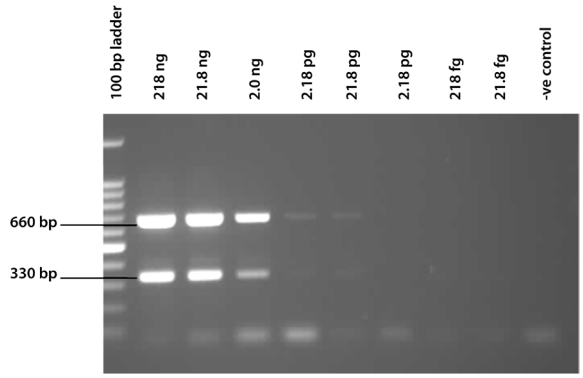

Figure 2: The sensitivity of mPCR in terms of the amount of genomic DNA mixture used as template. The agarose gel revealed that the mPCR was able to detect up to 21.8 pg of genomic DNA.

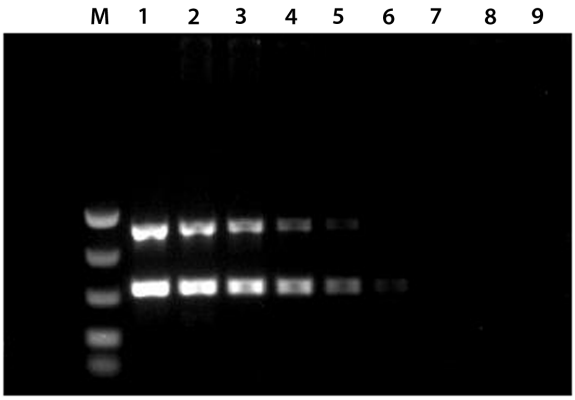

Figure 3: The sensitivity of the mPCR tested on spiked urine samples. M: PCR marker (NEB), Lane 1: 1×10^8 leptospires/ml, Lane 2: 1×10^7 leptospires/ml, Lane 3: 1×10^6 leptospires/ml, Lane 4: 1×10^5 leptospires/ml, Lane 5: 1×10^4 leptospires/ml, Lane 6: 1×10^3 leptospires/ml, Lane 7: 1×10^2 leptospires/ml, Lane 8: 1×10 leptospires/ml, Lane 9: 1 leptospires/ml.

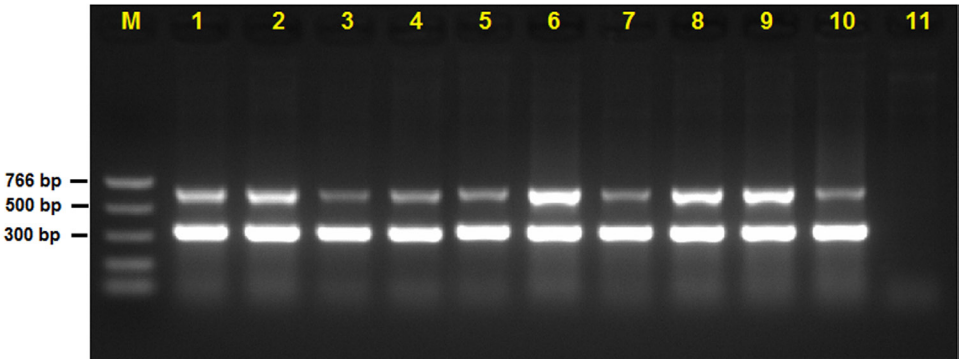

Figure 4: The specificity of the mPCR on *Leptospira* species. 10 serovars of bacteriologically identified *Leptospira* were used from Malaysia. Lane M: PCR marker (New England Biolab, US), Lane 1: *L. interrogans* serovar Canicola, Lane 2: *L. interrogans* serovar Pomona, Lane 3: *L. interrogans* serovar Australis, Lane 4: *L. interrogans* serovar Bataviae, Lane 5: *L. interrogans* serovar Pyrogenes, Lane 6: *L. interrogans* serovar Grippotyphosa, Lane 7: *L. interrogans* serovar Icterohaemorrhagiae, Lane 8: *L. interrogans* serovar Hebdomadis, Lane 9: *L. borgpetersenii* serovar Ballum, Lane 10: *L. kmetyi* serovar Malaysia, Lane 11: Negative control.

including *Leptospira*. This method offers several key advantages over the gold standard techniques of culture and MAT, such as a faster turn-around time, less contamination, and elimination of the need for the production of reference hyperimmune antisera to determine the identity of the cultured organism. To date, most of the reported conventional or nested PCR diagnosis are based on the detection of a single target, such as the 16S rRNA gene (17,18,28) or the 23S rDNA (29), or using G1/G2 primer pairs (13,30).

In this report, we described the development of an mPCR for the rapid detection of leptospiral infection based on the amplification of 2 genes: 16S rRNA gene and *LipL*32 gene. The mPCR used in this study offers further advantage over that of conventional PCR because it uses 2 sets of primers that increase the specific amplification (330 bp and/or 660 bp). Therefore, pathogenic strains can be detected rapidly for diagnostic purposes. It was also shown that the mPCR is a notably sensitive test, detecting up to 21.8 pg of genomic DNA and 1×10^3 leptospires/ml in seeded urine. Although real-time PCR has increasingly gained popularity (due to the elimination of the agarose gel electrophoresis step), the method is still relatively expensive for a small laboratory, especially in the third-world countries where the disease is predominant. Therefore, conventional PCR is still a better choice because this methodology is not technically demanding and uses only commercially available reagents. Therefore, this technique can be applied to diagnostic laboratories to help in identifying pathogenic leptospires, especially in developing countries.

The mPCR uses 2 sets of primers, which are based upon amplification of the *Leptospira* 16S rRNA gene that is conserved throughout the bacterial kingdom, as well as another set of primers detecting the leptospiral major outer-membrane lipoprotein *LipL*32 gene. The *LipL*32 gene is highly specific and is absent from nonpathogenic *leptospira* or any other commensal pathogenic bacteria. The leptospiral major outer-membrane lipoprotein (*LipL*32) is expressed during infection by all pathogenic strains and can prove to be an important candidate antigen for the development of a sensitive and specific test for leptospirosis (31,32).

Even though the study started with the detection of *Leptospira* species using extracted genomic DNA, the results were notably encouraging, and we believe that this method can be used as a valuable tool in the early diagnosis of human leptospirosis. However, clinical evaluation to confirm the potential of the PCR protocol is needed. To monitor the effectiveness of DNA extraction and the presence of any inhibitory factors in the PCR, an internal

control that will be co-amplified is to be included in this multiplex PCR. The conversion of the current method into a thermo-stabilised PCR will be undertaken in future work.

Conclusion

In summary, the mPCR was shown to be a promising adjunct to the early diagnosis of leptospirosis. The *LipL*32 gene can be another target for the efficient detection of leptospiral infection because the 2 sets of primers in an mPCR increases the sensitivity and specificity of the test. On the basis of its sensitivity and specificity, the mPCR method described here should be a useful tool for the early diagnosis of leptospirosis, irrespective of serovar.

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Conception and design: MS, THT, KLL
Obtaining of funding, analysis and interpretation of the data: THT
Provision of study materials or patients, collection and assembly of the data: MR, SAA
Drafting of the article: DAS, SAA
Critical revision of the article: SAA
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Original Article

Role of the Lewis and ABO Blood Group Antigens in *Helicobacter pylori* Infection

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Abstract

Background: ***Helicobacter pylori*** **infection is a major risk factor for chronic gastritis and gastric cancer. Some findings show increased frequencies of these diseases in individuals with type O blood and in secretors (expressing Le^b antigen), but other studies have not found any relationship between blood groups and this infection. Given that *H. pylori* infection and gastric cancer are common in Iran, the assessment of the pathogenesis of this infection in relation to these blood groups could be valuable.**

Methods: **In a cross-sectional study, we determined the ABO and Lewis blood groups of participants using the tube method and evaluated the level of anti-*H. pylori* immunoglobulin G using an enzyme-linked immunosorbent assay. This study included 171 Iranian blood donors from Mashhad, Iran, during 2010. The significance of the differences in the frequencies of the Lewis and ABO phenotypes between individuals infected with and without *H. Pylori* infection were tested using the Chi-square test. A *P*-value < 0.05 was considered significant.**

Results: ***H. pylori*** **infection was found in 76.6% of the study subjects (*n* = 131). The most common ABO blood group was O (33.9%), and the most common Lewis blood group was Le(a-b+) (54.7%). The frequencies of the ABO, Lewis, and secretion phenotypes were not significantly different between the infected and uninfected subjects.**

Conclusion: **We did not find any significant relationship between the Lewis, ABO, and secretion phenotypes and *H. pylori* infection.**

Keywords: *ABO blood groups, blood group antigens, Helicobacter pylori, Lewis blood group, secretor blood group*

Introduction

Helicobacter pylori infection is a high-prevalence worldwide; nonetheless, it is more common in underdeveloped and developing countries than in developed countries (1–3). *H. pylori* infection is most common in adults, with a prevalence of more than 90% in some countries (4). In Iran, the prevalence of this infection in adults has been reported to be approximately 80% (5,6). *H. pylori* infection is a major risk factor for chronic gastritis, peptic ulcers, and gastric cancer (7–9), which is the most common cancer in northern and northwestern Iran (6).

Lewis antigens, like ABO blood group antigens, are expressed in fluids and tissues such as the endothelium and the bowel mucosa. *H. pylori* expresses several lipopolysaccharides on its outer membrane that mediate the adhesion of the bacterium to the gastric epithelium and allow persistent colonisation (10). *H. pylori* binds to the H and Le^b blood group antigens in gastric mucosa; this binding most likely explains the increased incidence of gastritis and gastric cancer in individuals with type O blood and in secretors (expressing the Le^b antigen) (11,12). However, some other studies have not observed any relationship between *H. pylori* infection and the Lewis (4) and ABO blood groups (13). Therefore, the associations between the Lewis and ABO blood groups and *H. pylori* infection are controversial. There exists heterogeneity in the expression of outer membrane proteins, especially BabA, among different *H. pylori* strains, such that there is heterogeneity in the capacity of *H. pylori* to bind to the Le^b antigen on the surface of gastric epithelial cells. This heterogeneity may be a factor that explains some of the differences in the clinical outcomes of this infection (14). Given that *H. pylori* infection and gastric carcinoma are high-prevalence diseases in Iran, the assessment of the pathogenesis of *H. pylori* infection in relation to the blood groups could be valuable.

Materials and Methods

This cross-sectional study was financially supported and ethically approved by the research vice chancellor of Mashhad University of Medical Sciences, Iran. The study population included 171 healthy adult blood donors who were admitted to the Imam Reza Teaching Hospital and Blood Transfusion Center, Mashhad (a large city located in northeastern Iran), during 2010. Subjects who had a positive direct globulin test, were receiving treatment for *H. pylori* infection, or had a history of blood transfusion during the 3 months prior to admission were excluded from this study. We also excluded lipemic, icteric, and hemolytic samples. After obtaining informed consent, 2 mL of blood containing ethylenediaminetetraacetic acid was collected from each subject for blood group typing, and 2 mL blood without anticoagulant was collected for serologic evaluation of *H. pylori*. Red cell phenotyping was performed using commercial monoclonal antibodies in a direct agglutination test using the tube method according to manufacturer's protocol (Biotest AG, DE). Based on the expression of the Le^b antigen, subjects were divided into secretor and non-secretor groups. Because the secretory status was not obvious for the Le(a-b-) phenotype, subjects with this phenotype were not included in either of these groups (11).

Serum samples were tested for anti-*H. pylori* immunoglobulin G using an enzyme-linked immunosorbent assay kit (Euroimmun AG Lubeck, DE). According to the kit's documentation, this test does not exhibit any cross-reactivity; however, high levels of lipemia, jaundice, and hemolysis may influence the results.

Statistical analyses

First, the prevalences of Le^a and Le^b antigen production, the Lewis phenotypes, and *H. pylori* infection were determined. Then, the correlations between *H. pylori* infection and the Lewis antigens as well as the Lewis and ABO phenotypes were tested by Fisher's exact test. A P-value < 0.05 was considered significant. All results were analysed by SPSS version 16 (SPSS Inc., Chicago, IL, US).

Results

We evaluated 171 individuals, 94.3% of whom were male and 5.7% of whom were female. The age range was 19–61 years with a mean (SD) of 33.8 (1) years. *H. pylori* infection was identified in 76.6% of the subjects (n = 131). No significant association was observed between sex and *H. pylori* infection. The most common ABO blood group was O (33.9%), followed by A (29.5%), B (28.7%), and AB (7.9%), and the most common Lewis blood group was Le(a-b+) (54.7%), followed by Le(a+b-) (34.9%), Le(a+b+) (8.9%), and Le(a-b-) (1.6%). Of 169 donors, 106 (62.7%) were secretors and secreted Lewis and ABO antigens in secretions.

As shown in Table 1, the frequencies of the ABO, Lewis, and secretion phenotypes were not significantly different between the infected and uninfected subjects. The Le(a-b-) phenotype was rare (n = 2), and the secretion status of this phenotype cannot be inferred; therefore, individuals with this phenotype were not included in the Lewis and the secretion phenotype analyses.

Discussion

The blood group antigens are important in the pathogenesis of some diseases (15,16). The Lewis antigens are biochemically related

Table 1: Comparison of the distributions of ABO, Lewis and secretion phenotypes between the 2 subject groups (with or without *Helicobacter Pylori infection*)

Characteristics	Total	Uninfected *n* (%)	Infected *n* (%)	*P*- value[a]
ABO phenotypes	171			0.669
O		15 (37.5)	48 (36.6)	
A		10 (25.0)	38 (29.0)	
B		11 (27.5)	31 (23.7)	
AB		4 (10.0)	14 (10.7)	
Lewis phenotypes	169			0.945
Le(a+b-)		16 (41.0)	47 (36.2)	
Le(a-b+)		21 (53.8)	71 (54.6)	
Le(a+b+)		2 (5.1)	12 (9.2)	
Secretion phenotypes	169			0.581
Secretor		23 (59.0)	83 (63.8)	
Non-secretor		16 (41.0)	47 (36.2)	

[a] *P* - value

to the ABO blood antigens. The *secretor* (*Se*) gene, encodes a fucosyltransferase that adds fucose to the terminal galactose of the type 1 precursor chain, forming a type 1 H chain. The Lewis gene encodes fucosyltransferase type III that can add fucose to type 1 precursor chains, forming the Le^a antigen, or fucose to type 1 H chains, forming the Le^b antigen. Persons lacking the *Se* gene, referred to as non-secretors, cannot produce type 1 H chains or the antigen derived from this type of chain, Le^b (11,12,17); therefore, non-secretors can only express the Le^a antigen. For this reason, we can use saliva for the determination of the Lewis phenotype in adults.

Some studies have shown that *H. pylori* binds to H and Le^b antigens (secretors) in the gastric mucosa. The binding of blood group antigen B to the outer membrane of *H. pylori* mediates the binding of *H. pylori* to Le^b antigens expressed on the gastric mucosa (10,18); this binding most likely causes the increased incidence of gastritis and gastric cancer in individuals with the O blood group and the Le(a-b+) phenotype (12).

Despite this, we did not observe any significant associations between *H. pylori* infection and the Lewis and ABO blood groups, as well as the secretion status (Table 1). The frequencies of the ABO blood group phenotypes in Iran have been reported to be the following: O in 37.62%, A in 30.25%, B in 24.36%, and AB in 7.77% of the population (19). These frequencies are similar to our results and those of other studies conducted in Iran (20). Heneghan et al. (17) determined the Lewis and ABO blood group phenotypes of 207 patients undergoing upper endoscopy and, similar to our study, did not observe any significant association between these blood groups or secretor status and *H. pylori* infection (17). Mattos et al. (4) studied the frequencies of the ABO and Lewis blood group phenotypes and secretor status in patients with or without *H. pylori* infection subjects by using breath and urea tests. They showed that *H. pylori* infection is more common in the O blood group patients, but they did not find significant associations between this infection and the Lewis blood groups and secretor status (4).

A study by Rothenbacher et al. (10) investigated the role of Lewis antigens in ongoing *H. pylori* infection in 712 women of different nationalities who were admitted to the Department of Gynecology and Obstetrics, University of Ulm, Germany, between November 2000 and November 2001; in contrast to the results of many other studies, they found a higher frequency of *H. pylori* infection in individuals with the Le(a+b-) phenotype than in individuals with the Le(a-b+) phenotype. Therefore, they presented the hypothesis that individuals with a Le(a+b-) phenotype secrete only Le^a and no other ABH substances in secretions such as

gastric fluids; in contrast, individuals with the Le(a–b+) phenotype (secretors) secrete Le^a as well as Le^b and ABH substances in body fluids. Thus, it is possible that the Le^b present in other body secretions such as gastric mucus may bind to specific glycoproteins of *H. pylori* and hinder the binding of *H. pylori* to the gastric mucosa (10).

Recent findings on strains of *H. pylori* from different areas of the world have revealed that different strains differed by approximately 1500-fold with respect to binding affinities, and there was considerable diversity related to the babA gene sequences (14,16,21). Not all strains are equally specific for O and Le^b; many strains from outside South America can bind to A and Leb in addition to O and Le^b. For example, Peruvian strains are related to Spanish strains but not to Asian strains (16,21). A study by Con et al. (22), in which 95 Costa Rican and 95 Japanese *H. pylori* isolates were genotyped, revealed a higher frequency of babA2 in Japan (96.8%) than in Costa Rica (73.7%). In comparison, the frequency of babA2/B was higher in Costa Rica (11.6%) than in Japan (1.1%). Con et al. (22) also suggest that frequencies of babA2 and babA2/B exhibit geographic differences (22). Another virulence factor characterised recently in *H. pylori* is a sialic acid–binding adhesin, SabA. The frequency of SabA also exhibits geographic differences and is more common in European than Japanese *H. pylori* isolates (23,24). As a result, this diversity in *H. pylori* strains may explain why our findings were different from those of some other studies from different geographic area. We suggest that a future study should characterise the strains of *H. pylori* in infected patients in addition to determine the ABO and Lewis blood groups.

Conclusion

We did not observe any significant relationship between the Lewis, ABO, and secretion phenotypes and *H. pylori* infection.

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Authors' Contributions

Conception and design, analysis and interpretation of the data, statistical expertise: MRK
Obtaining of funding, collection and assembly of the data: AMR
Provision of study materials, drafting of the article: MHS
Critical revision of the article: HA
Final approval of the article: ZB
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Original Article

Evaluation of X-Ray Beam Quality Based on Measurements and Estimations Using SpekCalc and Ipem78 Models

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Abstract

Background: **Different computational methods have been used for the prediction of X-ray spectra and beam quality in diagnostic radiology. The purpose of this study was to compare X-ray beam qualities based on half-value layers (HVLs) determined through measurements and computational model estimations.**

Methods: **The HVL estimations calculated by IPEM78 (Spectrum Processor of the Institute of Physics and Engineering in Medicine's Report 78) and SpekCalc software were compared with those determined through measurements. In this study, the HVLs of both Philips (Phil) (Philips Healthcare, Best, NL) and General Electric Company (GE) (GE Global Research, Niskayuna, US) diagnostic range X-ray machines (50 kVp to 125 kVp) were evaluated.**

Results: **In the HVL estimations, SpekCalc and IPEM78 showed maximum differences of 10% and 9%, respectively, compared with direct measurements. Both models provided means and SDs of HVLs that were within 5% of the HVL measurements of GE and Phil machines.**

Conclusion: **Both computational models provide an alternative method for estimating the HVL of diagnostic range X-ray. These models are user-friendly in predicting HVLs, which are used to characterise the quality of the X-ray beam, and these models provide predictions almost instantly compared with experimental measurements.**

Keywords: *beam quality, effective energy, HVL, IPEM78, SpekCalc*

Introduction

X-rays play an important role in modern technology, especially for medical imaging purposes. Medical sources of ionising radiation are the largest contributor to the population dose from artificial sources, and most of this radiation comes from diagnostic X-rays (1). The X-ray spectrum and beam quality are must-know parameters for studying the dosimetric properties of X-ray beams in diagnostic radiology. In order to completely describe the X-ray beam spectrum, the spectral photon fluence needs to be determined. A spectrometer is needed to measure the true spectral photon fluence; however, spectrometry is too expensive and time-consuming for routine application to X-rays. Therefore, determination of the half-value layer (HVL) is often used to describe the X-ray beam quality. The HVL of a beam is the thickness of material required to reduce the intensity of an X-ray or gamma-ray beam to one-half of its initial value (2,3). In kilovoltage X-ray, determination of the HVL of the X-ray beam can be used to characterise the effective energy by converting the HVL to the linear attenuation coefficient or mass attenuation coefficient. The effective energy of a polyenergetic beam is equal to the energy of a monoenergetic X-ray beam that is attenuated at the same rate as the polyenergetic beam (4). The effective energy is used to describe the penetration of a polyenergetic X-ray.

Direct measurement of X-ray spectra requires expensive equipment as well as careful attention and planning during the experimental measurement setup, which is generally not practical in clinical diagnostic radiology departments with limited physicist support. Because direct measurement is time-consuming and remains a difficult task, an effort to predict X-ray spectra from different energy ranges and with various target/filter combinations in diagnostic radiology began several decades ago and still represents an active area of research. Detailed knowledge of X-ray spectra is required for mathematical modelling and optimisation of imaging systems in diagnostic radiology. Generally, X-ray prediction models can be divided into 3 categories: empirical, semi-empirical, and Monte Carlo models. Empirical models are based on the use of measured data for the prediction of X-ray spectra. Semi-empirical models are

based on a theoretical formulation to calculate the X-ray spectra by mathematical derivation followed by tuning in the equations' parameters using measured data (5). IPEM78 (Spectrum Processor of the Institute of Physics and Engineering in Medicine's Report 78) is a software that simulates X-ray spectra using a semi-empirical model based on the Birch and Marshall model (6). IPEM78 results in higher transmission curves for all tube voltages compared with measured spectra, and the differences increase with tube voltage. SpekCalc (Institute of Cancer Research in London, UK) is a software programme used to calculate X-ray spectra from a tungsten anode X-ray tube. SpekCalc relies on deterministic equations for bremsstrahlung productions in combination with numerically pre-calculated electron distributions (7).

The purpose of this study is to compare the results of HVL estimations of IPEM78 (semi-empirical model) and SpekCalc (deterministic model) with HVLs determined from measurements. These 2 X-ray prediction models were evaluated as alternative and quick methods to determine X-ray beam quality in the clinical environment. The determined HVLs were compared with one another because the HVL is the parameter used to describe the quality of the X-ray spectrum. The effective energies for the range of X-ray energy peaks from 50 kVp to 125 kVp were also determined based on the linear attenuation coefficients determined experimentally.

Materials and Methods

Materials

This study was conducted with a (Phil) (model SRO 33 100 X-ray machine with ROT 350 Optimus 80-kW high frequency generator) and a General Electric Company (GE) (model 2336058 X-ray machine with housing 46-15540VG48 and MPH 50 high frequency generator) X-ray machines. The Phil machine has an anode angle of 13°. The permanent filtration inside the X-ray tube is 0.66 mm aluminium (mm Al) equivalent, the tube housing is 2.5 mm Al equivalent, and the additional filtration is 2.0 mm Al equivalent. The GE X-ray machine has an anode angle of 13°. The inherent filtration inside the tube is 0.8 mm Al equivalent at 150 kV and the tube housing is 0.3 mm Al equivalent at 150 kV. The filtration inside the collimator is 1.5 mm Al equivalent at 80 kV.

SpekCalc software was used to calculate the X-ray spectra. The spectra are presented for tungsten targets at tube voltages from 40 kV to 300 kV and target angles with a maximum of 90° with respect to the beam axis. The energy interval can be customised by the user. The SpekCalc graphical user interface (GUI) is shown

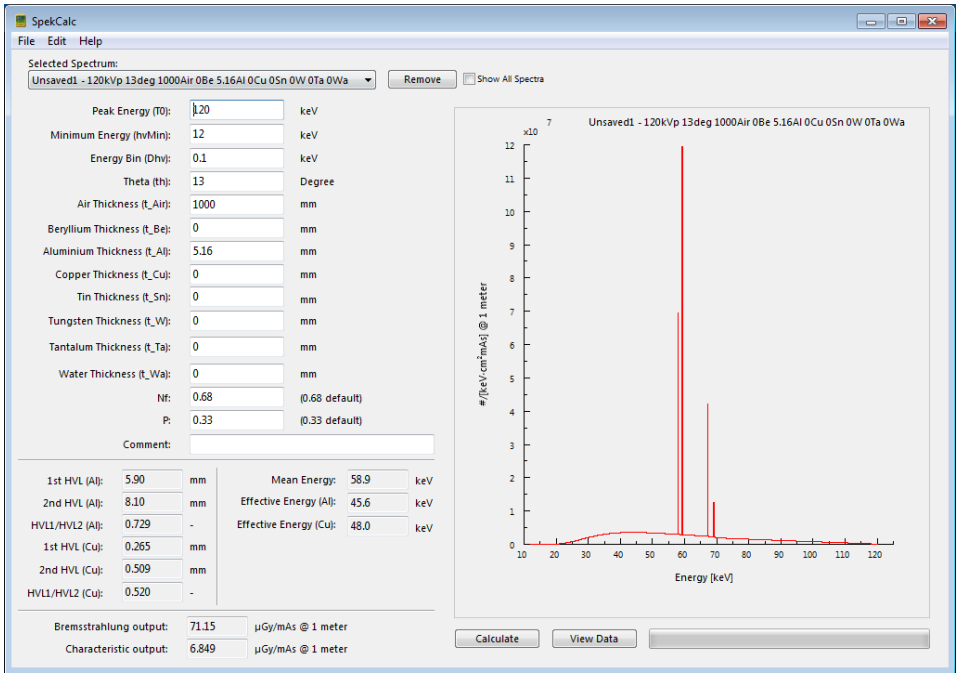

Figure 1: SpekCalc graphical user interface.

in Figure 1. IPEM78 uses an XCOM programme to calculate linear attenuation coefficients for various materials and contains sets of radiology and mammography X-ray spectra with considerably wider ranges (6). These spectra are presented for tungsten targets at tube voltages from 30 kV to 150 kV and target angles from 6° to 22°. Different materials can be chosen as additional filters. All spectra are provided at an energy interval of 0.5 kV. Voltage ripple is an input parameter for IPEM78. The IPEM78 GUI is shown in Figure 2.

Measurement of HVL

A Rad-Check Plus X-ray exposure meter (model 06-526-2200 [Fluke Biomedical, US]) was used as a dosimeter to measure the output of the X-ray machines. Aluminium attenuators of 10 × 10 cm with thicknesses of 0.5 mm and 1.0 mm were used in this study. The density of the aluminium attenuators is 2.699 g/cm^3.

The Rad-Check Plus exposure meter was positioned 100 cm perpendicular to the X-ray tube. The internal chamber of the Rad-Check Plus exposure meter was fully collimated within the X-ray field and was positioned in the centre of the 10 × 10 cm field, as shown in Figure 3. The first measurement was done without the aluminium attenuator. Next, measurement was repeated with a 0.5 mm Al attenuator in place between the X-ray tube and the exposure meter. The exposure was repeated while incrementing the aluminium thickness by 0.5 mm each time until the values approached the expected HVL value. The exposure measurements were subsequently repeated for a range of peak energies from 50 kVp to 125 kVp. A final exposure without an aluminium attenuator was repeated for every voltage to confirm an output stability of less than 2% from the first exposure without the aluminium attenuator. The relative intensity of the X-ray beam without an aluminium attenuator versus the aluminium attenuator thickness for every tube voltage was plotted on semi-log graphs, as shown in Figure 4 and Figure 5, for both GE and Phil machines respectively.

Determination of the linear attenuation coefficient (μ) and the HVL

The linear attenuation coefficient (μ) of aluminium for the corresponding tube voltage was determined by plotting a best-fit line using Graphpad Prism 5 (GraphPad Software Inc., California, US), as shown in Figures 4 and 5. The HVL was determined from the linear attenuation coefficient.

Determination of the effective energy

The effective energy of the X-ray machine was determined from the linear attenuation coefficient of the aluminium attenuator for various voltages using data from National Institute of Standards and Technology, as shown in Figure 6 (8). Later, the effective energy of both broad and fine focuses of the GE and Phil X-ray machines were compared.

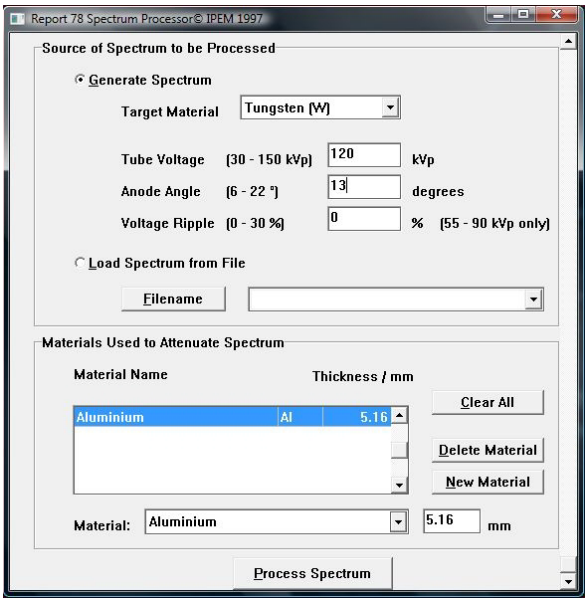

Figure 2: IPEM78 graphical user interface.

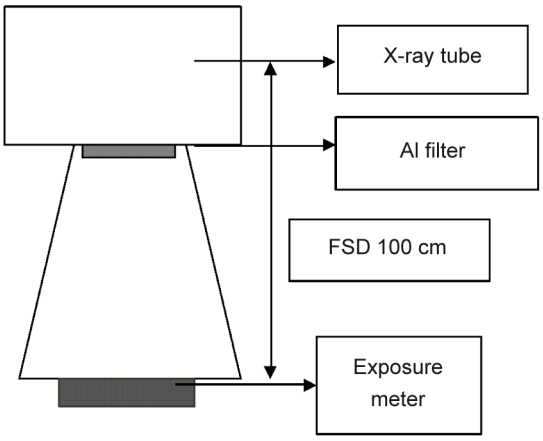

Figure 3: The experimental setup for half-value layer measurement. Abbreviation: FSD = Focus-surface distance.

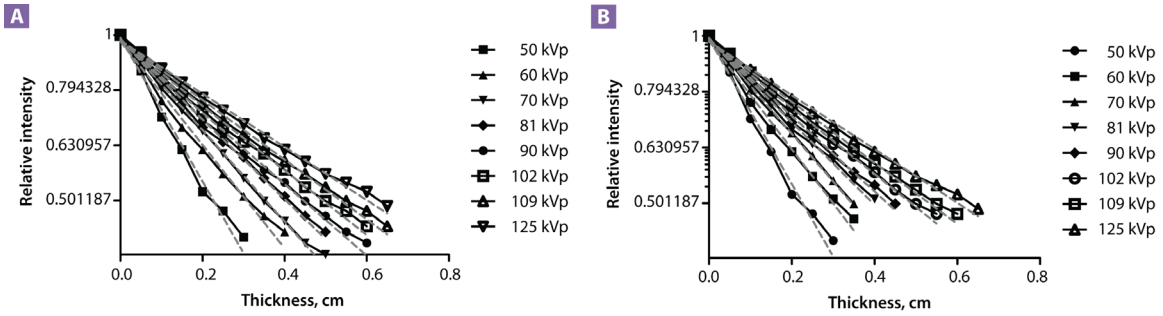

Figure 4: Transmission curves for the X-ray beam of a Phil X-ray machine corresponding to tube voltages ranging from 50 kVp to 125 kVp with (A) fine focus and (B) broad focus. The solid lines show the measured data, and the dashed lines show the best-fit line for half-value layer determination (in centimeter aluminium equivalent).

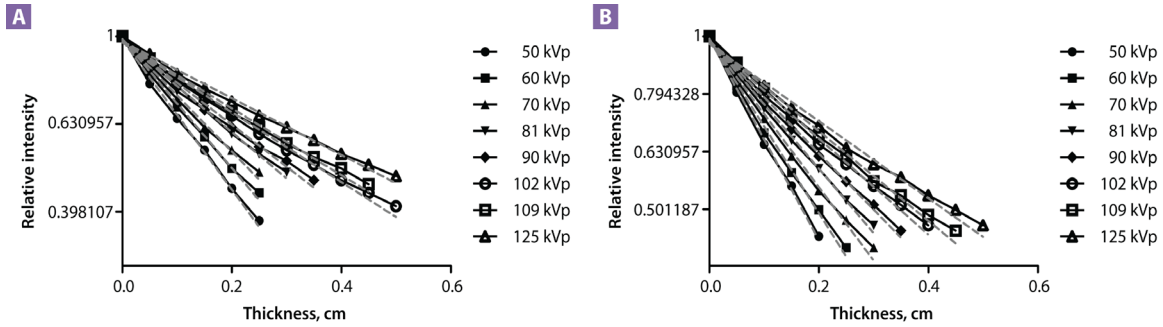

Figure 5: Transmission curves for the X-ray beam of a GE X-ray machine corresponding to tube voltages ranging from 50 kVp to 125 kVp with (A) fine focus and (B) broad focus. The solid lines show the measured data, and the dashed lines show the best-fit line for half-value layer determination (in centimeter aluminium equivalent).

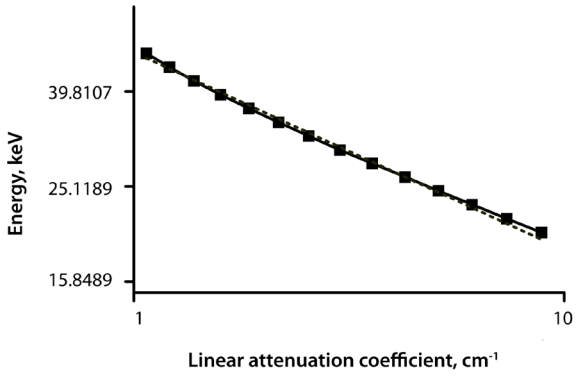

Figure 6: The energy of the X-ray beam versus the linear attenuation coefficient for effective energy determination based on National Institute of Standards and Technology (NIST) data. The solid line shows the data from NIST, and the dashed line shows the best-fit line for determination of the effective energy.

Evaluation of SpekCalc and IPEM78 for HVL estimations

The X-ray spectra calculated by the SpekCalc and IPEM78 models were evaluated by comparison with the measured spectra. The calculated HVLs were compared with the measured HVLs. The beam quality depends on tube voltage, filtration and anode angle; hence, both computational models were run to simulate spectra with the same parameters as the machines used in the direct measurements. The beam quality determined by direct measurement was taken to be the standard. The mean HVL ratios for all tube voltages in this study for both Phil and GE machines were calculated, and SDs were determined. For the accuracy comparison of the SpekCalc and IPEM78 models, mean HVL ratios were calculated for both broad and fine focuses of the 2 machines used, and SDs were subsequently determined.

Results

Comparison of effective energy

The HVLs determined from the direct measurements were used to determine the effective energies. The determined effective energies are summarised in Table 1. The effective energies of the Phil machine were higher than those of the GE machine for the entire range of tube voltages. For both machines, most of the effective energies observed when using a broad focus were slightly lower than those observed when using a fine focus.

Evaluation of SpekCalc and IPEM78 for HVL estimations

The HVL ratios calculated by comparing the results of the computational models (SpekCalc and IPEM 78) to the results of the experimental measurements for a range of tube

Table 1: Comparison of the effective energies in Phil and GE X-ray machines at tube voltages in the diagnostic range of radiology energy

Tube voltage (kVp)	Phil X-ray machine			GE X-ray machine		
	Effective energy (keV)			Effective energy (keV)		
	Fine focus	Broad focus	Deviation (%) [a]	Fine focus	Broad focus	Deviation (%) [a]
50	30.49	30.49	0.00	27.31	27.03	-1.04
60	34.87	33.11	-5.07	29.01	28.75	-0.89
70	36.68	35.81	-2.37	30.70	30.80	0.34
81	38.79	37.60	-3.08	33.27	32.46	-2.43
90	40.60	39.80	-1.97	34.58	34.33	-0.72
102	42.32	42.24	-0.18	37.30	36.62	-1.84
109	43.70	43.63	-0.16	38.01	37.66	-0.92
125	45.83	45.88	0.11	40.63	40.04	-1.45

[a] The deviations were related to the fine focus.

Table 2: Comparison of half-value layer (HVL) estimations from SpekCalc and IPEM78 models to measurements of tube voltages of Phil and GE X-ray machines. The estimations and measurements were made in the diagnostic range of radiology energy

Tube voltage (kVp)	Phil X-ray machine				GE X-ray machine			
	HVL ratio		Broad focus		HVL ratio		Broad focus	
	SCM	IPM	SCM	IPM	SCM	IPM	SCM	IPM
50	1.10	1.09	1.10	1.09	0.99	1.02	1.02	1.04
60	0.95	0.95	1.07	1.08	1.01	1.05	1.03	1.07
70	0.96	0.98	1.02	1.04	1.00	1.06	0.99	1.05
81	0.97	1.00	1.04	1.08	0.95	1.02	1.01	1.09
90	0.96	1.00	1.01	1.05	0.96	1.05	0.98	1.07
102	0.98	1.02	0.98	1.03	0.91	1.01	0.95	1.05
109	0.96	1.01	0.97	1.01	0.93	1.04	0.95	1.06
125	0.97	1.02	0.97	1.01	0.92	1.03	0.95	1.07
Mean	0.98	1.01	1.02	1.05	0.96	1.03	0.98	1.06
SD	0.048	0.040	0.049	0.033	0.038	0.019	0.030	0.013

Abbreviations: HVL = half-value layer, IP = IPEM78 estimation, M = measurement, SC = SpekCalc estimation.

voltages from 50 kVp to 125 kVp on 2 different machines (Phil and GE) are tabulated in Table 2. SpekCalc showed a maximum of 10% difference for 50 kVp tube voltage compared with the HVL based on direct measurement of the Phil machine. Similarly, IPEM78 showed a maximum of 9% difference in HVL estimations at 50 kVp and 81 kVp for the Phil and GE machines, respectively. All the means of HVL ratios for both the Phil and GE X-ray machines for the tube voltages studied were less than 5% difference, except the estimation by IPEM78 for the GE X-ray machine with broad focus, which showed a difference of 6%. The SDs of the means of HVL ratios for beam quality estimations were less than 5% difference. The means and SDs used to evaluate the accuracy of the SpekCalc and IPEM78 models for estimating the HVLs for both Phil and GE X-ray machines are summarised in Table 3. The mean HVL ratio for the SpekCalc model was calculated using the HVL ratios of both fine and broad focuses for both machines. The same method was used to determine the mean HVL ratio for IPEM78 model. The HVL ratios were subsequently used to calculate the SD for each model. Both the SpekCalc and IPEM78 models showed a percentage difference of the means and SDs within 5% of the HVL from the directly measured values for both the Phil and GE X-ray machines.

Discussion

There is a maximum of 5.07% difference of the effective energies between the fine focus and broad focus for both Phil and GE X-ray machines. For both X-ray machines, most of the effective energies were slightly lower when using a broad focus compared with when using a fine focus. The effective energies of the Phil X-ray machine were higher than the GE X-ray machine because of the thicker filtration in the aluminium equivalent inside Phil's X-ray tube.

SpekCalc mostly underestimated the beam quality for both the Phil and GE X-ray machines.

Table 3: Comparison of SpekCalc and IPEM78 models for half-value layer (HVL) estimation in both Phil and GE machines.

Computational model	Mean HVL ratio	SD
SpekCalc	0.99	0.03
IPEM78	1.04	0.02

For both machine types, the underestimation especially occurred at higher tube voltages, but also occurred at lower tube voltages when used with broad focus. Poludniowski et al. (7) have obtained similar results. SpekCalc showed an agreement within 5% of the direct measurement for estimating the beam quality. IPEM78 overestimated the beam quality for both X-ray machines at all tube voltages, except for the Phil X-ray machine at 60 kVp and 70 kVp with a fine focus. IPEM78 has previously been shown to overestimate the beam quality from tube voltages ranging from 50 kVp to 250 kVp (7). IPEM78 estimated the beam quality to be higher than the measured beam quality in a previous report by Ay et al. (5). However, in this study, IPEM78 showed an agreement within 5% of the direct measurement, except at 81 kVp with broad focus of the GE X-ray machine and at 50 kVp with both broad and fine focuses of the Phil X-ray machine.

The total filtration of the X-ray machine is required as an input parameter for all computational models. The determination of total filtration is important because its value will influence the theoretical results. In this study, the total filtration of the Phil X-ray machine was obtained from the manual of the machine, and the total filtration for the GE X-ray machine was obtained from the label on the X-ray tube. The filtrations were not the actual thicknesses and materials of the filter inside the tube but the thickness in aluminium equivalents. Therefore, without knowing the actual filtration inside the X-ray tube, the thickness in aluminium equivalents of the inherent filtration was used as the input parameter for the SpekCalc and IPEM78 models. The use of these filtrations could affect the beam quality estimation when using these softwares. However, for a diagnostic range X-ray machine with a focus to detector distance of 104 cm, the total filtration in mm Al of the X-ray tube from tube voltages from 50 kVp to 125 kVp does not vary notably, except at 50 kVp (9).

Compared with the measured beam quality, SpekCalc showed that the percentage difference of the mean is 1% underestimation, and the percentage difference of the SD is 3%, while IPEM78 showed that the percentage difference of the mean is 4% overestimation, and the percentage difference of the SD is 2%. Overall, both the SpekCalc and IPEM78 models showed that both the means and SDs were within 5% for beam quality estimations for both Phil and GE X-ray machines. These 2 calculation methods are reliable as computational models for predicting the HVLs that are used to characterise the beam

quality of X-ray spectra generated with different tube voltages in the clinical environment.

The limitation of this study is the difficulty in determining the actual total filtration of the X-ray tubes for both Phil and GE machines. The total filtration for both of the X-ray tubes was given in mm Al equivalent. The total filtration of a machine must be determined because it is required as an input parameter for SpekCalc and IPEM78. The total filtration value will influence the predicted result. The beam quality estimations with the SpekCalc and IPEM78 models will also be influenced if the actual filtration inside the X-ray tube is not known. For future research, there must be a proper way to determine the actual total filtration of the X-ray machine studied.

Conclusion

Both SpekCalc and IPEM78 showed mean and SD differences within 5% of the measured HVL values for the Phil and GE machines. However, SpekCalc showed better agreement with the measured HVLs compared with IPEM78. The successful use of SpekCalc and IPEM78 for HVL estimation used for the instant prediction of X-ray beam quality is dependent on the accuracy in determining the actual total filtration in the X-ray machine. The actual total filtration of the X-ray machine must be determined and used for future studies for better accuracy in HVL prediction.

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Authors' Contributions

Conception and design, drafting of the article: CSC
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Original Article

A Study of Psychological Distress in Two Cohorts of First-Year Medical Students that Underwent Different Admission Selection Processes

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Abstract

Background: **Medical training is often regarded as a stressful period. Studies have previously found that 21.6%–50% of medical students experience significant psychological distress. The present study compared the prevalence and levels of psychological distress between 2 cohorts of first-year medical students that underwent different admission selection processes.**

Methods: **A comparative cross-sectional study was conducted by comparing 2 cohorts of first-year medical students; 1 group (cohort 1) was selected based purely on academic merit (2008/2009 cohort) and the other group (cohort 2) was selected based on academic merit, psychometric assessment, and interview performance (2009/2010 cohort). Their distress levels were measured by the General Health Questionnaire, and scores higher than 3 were considered indicative of significant psychological distress.**

Results: **The prevalence (P = 0.003) and levels (P = 0.001) of psychological distress were significantly different between the 2 cohorts. Cohort 1 had 1.2–3.3 times higher risk of developing psychological distress compared to cohort 2 (P = 0.007).**

Conclusion: **Cohort 2 had better psychological health than cohort 1 and was less likely to develop psychological distress. This study provided evidence of a potential benefit of multimodal student selection based on academic merit, psychometric assessment, and interview performance. This selection process might identify medical students who will maintain better psychological health.**

Keywords: *medical, psychology, school admission criteria, student*

Introduction

The World Health Organization (WHO) has stated that, "*Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.*" (1), and "*mental health can be defined as a state of well-being enabling people to realize their abilities, cope with normal stresses of life, work productively and fruitfully, and make contributions to their communities.*" (2). Mental health is crucial to the overall and individual well-being, directly or indirectly, contributes to the overall well-being of societies and countries (2). In 2003, the WHO reported that mental illness is the fourth leading contributor to the global burden of diseases; approximately 450 million people suffer from a mental or behavioural disorder and nearly 1 million people commit suicide each year (2,3). The WHO projected that in 2020 mental illness will be the second leading contributor to the global burden of diseases (3). These facts could indicate a substantial increase in stress in individuals' daily lives. Medical students and professionals are not immune to this daily stress; in fact, studies found that the prevalence of mental disorder among these populations are higher compared to the general population (5–8).

Previous studies have revealed a rate of psychological distress among medical students ranging from 21.6%–50% (5,6,10–12). Medical students are particularly vulnerable at transitional periods such as their first year of medical school, when they face a period of adjustment to the new environment of

medical training (6,9–14). The prevalence of psychological distress among medical students at the end of their first-year of medical training has been shown to double compared to the prevalence at the beginning of the year (9,10). Studies also reported a high percentage of psychological distress among medical students at other stages of medical training (10–13). Psychological distress among medical students was associated with anxiety and depression (14,15), interpersonal conflict (16), sleeping problems (17), and lower academic and clinical performance (18). Psychological distress also has a negative impact on students' abilities to develop a rapport with patients, to concentrate and focus on their training, and to make decisions, which in turn leads to dissatisfaction during their clinical practice later on (16). Psychological distress was also linked to suicide (19), drug abuse (20,21), and abuse of alcohol (22). The psychological distress that leads to these unwanted consequences has been related to some aspects of medical training (14). Generally, psychological distress hinders the noble ambitions and values of students pursuing medical education.

The aim of medical education is to produce healthy and competent doctors to serve the society. The student selection process, therefore, is essential to medical training because the quality of students admitted to medical schools determines the quality of doctors who graduate (23). Methods of selection are generally grouped into cognitive and non-cognitive methods. Cognitive method focus on previous academic performance, whereas non-cognitive methods focus on less concrete variables using measurement methods such as psychometric assessments and interviews. Most medical schools prefer to select their medical students based on previous academic achievement because it is a better predictor of the student success in medical study (24–26). However, good academic achievement does not necessarily predict a doctor's professional performance (24,27), and the predictive capacity of previous academic achievement for successful medical study diminishes with progression through the course of medical training (24). A 9-year prospective study found that information gained through psychometric test and interview was associated with measured outcomes and that those who performed well during the interview had greater chances of completing their studies at medical school with honours (28).

Starting from June 2009, the School of Medical Sciences, Universiti Sains Malaysia was given the authority to semi-independently select their own medical students by the Malaysian government. The school began selecting students based on three criterias; previous academic performance, psychometric assessment, and interview performance, whereas previous cohorts had been selected based solely on previous academic achievement. This study aimed to compare the prevalence and levels of psychological distress between 2 cohorts of the first-year medical students selected through 2 different student admission processes. 1 batch was selected based solely on previous scholastic merit (cohort 1), and the other was selected based on academic merit, psychometric assessment, and interview performance (cohort 2). To our knowledge, no reports comparing these types of student selection exist in the literature. It is hoped that this article will contribute to the literature regarding medical student admission and mental health.

Materials and Methods

Design

A comparative cross-sectional study was conducted.

Sample

The study samples were cohort 1 and cohort 2 in the School of Medical Sciences, Universiti Sains Malaysia (USM).

Cohort 1 students were selected based solely on their previous academic merit; specifically, their final Cumulative Grade Point Average of the Science Foundation Course of the Malaysian Ministry of Education, or equivalents, which were the High School Certificate of Malaysia (HSC) or Advanced Level General Certificate of Education (A-Level).

Cohort 2 students were selected based on previous academic merit (similar to cohort 1) in addition to psychometric assessment and interview performance. The Malaysian Universities Selection Yearly Inventory (MUnSYI) was used as the psychometric assessment to assess the suitability of candidates for medical study. Unfortunately, the details of the MUnSYI are not available to the public because it is protected under the Official Secrets Act 1972 (Act 88) of Malaysian Law. A short list of applicants, selected based on their previous academic merits and the psychometric

assessment, were then called for an interview. The main objectives of the interview were as follows: 1) to assess the interest, general knowledge, and expectations of applicants about medical education and a medical career, 2) to assess the personal attributes of the applicants in relation to their suitability for studying medicine at USM, 3) to assess the applicants' adequacy in communicating in both Malay and English languages as basic requirements for a successful medical study, and 4) to observe any physical traits that might hinder the applicants from completing the medical studies or performing clinical functions.

Every enrolled medical students from cohort 1 and cohort 2 were invited to participate. 215 students were enrolled in cohort 1, and 196 students were enrolled in cohort 2. Both cohorts underwent a similar curriculum structure in terms of content, teaching, and learning methods and assessment. Both cohorts also studied in the same physical learning environment.

Researchers obtained permission and clearance from the School of Medical Sciences and the Human Research and Ethics Committee of USM prior to the conduct of the study.

Data collection

The 12-item self-administered General Health Questionnaire (GHQ-12) was used in this study. Demographic data pertaining to sex (male and female), race (Malay, Chinese, Indian, and other), and entry qualifications (matriculation, HSC, or A-Level) were obtained from the participants. Data for both groups were collected within 2 months after enrollment so that researchers could measure the students' baseline distress levels upon entry to medical school. This time point was selected as the baseline because it was considered a non-stressful period for the medical students.

The GHQ-12 is a widely used instrument to measure mental health status (29). It has been validated in many populations, including medical students (29–32). The internal consistency coefficients of the questionnaire have ranged from 0.78–0.95 in various studies (33). The items of GHQ-12 assess 12 manifestations of stress, and respondents are asked to rate the presence of each manifestation in themselves during recent weeks. Respondents choose from four responses: 'not at all', 'no more than usual', 'rather more than usual', and 'much more than usual'. The scoring method is binary; the 2 least symptomatic answers are scored as 0 and the 2 most symptomatic answers are scored as 1; i.e., 0-0-1-1. The minimum and maximum scores of the GHQ-12 are 0 and 12, respectively. Higher GHQ-12 scores indicate poorer mental health status. In previous studies the sensitivity and specificity of the GHQ-12 score at a cut-off point of 4 have been shown to be 81.3% and 75.3%, respectively, with a positive predictive value of 62.9%. Therefore, students who scored 4 or more were considered to have 'distress' (29–32).

The investigators administered the GHQ-12 to the 215 new first-year medical students of cohort 1 and to the 196 new first-year medical students of cohort 2 at approximately 2 months after enrollment. Completion of the questionnaire was voluntary and did not affect the students progress in the course. Data were collected in two face-to-face sessions with the students in a lecture hall via guided self-administration. Students took less than 10 minutes to complete the questionnaire, and questionnaires were collected immediately after they were completed.

Statistical analysis

Data were analysed using SPSS version 18 (SPSS Inc., US). An α-level of $P < 0.05$ was adopted. Descriptive statistics were conducted for the analysis of demographic data and the prevalence of psychological distress. For the purpose of statistical analysis, race was grouped into either Malay or non-Malay, and entry qualification was grouped into matriculation or non-matriculation. Histograms were constructed and normality tests (Kolmogoroz-Smirnov and Shapiro-Wilk) were performed to test for normality of the distributions of GHQ-12 scores for each cohort. The distribution of GHQ-12 scores in both cohorts were skewed to the left; however, the normality tests were significant ($P < 0.001$); therefore the Mann-Whitney test was used to compare the median GHQ-12 score between the 2 cohorts of medical students. The Chi-square test was used to test for differences in demographic variables (sex, race, and entry qualification) and for differences in the prevalence of psychological distress between the 2 cohorts. Multiple binary logistic regression (stepwise and enter method) was conducted to compare the risk of developing distress between the 2 cohorts.

Results

A total of 215 (99.1% of the class) students from cohort 1 and 196 (100% of the class)

students from cohort 2 participated in this study.

The demographic profile of the participants is shown in Table 1. The distributions of gender and entry qualification did not differ significantly between cohorts ($P > 0.05$). However, the distribution of ethnic groups was significantly different between the 2 cohorts ($P < 0.001$).

Mann-Whitney test analysis showed that there was a significant difference of the median GHQ-12 score between cohort 1 (median = 2, IQR = 4) and cohort 2 (median = 1, IQR = 3) ($Z = -3.2$, $P = 0.001$).

The prevalence of medical students having significant psychological distress (CI 95%; lower limit, upper limit) in cohort 1 and cohort 2 were 26.3% ($n = 56$; 23.6%, 29.0%), and 14.3% ($n = 28$; 12.6%, 16.0%), respectively. A Pearson Chi-square test analysis showed that the prevalence of psychological distress was significantly different between the 2 cohorts (X^2 (df) = 9.02 (1), $P = 0.003$), as shown in Figure 1.

Multiple binary logistic regression showed that cohort 1 had a 2.019 times higher risk of developing distress compared to cohort 2 ($b = 0.704$, *Wald* (df) = 7.316 (1), $P = 0.007$), as shown in Table 2.

In sum, the results indicated that cohort 2 had better psychological health compared to cohort 1.

Discussion

The prevalence of psychological distress among medical students of cohort 2 (14.3%) was lower compared to the prevalence in cohort

Table 1: Demographic profiles of the 2 student cohorts

Variable		Cohort 1 (n = 213)	Cohort 2 (n = 196)	X^2 statistics (df)	P-value [a]
Sex, n (%)	Male	84 (39.4)	68 (34.7)	0.89	0.321
	Female	129 (60.6)	128 (65.3)	(1)	
Race, n (%)	Malay	140 (65.7)	105 (53.6)	6.28	0.012
	Non-malay	73 (34.3)	91 (46.4)	(1)	
Entry qualification, n (%)	Matriculation	177 (83.1)	174 (88.8)	2.70	0.100
	Non-matriculation	36 (16.9)	22 (11.2)	(1)	

[a] Pearson Chi-square test.

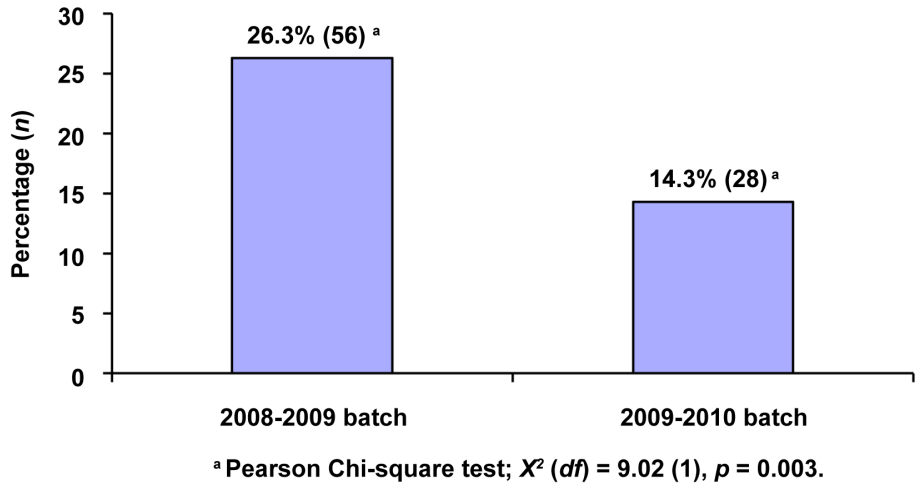

Figure 1: Comparison of prevalence of psychological distress in 2 cohorts of first-year medical students at the beginning of their training.

Table 2: Factors related to psychological distress among the 2 student cohorts

Factor		*b*	*Wald*	*df*	*P*-value [a]	Odds ratio	95% CI for odds ratio	
							Lower	Upper
Cohort	2009/2010				Reference group			
	2008/2009	0.704	7.316	1	0.007	2.019	1.211	3.366
Race	Malay				Reference group			
	Non-malay	-0.238	0.651	1	0.420	0.789	0.443	1.404
Entry qualification	Matriculation				Reference group			
	Non-matriculation	0.628	2.862	1	0.091	1.875	0.905	3.883
Sex	Female				Reference group			
	Male	0.022	0.007	1	0.934	1.022	0.610	1.711
Constant		-1.776	52.898	1	< 0.001	0.170		

[a] Multiple Binary Logistic Regression (stepwise enter method) was applied.
X^2 (df) = 12.06 (4), p = 0.017, -2 Log likelihood = 403.29.

1 (26.3%) and was also lower compared to the prevalence in previously reported samples, which have ranged from 21.6%–50% (5,10,11,34–36). The current study only examined psychological distress at a very early stage of medical training. Because previous studies have indicated that psychological distress can vary at different stages of medical training (10–13), the current samples should be followed during their clinical training years; such follow-up would provide stronger and more constructive evidence to support the current finding.

The significantly lower number of medical students having psychological distress in cohort 2 compared to cohort 1 suggested better psychological health in this cohort. This was further supported by cohort 2, which have significantly lower risk of developing psychological distress compared to cohort 1. These findings indicated that the multimodal selection process based on academic merit, psychometric assessment, and interview performance was able to identify medical students with better psychological health better than the selection process that was based solely on academic merit. To our knowledge, this is the first study to report such a finding. It is important to highlight that previous studies found the prevalence of psychological distress among medical students at the end of the first year of study to be twice as high compared to the beginning of the first year (9,10).

The current results are not enough to confirm the advantage of the expanded student selection process. Such confirmation requires follow-up of these medical students over a longer duration. A prospective study design is necessary to explore the long-term differences between the 2 selection processes. Many researchers proposed that selecting psychologically healthy candidates will buffer the negative effects of some aspects of medical training (5,10–12,14,37). Accordingly, better identification of medical students with good psychological health might eventually produce future doctors who are psychologically healthy. Downie & Chartlon (1992) echoed that the type of medical students recruited at the beginning of training will determine the type of doctors produced at the end (23).

The aim of the student admission process is not to pick candidates for specific jobs, but rather to choose persons of strong potential who are healthy (physically, emotionally, psychologically, and mentally), who will eventually find their interest and niche somewhere in medicine and who will subsequently take the field of medicine to a higher level (38). In accord with that notion, findings from the current study provide initial evidence that multimodal student selection can successfully identify the medical students that are psychologically healthy. This finding is commensurate with recent evidence that cognitive superiority alone does not protect medical students from distress even up to the internship level (39).

This study has several limitations that should be considered in interpreting its findings and in designing future studies. The first is related

to the study design. The cross-sectional design used in this study produces only a snapshot of a particular time; therefore, a longitudinal study design is necessary to explore the advantages of the new student admission process over time. The second limitation concerns other confounding factors such as socio-economic status, parent education level, stress at home, distress level prior to entry of medical training, psychiatric status prior to medical training, personality and family relationships. These factors should be controlled either during sample selection or during data analysis to isolate the effects of the new multimodal student admission process. The third limitation is that data were collected face-to-face, which may not be seen by participants as completely anonymous (even though participants did not provide names on the questionnaire). This data collection procedure might have led to response bias. The fourth limitation is that our single psychological health measurement was unlikely to provide a comprehensive picture of psychological health. Other psychological health measurements should be used during follow up in future studies.

Conclusion

Cohort 2 had better psychological health than cohort 1. Cohort 2 were less vulnerable to develop psychological distress compared to cohort 1. This study provides evidence that multimodal student selection might better identify medical students with good psychological health.

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Authors' Contributions

Conception and design, provision of study materials; collection, assembly, analysis, and interpretation of the data; critical revision and final approval of the article; administrative, technical, or logistic support: MSBY, AFAR, AAB, SBI, ARE
Obtaining of funding: AAB, SBI
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Original Article

Perceptions of Receiving Bad News about Cancer among Bone Cancer Patients in Sarawak General Hospital - A Descriptive Study

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Abstract

Background: **This study aimed to determine the perceptions and expectations of bone cancer patients with respect to their doctors and the breaking of bad news as well as the environment in which the news was delivered.**

Methods: **A cross-sectional study using a pretested 41-item questionnaire was conducted using convenience sampling among bone cancer patients in Sarawak General Hospital. Face-to-face interviews were conducted after consent was obtained. Data were analysed using SPSS version 16 (SPSS Inc., IL, US).**

Results: **A total of 30 patients were interviewed. The majority of the respondents were younger than 40-years-old, Malays, and female. All of the respondents perceived that they received news in a comfortable place, agreed that the doctor used simple language and appropriate words during the interaction, and believed that the way the doctor delivered the news might influence their life. The majority of the respondents reported that their news was received without interruption, that the doctor was sitting close but without making physical contact, and time was given for patient to ask questions and they were informed accordingly.**

Conclusion: **Delivering bad news regarding cancer is an important communication skill and a complex task that can be learned and acquired. Specially tailored training is proposed to improve medical practice in this area.**

Keywords: *bone neoplasms, communication barrier, health care, truth disclosure*

Introduction

Cancer is one of the leading causes of death in the world today. The estimated cancer incidence in Malaysia is 30 000 cases annually with a prevalence of 90 000 (1). Bone cancer is relatively uncommon and involves tumour growth in the bone resulting in pain, hypercalcemia, anemia, skeletal fractures, and spinal related injuries that can affect mobility and subsequently the patient's functional status, quality of life, and survival (2). The most common type of bone cancer is osteosarcoma; mainly affects children and young adults, chondrosarcoma; usually afflicts adults over 40 years of age, and Ewing's sarcoma; which is commonly found in children and teenagers (3).

As cancer is a complicated illness that often leads to a poor prognosis, it is a major challenge to healthcare providers, particularly at the point when they have to break bad news to the patient. Bad news can be regarded as unfavourable news that in the context of medicine has been defined as "any news that drastically and negatively alters the patient's view of her or his future" (4). It is often a dilemma for the physician in charge to be able to break the bad news to patient and family members without giving a sense of false hope. Effective breaking of bad news must consist of the ability to break the news compassionately, clearly, and at the same time provide emotional support, respond to questions, and maintain a sense of hope. A good breaking of bad news should avoid

misunderstandings with regard to the disease, treatment, management, and prognosis, which would contribute to better treatment compliance and emotional adjustment (5).

Communication barriers such as educational level, socio-economic status, language, and gender may hinder the effectiveness of delivering bad news (3). Additionally, the patient's emotional state, the doctor's sensitivity, and perception can all be crucial factors to consider when delivering bad news (5). Moreover, cultural influences observed in countries like Japan, Pakistan, Turkey, and Saudi Arabia, often discourage the patient from knowing the truth to prevent emotional breakdowns (6–9). Thus, the breaking of bad news may pose different challenges.

Previous studies have described the challenges in the patients' perceptions of the breaking of bad news (7,8,10). However, most of these studies have focused on breaking bad news for more common types of cancer in developed countries. As cultural differences and the type of cancer may affect the patients' perception on doctor's effectiveness in breaking bad news, currently available findings may not be applicable in Malaysia. This study aimed to determine the perceptions and expectations of bone cancer patients with respect to their doctors and the breaking of bad news, as well as the environment in which the news were delivered.

Materials and Methods

A cross-sectional study using a pretested 41 item questionnaire adopted from Ptacek and Ptacek (10) was performed. The questionnaire consists of 5 subscales that measured the perception of bone cancer patients on the breaking of bad news: (a) Environment (7 questions), (b) Physician behaviours (7 questions), (c) Physician speech (9 questions), (d) Patient-centred (9 questions), and (e) Miscellaneous (3 questions). A yes-no response was obtained for each item. Using a back-to-back method, the questionnaire was translated into the Malay language to facilitate the interview process. A pilot study was not conducted due to the limited number of bone cancer patients at the time of the study. The questionnaire was reported to be reliable with a Cronbach's alpha of 0.89 and an average inter-item correlation score of 0.36 (11). The content validity of the questionnaire was achieved from the extensive literature as previously reported by Ptacek and Ellison (11) and Ptacek and Eberhardt (12).

This study was conducted in the orthopedic ward of the Sarawak General Hospital, the regional hospital that offers specialist treatment for osteosarcoma and soft tissue sarcoma patients in Sabah and Sarawak. The ward consists of 72 beds that accommodate both male and female patients. The patients were normally diagnosed in the outpatient clinic, followed by the breaking of news regarding the diagnosis and treatment. Only the patients admitted for treatment were recruited for this study.

Ethical approval for this study was obtained from the Ministry of Health Malaysia (NMRR-10-931-7508). All sarcoma patients admitted to the ward who gave consent were recruited for this study. Patients who were ill, mentally challenged, or refused to participate were excluded from the study. After obtaining informed consent, a face-to-face interview was conducted. The second researcher performed all face-to-face interviews using the questionnaire. A total of 30 patients were interviewed during the 2 months data collection period. Data were entered and descriptive analyses were performed using SPSS version 16.

Results

All respondents were interviewed between January and February 2010. The socio-demographic data of the respondents are presented in Table 1. More than 75% of the respondents were younger than 40-years-old, and the majority of the respondents were Malay, followed by other Sarawak natives (23.3%). A total of 63.3% of the respondents were women, the majority of whom were either single or married. Approximately 40% of the respondents were working and 60% had a secondary level of education.

Table 2 presents the health profile of the respondents. An equal number of patients were diagnosed with osteosarcoma and soft tissue sarcoma (36.7%, respectively) while the rest were diagnosed with Ewing's sarcoma and synovial sarcoma. The majority of the respondents were informed of their diagnosis more than 4 months previously (43.3%). All respondents at the time of the study were receiving intravenous chemotherapy as their treatment.

Table 3 presents the findings of patients' perceptions and expectations of the doctor when breaking bad news and the environment in which the news was delivered. All of the respondents perceived that they received the news in a comfortable place, agreed that the

Table 1: Socio-demographic characteristics of the respondents (n=30)

Socio-demographic characteristics	Number of respondent (n)	Percentage of respondent (%)
Age (years)		
≤ 20	8	26.7
21–30	6	20.0
31–40	9	30.0
> 40	7	23.3
Races		
Malay	11	36.7
Pribumi Sarawak (Iban & Bidayuh)	7	23.3
Chinese	5	16.7
Others	7	23.3
Gender		
Male	11	36.7
Female	19	63.3
Marital status		
Single	14	46.7
Married	14	46.7
Divorced	2	6.6
Occupation		
Currently employed	12	40.0
Unemployed	8	26.7
Studying	10	33.3
Educational level		
Primary school	3	10.0
Secondary	18	60.0
Diploma and above	9	30.0

Table 2: Health status of the respondents (n=30)

Health profile	Number of respondent (n)	Percentage of respondent (%)
Cancer type		
Osteosarcoma	11	36.7
Soft tissue sarcoma	11	36.7
Synovial sarcoma	6	20.0
Ewing's sarcoma	2	6.6
Duration of diagnosis (months)[a]		
< 1	7	23.3
1–4	10	33.3
> 4	13	43.3

[a] The duration of diagnosis is the duration of time since the patient was informed of his/her diagnosis.

Table 3: Perceptions of the patients (n=30)

Characteristic	Percentage of "Yes" answer (%)
Environment	
Did you receive the news in the ward?	96.7
Did you receive the news in a comfortable place?	100
Did you receive the news in a private location?	10.0
Did the doctor deliver the news by himself?	96.7
Did the doctor make certain there were no interruptions while breaking the news?	93.3
Did the doctor deliver the news at the location he selected?	13.3
Did anyone accompany you when the doctor delivered the news?	86.7
Did any nurse accompany the doctor when breaking the news?	6.7
Physician behaviours	
Did the doctor decide where he/she wanted to deliver the news?	10.0
Were you given written material about the condition or services?	70.0
Did the doctor sit close to you while breaking the bad news?	96.7
Did the doctor check if you had any questions?	20.0
Did you feel that the doctor hid his real feelings about the disease during the interaction?	16.7
Did the doctor use non-verbal cues or body language indicating that bad news was forthcoming?	6.7
Did the doctor have any physical contact while breaking the news, such as holding your hand?	10.0
Physician speech	
Did the doctor use simple language during the interaction?	100
Did you understand the news and implications when the doctor broke the news?	86.7
Did the doctor deliver the news in a warm and caring manner?	96.7
Did the doctor convey some hope to you?	96.7
Did the doctor use appropriate words during the interaction?	100
When you asked a question, did you think the doctor had the ability or knowledge to answer?	96.7
Did you think the doctor took his time or rushed when delivering the news?	83.3
Did the doctor use humour/jokes to ease the situation during the interaction?	6.7
Based on your observation, did you think the doctor was struggling to find the right words when delivering the news?	16.7
Patient-centred	
Were you given a chance to ask questions?	86.7
Did the doctor show sensitivity to how you felt?	20.0
Were you given the opportunity to express your feelings?	30.0
Did the doctor show that he/she thought about your needs during the interaction?	33.3

Characteristic	Percentage of "Yes" answer (%)
Did the doctor take seriously your personality and emotions when delivering the news?	26.7
Did the doctor take into account that you already knew about the news?	13.3
Did the doctor give you the option of how the news should be delivered?	13.3
Did you think the manner in which the doctor delivered the news might influence your life?	100
Did you think the doctor only took care of his/her own needs during the interaction?	0
Miscellaneous	
Were you sad when the doctor delivered the news?	93.3
Was the doctor nervous when you received the news?	3.3
When you received the news, did you blame the doctor for the unexpected news?	0

[a] The duration of diagnosis is the duration of time since the patient was informed of his/her diagnosis.

doctor used simple language and appropriate words during the interaction, and believed that the manner in which the doctor delivered the news might influence their life. The majority of the respondents reported that they received the news in the ward, agreed that the doctor delivered the news by him/herself without interruption during the news breaking and that they were accompanied by someone (86.7%–96.7%). However, most of the bad news were not delivered in a private location, the location was not chosen by the doctor (10%–13.3%) and no nurse accompanied the doctor.

In terms of physician behaviours, the majority of the respondents reported that the doctor sat closely to them, but only 10% had physical contact such as holding hands during the breaking of bad news. Approximately 70% of the patients were given written materials about the illness and the health care services available. Less than 20% of the patients felt that the doctor hid his/her real feelings about the disease or used non-verbal cues during the delivery of bad news.

Based on the responses for each subscale, the physician's speech was perceived to be the most favourable. The majority of the patients (83.3%–100%) reported that the doctor used simple language, delivered the news in a warm and caring manner, conveyed hope to them, was able to answer questions, took his/her time in delivering the news, and explained the implications properly. Many patients did not think the doctor was struggling to find the words or use humour/jokes to ease the situation during the delivery of the bad news.

On the patient-centred subscale, only 2 items were rated above 85% by the respondents: patients were given a chance to ask questions and patients believed that the manner in which the doctor broke the news might influence their life. Less than 15% of the respondents reported that the doctor took into account what they knew or gave them the option on how the news would be delivered. Approximately 20% of the respondents felt that the doctor allowed them to express their feelings and none of the patients thought the doctor only took care of his/her own needs during the interaction. On the miscellaneous subscale, almost all of the respondents admitted they were sad when receiving the bad news, but none of them blamed the doctor for the unexpected news.

Discussion

This preliminary study provides an important local perspective on the perception of sarcoma patients regarding the breaking of bad news by their doctor. Although privacy was limited, more than 95% of the respondents reported that the environment (the ward) in which they received

bad news was comfortable, and particularly so when the doctor made certain that there were no interruptions during the process. The literature suggests that a comfortable environment is a significant independent predictor of satisfaction for the delivery of bad news (10). The ideal location for breaking news should be comfortable and without interruption to ensure patients are in the best condition to receive the news (10). Only 6.7% of the respondents received bad news in the presence of a nurse. This finding is of concern. Although breaking bad news is the doctor's responsibility, using a multi-professional team is also important (13). When cancer patients receive their diagnosis, they tend to lose part of the information due to their reactions to the news (13), and they will subsequently turn to nurses to obtain the missing information or to confirm the information that they have heard (14). In addition, studies have also shown that nurses can be the interpreters when patients do not understand what is explained to them due to the complexity of the medical terminology used in breaking the news (15).

Physicians were reported to break the bad news themselves, using simple and easy language and proper body language (sitting close, warm, and caring manner). These findings indicated that the doctors were perceived to be competent in the task of breaking bad news. However, only a small percentage of the respondents indicated that the doctors initiated physical contact such as holding their hands. This finding is not surprising, as using physical contact to offer comfort is not part of the Malaysian culture. Two-thirds of the respondents reported that their doctors did not show any sensitivity to their feelings or consider their needs or emotions during the interaction, which prevented them from expressing their feelings. One possible explanation could be that the doctors were trying to maintain professional distance to prevent any outburst of emotion that might be difficult to handle (10). Other physicians may feel that psychological assistance is beyond their job description (16).

The breaking of bad news to cancer patients is an important communication skill, but it is also a complex communication task. In addition to having the ability to break news verbally, the doctors also need to have effective non-verbal skills. These include responding to a patient's emotional reactions, involving the patient in decision making, helping patients to cope with many issues, and addressing the dilemma of not giving false hope to the patients. It is recognised that breaking bad news is one of a doctor's most difficult duties, yet most doctors are not formally trained for the task (17). Among those doctors who directly interact with cancer patients, specially tailored training has proven to be helpful and beneficial in their daily practice (18).

Approximately 13% of the doctors took into account that their patients already knew the news. Had the doctor inquired, the patient would have informed the doctor about knowing their diagnosis. This would foster a better doctor-patient relationship in cancer treatment and save the doctor time for other useful activities. Additionally, only approximately 13% of doctors gave the patient the option on how the news should be delivered. These findings indicated that some doctors might still practice paternalism in the doctor-patient relationship where they see themselves in a superior position to their patients (19).

Conclusion

Despite high levels of self-reported satisfaction by patients on some of the aspects of breaking of bad news, there are some areas of concern. The findings suggest that special attention should be given in creating a more conducive environment and specific training to help the physicians to be more confident and competent in delivering of bad news. Doctors need to take into consideration their patients' prior knowledge about their cancer in order to be more effective in breaking the bad news. In addition doctors need to allow their patients to express their feeling, which is very important after receiving a bad news.

This study has 2 limitations. First, the study was based on convenience sampling performed in a single locality, and therefore, generalisation of the findings is limited. Second, given the self-reporting methodology used, self-reporting bias might have occurred. Despite these limitations, to the best of our knowledge this is one of the first studies performed on this issue conducted in Sarawak. Additional research should include a larger scale, different cancer types and the use of mixed methods for data collection. Use of mixed-methods research would have been ideal to capture important data on patients that cannot be measured solely by quantitative research methods. Given the potential importance of this topic to the well-being of both patients and healthcare providers, more studies should be performed in the future.

Authors' Contribution

Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, statistical expertise, and administrative, technical, or logistic support: CWL
Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, statistical expertise, administrative, technical, or logistic support, and collection and assembly of data: NBD
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Original Article

Factor Structure and Reliability of the Malay Version of the Perceived Stress Scale among Malaysian Medical Students

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Abstract

Background: **The Perceived Stress Scale 10 (PSS-10) is a validated and reliable instrument to measure global levels of perceived stress. This study aims to assess the internal consistency, reliability, and factor structure of the Malay version of the PSS-10 for use among medical students.**

Methods: **The original English version of the PSS-10 was translated and back-translated into Malay language. The Malay version was distributed to 242 Bachelor of Medical Science students in a private university in Malaysia. Test–retest reliability was assessed in 70 students. An exploratory principal component factor analysis with varimax rotation was performed. Reliability was tested using the intraclass correlation coefficient (ICC).**

Results: **All 242 students participated in the initial questionnaire study (validity and factor structure), and 70 students participated in the test–retest reliability of the study. Exploratory factor analysis yielded 2 factors that accounted for 57.8% of the variance. Cronbach's alpha coefficients for the 2 factors were 0.85 and 0.70, respectively. The reliability test showed an ICC of 0.82 (95% CI: 0.70, 0.89).**

Conclusion: **The Malay version of the PSS-10 showed adequate psychometric properties. It is a useful instrument for measuring stress among medical students in Malaysia.**

Keywords: *Malaysia, medical, psychological, reliability and validity, stress, students*

Introduction

Medical education is stressful and demanding. Previous studies have shown high levels of stress among medical students (1,2). Stress may affect academic performance and students' physical and mental health (3). Health behaviour may also be affected by stress, as reported by previous studies (4,5). A significant association has been found between stress and sleep disturbances, eating habits (such as infrequently eating breakfast), a lack of physical exercise, alcohol consumption, and smoking and drug consumption (6). Recent studies have also found that perceived stress was associated with low quality of life (7) and with premature death (8). A study found that 2.7% of Swedish students had attempted suicide (2).

In 1984, Lazarus and Folkman (9) proposed that psychological stress involves the relationship between an individual and an environment that is appraised by the individual as threatening or overwhelming to his resources and well-being. Accordingly, both internal and external conditions must exist for a stress response to occur; the relation and interaction of these conditions generate the occurrence of stress (10). Stress occurs when an individual is confronted by a situation that the individual perceives as overwhelming (10). The degree of stress is related to the intensity of this threat and to the beliefs and expectations that individuals believe may be achieved or thwarted (9).

The importance of research on perceived stress suggests the need for valid and reliable instruments to measure and assess global

perceptions of stress. Cohen et al. (11) stated that an assessment scale for global perceptions of stress could provide a variety of valuable functions. These authors suggested that Lazarus' proposals about stress were not accompanied by valid measurements of perceived stress. Hence, they created the Perceived Stress Scale (PSS) to measure the degree to which life events are appraised as stressful. This scale is one of the few scales that assess generalised perceptions of stress (12).

The PSS measures the degree to which life events are appraised as stressful (12). This method of assessing stress reflects the definition of psychological stress proposed by Lazarus and Folkman (9). In this scale, perceived stress is viewed as an outcome variable that measures the level of stress experienced as a function of objective stressful events, coping processes, and personality factors (6). Additionally, the scale can provide information about the processes through which stressful events influence pathology. It can be used in conjunction with an objective scale to determine whether self-appraised stress mediates the relationship between objective stress and illness (6). This scale was specifically designed for use with community samples with at least a junior high school education (11).

Regarding the validity and reliability of the original (English) version of the PSS, a study by Cohen and Williamson (6) included exploratory factor analysis with principal component analysis and varimax rotation as part of the statistical analysis procedures. The results showed 2 factors that conjointly accounted for 41.6% of the variance (25.9% for the first factor and 15.7% for the second factor). Cronbach's alpha for the total scale was 0.78.

This scale has become one of the most widely used instruments for measuring perceived stress and has been translated into several languages; including Spanish, Turkish, Japanese, and Chinese (13–16,19). The PSS-10 was used in our study because it is a brief, easy-to-use version with equivalent psychometric properties to the PSS-14, as recommended by Cohen and William (6). The objectives of this study were to assess the internal consistency, reliability, and factor structure of the Malay version of the PSS-10 for use among medical students.

Subjects and Methods

Participants

Of the 249 students enrolled in the Bachelor of Medical Science program at a private university in Malaysia, all 242 students who were present on the day of the data collection participated in this study. 7 students who were absent on the day of the data collection were excluded from this study. After permission was obtained from the ethical committee of the faculty for access to the students, the investigators visited the students before or after a lecture and distributed the questionnaire to students who agreed to participate.

Instruments

Perceived Stress Scale

The PSS-10 assesses perceived stressful experiences or stress responses over the previous month with a 5-point Likert scale (0 = never and 4 = very often). PSS-10 scores are obtained by reversing the responses (e.g., 0 = 4, 1 = 3, 2 = 2, 3 = 1, and 4 = 0) to the 4 positively stated items (items 4, 5, 7, and 8) and then summing across all scale items. The scores range from 0–40, with higher scores indicating greater stress.

Translation

This study used a forward–backward translation procedure. In this procedure, a forward translation was produced from the original language (English) to Malay language. The Malay language version was then translated back into the English language and compared to the original version. Errors in the target language version were identified through changes in meaning that arose in the back translation. This procedure was repeated until a satisfactory translation was obtained. The final version was reviewed by an expert. The final Malay version was pilot tested on 10 students who did not participate in the study. These students were asked to complete the questionnaire for the pilot study. Additional grammatical errors and misspellings were subsequently corrected.

Procedure

The students were informed verbally of the research objectives and benefits. They were informed that they had the option to participate in the study and that their participation would not affect their progress in the course. Confidentiality was assured and written consent was obtained. Test–retest reliability was conducted among 74 students. These students were asked to choose and remember a code name to maintain their anonymity. 3 weeks after the initial testing, retesting was conducted by distributing the same questionnaire. The

students were asked to use the same code as in the previous test. Questionnaires without an accurate code were excluded. 70 questionnaires were considered valid for the reliability study.

Statistical analysis

The data analysis was performed using SPSS version 16 (SPSS Inc., IL, US). Total scores were obtained by summing across all 10 items after reversing the scores on the 4 positive items. A test of normality was conducted, and an exploratory factor analysis of the 10-item questionnaire was performed using a principal component method with varimax rotation (6,17). Correlation analyses, the Kaiser-Meyer-Olkin (KMO) and Bartlett's Test of Sphericity were used. Cronbach's alpha was used to test the internal consistency of the questionnaire. Reliability was tested using the intraclass correlation coefficient (ICC) for the sum scores. The values of the ICC vary from 1 (perfectly reliable) to 0 (totally unreliable) (18).

Results

Socio-demographic characteristics and stress level measured by the PSS-10

All 242 students who were present during the data collection participated in the validity study. 70 of the students also participated in the reliability study. Those 70 students were selected from the same cohort. The mean (SD) age of the respondents was 20.9 (6) years, with 116 respondents aged ≤ 20 years (47.9%). The majority of the respondents were female (74.8%) and Malay (75.2%), 149 were Muslims (80.2%), 14 were Christians (5.8%), 28 were Buddhists (11.6%), and 4 were Hindus (1.7%) (Table 1). The mean (SD) level of stress, measured by the PSS, was 18.9 (4,8). The distribution of the participants' scores on the PSS-10 is shown in Table 2.

Internal consistency and test-retest reliability of the PSS-10

Cronbach's alpha coefficient was 0.78 for the total scale, 0.85 for the first factor and 0.70 for the second factor. The analysis showed that the value of Cronbach's alpha did not improve by eliminating items. Regarding test-retest reliability, the analysis showed that the Malay version of the PSS-10 had an ICC of 0.82 (95 % CI: 0.70, 0.89).

Factor structure and construct validity of the PSS-10

The exploratory analyses of all 10 items yielded 2 factors with given values greater than 1 (3.8 and 1.9, respectively). The 2-factor solution accounted for 57.8% of the variance. The first factor accounted for 38.3% of the variance and included 6 items representing "stress" (items 1–3, 6, 9, and 10) (Table 3). Factor loading ranged from 0.67–0.84, and none of these items loaded significantly onto the second factor (Table 4). The second factor included 4 items representing "control" (items 4,5,7, and 8) and accounted for 19.5% of the variance with factor loadings ranging from 0.67–0.78. For all items, factor loadings were greater than 0.65, and the item's share of communality for 1 factor was at least 20% higher than its share of communality for any other factor. The item loadings are presented in Table 4. The mean (SD) of the first factor was 11.9 (4.4), and the scores ranged from 0–24; 6 participants (2.5%) scored 0 and 1 participant (0.4%) scored 24. For the second factor, the mean (SD) was 7.0 (2.7), and the scores ranged from 0–16; 1 participant (0.4%) scored 0 and 7 participants scored 16 (Table 5). The Kaiser-Meyer-Olkin measure of sampling adequacy tests (KMO) and Bartlett's Test of Sphericity were performed. The analyses showed that the KMO was 0.77 and Bartlett's Test of Sphericity

Table 1: Socio-demographic characteristics of the respondents (n = 242)

Variable	Total (n)	Percentage (%)
Gender		
Male	61	25.2
Female	181	74.8
Age (years)		
≤ 20	116	47.9
> 20	126	52.1
Race		
Malay	182	75.2
Chinese	12	5.0
Indian	32	13.2
Other	16	6.6
Religion		
Muslim	149	80.2
Christian	14	5.8
Hindu	4	1.7
Buddhist	28	11.6
Semester		
1–3	178	73.6
4–6	64	26.4

Table 2: Distribution of scores of the participants on the PSS-10 (n = 242)

Item	Score				
	0, *n* (%)	1, *n* (%)	2, *n* (%)	3, *n* (%)	4, *n* (%)
1. In the last month, how often have you been upset because of something that happened unexpectedly?	11 (4.5)	29 (12.0)	133 (55.0)	54 (22.3)	15 (6.2)
2. In the last month, how often have you felt that you were unable to control the important things in your life?	20 (8.3)	49 (20.2)	128 (52.9)	34 (14.0)	11 (4.5)
3. In the last month, how often have you felt nervous and "stressed"?	18 (7.4)	27 (11.2)	148 (48.8)	61 (25.2)	18 (7.2)
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	21 (8.7)	98 (40.5)	102 (42.1)	10 (4.1)	11 (4.5)
5. In the last month, how often have you felt that things were going your way?	17 (7.0)	85 (35.1)	112 (46.3)	16 (6.6)	12 (5.0)
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	18 (7.4)	45 (18.5)	125 (51.7)	49 (20.2)	5 (2.1)
7. In the last month, how often have you been able to control irritations in your life?	9 (3.7)	84 (34.7)	114 (47.1)	15 (6.2)	20 (8.3)
8. In the last month, how often have you felt that you were on top of things?	14 (5.8)	49 (20.2)	128 (52.9)	30 (12.4)	21 (8.7)
9. In the last month, how often have you been angered because of things that were outside of your control?	19 (7.9)	63 (23.6)	95 (39.3)	48 (19.8)	17 (7.0)
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	28 (11.6)	44 (18.2)	114 (47.1)	40 (16.5)	16 (6.6)

Abbreviation: PSS = Perceived Stress Scale

Table 3: Total variance explained; Principal component analysis

Component	Initial Eigenvalues	Extraction Sums of Squared Loadings	Cumulative (%)	Total	Variance (%)
	Total	Variance (%)			
1.	3.832	38.322	38.322	3.832	38.322
2.	1.945	19.448	57.770	1.945	19.448
3.	0.893	8.925	66.696		
4.	0.822	8.221	74.917		
5.	0.617	6.166	81.082		

was significant ($P < 0.001$). These findings indicate sampling adequacy, and the items can be considered appropriate for factor analyses.

Discussion

The aim of the present study was to develop an adapted Malay version of the English PSS-10 scale. Overall, the results of this study support the validity and reliability of the Malay version of the PSS-10. This study found that the Malay version of the PSS-10 had 2 factors that accounted for 57.8% of the variance (38.3% and 19.5%, respectively). According to Cohen's original analysis, the 2 factors accounted for 25.9% and 15.7% of the variance, respectively

Table 4: Rotated factor loadings of PSS items and the corrected item-total correlation

Item	Factor 1 (α = 0.85)	Factor 2 (α =0.70)	Corrected item-total correlation
1. In the last month, how often have you been upset because of something that happened unexpectedly?	0.710	-0.131	0.506
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0.803	-0.083	0.601
3. In the last month, how often have you felt nervous and "stressed"?	0.742	-0.109	0.557
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	-0.001	0.776	0.237
5. In the last month, how often have you felt that things were going your way?	0.004	0.730	0.245
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0.745	-0.001	0.591
7. In the last month, how often have you been able to control irritations in your life?	-0.014	0.703	0.384
8. In the last month, how often have you felt that you were on top of things?	-0.151	0.672	0.355
9. In the last month, how often have you been angered because of things that were outside of your control?	0.804	-.0131	0.568
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0.836	-0.021	0.622

Abbreviation: PSS = Perceived Stress Scale

Table 5: Floor and ceiling of the 2 factors of the PSS (n=242)

Factor	Number item	Mean (SD)	Minimum	Maximum	Range	Reaching floor, n (%)	Reaching ceiling, n (%)
Factor 1	Items 1, 2, 3, 6, 9, and 10	11.9 (4.4)	0	24	24	6 (2.5)	1 (0.4)
Factor 2	Items 4, 5, 7, and 8	7.0 (2.7)	0	16	16	1 (0.4)	7 (2.9)

Abbreviation: PSS = Perceived Stress Scale

(6). Previous research on different language versions of the PSS-10 found that the PSS-10 had 2 latent factors and that 2 factors accounted for 52% to 58% of the variance (13–16,19). The minimum acceptable value for factor loading is 0.30 (20). In 1988, Cohen and Williamson (6) found that the factor loadings of the scale items were 0.42 and higher. In the current study, all items met this criteria, and the factor loadings were high (ranging from 0.67–0.84). Previous studies found a minimum factor loading of 0.32 and a maximum of 0.88 (13–16,19).

In this study, the first factor weighted most heavily items that were negatively worded (e.g., been upset, unable to control things, felt nervous, and stressed) and the second factor reflected positively worded items (e.g., able to control irritation and ability to handle personal problems). Similar findings were reported by Cohen and Williamson (6). Hewitt et al. (21) called the first factor "perceived distress" because it included items referring to negative affective reactions. In contrast, the second factor was labelled "perceived coping" because it included items reflecting perceptions of coping ability for stressful events. Cronbach's alpha coefficient was 0.78 for the 10 items of the Malay PSS, which was similar to that reported for the original version (0.78) (6). Cronbach's alpha coefficient was 0.85 for the first factor and 0.70 for the second factor. Both are acceptable and not far from the values reported in the original version (0.72–0.81) (21). A Cronbach's alpha of 0.70 or more was considered acceptable (22). The test-retest reliability in this study for the 3 week interval was good (ICC above the criterion of 0.75) (23). A 3-weeks interval for test-retest reliability was used in this study to ensure comparability with other studies (14). Cohen et al. (11) found a test-retest reliability of 0.85 and 0.55 for 2-days and 6-weeks intervals, respectively.

Limitations of the study

The use of a homogeneous sample of undergraduate students from only 1 university and 1 college may have affected the generalisability of this study. Another limitation of this study is the absence of concurrent validity assessment, which is recommended for future studies.

Conclusion

The present study of a sample of undergraduate university students demonstrates that the Malay version of the PSS-10 is a reliable and valid measure of stress among medical students in Malaysia. Future research should involve more diverse, heterogeneous samples to rule out the effect of sample homogeneity on the results. Research on the concurrent validity of this measure is recommended.

Authors' Contributions

Conception and design, analysis and interpretation of the data, drafting of the article, and Collection and assembly of data: SARAD
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Original Article

A Pilot Investigation of the Operationalized Predicaments of Suicide (OPS) Framework

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Abstract

Background: **Suicide may be conceptualized as an escape from intolerable predicaments, in particular, mental illness and environmental stressors. The operationalized predicaments of suicide (OPS) is a 4 category framework designed to assist in the classification of suicide. The objective was to examine whether this framework is potentially useful.**

Method: **18 psychiatrists from 6 different countries examined 12 written coroners' reports of suicide and rated each report according to the OPS. 16 of these raters then also completed a qualitative questionnaire regarding the framework.**

Results: **In 89.8% of cases the raters where able to make a decision regarding the drivers which led to the suicides. The respondents displayed modest inter-rater correlation (Kappa = 0.42; *P* < 0.0001). In the qualitative section, respondents supported the face validity of OPS and considered it potentially useful. Feedback allowed improved wording of the OPS instructions.**

Conclusion: **The OPS has potential as a useful framework. The OPS instructions have been improved and further studies are justified.**

Keywords: *mental health, suicide, public health, social medicine*

Introduction

Suicide accounts for 1.5% of all deaths and is the tenth leading cause of death worldwide (1), but remains incompletely understood. Suicide occurs more commonly in people with mental illness than people without mental illness, and the life-time risk of suicide for people with major depression is around 3%–4% (2). However, suicidality is distinct from depression (3) and adverse life events increase the suicide risk, independent of any mental illness (4,5).

Shiner et al. (6) recommended coroners' reports as a "reasonable basis" for research focused on understanding the social circumstances of suicide, and Scourfield et al. (7) concluded that they "offer an opportunity for suicide research". The duties and procedures of coroners differ, to some extent, from one jurisdiction to another. However, throughout Australia, reportable deaths are examined in a similar manner and with the highest care and integrity. They have been used in quality suicide research (8,9).

In keeping with a diversity of perspectives in the literature, our group has published the view that suicide can be conceptualized as an escape from intolerable predicaments or stressors (10). We have identified the 2 main types of intolerable predicaments, 1 is untreated or unresponsive mental illness, and the other is environmental or non-mental illness stressors (11).

The operationalized predicaments of suicide (OPS) is a simple classification system devised by the authors to differentiate such concepts. It is based on observations in the literature that mental illness (12,13) and environmental stressors (4,5) may separately trigger suicide; it also allows those stressors to be combined (a common clinical observation).

The present study seeks to determine whether

the OPS may be a useful or safe framework for suicide research. The aims of the current pilot study: (1) to apply the OPS to the classification of actual coronial reports by an international sample of highly experienced psychiatrists, (2) to explore inter-rater consistency of ratings, (3) and to obtain qualitative comments on the application of the framework.

Subjects and Methods

Ethical approval

As a preliminary exploration of a clinical concept with clinicians, this pilot study was deemed a quality assurance exercise and did not require ethics committee approval. The cases were publicly available on the web.

OPS

OPS is an arrangement of 4 categories, which may assist in the conceptualization and classification of triggers or drivers of suicide. The full details are presented in Appendix 1, a summary appears below:

- Category A (Cat A) distinguishes situations in which mental illness is likely a key trigger.
- Category B (Cat B) identifies situations in which social or environmental factors are likely to be a key trigger.
- Category C combined (Cat C) distinguishes situations when both mental illness and social or environmental are the key factors.
- Category U unclassifiable (Cat U) identifies situations when none of the above triggers is evident, or the information is insufficient or contradictory.

Respondents

18 psychiatrists (12 male, 6 female; with an average of 18.1 years of clinical experience) from 6 countries (Brazil = 1, Nepal = 1, Israel = 1, New Zealand = 1, Malaysia = 5, Australia = 9; see Acknowledgements for details) were recruited from among the scholarly contacts of the first author. All were in current clinical practice, half with teaching or research duties. All respondents were purposively recruited by email through the contacts of the first author and self-selected. They were invited and agreed to give their time to the enterprise.

Materials: Coroner's reports

In recognition of confidentiality requirements pertaining to coroner's reports, this pilot study was based entirely on de-identified reports freely available on the internet. 24 reports of completed suicide were identified, from Australian sources (limiting the sources to 1 country prevented international variation in reporting processes and formats). The first author reviewed all these reports and found that since coroners tend to publish findings that have relevance to the public interest, the sample disproportionately comprised suicides in custody. This study focused on whether experienced psychiatrists could agree on the main trigger or driver of a particular suicide. Accordingly, 12 reports were selected (South Australia = 5, Tasmania = 4, Queensland = 2, and Victoria = 1) which appeared (in the view of the first author) to involve a range of trigger or drivers; including mental disorder, social or environmental stressors, and some cases in which the trigger or drivers were ambiguous or unknown. (See Appendix 2 for web-addresses).

Procedure

All respondents were individually recruited and responded by email. They were provided with Appendix 1. This document advises responders to read the 12 coroner's reports of completed suicide and to rate each report using 1 of the 4 OPS categories listed above. It was not possible to train the participants face-to-face on how to use the OPS because of their different geographic locations.

The quantitative component of the study comprised of the categorization of the cases by the respondents. Each respondent returned their responses and were tabulated for analysis. The qualitative component of the study commenced when the completed OPS task was returned; each respondent was provided with a follow-up questionnaire regarding the nature and value of OPS. Each respondent was asked to address 9 questions about the framework. They registered a response to each question on a 4-option scale, and were also invited to make comments.

In brief, these follow-up questions touched on the usefulness of the OPS in the study of suicide, acceptability and appropriateness of concepts, and face validity of the framework. It also explored the suitability of coroner's reports in this task, including ambiguity, missing information, completeness of information, and suggestions for dealing with such information in future research. Qualitative analysis on the responses was undertaken independently by the authors to examine for recurring themes.

Each rater was codified by an assigned letter of the alphabet from A to R, and Minitab

15 statistical software (Minitab Inc., State College PA, USA) was used to calculate inter-rater (Fleiss' kappa) and percentage of overall agreement between the raters to ascertain trends and agreement in thought for each case and for all 12 cases.

Results

Quantitative

18 participants scored 12 cases (using coroners' reports and OPS) for a total of 216 decisions (Table 1). For the majority of decisions (n = 194, 89.8%), a classification could be made (Cat A, B, or C); and 22 decisions (10.2%) were that a classification could not be made (Cat U). Of the 194 ratings for the classifiable cases, just under half of the total ratings (n = 87, 44.8%) were attributed to a solely mental illness cause (Cat A), about one-third were an environmental cause (Cat B) (n = 68, 35.1%), and the remainder fifth fell into the combined mental illness and environmental causes category (Cat C) (n = 41, 19.0%).

For 7 cases (cases 2, 5–8, 10–12; 66.7%), between 1 and 6 participants (8.3%–50.0%) could not classify each case; and 5 cases (1, 3, 4, 9; 33.3%) were found classifiable by all 15 (100%) participants.

The overall percent agreement was determined to be 59.3% and statistical analysis using the Fleiss' Kappa statistic for inter-rater reliability was calculated to be Kappa = 0.42 (P < 0.0001), 95% CI (0.39, 0.45). When looking at each category separately, Category B received the highest inter-rater reliability statistic with Kappa = 0.70 (P < 0.0001), 95% CI (0.65, 0.75). Category U had by far the lowest with Kappa = 0.08 (P = 0.0002), 95% CI (0.04, 0.13). Table 2 summarises the inter-rater reliability for each category.

Qualitative follow-up

After rating the cases, 15 of 18 respondents (83.3%) chose to answer a follow-up questionnaire. From this, it appeared that most of

Table 1: The rating of 12 cases by 18 psychiatrists (A to R). Cat A, mental illness only; Cat B, social or environmental stressors only; Cat C, both mental illness and social or environmental stressors; and Cat U, unclassifiable (any reason)

No.	Cat A	Cat B	Cat C	Cat D
1	C,D,E,J,L,Q,R		A,B,F,G,H,I,K,M,N, O,P	
2	B,D,E,G,H,K,O,Q		L,N,P	A,C,F,I,J,M,R
3	A,B,C,D,E,F,G,I,K, L,M,O,P,Q,R		H,J,N	
4	A,M,O,Q	C,J,L,R	B,D,E,F,G,H,I,K,N,P	
5	N	A,B,C,D,F,I,J,K,L, M,O,P,Q,R	E	G,H
6	A,B,D,E,F,G,I,L,M, N,O,P,Q,R			C,H,J,K
7		A,B,C,D,E,F,G,H, I,J,K,L,M,N,O,P,Q		R
8	A,B,C,D,E,F,G,I,K, L,M,N,O,P,R			H,J,Q
9	C,D,E,G,J,K,L,M, O,Q	N	A,B,F,H,I,P,R	
10	A,B,C,D,F,G,J,K,L, M,O,P,Q		E,H,I,R	N
11			N,O	J,L
12		A,B,C,D,E,F,G,I,K, L,M,N,O,P,Q,R		H,J

Abbreviations: Cat A = Category A, Cat B = Category B, Cat C = Category C, Cat D = Category D.

Table 2: Inter-rater reliability statistics across the 4 OPS categories

Category	Kappa score	95% C.I	*P*-value
Cat A	0.41	0.36–0.46	< 0.0001
Cat B	0.70	0.65–0.75	< 0.0001
Cat C	0.24	0.19–0.29	< 0.0001
Cat U	0.08	0.04–0.13	0.0002
Overall	0.42	0.39–0.45	< 0.0001

Abbreviations: Cat A = Category A, Cat B = Category B, Cat C = Category C, Cat D = Category D, OPS = operationalized predicaments of suicide.

the respondents (12 of 15) found the OPS useful in the study of suicide. Comments included that it was consistent with clinical practice, "*it reflects 'categories' seen in regular clinical practice*", and assisted in conceptualising suicide other than as a consequence of psychopathology. The majority of respondents (14 of 15) found the concepts underpinning OPS as to be acceptable. Most (10 of 15) respondent psychiatrists noted that the 2 main descriptor types were sufficient for categorising the 12 pilot coronial case reports. Comments reflected that respondents had some questions over the diagnosis and severity or the extent of a mental disorder as described in the reports, and the effect this might have in identifying a descriptor. All respondents found the OPS had face validity, "*It definitely has conceptual face validity*". The OPS was noted as consistent with psychiatrists' clinical experience, "*I do agree as it does reflect (at least my) daily clinical practice experience*".

When asked about ambiguity around concepts and classification in the OPS, responses were far less consistent. Despite finding the OPS useful in the categorisation of completed suicide reports, respondent psychiatrists clearly experienced some ambiguity in applying the framework to coronial reports. In their written responses, they noted that a concern was missing information, or a lack of detail on issues relevant to make professional judgements, "*Coroner's reports are not limited in what they put in. It is what they leave out that makes the greatest difference of all*". Questions 6 and 7 addressed the issue of potentially missing information from coronial reports of completed suicides. Nearly all respondents said that in instances where they perceived insufficient information they chose an "unclassifiable" category, "*I think it best not to make any assumptions about information*". About half of the respondents indicated the potential value of rules or guidelines for dealing with potentially missing information (6 'Yes', 4 'Possibly'). Despite their reservations about missing information, nearly all respondents (13 of 15) expressed confidence in coroner's reports as useful in the study of suicide, "*I think they're ideal because they are thoughtfully written, by intelligent laypeople who are relatively untainted by psychobabble*". The majority of respondents also saw the value in some relative rating of the comprehensiveness of information provided in the respective reports for this purpose (12 'Yes', 3 'Possibly'). In summary, responses to the qualitative follow-up questionnaire supported the consistency in respondent ratings and validity of OPS.

Discussion

This pilot study of the application of the OPS framework was encouraging. It provided some indication of the benefit of clearly differentiating between social or contextual and mental illness aetiologies in understanding suicide, which is consistent with the literature and clinical experience of the respondents and authors. The OPS framework, therefore, suggests substantial validity as a tool to understand the etiology of suicide.

According to the guidelines (14), the inter-rater reliability was deemed moderate at Kappa = 0.42 with the best agreement observed in Cat B. However, this moderately-low reliability index is perhaps more dependent on the actual raters themselves rather than an intrinsic problem with the scale (15). This certainly indicates a degree of ambiguity of the task or categories in the OPS, which was also borne out in the qualitative follow-up responses. Cat B received the highest inter-rater agreement of the 4 categories, suggesting that the OPS scaffold was effective amongst the raters when it came to identification of environmental influences

on suicide cases. Conversely, Cat U received a poor level of agreement implying a high level of subjectivity and variability overall and for each case. This is also a mark of the significant interpretation differences for each case, despite the basic framework of OPS.

With the benefit of the qualitative feedback obtained during this study, slight adjustments have been made to the OPS Instructions and terms (and are reflected in Appendix 1). For example, 1 participant suggested that the term 'mental illness' be used in preference to 'mental disorder', noting that mental illness is generally regarded as having a tighter definition. It is anticipated that incorporation of suggestions and further refinement will increase the inter-rater reliability in future applications.

There was agreement that the absence of details about the mental health or environmental circumstances of the deceased in the reports led to some uncertainty (whether absent information should be taken as meaning no important information had been overlooked). Accordingly, the OPS instructions have been revised to theeffect that absent information should not automatically be taken to indicate no such important information existed, but that when a report is generally comprehensive, the rater may judge it safe to interpret the absence of information as meaning no important information has been overlooked.

There was strong agreement that coroners' reports are potentially useful in the study of suicide, and that in addition to assessing the information available from coroners' reports, that there would be an advantage in participants rating each report with respect to quality (which could be the basis of further avenue of research). This was in agreement with the opinions of workers in the field from the previous studies by Shiner et al. (6) and Scourfield et al. (7).

The cases for examination were selected according to content rather than a random process. As stated, these were publicly available reports (obviating confidentiality concerns) and needed to be individually selected because their publication was designed to serve the public good, and a particular emphasises was placed on certain types of cases (such as the deaths of males in custody). Content selection was not seen as a concern, however, as this study is not focused on the proportions of cases meeting particular criteria. Instead, it is focused on OPS. Cases were selected by the first author to reflect various sets of circumstances: apparent mental disorder, apparent social or environmental stressors, community and custody situated. What proportions of cases meet the various classification criteria is a matter for a random or complete sample study, which is in preparation.

Limitations of the pilot study include that face-to-face training in the OPS was not possible, due to the different geographic locations of the participants. On occasions, participants made comments which were at variance with the rating they made, indicating that in some instances, understanding of OPS was not complete. However, there was broad agreement in the classification of cases and qualitative feedback. Given that over half the participants had English as a second or third language and that face-to-face training was not possible, this broad agreement suggests the OPS has the advantages of simplicity and utility.

In this pilot study, the OPS has face validity and moderate inter-rater reliability, and highlights the notion that suicide can be triggered or driven by either both of mental illness and social or environmental stressors. Its potential usefulness in future studies of suicide is supported by the opinions of a cosmopolitan group of participants. The wording of the instructions for OPS has been improved, which is intended to improve reliability for future applications.

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Authors' Contribution

Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content,

final approval of the article, and provision of study materials or patients: SP
Analysis and interpretation of the data, critical revision of the article for important intellectual content, statistical expertise: PK
Final approval of the article, statistical expertise, and collection and assembly of data: AL
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Appendix 1

Operationalized predicaments of suicide (OPS)

Instructions

OPS is an experimental method of classifying suicide. It is investigating the concept that suicide represents an escape from painful predicaments. 2 main predicaments have been described, (1) untreated or unresponsive mental illness, and (2) social or environmental stressors.

In this application of the OPS to 12 coroners' reports of completed suicides, we are asking you to assign each of the attached reports to one of the following categories. In many reports, some information you may desire will be absent. Absent information should not automatically be taken to indicate no such important information existed (that is, it may have existed but not been reported). However, given the nature of the coronial process, when the report is generally comprehensive, you may judge it safe to interpret the absence of information as meaning no important information has been overlooked.

Framework

Category A

A mental illness is clearly or probably present, and probably played a major role in triggering the suicide.

No environmental or social (non-mental illness) stressor played a major role.

Category B

An environmental or social (non-mental illness) stressors is clearly or probably present, which probably played a major role in triggering suicide.

No mental illness played a major role. For current purposes, terminal illness and intractable pain are considered as 'external' stressors.

Category C (combined)

Mental illness and environmental or social (non-mental illness) stressors are both present, and both probably played a role in triggering the suicide. In these circumstance it is difficult to decide which (if either) was the main trigger for the suicide. If the influence of one is clearly predominant and the other is clearly trivial, another category may be chosen.

Category U (unclassifiable)

There is insufficient or contradictory information. Also, if there is no evidence for either mental illness or environmental or social (non-mental illness) stressor, this is the appropriate designation. Category U can be used when dealing with uncertainty.

Appendix 2

Case access details

Case 1. Magistrates court of Tasmania record of investigation into death. http://www.magistratescourt.tas.gov.au/decisions/coronial_findings/i/2008_tascd_106_-_intentional_firearm [accessed on September 1, 2011].

Case 2. South Australia findings of inquest. http://www.courts.sa.gov.au/courts/coroner/findings/findings_2000/graetz.finding.htm [accessed on September 1, 2011].

Case 3. Queensland courts office of the state coroner findings of inquest. http://www.courts.qld.gov.au/__data/assets/pdf_file/0011/86591/cif-partridge-pb-20051222.pdf [accessed on September 1, 2011].

Case 4. Magistrates court of tasmania record of investigation into death. http://www.magistratescourt.tas.gov.au/decisions/coronial_findings/h/holloway,_maxine_frances_-_2011_tascd_125 [accessed on September 1, 2011].

Case 5. South Australia findings of inquest. http://www.courts.sa.gov.au/courts/coroner/findings/findings_2000/hutchinson.finding.htm [accessed on September 1, 2011].

Case 6. Coroners court of Victoria redacted, http://www.coronerscourt.vic.gov.au/wps/wcm/connect/justlib/Coroners+Court/resources/d/8/d8fe51804661da829e229ed6abc0bba5/VH_225410.pdf [accessed on September 1, 2011].

Case 7. Queensland courts office of the state coroner findings of inquest. http://www.courts.qld.gov.au/__data/assets/pdf_file/0007/86794/cif-miller-mj-20091209.pdf [accessed on September 1, 2011].

Case 8. South Australia findings of inquest. http://www.courts.sa.gov.au/courts/coroner/findings/findings_2009/Hope_Maria_Kate.pdf [accessed on September 1, 2011].

Case 9. South Australia findings of inquest. http://www.courts.sa.gov.au/courts/coroner/findings/findings_2003/gillies.finding.htm [accessed on September 1, 2011].

Case 10. Magistrates court of Tasmania record of investigation into death. http://www.magistratescourt.tas.gov.au/decisions/coronial_findings/n/nichols,_timothy_david_-_2010_tascd_387 [accessed on September 1, 2011].

Case 11. South Australia findings of inquest. These findings deal with 2 people (1 male, the other female) who took their lives using the same method. Only material pertaining to the death of the male was used in this study. http://www.courts.sa.gov.au/courts/coroner/findings/findings_2011/Morris_Julia_Hisae_and_Jast_Raymond_Glen.pdf [accessed on September 1, 2011].

Case 12. Magistrates court of Tasmania record of investigation into death. http://www.magistratescourt.tas.gov.au/decisions/coronial_findings/i/intentional_overdose_-_2006_tascd_104 [accessed on September 1, 2011].

Original Article

The Perception, Level of Safety Satisfaction and Safety Feedback on Occupational Safety and Health Management among Hospital Staff Nurses in Sabah State Health Department

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Abstract

Background: **This study aimed to determine the perception and level of safety satisfaction of staff nurses with regards to Occupational Safety and Health (OSH) management practice in the Sabah Health Department, and to associate the OSH management dimensions, to Safety Satisfaction and Safety Feedback.**

Methods: **A cross-sectional study using a validated self-administered questionnaire was conducted among randomly respondents.**

Results: **135 nurses responded the survey. Mean (SD) score for each dimension ranged from 1.70 ± 0.68–4.04 ± 0.65, with Training and Competence dimension (mean [SD], 4.04 ± 0.65) had the highest while Safety Incidence was the least score (mean [SD], 1.70 ± 0.68). Both mean (SD) scores for Safety Satisfaction and Safety Feedback was high, 3.28 ± 0.51 and 3.57 ± 0.73, respectively. Pearson's correlation analysis indicated that all OSH dimensions had significant correlation with Safety Satisfaction and Safety Feedback (*r* coefficient ranged from 0.176–0.512) except for Safety Incidence.**

Conclusion: **The overall perception of OSH management was rather low. Significant correlation between Safety Satisfaction and Safety Feedback and several dimensions, suggest that each organization to put in place the leaders who have appropriate leadership and supervisory skills and committed in providing staff training to improve staff's competency in OSH practice. In addition, clear goals, rules, and reporting system will help the organization to implement proper OSH management practice.**

Keywords: *hospital administration, nurses, occupational health, safety management, workplace*

Introduction

Based on World Health Organization (1), over 59 millions health workers are exposed to various type of health and safety hazards every day including biological, chemical, and physical hazards. Prevention of occupational injuries among the healthcare workforce is vital to provide high quality patient service, improve morale, and enhance productivity by reducing time-loss and other absenteesim (2). Nurses, the largest group of health care providers, deliver care to patients in a variety of health care facilities. In recent years attention has been paid to the occupational risks and injuries of nurses. Injuries and resultant compensation to workers are expensive. In long-term care facilities in the United States, nurses' back injuries are estimated to cost US$6 million in indemnity and medical payment (3).

One of the main contributing factors which influences the Safety Satisfaction of health care providers is job satisfaction. Job satisfaction affects nurses' retention and turnover, their morale level, productivity, commitment, and performance,

which in turns affects patients' safety (4). A health and safety survey showed a majority of nurses indicated that perception on working conditions interfered with their ability to deliver quality care (5). These respondents also reported that health and safety concerns influenced their decisions about the kind of nursing work performed and their continued practice in the field of nursing. In addition, the respondents also stated that the perception of unsafe working conditions may hinder recruitment and retention of qualified staff.

It is important to gauge how healthcare workers perceive the issues of safety and health in their workplace. Evidence shows that the work nature of health workers, involving long working hours and overtime, can create stress and work-personal life imbalance (6). Inadequate nursing staff, poor working environment, and lack of management support impact patient safety and health care delivery (7). Increasing work pressure results in decrease in morale and productivity of nurses (8). Monitoring nurses' working conditions and improving the organizational climate of hospitals is likely to improve nurses' safety and hospital profitability and the quality of patient care delivered (9).

Sabah, the second largest state in Malaysia, is located in the north of the island of Borneo with a multi-ethnic population of 320 1000 in 2009 (10). Health care is provided through 22 government hospitals which include 1 psychiatric hospital, 83 primary health clinics, 38 dental clinics, 20 maternal and child health clinics and 189 rural clinics. In 2006, there were 13 076 health staffs working in Sabah Health Department, with 8041 (61.8%) in the hospitals and 4675 (35.9%), in different health clinics (11).

In Sabah, staff nurses in the job category of U29 (with a minimum qualification of diploma in nursing) form the largest group (31.5%) of frontline hospital workers (11). In providing patient care, these nurses are exposed to many occupational-related safety and health problems. A report by Lim (12) in 2000, the Sabah State Health Department showed that the highest percentage (74.5%) of needle stick injury occured among nurses. Although emphasis on occupational safety and health is in place in Malaysia, there has not been substantiate evaluation of the perception of occupational safety and health management among the employees, including nurses, in Sabah State Health Department. This study aimed to determine the perception and level of safety satisfaction of staff nurses with regards to occupational safety and health (OSH) management practice in the Sabah Health Department, and to associate the OSH management dimensions, to Safety Satisfaction and Safety Feedback.

Material and Methods

This was a cross-sectional study conducted among the hospital staff nurses with a minimum of 6 months work experience. Using Statcalc in Epi Info version 6 (Atlanta, GA), with a population size of 3391 nurses, the expected prevalence of occupational related injury of 30% and the precision of 10%, and the confidence level at 95%, the total sample size is 79 nurses. A letter was then sent to all the 22 hospitals to invite participation and request a response within 2 weeks. Only 7 hospitals consented to participate. Sampling frame was obtained from each of the 7 hospitals and random sampling was conducted to select 20 respondents from each hospital. Each respondent was given an informed consent form together with a questionnaire through their respective supervisors. The respondents returned their completed questionnaires to the researcher through their respective administrative office.

Data collection was done using a set of self-administered questionnaires adopted with permisson from Nor Azimah et al.'s study (13). The questionnaires examined the perception of employees of the management of OSH in public hospitals in Malaysia. The questionnaires consisted of 2 sections: (1) 6 items on socio-demographic data of respondents; (2) 85 items on perception of different dimensions of the implication of OSH management dimensions. The OSH dimensions were grouped into 10; namely Leadership Style, Safety Responsibility, Management Commitment, Role of Supervisor, Training and Competence, Safety Communication, Health and Safety Goals, Safety Rules and Reporting, Work Pressure, and Safety Incidents which represented the independent variables while Safety Satisfaction and Safety Feedback represented the dependent variable. The items on OSH management were scored on a 5 point Likert-type scale where 1 indicates strongly disagree/highly dissatisfied and 5 indicates strongly agree/highly satisfied. Pilot test on the questionnaire was conducted with overall Cronbach's alpha of 0.77, and for the different dimensions, Cronbach's alpha ranged from 0.60–0.90. Content validity was based on literature and verified by lecturers and clinicians familiar with the subjects.

Ethical approval and permission to conduct the research was obtained from the Sabah State Health Department, Clinical Research Centre Sabah, and the National Medical Research Register (NMRR-09-1053-4962). Statistical analysis was done using SPSS version 18 (SPSS Inc., IL, US) for descriptive report and inferential statistical analysis. Demographic profiles and workplace information were examined using frequency and percentage. The mean (SD) for the demensions were assessed. The association between independent and dependent variables were analyzed using Pearson's correlation. The level of significance was set at 5% (2 sided).

Results

A total of 135 respondents participated in the study giving a response rate of 96% (135 of 140). The mean (SD) age of the respondents was 35.4 ± 8.17 years, with majority from the age group of 40-years-old and above. The majority of the respondents were female (97.8%) and Kadazan (56.3%) (Table 1). About 62% of the respondents worked in general wards and Intensive Care Unit/Critical Care Unit. More than 80% of the respondents had working experience between 1–15 years. 60% of the respondents had worked in their current hospital for a duration of 1–10 years (Table 2).

Table 3 depicts the score of the 10 dimensions used to measure OSH management as perceived by the respondents. The finding showed that Training and Competence had the highest mean (SD) score of 4.04 ± 0.65. Safety Incidents, on the other hand, had the lowest mean (SD) score of 1.70 ± 0.68. Overall, the mean score of respondents' perception ranged between 1.70–4.04 which indicated the responses centred around a mixture of scores on "disagree/not satisfied" and "agree/satisfied".

Pearson's correlation analyses were used to determine the relationship between the study factors. The results of this analyse are shown in Table 4. The dependent variable, Safety Satisfaction and Safety Feedback had a significant correlation with all but 3 independent variables; Safety Communication, Work Pressure, and Management Commitment.

Table 1: Demographic profiles of participants (n = 135)

Socio-demographic characteristic	Number of participant (n)	Percentage of participant (%)
Age group (years)		
20–24	8	5.9
25–29	27	20.0
30–34	34	25.2
35–39	30	22.2
40 & above	36	26.7
Gender		
Male	3	2.2
Female	132	97.8
Race		
Kadazan	76	56.3
Others	32	23.7
Malay	14	10.4
Bajau	7	5.2
Rungus	4	3.0
Murut	1	0.7
Chinese	1	0.7

Table 2: Workplace profiles of participants (n = 135)

Workplace profile	Number of participant (n)	Percentage of participant (%)
Place of Work		
Hospital wards/ICU/CCU	84	62.2
OPD	19	14.0
OT/Labour room/ Procedure room	14	10.4
Administrative office	2	1.5
Others	16	11.9
Years of working as staff nurse, U29 (years)		
Below 1	3	2.2
1–5	41	30.4
6 –10	43	31.9
11 –15	30	22.2
16 –20	8	5.9
21 & above	10	7.4
Experience working in the current hospital (years)		
Below 1	17	12.6
1 –5	52	38.5
6 –10	29	21.5
11 –15	20	14.8
16 –20	7	5.2
21 & above	10	7.4

Abbreviations: CCU = Critical Care Unit, ICU = Intensive Care Unit, OPD = out patient deparment, OT = operation theater.

Table 3: Perception of OSH management

Dimensions	Mean	SD	Range
Training & Competence	4.04	0.65	2.25–5.00
Safety Rules & Reporting	3.70	0.64	2.20–5.00
Safety Responsibility	3.62	0.62	2.20–5.00
Role of Supervisor	3.62	0.66	2.00–5.00
*Feedback on Safety	3.57	0.73	1.50–5.00
Health & Safety Goals	3.56	0.76	1.60–5.00
Leadership Style	3.39	0.66	1.60–5.00
*Safety Satisfaction	3.28	0.51	2.06–4.82
Management Commitment	3.15	0.60	1.83–5.00
Safety Communication	3.23	0.47	2.25–4.50
Work Pressure	2.76	0.48	1.83–4.67
Safety Incidents	1.70	0.68	1.00–4.00

* *Dependent variable*. Abbreviation: OSH = occupational safety and health.

Table 4: Interscale correlations of the OSH management dimensions, Safety Satisfaction, and Safety Feedback.

Independent variable	Dependent variable	
	Safety satisfaction	Safety feedback
Safety Incidents	-0.141	-0.184*
Health Safety Goal	0.350**	0.512**
Training & Competence	0.240**	0.337**
Safety Rules & Reporting	0.432**	0.453**
Safety Communication	0.106	0.164
Work Pressure	0.112	0.255**
Leadership Style	0.307**	0.336**
Role of Supervisor	0.416**	0.415**
Management Commitment	0.176*	0.056
Safety Responsibility	0.291**	0.420**

* Significant at the 0.05 level (2-tailed), ** Significant at the < 0.01 level (2-tailed).
Abbreviation: OSH = occupational safety and health.

Discussion

The overall perception of occupational safety and health among the staff nurses was reported to be similar to that in a study done by Nor Azimah et al. (14). On the mean score of the dimensions of OSH management (Table 3), respondents were highly satisfied with the Training and Competence dimension. This dimension has 3 items: (1) respondents' perception of their understanding about safety requirements, (2) health and safety risks in their job and (3) what to do to ensure high standards of health and safety. Respondents also tend to agree strongly that their training had covered their job related health and safety risks. This dimension scored more highly compared to Nor Azimah et al.'s (14) and was probably a reflection of the active OSH programme promotion and training in Sabah. Training is important as employees who receive safety training suffer fewer work-related injuries than their untrained counterparts (15), as it allows employees to acquire greater competencies to control work and perform jobs more safely (16).

The Safety Incidents dimension had 7 items. 2 items required the respondents to indicate the number of incidences that they perceived could harm the staff (2 items). 5 items related to personal injuries occurring during the previous 5 years as a result of moving and handling of patients, needle stick and sharp injuries, slip, trips or falls, work related stress, or exposure to dangerous substances. Congruent with Nor Azimah et al's (14) study, this study also reported very low incidence (Table 3). A score of 1.72 indicated that respondents either experienced few injuries themselves or perceived few incidences that would harm staff 1 or 2 times in the past year. This finding was similar to those reported by de Castro et al. (17).

Respondents rated Safety Satisfaction slightly lower with a mean (SD) score of 3.28 ± 0.51 than Safety Feedback mean (SD) score of 3.57 ± 0.73. This finding may indicate that although respondents agreed or strongly agreed with the feedback but they might not be highly satisfied with the safety system.

Similar to Nor Azimah et al.'s (14), the respondents of this study scored low on Work Pressure. A score of 2.76 indicated that respondents did not perceive they have enough staff to handle workload, satisfied with their work schedule, or able to take scheduled rest breaks.

Pearson's correlation analysis results indicated that all OSH dimensions had positive correlation with Safety Feedback and Safety Satisfaction (r coefficient ranged from 0.176–0.512) except Safety Incidents. Among the significant findings, Leadership Style and Role of Supervisor were found to have positive correlation with Safety Satisfaction and Safety Feedback (see Table 4). This was expected as effective Leadership Style would result in effective supervision and Safety Satisfaction and

Safety Feedback. Literature also reported that appropriate Leadership Style could help to reduce incidents or injuries in the workplace (16) and thus, improve employees' safety satisfaction.

Significant positive correlation was also found between Safety Satisfaction and Training and Competence. This may indicate that when Training and Competence was perceived to increase, the Safety Satisfaction would also increase. Training and Competence was also found to have significant correlation with Safety Feedback which may also indicate that an increased in Training and Competence in safety would motivate an increased in Safety Feedback. The other independent variable with significant relationship with Safety Satisfaction and Safety Feedback were Safety Rules and Reporting, Health and Safety Goal, and Safety Responsibility. Respondents who perceived the importance of safety rules and reporting, goal and responsibility have higher Safety Satisfaction and Safety Feedback. To improve work outcomes and accuracy, assessment of work place health and safety, a good reporting system must be in place with clear health safety goals (17). Nurses must then be encouraged to report injuries and take responsibility for injury prevention.

Unlike Nor Azimah et al.'s (14) study, this study found more dimensions which were not significantly correlated with each other. Safety Satisfaction was found to have no significant correlation with 3 independent variables of OSH management: Safety Incidence, Safety Communication, and Work Pressure. Safety Feedback had no significant correlation with Safety Communication and Management Commitment. Safety Incidence had a negative correlation with Safety Satisfaction and Safety Feedback, indicating that as Safety Incidence increased, the Safety Satisfaction would decrease or when Safety Feedback increased, the Saftey Incidence would decreased. The positive correlation between Work Pressure and Safety Satisfaction indicated that if respondents agreed that they have less work pressure, their satisfaction with safety would also increase. However, this relationship was not significant.

Although Management Commitment has been perceived as the main contributor in establishing a thriving and pervasive safety climate within an organization, this study indicated otherwise. Management Commitment in this study was found to have no significant relationship with Safety Feedback. This finding was found to be incongruent with Nor Azimah et al.'s study (14). One possible explanation was that the respondents did not believe it was the role of management to be determining factors that influenced their knowledge and competence in occupational health and safety. The need to improve and protect themselves and establish a strong safety culture could be considered as part of their intrinsic needs, rather than as extrinsic needs enforced by the management. Another possible explaination for this finding could be that the role of management in implementing the rules and regulations pertaining to safety at work and establishment of safety culture within the organization were unclear, thus, respondents did not perceive Management Commitment as important.

Conclusion

This study revealed that the overall perception of OSH management in Sabah was rather low. The score on Training and Competence was high reflecting that Sabah Health Department had placed emphasis on training. The score of Safety Satisfaction and Safety Feedback were above average indicating that the respondents were satisfied with OSH management. The study also revealed significant correlation between Leadership Style, Role of Supervisor, Health and Safety Goal, Training and Competence, Safety Rules and Reporting, and Safety Satisfaction and Safety Feedback. These findings suggest the need of every health care organisation to have competent and committed leaders with appropriate supervisory skills to ensure effective OSH practice. In addition, organisations need to conduct proper training to improve the competency of the staff on OSH practice. An organisation that has clear health safety goals would enhance staff's safety satisfaction. Clear safety rules and proper reporting system would encourage staff to report injuries and take responsibility of their own safety. This study might lack generalisation as the study population included only staff nurses of government hospitals from 1 state. As it was a preliminary study, further study should include bigger sample involving other categories of hospital staff from different health care setting.

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Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, and statistical expertise: CWL
Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, statistical expertise, administrative, technical, or logistic support, and collection and assembly of data: NG
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Brief Communication

Mild Paediatric Head Injury: The Diagnostic Value of Physical Examinations Compared with Computed Tomographic Scans

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Abstract

The study objective was to determine the diagnostic value of physical examinations for positive computer tomography (CT) scans in children with mild head injuries. Retrospective data of patients evaluated for mild head injuries with loss of consciousness (LOC) or amnesia were reviewed. Estimations of prevalence, sensitivity, specificity, and predictive values were calculated. Agreement between the physical examinations and CT brain scans was calculated using the Kappa test. 225 patients were included in the study. Of this group, 19.56% of patients had positive CT scans, and 7.56% had normal physical examinations. 15 underwent neurosurgical intervention. For positive CT scans, sensitivity and specificity were 61.36% and 60.22%, respectively. Agreement between physical examinations and CT scans was Kappa = 0.147 ($P < 0.05$), 95% CI (0.035, 0.259). The present study demonstrated that physical examinations were significantly associated with positive CT scans ($P = 0.01$). However, the calculated Kappa value showed only slight agreement between these 2 variables, and the low sensitivity and specificity of the physical examinations suggest that intracranial pathology in children with mild head injuries and LOC or amnesia cannot be excluded based on physical examinations alone.

Keywords: *CT scan, diagnostic value, mild head injury, physical examination, sensitivity, specificity*

Introduction

Few studies have been conducted on patients with mild head injuries compared with moderate and severe head injuries. A large number of hospital admissions and radiological investigations involve mild head injuries in children despite the fact that most do not involve long-term neurological deficits.

Several studies have attempted to determine clinical criteria that can reduce the cost of evaluating and treating these patients (1–10). Although conducting a computer tomography (CT) scan is acceptable in pediatric trauma patients with a Glasgow Coma Scale (GCS) lower than 13, deteriorating consciousness or focal deficits, the guidelines for scanning children with milder head injuries have remained controversial and poorly defined (11). The incidence of delayed surgery for children with extradural or acute subdural hematoma has resulted in increasing morbidity and mortality, further emphasising the importance of this controversy (12–14). A previous study concluded that the following clinical variables could not be consistently associated with intracranial injury (ICI), loss of consciousness (LOC), vomiting, headache, and amnesia (22). They found that ICI occurred in 4% of children, in which 1% of it needed surgical intervention, despite having normal clinical examinations. Similarly, Keskil et al. (21) were not able to find any dependable identifying clinical features for ICI and determined that CT scanning was the only reliable means of reducing avoidable mortality and morbidity.

The objective of this study was to determine the diagnostic value of physical examinations compared with positive CT scans in children with mild head injuries (GCS scores of 13–15) and LOC or amnesia in the emergency department. There were 2 specific objectives of this study: to (1) determine the sensitivity,

specificity, and (2) predictive values of a normal physical examination after mild head injury with LOC and to determine the correlation between physical examinations and CT brain scans in children with mild head injuries.

Subjects and Methods

This was a cross-sectional study using secondary data. This study was a retrospective case review of pediatric patients who presented to the Accident and Emergency Department of Hospital Kuala Lumpur (HKL) with mild closed-head injuries between January 2007–June 2009.

Subjects were children aged between 1–12 years with mild closed-head injuries (GCS 13–15) and a history of LOC or amnesia who had received head CT scans as part of their evaluation. All patients diagnosed with a head concussion and mild head injury were identified for the study population. Data concerning age, gender, mechanism of the injury, GCS at arrival, symptoms presented, physical findings, head CT results, and further management of the subjects were collected.

Results

In this study, 27 patients (27.3%) with positive physical examinations (PE) showed positive CT scans and 72 patients (72.7%) had negative CT scans. 17 (13.5%) of 126 patients with negative PEs had positive CT scans and 109 (86.5%) had negative CT scans. A Chi-square test was applied to analyse the association between these 2 variables. The results showed a significant association between physical examinations and CT scans (P = 0.01), as shown in Table 1.

The likelihood ratio (LR) indicates the test-value for increasing certainty of a positive diagnosis. In this study, the calculated LR was 1.5. The prevalence of positive CT scans was 19.56%. Sensitivity was 61.36% and specificity was 60.22% (Table 2).

Agreement between the physical examination and CT scan was Kappa = 0.14 (P = 0.01) (Table 3). This measure of agreement, while statistically significant, is only slightly convincing. Although not displayed in the output, we can calculate a 95% confidence interval using the generic formula for 95% confidence intervals: estimate ± 1.96 SE.

Using this formula and the results in the table, the approximate 95% confidence interval for Kappa was 0.035, 0.259. Agreement between physical examinations and CT scan was Kappa = 0.14 ($P < 0.05$), 95% CI (0.035, 0.259).

Discussion

Amongst children with minor head injuries, it is uncommon to observe LOC, but it is related to increased risk for intracranial injury. Since

Table 1: Association between physical examinations and CT scans in 225 patients

Physical examination	CT scan finding, *n* (%)		*P*-value[a]
	Positive	Negative	
Positive	27 (27.3)	72 (72.7)	0.01
Negative	17 (13.5)	109 (86.5)	0.01

[a] Pearson's Chi-square test. Abbreviation : CT = computer tomography.

Table 2: Cross tabulation of physical examinations versus CT scans

Physical examination	CT scan finding, *n*		Total, *n*
	Positive	Negative	
Positive	27	72	99
Negative	17	109	0.01

Abbreviation : CT = computer tomography.

1. Sensitivity = 27 / (27 + 17) x 100 = 61.36%
2. Specificity = 109 / (109 + 72) x 100 = 60.22%
3. Positive predictive value (ppv) = 27 / 99 x 100 = 27.22%
4. Negative predictive value (npv) = 109 / 126 x 100 = 86.50%
5. Prevalence = 44 / 225 x 100 = 19.56%

Table 3: Symmetric measures of agreement using the Kappa test

Paramater	Value	Asymptotic standard error[a]	Approximate T[b]	Approximate Sig.
Measure of agreement, Kappa value	0.147	0.057	2.587	0.010
No. of valid cases	225			

[a] Not assuming the null hypothesis.
[b] Using the asymptotic standard error assuming the null hypothesis.

CT scanning began, studies have suggested that up to 28% of children with LOC or those who demonstrate amnesia at the time of evaluation present with intracranial injury that can be detected on a CT scan (3,12,20). Although most of these intracranial lesions remain clinically irrelevant, between 2% and 8% of those with mild head injuries and LOC might require neurosurgical intervention (12).

The present study showed that physical examinations were significantly associated with positive CT scans (P = 0.01). However, a further assessment of the predictive ability of normal physical examinations and their unacceptably low sensitivity and specificity (61.4% and 60.2%, respectively) suggests that intracranial pathology in children with minor head injuries cannot be excluded based on physical examinations alone. Sensitivity and specificity are important measures of the diagnostic accuracy of a test but cannot be used to estimate the probability of disease in an individual patient. The effectiveness of a test depends on its ability to identify people with disease; the sensitivity of a test is determined by observing only those with disease. Thus, a test with high sensitivity is valuable for excluding a disease if subject's test was negative. To define specificity, the proportion of people without the disease whose test was negative is of interest. Thus, a test with high specificity is valuable for excluding a disease if subject's test was positive.

In this study, the positive and negative values were 0.27 and 0.87, respectively. This indicates that in this study population, in which a 19.56% prevalence of positive CT scans was observed, a child who has a positive physical examination has 27% chance of having a positive CT scan. Likewise, a child who has a negative physical examination has 87% chance of not having a positive CT scan. We can presume from the above data that the negative predictive value (NPV) might also be termed as the probability of not having a disease given a negative test. Therefore, it is vital to note that 'the post-test probability of disease given a negative test' is the converse of NPV (1-NPV), and is not equal to NPV.

This study also showed that the post-test probability of disease given a negative physical examination was 13%, indicating that a child who has a normal physical examination has a 13% chance of having a positive CT scan. This is a high percentage and cannot be ignored given the detrimental effects of overlooking intracranial injuries in developing and growing children. The calculated likelihood ratio was 1.5. This suggests that a child with a positive physical examination is 1.5 times more likely to have a positive CT scan. A high probability ratio implies that the test is useful but does not necessarily confirm that a positive test is a positive indicator of disease existence. Because probability ratios are derived from sensitivity and specificity, they are stable operating test characteristics that are unaffected by disease frequency.

Although there was an association between physical examinations and CT scans, only slight agreement was observed between these 2 observations (Kappa = 0.15), as values less than zero indicate less than chance agreement (Table 4) (23). Most statisticians select Kappa values of at least 0.6 and many, higher than 0.7, before declaring an acceptable level of agreement. This agreement test has further strengthened the conclusion that intracranial pathology in children with minor head injuries cannot be excluded based on physical examinations alone. Kappa values does not differentiate amongst the different types and sources of disagreement because it is affected by frequency. It may not be appropriate to compare Kappa values between different studies or populations; however, Kappa values can provide more information than simple deductions of the raw proportions of agreement.

Conclusions

This study showed that positive physical examinations were significantly associated with positive CT scans (P = 0.01). However, the calculated Kappa value showed only slight

Table 4: Qualitative terms for Kappa values.

Kappa value	Qualitative value
< 0	Less than chance agreement
0.0–0.2	Slight agreement
0.2–0.4	Fair agreement
0.4–0.6	Moderate agreement
0.6–0.8	Substantial agreement
0.6–1.0	Near-perfect agreement

agreement between these 2 variables, and the low sensitivity and specificity of physical examinations suggest that intracranial pathology in children with mild head injuries and LOC or amnesia cannot be excluded based on physical examinations alone.

Authors' Contribution

Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, obtaining of funding, administrative, technical, or logistic support, and collection and assembly of data: FF

Drafting of the article, critical revision of the article for important intellectual content, final approval of the article, provision of study materials or patients, and administrative, technical, or logistic support: MSMH

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Case Report

Fetal Intra-Abdominal Umbilical Vein Varix in Monochorionic Twins: Is it Significant?

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Abstract

A 30-years-old Taiwanese female in her second pregnancy spontaneously conceived a monochorionic twin pregnancy. A routine ultrasound at 27 weeks of gestation revealed a selective intrauterine growth restriction (sIUGR) fetus and an appropriate gestational age (AGA) fetus. The AGA fetus was found to have a fetal intra-abdominal umbilical vein (FIUV) varix. Serial ultrasounds showed no changes in the FIUV varix. 2 weeks later, the pregnancy progressed to twin–twin transfusion syndrome (TTTS). Repeated amnioreductions were required at 29 and 30 weeks gestation. The babies were delivered by caesarean section at 31 weeks due to fetal distress in the sIUGR fetus. Both fetuses survived the neonatal period with problems of prematurity. The FIUV varix disappeared a few days after delivery.

Keywords: *intra-abdominal, multiple pregnancies, ultrasound, umbilical vein, varix*

Introduction

The evolution of ultrasound techniques has improved the diagnosis and follow-up management of fetal intra-abdominal umbilical vein (FIUV) varix. The detection of a cystic mass along the natural course of the umbilical vein with grey scale ultrasound raises the suspicions of a FIUV varix. However, colour and pulsed Doppler can further define the venous vascular anomalies, and these techniques are useful for detecting and monitoring thromboses (1).

FIUV varix is defined as an umbilical vein diameter of more than 9 mm or when the diameter is larger than the intra-hepatic portion of the vein by 50% or more (2). It has been associated with intrauterine fetal death, structural fetal anomalies, chromosomes anomalies, trisomy 21, hydrops fetalis, and intrauterine growth restriction (IUGR) (3). Favourable outcomes were reported especially when there were no co-existing fetal abnormalities (4). The management of FIUV varix, especially the follow-up and timing of delivery, is still controversial.

More than 100 cases of FIUV varix have been reported in singleton pregnancies, but to date, no reported cases have specifically involved multiple pregnancies. We report a case of monochorionic twins with a selective intrauterine growth restriction (sIUGR) fetus and an appropriate gestational age (AGA) fetus with a FIUV varix. The pregnancy then progressed to twin–twin transfusion syndrome (TTTS).

Case Report

A 30-years-old Taiwanese, gravida 2 para 1 female was managed at our tertiary care centre for a monochorionic twin pregnancy. Her first pregnancy was uneventful, and she had no previous history of twins or congenital anomalies. She was a non-smoker, and her marriage was non-consanguineous. Her blood group is B rhesus positive, and her husband's blood group is A rhesus negative.

A routine ultrasound at 12 weeks gestation

revealed a monochorionic diamniotic twin pregnancy. In Taiwan, amniocentesis is routinely offered for women above 35 however it is also performed upon couple request. In this case, it was performed at 16 weeks on couple request and confirmed that both fetuses were carrying the 46, XX karyotype. A detailed ultrasound at 18 weeks showed neither congenital anomalies nor complications of the pregnancy.

The 2 weekly serial ultrasounds were normal until 27 weeks of gestation; then, 1 of the fetuses was found to have sIUGR (fetal weight below the 3rd percentile and fetal weight discordance of 39%). The sIUGR-twin had an amniotic fluid maximum vertical pocket (MVP) of 4.0 cm and absent end-diastolic velocity (aEDV) of the umbilical artery. However, the mid-cerebral artery peak systolic velocity and ductus venosus flow were normal.

The other fetus was AGA with an amniotic fluid MVP of 7.5 cm and normal umbilical artery flow. However, there was an intra-abdominal cystic mass that measured 1.52 × 1.26 cm. The presence of turbulence Doppler flow suggested a FIUV varix, and fortunately, there was no evidence of thrombosis (Figures 1 and 2).

Repeat ultrasound 2 weeks later, at 29 weeks gestation showed that the FIUV varix remained the same size with no thrombosis; however, the amniotic fluid MVP increased to 12 cm and the sIUGR-twin appeared to be stucked against the uterine wall. A diagnosis of TTTS was then made. Amnioreductions were performed twice, at 29 weeks and 30 weeks of gestation, and betamethasone was administered to promote fetal lung maturity. The fetuses were closely monitored with serial non-stress cardiotocograph tests and Doppler ultrasounds.

At 31 weeks, the FIUV varix in the AGA-twin remained the same. Unfortunately, the twins were delivered with an emergency caesarean section, as there were multiple spontaneous fetal heart decelerations of the sIUGR-twin. The outcomes of the babies are summarised in Table 1.

Discussion

Many reports on FIUV varix have involved singleton pregnancies. Of 91 cases reviewed by Fung et al. (5), 31.9% were detected prenatally by ultrasound of cardiovascular anomalies, hydropic features, and anaemia. In addition, 9.9% exhibited chromosomal anomalies, 13% exhibited perinatal losses, and only 59% had a normal obstetrics outcome. Therefore, those authors recommended detailed sonography, karyotyping, and intensive surveillance including colour Doppler ultrasound from the moment of diagnosis until delivery, especially in cases that present before 26 weeks (5). This recommendation is supported by Byers et al. (4) who also advocated searching for other anomalies, especially markers of aneuploidy. In isolated FIUV varix, Fung et al. (5) found 8.1% of unexplained intrauterine deaths between 29 and 38 weeks of gestation. There was an increased incidence of intrauterine death,

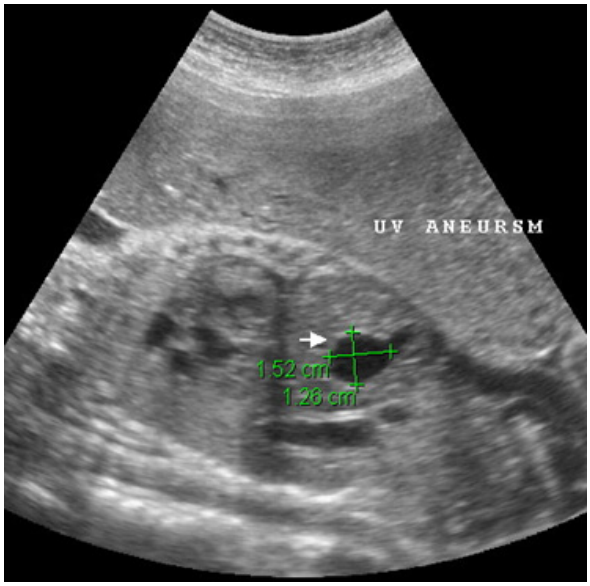

Figure 1: Ultrasound image showing the intra abdominal cystic mass.

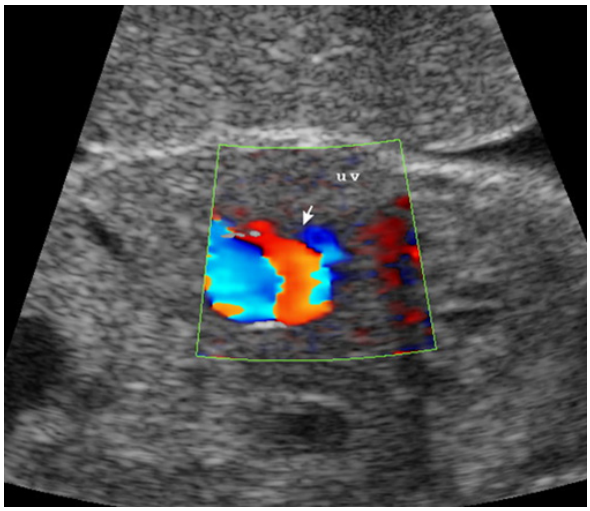

Figure 2: Ultrasound image showing turbulence flow on colour Doppler in the cystic mass.

Table 1: Outcome of the babies during delivery and neonatal period

Parameters	Twin with varix (AGA / recipient)	Co-twin (sIUGR / donor)
APGAR score	$7^{1\ min}$ $8^{5\ min}$	$8^{1\ min}$ $9^{5\ min}$
Weight	1.515 g (25%–50%)	820 g (< 10%)
Birth weight discordant	45%	
Ponderal index	2.9 (> 90%)	2.5 (50%–75%)
Fetal/placenta ratio	3.8	5.4
Problems at birth until neonatal life	• Respiratory distress • Coagulopathy	• Respiratory distress • Hypoglycemia • Hypoalbuminemia
Repeated ultrasounds of brain	Basically was an extremely premature brain	Basically was an extremely premature brain
Ultrasound of abdomen	No umbilical vein varix on 5th day of life	Ultrasound was not performed as it was not necessary
Discharge	Day 43	Still warded for prematurity at day 43

Abbreviations: AGA = appropriate gestational age, APGAR = appearance, pulse, grimace, activity, respiratory, sIUGR = selective intrauterine growth restriction.

thrombosis of the umbilical vein, and abnormal antenatal CTG especially when the diagnoses were made before 26 weeks. However, Byers et al. (4) reported a favourable obstetrics outcome in an isolated FIUV varix.

Only 5 reports of FIUV varix series included 1 or 2 cases of FIUV varix in multiple pregnancies, as shown in Table 2. The FIUV varix in monochorionic pregnancies were mainly diagnosed at mid-trimester ranging from 23 weeks to 34 weeks. The majority of them were delivered prematurely probably because of complications of the twin pregnancy itself. In the 3 cases of monochorionic twins complicated by TTTS or sIUGR, the FIUV varix always occurred in the AGA or recipient fetuses. This finding may merely be a coincidence, or it might be the possible result of a direct mechanical response to the increased feto-placental circulation, which could act as a protective reservoir mechanism because the 3 affected fetuses were born alive. Our case was diagnosed prior to the occurrence of TTTS, and this suggests that the protective mechanism for the fetus occurred earlier than the clinically detected TTTS.

Sepulveda et al. (2) reported 1 case of extensive thrombosis in a fetus with rhesus isoimmunisation following blood transfusion. This case indicates that FIUV varix might aggravate thrombotic events and extra care is needed for any fetal procedure through the umbilical vein, such as intrauterine blood transfusions.

Whether the occurrence of FIUV varix in twins with high hemodynamic circulation was a coincidence or whether FIUV varix alters the prognosis of the fetuses are questions that require further prospective studies.

In the singleton series, Yagel et al. (6) advocated a close monitoring of FIUV varix fetuses with early delivery at 34 weeks gestation. Delivery after the establishment of fetal pulmonary maturity or labour induction by 40 weeks gestation were also suggested by others (5–7), even in cases involving an isolated FIUV varix.

The complications of umbilical vein varix reported in singleton pregnancies might not be observed with the multiple pregnancies especially in the monochorionic twins. The monochorionic twins generally would have had close fetal surveillance and delivered at an earlier gestational age before any adverse effect of FIUV varix could be seen.

In monochorionic twin pregnancies, FIUV varix is significant and could be a good predictive factor for fetal survival, but this requires further prospective studies.

Table 2: Literature review of umbilical vein varix in multiple pregnancy

Study	Chorionicity	Antenatal complication	Gestational age at diagnosis	Size of FIUV varix	Twin with FIUV varix	The co-twin
Estroff and Benacerraf, 1992 (8) 1 of 5 cases	n/a	• None	29 weeks	15 mm	• Healthy baby	• Normal
Sepulveda et al., 1998 (2) 1 twin of 10 cases	n/a	• Rhesus incompatibility	30 weeks	15 mm	• Died shortly after intrauterine blood transfusion at 32 weeks • Post-mortem extensive thrombosis in FIUV varix	• n/a
Viora et al., 2004 (9) 1 twin of 12 cases	Monochorionic	• IUGR • Delivered at 35 weeks and 6 days	28 weeks 3 days	n/a	• AGA • Alive • Female • 1780 g	• IUGR • Alive • Female • 1050 g
Fung et al., 2005 (5) 1 twin of 13 cases	Monochorionic	• None delivered at term	34 weeks	10 mm	• Alive • Extra-thumb	• Alive
Byers et al., 2009 (4, personal communication) 2 twin cases of 52 FIUV varix cases	Monochorionic	• TTTS • Delivered at 33 weeks due to worsening diabetes • Mother had PCOS, diabetes on insulin, and chronic hypertension	31 weeks 3 days	12.7 mm	• Recipient alive	• Donor alive
	Monochorionic	• TRAP • Delivered at 28 weeks and 5 days due to deterioration of pump twin	23 weeks 5 days	12 mm	• Pump twin with single umbilical artery, tricuspid regurgitation, cardiac enlargement, and reversal flow of ductus venosus • APGAR score $7^{1\ min}$ $8^{5\ min}$	• Acardia

Study	Chorionicity	Antenatal complication	Gestational age at diagnosis	Size of FIUV varix	Twin with FIUV varix	The co-twin
Ismail et al., 2012 (current study)	Monochorionic	• sIUGR→TTTS • Repeated amnio reductions • Delivered at 31 weeks 4 days due to fetal distress of sIUGR-twin	27 weeks	15 mm	• AGA • Recipient twin coagulopathy • Female	• sIUGR • aEDV/ fetal distress • Female • Alive

Abbreviations: aEDV = absent of end diastolic velocity, AGA = appropriate gestational age, APGAR = appearance, pulse, grimace, activity, respiration, FIUV = fetal intra-abdominal umbilical vein, n/a = not available, PCOS = polycystic ovarian syndrome, sIUGR = selective intra-uterine growth restriction, TRAP = twin reversed arterial perfusion, TTTS = twin–twin transfusion syndrome.

Authors' Contributions

Conception and design: ZN
Provision of patients: YLC, SDC
Analysis and interpretation of the data: HI, YLC, SDC
Drafting of the article: HI
Critical revision of the article: HI, ZN

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Case Report

Giant Myofibroblastoma of the Male Breast: A Case Report and Literature Review

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Abstract

Myofibroblastomas are soft-tissue neoplasms that are thought to arise from myofibroblasts. They are mostly observed in males 41–85 years of age; however, this lesion also occurs in women. The usual clinical presentation is a unilateral painless lump that is not adherent to overlying or underlying structures. Microscopically, myofibroblastomas can be divided into 5 subtypes: classical, epithelioid, collagenised, cellular, and infiltrative. Mammary ducts and lobules are absent in the typical histological subtypes and the adjacent breast parenchyma may form a pseudocapsule. The majority of myofibroblastomas are immunoreactive for CD34, desmin, smooth muscle actin, and vimentin and are negative for cytokeratin and S-100 protein. We present a case of a giant myofibroblastoma arising in the background of gynecomastia in an adult male.

Keywords: *breast, gynecomastia, mesenchymal, myofibroblastoma, spindle cell*

Introduction

Myofibroblastoma is a rare, benign mesenchymal tumour of the breast that is thought to arise from myofibroblasts (1). Cases in the literature are mostly reported in males 41–85 years of age; however, this lesion also occurs in women (2). In addition to the breast, myofibroblastomas have also been reported at extramammary sites such as the popliteal fossa, head, neck, vulva, buttocks, groin, and paratesticular region (3). Since its first description by Wargotz et al. (2), less than 70 cases have been reported in the literature (2). Grossly, they are usually well circumscribed and small, seldom exceeding 3 cm. Microscopically, a myofibroblastoma of the breast is a mesenchymal tumour that is well demarcated from the adjacent parenchyma, lacks epithelial breast elements, and is composed of fascicles of spindle cells separated by thick collagen bands (4). Cases of associated myofibroblastoma and gynecomastia are very rare, and only a few cases have been reported in the literature (5).

Case Report

A 62-years-old man presented with a 9-year history of a large lump in the right mammary region. He was taking oral hypoglycemics and antihypertensives. He was recently diagnosed with hypothyroidism. The patient underwent an open nephrolithotomy in 1976 for a renal calculus. In addition, he had undergone angioplasty and stenting in 1996 for coronary artery disease. There was no family history of breast cancer. The lump initially appeared as a small and asymptomatic swelling 5 years prior, and a trucut biopsy performed at a private hospital suggested gynecomastia. The patient presented to us with an extremely large lump underneath the areola measuring 18 × 14 cm in maximum diameter (Figure 1). The lump was nontender, lobulated, well defined, and freely mobile with respect to the underlying muscular plane. No regional lymph nodes were palpable. Routine laboratory investigations were within normal limits. A mammogram of the breast revealed a large dense lesion with no microcalcifications. Ultrasonography showed a well-defined heterogeneous hyperechoic mass measuring 16 × 12 cm. An ultrasound of the scrotum was suggestive of a moderately sized bilateral hydrocele. A trucut biopsy of the breast performed during the present admission showed fibroadipose tissue. Therefore, the tumour was completely excised along with the nipple and areola. The post-operative period was uneventful. A gross tissue examination revealed a 16 cm

nodular lobulated tumour with a reddish-brown to whitish-yellow cut surface. A microscopic examination indicated that the tumour cells were arranged in an ill-defined fascicular pattern and were separated by thick collagen bundles (Figure 2). The cells were mostly spindle shaped and monomorphic. Adipose tissue was observed at the periphery of the tumour. No breast epithelial elements or necrosis were identified within the tumour. The tumour cells showed scant mitoses and immunopositivity for smooth muscle actin, vimentin, Bcl-2, and CD34 (Figure 3) and were negative for cytokeratin and S-100 protein. Based on the morphology and immunohistochemical results, a diagnosis of myofibroblastoma was made.

Discussion

A myofibroblastoma is a rare, benign mesenchymal tumour of the breast that is composed of myofibroblasts (1,2). Cases in the

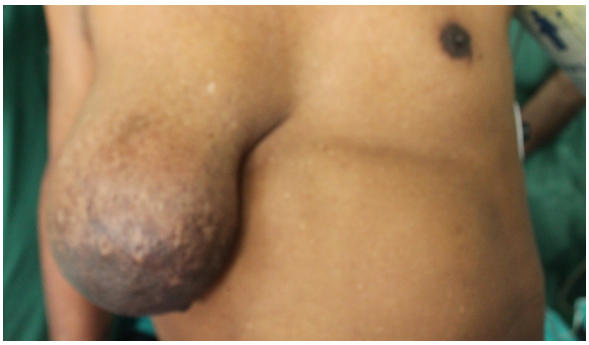

Figure 1: A large, pendulous right breast.

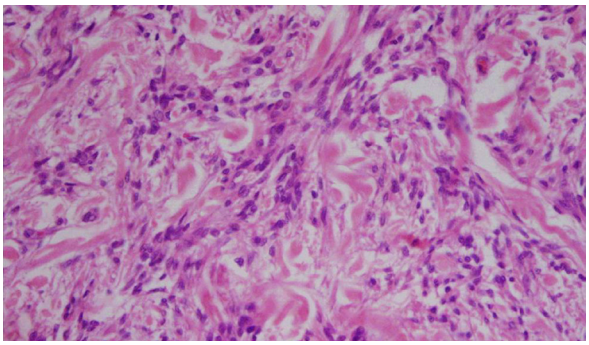

Figure 2: Haphazardly arranged short fascicles of oval-to-spindle-shaped cells separated by thick eosinophilic collagen bands (haematoxylin and eosin staining, 400 × magnification).

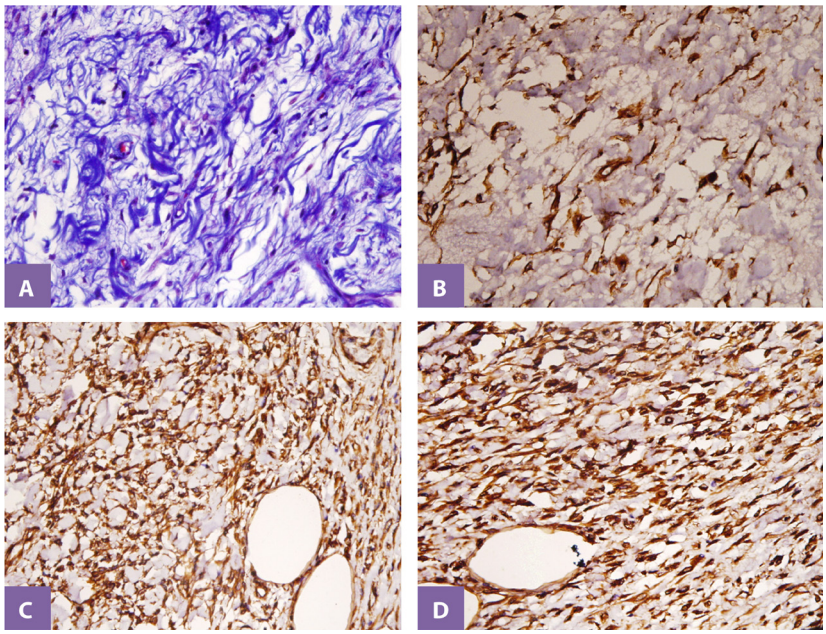

Figure 3: (A) Thick collagen bands, Masson's trichrome stain (200 × magnification). (B) Tumour cells immunopositive for vimentin (200× magnification). (C) CD34 immunopositivity in tumour cells (200 × magnifications). (D) Tumour cells immunopositive for BCL2 (200 × magnification).

literature are mostly reported in men, 41–85 years of age; however, this lesion also occurs in women (2). The usual clinical presentation is a unilateral painless lump that is not adherent to overlying or underlying structures. Bilaterality and unilateral multicentricity are rare. The association between myofibroblastoma and gynecomastia is very rare (5). Radiologically, myofibroblastomas are homogenous, lobulated, and well-circumscribed lesions, typically lacking microcalcification. Ultrasonography cannot often differentiate a myofibroblastoma from a fibroadenoma (6). Microscopically, myofibroblastomas can be divided into 5 subtypes: classical, epithelioid, collagenised, cellular, and infiltrative. Mammary ducts and lobules are absent in the typical histological subtypes and the adjacent breast parenchyma may form a pseudocapsule. Myofibroblast proliferation may also be observed in inflammatory reactions, fibromatosis, and some sarcomas (7). Microscopic analyses have also demonstrated that myofibroblasts resemble myoepithelial cells, but they can be distinguished either by immunohistochemical staining or electron microscopic characteristics (8). The majority of myofibroblastomas are immunoreactive for CD34, desmin, smooth muscle actin, and vimentin and are negative for cytokeratin and S-100 protein. The epithelioid variant may be negative or only focally positive for CD34. Rarely, a myofibroblastoma also shows nuclear positivity for the oestrogen, progesterone and androgen receptors (9). Compared to malignant spindle-cell tumours, myofibroblastomas are usually less cellular and do not show a high mitotic rate, atypical mitoses, anaplasia, or necrosis. (10). Myofibroblastomas behave in a benign fashion and an excision biopsy is usually adequate for this tumour. No recurrence or metastasis has been described in the literature.

Conclusion

A careful clinical and histopathological examination along with the use of immunohistochemical and ultrastructural techniques are necessary to correctly diagnose a unilateral, extremely large male breast lump, which may clinically simulate gynecomastia, phyllodes tumour, or carcinoma. Moreover, this diagnosis may be missed radiologically or in fine-needle aspiration cytology and biopsy specimens.

Authors' Contribution

Conception and design: KK
Analysis and interpretation of the data: VS
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Case Report

Simultaneous Non-Traumatic Perforation of the Right Hepatic Duct and Gallbladder: An Atypical Occurrence

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Abstract

Simultaneous non-traumatic perforation of the extrahepatic bile duct and the gallbladder is an uncommon occurrence that has been infrequently reported. We describe a patient with a spontaneous perforation of both the extrahepatic bile duct and the gallbladder. A contrast-enhanced computed tomography (CECT) scan of the abdomen and endoscopic retrograde cholangiopancreatography (ERCP) demonstrated a perforation of the gallbladder and a free leak from the right hepatic duct, respectively. Endoscopic biliary drainage following a sphincterotomy and biliary stent placement led to a dramatic improvement in the patient's general condition. He was subsequently scheduled to undergo an elective cholecystectomy. Repeat ERCP performed at 4 weeks after the initial stenting showed a normal cholangiogram and a distally migrated stent, which was there after removed. However, early stent removal led to re-perforation of hepatic duct and gallbladder. A repeat endoscopic biliary drainage did not help, and the patient developed biliary peritonitis. Surgical exploration revealed a perforation at the fundus of the gallbladder, 400 ml of biliopurulent collection and a frozen Calot's triangle. A subtotal cholecystectomy, gall stone removal, and a thorough peritoneal lavage were undertaken. The patient improved postoperatively. The second biliary stent was removed after 4 months. This case report highlights the role of endoscopic biliary drainage in the management of an extrahepatic bile duct perforation and warns against the early removal of a biliary stent.

Keywords: *CT scan, ERCP, gallbladder, hepatic duct, perforation*

Introduction

A non-traumatic perforation of the biliary tract is a rare occurrence that commonly involves the gallbladder. Only a few case reports have described a non-traumatic perforation of the extrahepatic bile duct, and most have been observed in neonates and children due to congenital anomalies. Since the first description of a non-traumatic perforation of the extrahepatic bile duct, only 70 cases have been reported in the English literature (1). The probable causes include high intra-ductal pressure due to obstruction of the ampulla by a tumour or calculus, pregnancy, and necrosis of the duct wall secondary to vascular thrombosis (2). To the best of our knowledge, a simultaneous non-traumatic perforation of the extrahepatic bile duct and gallbladder has not yet been reported. We present a case of a simultaneous non-traumatic perforation of the extrahepatic bile duct and gallbladder in a 45-years-old man and discuss its management.

Case Report

A 45-years-old man who was a resident of Delhi and a street vendor by profession, presented with pain in the right upper abdomen, jaundice, and fever of 15 days duration. There was no past history suggestive of biliary colic, or jaundice. A physical examination revealed tachycardia (104 min), icterus and a tender right hypochondrial lump that was continuous with the liver. His serological parameters were as follows: hemoglobin, 7.2 gm%; total

leukocyte count, 29, 100 mm^3; total bilirubin, 30.3 mg% (direct, 18.3 mg%); alkaline phosphatase, 1086 IU; and prothrombin time, 2.3 (INR). Contrast-enhanced computed tomography (CECT) of the abdomen supplemented with ultrasonography (USG) demonstrated hepatomegaly (14.7 cm). The gallbladder was grossly distended (Figure 1). A hypodense pericholecystic collection was observed communicating with the gallbladder at the level of its fundus on the right side, suggesting gallbladder perforation (Figure 2). The distended gallbladder and the pericholecystic collection appeared to compress the confluence of the right and left hepatic ducts and the common hepatic duct. Upstream dilatation of the right and left hepatic ducts and dilatation of the intra-hepatic biliary radicles were also observed. A calculus was floating in the body of the gallbladder. Free fluid was not present in the paracolic gutters or pelvis. The patient underwent endoscopic retrograde cholangiopancreatography (ERCP), which demonstrated that the entire length of the common bile duct was compressed by an extrinsic mass, with a free leak of contrast media from the right hepatic duct (Figure 3). The common bile duct (CBD) was free of stones. A guide wire was placed across the site of the leak into the right hepatic duct. A 7 Fr, 12 cm stent was placed with the proximal end above the site of the leak. Endoscopic biliary drainage led to a dramatic improvement in the patient's general condition with gradual resolution of the lump and the jaundice. The pericholecystic collection disappeared after 4 days, as confirmed upon repeat USG. The patient was scheduled for an elective cholecystectomy. His serum bilirubin decreased from the initial value of 30.3 mg% to a plateau averaging 5.0 mg% after 4 weeks. CECT of the abdomen showed distal migration of the biliary stent, which abutted the lateral wall of the duodenum. There was mild intrahepatic biliary radicle dilatation. A repeat ERCP was undertaken, which showed a normal biliary tract; the stent was removed. Unfortunately, 2 days later, the patient developed severe pain in the right upper abdomen. An examination revealed a tender, firm right hypochondrial lump. A repeat abdominal ultrasound showed gallbladder thickening with a small pericholecystic collection. The common duct was not visualised clearly. A repeat ERCP demonstrated a free leak of contrast from the right hepatic duct. A guide wire was placed across the site of the leak into the right hepatic duct and a 7 Fr, 12 cm stent was placed with the proximal end above the site of the leak. However, this time, the patient did not respond well and developed biliary peritonitis. Surgical exploration revealed a perforation at the fundus of the gallbladder, 400 ml of biliopurulent collection and a frozen Calot's triangle. A subtotal cholecystectomy, gall stone removal and a thorough peritoneal lavage

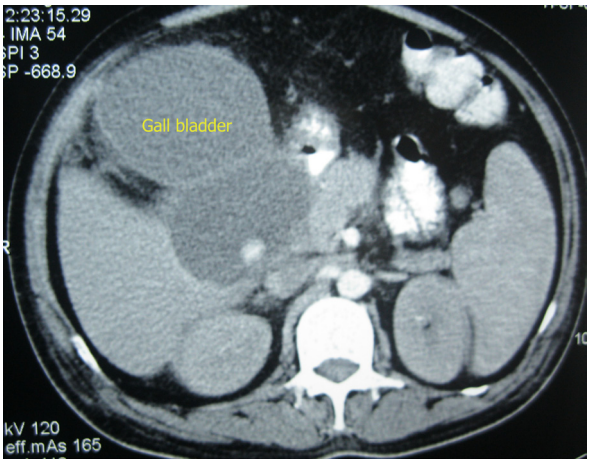

Figure 1: An axial section of an abdominal contrast-enhanced computed tomography showing a distended gallbladder. A large calculus is observed in the lumen of the gallbladder (sonographic correlation).

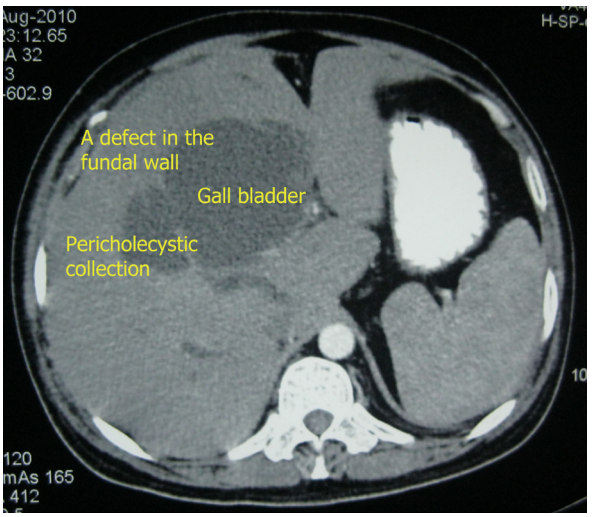

Figure 2: An axial section of an abdominal contrast-enhanced computed tomography showing a defect in the fundus of the gallbladder with a communication to a pericholecystic collection.

were undertaken. The patient improved and progressed well. The subhepatic drain stopped draining bile on the 10th day and was removed on the 12th day following surgery. ERCP performed after 16 weeks revealed a normal biliary tract, and the stent was removed. The patient was asymptomatic after 7 months of follow up. A histopathological examination of the gallbladder demonstrated chronic cholecystitis.

Discussion

Various approaches for the management of bile duct perforations have been described, but these approaches need to be tailored according to the general condition of the patient, the extent of the peritonitis, and the imaging findings. Patients presenting with generalised peritonitis require surgical exploration, thorough lavage and drainage of the peritoneal cavity, a sutured closure of the perforation, if possible, and treatment of any associated biliary pathology. Most of these patients have associated choledocholithiasis, which may require either a choledocholithotomy with T-tube drainage (3) or a choledochoduodenostomy (4). A perforation may also be closed over a T-tube if there is no associated biliary pathology (5). Suture repair may not be possible if severe inflammation is present at the perforation site. A more proximal perforation of the hepatic duct may also preclude the feasibility of primary repair. These patients may be managed with biliary decompression with T-tube drainage provided there is no distal obstruction. Patients who have a localised collection may be treated with percutaneous drainage of the collection and endoscopic sphincterotomy with stenting (6). Percutaneous transhepatic gallbladder drainage has been advocated as an initial alternative to surgery to treat gallbladder perforations in high-risk patients (7). The timing of biliary stent removal has been variable in previous reports of bile duct perforation. Bernas et al. (8) reported a case of spontaneous bile duct perforation in a 3-years-old toddler. They managed the case with endoscopic biliary stenting and removed the stent successfully 7 weeks after the procedure. Karvonen et al. (6) waited 3 months for stent removal while successfully managing a case of spontaneous bile duct perforation with endoscopic biliary stenting and percutaneous drainage of a subhepatic collection in a 67-years-old man.

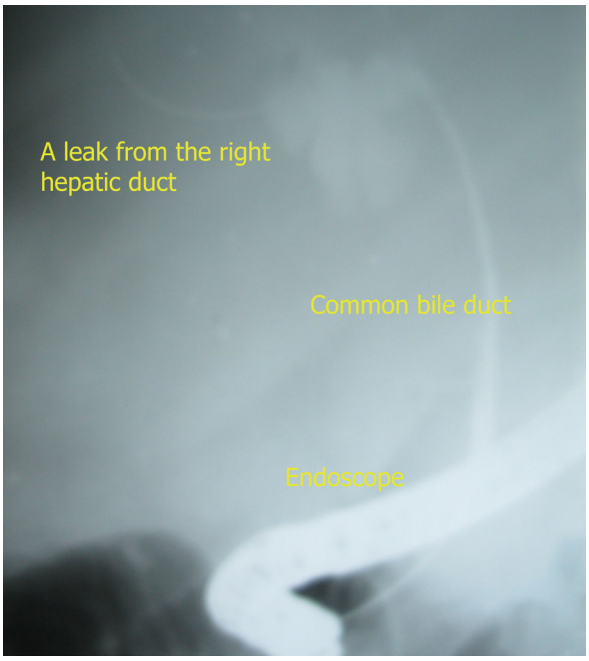

Figure 3: An endoscopic retrograde cholangiopancreatography image showing the entire length of a compressed common bile duct and the free leak of contrast from the right hepatic duct.

Our patient presented with localised peritonitis in the right hypochondrium and CECT suggested gallbladder perforation and a localised pericholecystic collection causing extrinsic CBD compression with proximal biliary radical dilatation. Although there was a gallbladder perforation, its huge distension may have been caused by a large pericholecystic collection that compressed the entire bile duct and the cystic duct. Due to the significantly abnormal liver function tests, we planned for endoscopic stenting followed by a laparotomy and cholecystectomy. Endoscopic stenting caused a dramatic improvement in the condition of our patient, leading to the postponement of surgical intervention to allow further optimisation of the patient. However, stent removal at 4 weeks led to a re-perforation and biliary peritonitis. This highlights the role of endoscopic drainage in these patients and underscores the importance of delayed removal of the biliary stent.

Conclusion

We conclude that endoscopic biliary drainage should be considered as an option in the management of non-traumatic perforation of the extrahepatic duct with a caveat that early stent removal may cause re-perforation.

Authors' Contribution

Conception and design: PKG
Acquisition of data: PKG, SP
Analysis and interpretation of data: PKG, BKJ, ASP, VR
Drafting the article: PKG, SP
Critical revision: BKJ, VR, ASP
Final approval of the draft: PKG, BKJ, SP, VR, ASP

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Case Report

Fournier's Gangrene: A Case of Neglected Symptoms with Devastating Physical Loss

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Abstract

Fournier's gangrene is a severe life-threatening infection involving the perianal area, perineum, and external genitalia. It demands prompt recognition, critical care therapy, surgical therapy, and a combination of antibiotics. The infection commonly spreads via the fascial planes and causes superficial vascular thrombosis within the Colles' fascia around the external genitalia. It can extend cephalad to involve the Scarpa's fascia and Camper's fascia in the abdominal wall. The treatment would include multiple debridements, which would result in disfiguring scars of the perineum and might lead to significant physical and psychological complications. We describe a case of a 58-years-old man presenting with Fournier's gangrene resulting from an infection of an impacted urethral stone. The patient previously had obstructive voiding symptoms for 1 month but chose to neglect them. The resultant infection was severe and caused penile and right testicular gangrene. He underwent multiple wound debridements, which included a total penectomy and right orchiectomy. Psychological and rehabilitative support was necessary for him to overcome his loss and disfigurement.

Keywords: *gangrene, genitalia, orchidectomy, perineum, psychology*

Introduction

Fournier's gangrene is a severe and life-threatening infection of the perineum and perianal region. Despite established management protocols, the mortality and morbidity range from 10%–20% and up to 60%, respectively. Patients who do survive the ordeal are frequently left with a disfiguring wound, a sense of altered body image, psychological trauma, and prolonged rehabilitation to normality. Here, we describe such a case in which delayed presentation of the disease resulted in devastating disfigurement and morbidity.

Case Report

A 58-years-old man had a one-month history of obstructive voiding symptoms. He worked as a security guard and was from a low socio-economic income group. He had not sought proper medical help but instead tried traditional remedies to overcome his symptoms. He then presented to the emergency department with acute urinary retention associated with 3 days of penile and scrotal swelling. He had no fever, hematuria, or previous instrumentation of the urinary tract. A physical examination demonstrated that he was tachycardic (120 beats/min) and hypotensive (80/60 mmHg). There was discolouration and swelling of his external genitalia with an associated priapism (Figure 1a). A diagnosis of Fournier's gangrene was made. He had severe metabolic acidosis and a random blood sugar level of 8.4 mmol/L. Following fluid resuscitation, he was treated with broad-spectrum antibiotics and inotropic support, and an immediate wound debridement was performed.

Intra-operatively, the skin overlying the external genital was gangrenous and removed. The corpus cavernosum was engorged with deoxygenated blood and the corpus spongiosum had extensive necrosis (Figure 1b). The superficial and deep dorsal penile veins were thrombosed. An impacted urethral stone was observed and removed from the membranous urethra (Figure 1c). It was unclear whether the corporal bodies of the penis and both testes were viable. They were therefore not removed to preserve the genital anatomy. A suprapubic catheter was

inserted to drain the bladder.

The patient post-operatively developed pneumonia. He then developed gangrene of the digits of both the lower and upper limbs, which resulted from a 20 mg/min noradrenaline infusion. Within 3 days, the right testis and the corporal bodies of the penis became gangrenous (Figure 1d). He underwent a total penectomy, right orchiectomy, and further wound debridement. Upon discharge, the wound had contracted with healthy granulation at its base. However, the patient was distraught due to the loss of the penis and right testis. The patient and his family received psychological counselling and are still under active observation and follow up.

Discussion

Fournier's gangrene is a devastating disease with an estimated mortality of 10%–20%, depending on the severity of presentation (1). It was initially described by Jean Alfred Fournier in 1883. He described 3 features of this disease, which include the abrupt onset of scrotal pain and swelling in a healthy adult, rapid progression to gangrene, and the absence of a definitive cause (2). It is now no longer considered idiopathic, as its etiology is usually a pathological process from the overlying skin, urinary tract, or colorectal area (1). The disease usually involves the scrotum (30%), perineum (50%), or anterior abdominal wall (20%). Predisposing factors, such as systemic immunosuppression, diabetes mellitus, chronic alcoholism, and steroid therapy favour its rapid progression (3).

Fournier's gangrene represents a polymicrobial infection. Both aerobic and anaerobic organisms are usually present. *Enterobacteriaceae, bacteroides* and *streptococcus* species are the most commonly isolated. The infection begins in an area adjacent to the site of bacterial entry and progresses as a spreading inflammatory reaction that involves the superficial and deep-tissue planes. As it progress, the infection causes endarteritis, leading to cutaneous and subcutaneous vessel thrombosis and tissue necrosis due to the synergistic actions of the

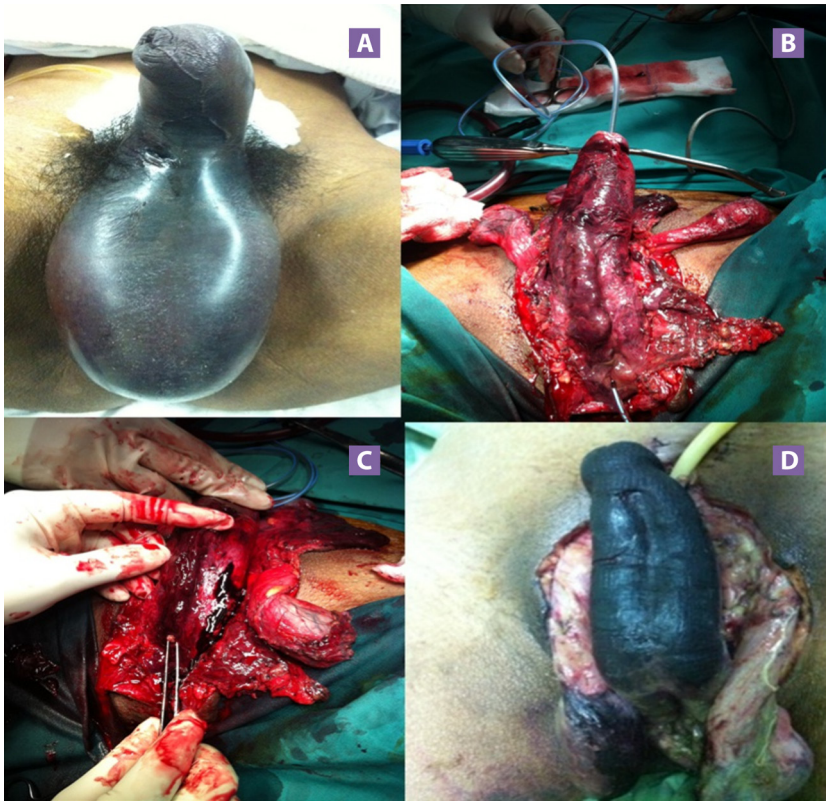

Figure 1: (A) Gangrene and swelling of the external genitalia. (B) Gangrenous corpus spongiosum and perineal necrosis. (C) A stone removed from the membranous urethra. (D) Penile and right testicular gangrene.

aerobic and anaerobic organisms; which produce various proteins and enzymes that lead to intravascular clotting. The microorganisms produce various endotoxins and exotoxins that cause prolonged vasoconstriction and a thrombotic occlusion of the blood vessels. These toxins are also released into the systemic circulation and resulting in systemic inflammatory response syndrome (SIRS) and septic shock. Certain bacteria, including *streptococci* and *staphylococci*, produce hyaluronidase, streptokinase, and streptodornas, which directly destroy connective tissue. Hydrogen and nitrogen gasses are produced by the anaerobes, resulting in crepitus (4). As such, potential antibiotic therapies include a metronidazole combination for anaerobic microorganisms and broad-spectrum third- or fourth-generation cephalosporins and an aminoglycoside, such as gentamicin, for gram-positive and gram-negative microorganisms, respectively.

Urogenital causes of Fournier's gangrene include urethral strictures, indwelling catheters, traumatic catheterisation, urethral calculi, and prostate biopsies. Stricture and calculi may produce minimal symptoms, and therefore go unrecognised unless the appropriate investigations are undertaken, such as urinary tract imaging and cystoscopy. Infected urine proximal to the obstruction enters the periurethral glands. The invading organisms then spread within the corpus spongiosum before penetrating the tunica albuginea to reach Buck's fascia. Infections then travel posteriorly along the dartos fascia to enter Colles' fascia (3,4). Colles' fascia is posteriorly attached to the perineal body, and therefore, infections arising from the urogenital structures do not reach the anal margin. By contrast, an infection with an anorectal focus penetrates the anal sphincter muscles to reach Colles' fascia before involving the scrotum. This difference helps to identify the likely origin of infection because the perianal involvement of Fournier's gangrene indicates an anorectal source of infection (4).

The corporal bodies and testes are rarely affected because they have independent blood supplies that originate intra-abdominally. However, severe infections may penetrate the urogenital diaphragm and the perivesicle space and gain entry into the inguinal canal via the internal and external fascia of the spermatic cord (4), which occurred in this patient's right side, causing testicular gangrene. An ischemic priapism was present and is believed to have resulted from a venous thrombosis of the superficial and deep dorsal veins.

Prompt recognition and treatment may limit the spread and metabolic consequences of a gangrenous infection. However, our patient, as in previously reported studies, showed a consistent delay of 1–7 days (mean of 2.5 days) between disease onset and the first debridement.

A total penectomy is rarely necessary, but an orchiectomy is reportedly performed in 21% of cases (1). Post-debridement, most patients have a flap or skin graft cover the tissue loss on the penis. The scrotal skin heals well and is usually left to regenerate itself (1,2). Our patient had both of the above-mentioned procedures performed, which gave him a sense of physical loss and altered body image. Psychological counselling was obtained for the patient and the family. Further rehabilitation was necessary to hasten his recovery process and allow him to return to work.

This case illustrates the severity and fast spread of necrotising fasciitis of the perineal region resulting from a neglected treatable condition. It is likely that low economic status, cultural beliefs, and a fear of modern medicine kept this patient away from early definitive treatment. Immediate recognition, prompt resuscitation, and extensive debridement with broad-spectrum antibiotic coverage are necessary to limit the spread and severity of a gangrenous infection. Nonetheless, the physical and psychological damage is sometimes already present. Major lifestyle adjustments may be needed and could include role reversal of the family breadwinner, a change in occupation and financial uncertainties. Thus, it is important that early psychological counselling, aggressive rehabilitation, and social support are obtained. These added supportive measures will allow the patient and family members to come to terms with their loss and keep them focused on their future aspirations and goals.

Conclusion

Fournier's gangrene is a surgical emergency which demands prompt recognition and aggressive treatment. A delay in diagnosis would result in devastating outcomes. The etiology is often found through proper investigations and not idiopathic as previously believed. Definitive management still includes multiple surgical debridement which saves lives but leaves traumatic scars on a patient.

Authors' Contributions

Conception and design and analysis and interpretation of the data: PS
Drafting of the article: KTW
Critical revision of the article for important intellectual content: TGC
Provision of study materials or patients: AR
Collection and assembly of data: JL

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Eulogy

Eulogy – Almarhum Prof. Dr. Syed Mohsin Sahil Jamalullail

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I have lost a close and loyal friend. We had undergone the ups and downs of life, overcomed the brickbats and yet, he remained positive of human kind until the very end. To understand these characteristics of the man, it perhaps would be pertinent for me to trace our long relationship from the very beginning.

It was in 1976, when I was just about completed the establishing the Department of Pathology and the academic programme of the first cohort of the medical student in Universiti Kebangsaan Malaysia (UKM). I was approached by the senior technologists of the faculty regarding their dilemma in not having a formal qualification and therefore, recognition by the authorities. If my memory serves me, only 2 of them had the requisite for appointment, i.e., the advanced certificate from the Institute of Medical Research (IMR) and the University of Malaya (UM). Their previous training had been "informal" at various medical facilities (including the British Army Laboratory) and their varied functions in UKM from Medical Muzium and Illustration to Animal House Management.

Being the only "pathologist" in UKM, I assembled a small committee from various laboratory disciplines. Mohsin, or 'Moh' as I used to call him, was one of them and he subsequently was the secretary by virtue of his command of Bahasa and his linkage to Dewan Bahasa dan Pustaka (DBP), the National Language Centre. We discussed at length on the structure of a full three-year Diploma Programme and the option for the serving technologists who were in their late thirties and forties. Within a year, we received the green light to proceed and the programme was successfully implemented. Moh worked closely with me as I chaired the committee for the Tenth Anniversary Celebrations of UKM under my role of Deputy Dean.

After my appointment as the Founding Dean in Universiti Sains Malaysia (USM) in July 1979, I came back to UKM and called up Moh, the late Saidi (my trainee), and Ong (I had made my acquaintance with him when he was the Scientific Officer in Kuala Lumpur Hospital). I told them of my need for abled assistants willing to work aggressively to meet the targets I had set out. I gave them 24 hours to decide. They came back to me in the affirmative.

I know very little of Moh's childhood days but we shared some commonality as our fathers were in the service and were frequently transferred. Temerloh (Pahang) and Anderson School (Ipoh), were 2 places that we both fondly remembered. He completed his Form 6 in Alor Star and proceeded to do his degree in Monash University, followed by his Masters in Melbourne University. He met his future wife in Monash. When they returned in 1976, he joined UKM as a lecturer in Pharmacology.

The first 6 months in USM was a busy period, preparing paper after paper for approval by the authorities (In which I've detailed extensively in my book - Medical Education in Malaysia: Changing the Mind Set). Our routine day ended no earlier than 9 pm and Moh was given charge of human capital and to identify our needs in the immediate, medium, and long terms.

In the midst of our work, we shared some light moments and that was when I recognised the true nature of Moh.

A particularly fond memory that I have of him, was when we first made a trip to Kota Bharu in 1979. We decided to explore the town center, which at the time only consisted of a square and only 3 main hotels - we took a rickshaw to savour the "night" life! With Moh, it didn't matter what we did, but the good company was irreplaceable. Despite all the hard work, we knew how to let our hair loose, and during our (semi-official) work functions Moh would always break in to his favourite song, Widuri – he was a pretty good singer!

Back at work, my aggressiveness unfortunately, did not go down too well with various parties in USM. We were labelled the Ewing family (after the television series, Dallas) - Moh was the Bobby Ewing, the likeable, approachable, sincere and soft-spoken son, and I was the Jock Ewing, the patriarch of the clan. He was the link to the USM crowd and organised games with the other schools. In football, we had in our team footballing legends such as Kamaruzaman Wan Su, Ramli Saad and Roslan from ENT. Moh was our heroic goalkeeper and he kept our opponents at bay.

After the first batch of students were enrolled in July 1981, and the second cohort completed their first year, I discussed with Moh on his future academic enhancement, reminding myself that my work in USM would be completed with the first graduating class and the establishment of the campus in Kubang Kerian.

I highlighted 2 options to him: the suitability of a medical degree versus a doctoral in a medical school, and Moh decided to do the former. He was accepted into the Middlesex Hospital programme, which, on hindsight was probably unsuitable.

He had asked me personally some years later, of the reasons for implementing the USM curriculum and managing it in that way, and my response was to remove the power from biased lecturers and disciplines in a faculty system to determine the passing or failing of students in the examinations.

Unfortunately, this was what happened to him but Moh did not let this dampen his spirits and came back to start footing research in Pharmacology. With the move to Kubang Kerian, he delved deeper into the merits and demerits of local plants. A testament to this would be his various publications and successful postgraduate students that he supervised. His work with Kitasato University earned him the Doctorate in 1995.

Besides his personal achievements, unknown to many, Moh was also a very generous man, having sponsored a postgraduate student. All in all, he lived his life as a man for all seasons, overcomed adversity, cared for his family and caring for all who crossed his path.

In spite of knowing that there were people who were backbiting him, he bore no grudges against them. He was a close and loyal friend, and while new friends come and go - it is too late for me now to inculcate new friendships such as the one we had, I will miss him very much.

My dear friend, may Allah shower you with His blessings. Al-fatihah.

Best regards,

Dato' Dr. Mohd Roslani Abdul Majid
Foundation Dean of The School of Medical Sciences, Universiti Sains Malaysia

Abstracts

Abstracts of Theses Approved for the MMed at the School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia

STUDY TO DETERMINE THE INFLUENCE OF DIFFERENT ANALGESIC DRUGS BETWEEN TRAMODAL SODIUM AND PARECOXIB SODIUM INTRAMUSCULAR ON EXPERIMENTAL PLEURODESIS INDUCED BY ERYTHROMYCIN OR BLEOMYCIN INTRAPLEURAL IN RABBITS

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MMed (Surgery)

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Introduction: Malignant pleural effusion, recurrent spontaneous pneumothorax, and recurrent benign pleural effusions were common complications encountered in the daily clinical practices especially those with advanced malignant diseases. These debilitating complications of advanced disease may contribute to poor quality of life, recurrence hospital stay, and increase hospital cost. However, optimal treatment is controversial and there is no universally standard approach.

Objectives: The aim of study is to determine the influence of different analgesic drugs between Tramadol Sodium and Parecoxib Sodium intramuscular on experimental pleurodesis induced by Erythromycin or Bleomycin intrapleural in rabbits.

Methods: A pilot study was designed where 28 White New Zealand rabbits were divided into 4 groups of 7 rabbits (each about 2 months of age weighing 2 to 4 kg) and scheduled to receive different agents as labelled into group A (Erythromycin and Parecoxib Sodium), B (Erythromycin and Tramadol Sodium), C (Bleomycin and Parecoxib Sodium) and D (Bleomycin and Tramadol Sodium) at right hemithorax. The left hemithorax was subjected as control measures labelled as CONTROL. After 30 days, the rabbits were euthanatised for evaluation of presence of pleural adhesions macroscopically and microscopically by blinded respective pathologist.

Result: This preliminary pilot study demonstrated that the degree of pleurodesis induced by the intrapleural injection of Erythromycin was superior compared to Bleomycin as sclerosing agent in the experimental rabbits (P = 0.003). The use of sustained systemic administration of concomitant analgesia in this study observed that centrally acting opiods, Tramadol Sodium surprisingly reduces the degree of pleurodesis as compare to selective cycloxygenase-2 inhibitors, Parecoxib Sodium (P = 0.009) which thought to be an anti-inflammatory agent .

Conclusion: As a conclusion, extrapolation of these results to human suggests that the use of intrapleural Erythromycin as potent chemical pleurodesis agent and insensitive to the action of concomitant analgesia of Parecoxib Sodium will give important clinical implication for the effectiveness of chemical pleurodesis in future.

Supervisors:
Assoc Prof Dr Ziyadi G
Dr Andee D

STUDY OF CONCENTRATION AND MORPHOLOGY OF MECHANORECEPTORS IN THE MUCOSA OF UNCINATE PROCESS OF THE HUMAN NOSE

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MMed (ORL–Head and Neck Surgery)

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Objective: To study the mechanoreceptors in the human nasal mucosa and to compare the mean concentration of mechanoreceptors in the uncinate process mucosa in patients with and without nasal polyp.

Method: Subjects were 12 adult patients; 6 participants in the study group (patient with nasal polyp) and 6 participants in control group (patients without nasal polyp). Both groups underwent functional endoscopic sinus surgery for their nasal pathology. During operation 1 × 1 cm from the uncinate process mucosa was excised then fixed with formalin and sent to the pathology laboratory for staining, each sample was stained for Calretinin-labeled antibody and Neurofilament-labeled antibody. After the staining process, the slides were examined by light microscope.

Result: There were no cells identified to be stained by Calretinin antibody in all 12 samples. However sample that stained with Neurofilament antibody showed the presence of the nerve terminals in the mucosa of all 12 samples. The mean concentration of nerve terminals was significantly higher in patients without nasal polyp (20.67 ± 5.046) than for patients with nasal polyp (11.67 ± 7.257).

Conclusion: As a conclusion, the results suggest that there are no specific cells in the nasal mucosa that act as mechanoreceptors. However the presence of the nerve terminals in the nasal mucosa and between the epithelial cells suggests that they are C-mechanoreceptors which are thought to be polymodal nerve terminals. In addition, reduction in the concentration of nerve terminals in patients with nasal polyp can be the reason for the reduction or absence of the feeling of

nasal obstruction in some patients with nasal polyp.

Supervisor:
Assoc Prof Dr Rosdan Salim
Co-supervisor:
Dr Ramiza Ramza
Dr Sharifah Emila

A RANDOMISED CONTROLLED TRIAL OF MGSO4 THERAPY FOR 24 HOURS VERSUS EARLY CESSATION IN PATIENTS WITH SEVERE PRE-ECLAMPSIA

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MMed (O & G)

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Introduction: Magnesium sulphate has been shown to be the optimal anticonvulsant in preventing the recurrence of seizures in eclampsia and in seizure prophylaxis in pre-eclampsia. Traditionally, seizure prophylaxis has been administered before delivery and continued postpartum for an arbitrary time, usually 24 hours.

Objectives: The primary objectives of this study were to evaluate the safety and effectiveness of using clinical parameters to signal cessation of postpartum magnesium sulphate therapy among patients with severe pre-eclampsia.

Methods: A randomised trial of postpartum magnesium sulphate therapy was conducted in Hospital Raja Perempuan Zainab II, Kota Bharu and Hospital USM, Kubang Kerian from December 2009 to September 2010. The control group received 24 hours of therapy and the intervention group received therapy until fulfilled clinical criteria for discontinuation of seizure prophylaxis. The independent *t*-test, Chi-square test and Fisher's exact test were used for analysis of data. A *P*-value was considered statistically significant.

Results: There were 52 patients in the control group and 50 patients in the intervention group. The intervention group had a significantly shorter duration of therapy ($P < 0.05$). There were no differences in the mean booking BMI, weight on admission, systolic blood pressure and platelet level between the 2 groups. However, there were significance differences in the mean age of the patients, delivery gestational age, diastolic blood pressure, and uric acid level between 2 groups. There was no patient in this study had eclampsia or required the reinitiation of therapy.

Conclusions: Clinical parameters can be used effectively and safe to shorten the duration of postpartum magnesium sulphate therapy in patients with severe pre-eclampsia.

Supervisor:
Associate Professor Dr Nor Aliza Abd. Ghaffar
Co-supervisor:
Dr Zainal Abidin Hanafiah

COMBINED SPINAL EPIDURAL ANALGESIA IN LABOR: COMPARISON BETWEEN INTRATHECAL OF 2 MG PLAIN BUPIVACAINE VERSUS HEAVY BUPIVACAINE WITH FENTANYL

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Introduction: Spinal opioid analgesia utilizing analgesics has been one of the major developments during the past decade in the management of acute and chronic pain. The relief of pain is due to the interaction of the opioid injected epidurally or intrathecally with a specific opioid receptor in the spinal cord.

Objectives: The use of opiates in the conjunction with the spinal or epidural local anesthetic such as bupivacaine afford prolonged post-operative pain relief (Aboulish et al., 1988, Akerman et al., 1988). A possible synergistic analgesic effect between the local anesthetic and opioids may have important clinical implications. However, this effect is difficult to evaluate in man (Akerman et al., 1988).

Methods: As there are only few studies on analgesic duration of plain bupivacaine, a double blind randomised prospective study was conducted on 90 patients who had undergone parturient in labour in Hospital Universiti Sains Malaysia , Kelantan. The aim of our study was to ascertain whether a smaller dose of intrathecal bupivacaine can preserve the quality of analgesia while generating fewer adverse effects. 90 patients with no complicating obstetric and medical problem, whose age ranges from 18–42 years were selected randomly into 2 groups. For group 1, the patients received 2 mg of plain intrathecal bupivacaine with 25 mcg fentanyl and group 2 received 2 mg intrathecal heavy bupivacaine with 25 mcg fentanyl. The pain was assessed on the variables at time 0 (time at the start of IT injection) and at 5, 15 and 30 minutes.

Conclusion: The result revealed that the use of 2 mg heavy bupivacaine with 25 mcg fentanyl produce adequate level of analgesia at T10 and no incidence of high sensory block. It was statistically significant comparing both groups with a *P*-value of 0.003. In terms of side effect, our study has shown less incidence of side effect including nausea and/or vomiting as well as incidence of pruritus is significantly reduced in the study population (nausea and/or vomiting *P*-value at 0.049 and pruritus *P*-value = 0.026.

Supervisor:
Dr Gnandev Phutane

COMPARISON OF EFFECTIVENESS AND SAFETY OF KETAMINE WITH MIDAZOLAM AGAINST HIGHER DOSE OF KETAMINE AS PROCEDURAL SEDATION FOR LUMBAR PUNCTURE IN PAEDIATRIC LEUKEMIC PATIENTS

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Introduction: Children with leukemia undergo several invasive procedures. Sedation is used to make these procedures more comforting to the patient as it is necessary for successful outcome. However sedatives can have devastating effects. In our centre as well as others, combination of ketamine with midazolam has been used for years without specific protocol.

Objectives: To compare the effectiveness and safety of combination ketamine and midazolam against higher dose of ketamine as procedural sedation for lumbar puncture in pediatric leukemic patients.

Method: A total of 29 paediatric leukaemia patients underwent 58 lumbar punctures in a double blinded crossover clinical trial. The 2 regimes compared were ketamine-midazolam (KM) regime who received combined intravenous midazolam 0.1 mg per kg with ketamine 1 mg per kg against ketamine-ketamine (K2) regime who received higher dose of intravenous ketamine (i.e. 2 mg per kg). The main outcomes measured were time to achieve the desired sedation (Ramsay level of sedation at 6), time to complete lumbar puncture, time to regain consciousness (Aldrete recovery score of at least 8), and adverse effects.

Result: 27 patients (93%) were successfully sedated with each of the regimens. Mean time taken for sedation and mean time to be fully conscious after sedation were significantly less ($P < 0.05$) in K2 regime. Mean time taken for sedation in K2 regime was 7.56 minutes ± 4.4 and in KM regime it was 8.74 minutes ± 3.6. Mean time to be fully conscious was 132 minutes ± 93.5 for K2 regime while it took 173 minutes ± 88.8 for patients in KM regime. There is no statistically significant difference in mean time taken to complete LP between the 2 regimes ($P = 0.06$). 2 patients in K2 regime developed tachycardia and 1 patient had pain after procedure while no patient in KM regimen had either of these. 5 patients from either of the groups had desaturation. This was not statistically significant (McNemer test = 0.250) but it could be clinically relevant. 8 patients (30%) in KM regime required top-up doses of ketamine and 7 patients (26%) required top-up doses of ketamine in K2 regime.

Conclusion: Ketamine as a sole agent is as effective and safe as combination of midazolam and ketamine. It should be considered in procedural sedation for lumbar puncture in pediatric leukemic patients. It has faster induction and reversibility but it cause more adverse reactions and do not reduce time taken for lumbar puncture. An initial dose of 2 mg per kg is safe to be used with another top up dose of 0.5 mg per kg. Top up doses are frequently required.

Supervisor:
Dr Mohd Suhaimi bin Ab Wahab
Co-supervisors:
Dr Norsarwany Mohamad
Assoc Professor Dr Saedah Ali

THE EXPRESSION OF INSULIN-LIKE GROWTH FACTOR-RELATED PROTEIN 1 (IGFBP-rP1) IN COLORECTAL CARCINOMA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Introduction: Insulin-like growth factor (IGF)-binding protein-related protein 1 (IGFBP-rP1) is a member of the IGF axis. IGFs have numerous functions such as potent mitogens, anti-apoptotic survival factor, promoting cell migration and in glucose metabolism. Type 2 diabetes mellitus or in hyperinsulinemia state is hypothesised to promote colorectal carcinogenesis directly or indirectly by increasing the insulin-like growth factor-1 (IGFBP-rP1), a potent mitogen and inhibitor of apoptosis.

Objectives: To determine the expression and association of IGFBP-rP1 protein in patients having colorectal carcinoma (CRC) with and without diabetes mellitus type 2 (DM2) in our population.

Methods: This is a case control study of 111 cases of CRC with or without clinically confirmed DM2 in Hospital Universiti Sains Malaysia (HUSM) Kelantan from January 2000–April 2010. The Chi-square test was used to compare the immunoreactivity of IGFBP-rP1 expression among CRC cases with or without type 2 DM, and its association by using multiple logistic regression test. All calculations performed by using SPSS version 18.0, *P*-value < 0.05 was taken as statistically significant.

Results: A significant difference in the expression of IGFBP-rP1 among CRC cases with and without DM2. The over-expression of IGFBP-rP1 staining was observed in (18/26) 69% of CRC cases with DM2, while in CRC cases without DM2 only (24/57) 42%. Univariable analysis showed significant finding for DM2 ($P < 0.022$) and cancer stage ($P < 0.005$). This result was further strengthened by using Multiple logistic regression test whereby both variables, DM2 ($P < 0.019$; adjusted OR = 3.50, 95% CI, 1.23–9.97) and cancer stage ($P < 0.005$; adjusted OR = 0.25, 95% CI, 0.10–0.66) were statistically significant.

Conclusion: In this study, we found that there was an increased in the expression of IGFBP-rP1 in

our colorectal cancer patients with DM2. This study supports the theory, that chronic hyperinsulinemia may indirectly promotes colorectal carcinogenesis via the IGFBP-rP1, which might play an important role in the initiation and promotion of the cancer.

Supervisor:
Prof Dr Nor Hayati Othman
Co-Supervisor:
Dr Sharifah Emilia Tuan Sharif

FACTORS AFFECTING CHOICE OF DELIVERY AMONGST PATIENTS AND DOCTORS AND FETOMATERNAL OUTCOME IN BREECH PRESENTATION IN TWO LARGE HOSPITALS IN MALAYSIA

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Objectives: To assess the factors leading to the preference of mode delivery in breech presentation amongst women and doctors in 2 large hospitals and its feto-maternal outcome.

Methods: 175 patients from Hospital Universiti Sains Malaysia (HUSM) in Kelantan and 164 patients from Hospital Tuanku Ja'afar (HTJS) in Seremban, Negeri Sembilan with a term breech presentation were interviewed with standard questionnaire on the preferred mode of delivery threshold for complication rates where patients switch preferences were documented. A total of 50 doctors were also interviewed with a standard questionnaire on the preferred mode. Difference in preference and factors affecting it were tested using Chi-square test.

Result: Assisted vaginal breech delivery, external cephalic version (ECV) and cesarean section was preferred mode in 36.6%, 38.9% and 24.5% of patients in HUSM and 8.5%, 28.7% and 62.8% in HTJS respectively. This confirmed a regional variation in preference. In HUSM and HTJS, a significant amount of women finally did not undergo the mode of delivery they desired (*P*-value = 0.001). Only 64.7% (44 out of 68 women) and 35.7% (5 out of 14 women) proceeded with AVBD, 23.4% (15 out of 64 women) and 42.6% (19 out of 47 women) proceeded with ECV. 93% and 98% had successful LSCS respectively. Education level, occupation, parity, religion, culture and believes were contributing factors to women in Kelantan while the wide availabity of knowledge through the internet and making a combined decision with their doctors were contributing factors in Seremban in decision making. The fetal outcome and maternal outcome were similar in both the Assisted Vaginal Breech Delivery group and cesarean section group (*P* = 0.33 and 0.243, respectively). Vaginal breech delivery was a preferred choice in 62% of the trainees who were confident in the management of vaginal breech delivery as long as a strict criteria of selection was done.

Conclusion: Most women are becoming more aware of breech presentation as a high risk pregnancy and would rather opt for cesarean section. Nevertheless, there are still women who are keen for vaginal breech delivery. Therefore, it is not the best option to subject all women to cesarean section for breech. With proper selection a good number of women with breech presentation will be able to achieve a vaginal delivery without complications. Supervision and credentialing of medical officers needs to be looked into and updated as it is proven that confidence and individual preferences of doctors do also play the final role in mode of delivery of term breech pregnancies.

Supervisors:
Prof Dr Nik Mohamed Zaki Nik Mahmood
Prof Dato Dr Sivalingam Nalliah
Dr Tham Seng Woh

MAGNETIC RESONANCE MEASUREMENT OF TOTAL INTRACRANIAL VOLUME AMONG MALAY POPULATION: ACCURACY OF ALTERNATIVE MEASUREMENT METHODS

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Introduction: Total intracranial volume (TIV) is defined as the volume within the cranium, including the brain, meninges, and cerebrospinal fluid. It provides a stable and accurate normalisation factor for estimating volumetric changes of brain structures in studies of ageing process, various neurological and neuropsychiatric diseases as it is constant and did not changed with increasing age and less vulnerable to pathological changes. With the advance of the technology, magnetic resonance (MR) imaging has made possible accurate measurements of the brain and its substructures. Various methods of MR volumetric measurement of TIV had been established and manual method is the best. The best manual MR volumetry is obtained by measuring each MR slices that cover the brain. However, obtaining TIV via the standard manual method is time consuming. Therefore alternative volumetric measurement methods which reduced the time consumption in measuring TIV without alteration of their accuracy and reliability should be established. This study had calculated the estimation of TIV using alternative measurement and standard methods. Thus, comparison of the accuracy of measuring TIV using alternative measurement methods with the standard measurement method can be evaluated.

Objectives: To compare the accuracy of MR volumetry of TIV using alternative measurement methods with the standard measurement method.

Methods: This was a cross-sectional comparative study of TIV measured using alternative measurement methods and standard measurement method among normal Malay population. The study involved the data from total of 59 subjects (32 females and 27 males) with the age ranging from 15 to 50 years old. All the patients' data were taken from archive images from PACS system. TIV measurement was performed manually using OsiriX version 3.2.1 using 3 methods namely Half Cranial Measurement Method on right and left side, Alternate Slice Measurement Method, and a Standard Measurement Method by 2 observers. The rater was initially undergone reliability. The mean and standard deviation (SD) of TIV measured using the alternative and standard methods were calculated, analysed and compared. Mean difference of TIV between genders were also calculated.

Result: Mean total intracranial volume of all subjects was 1375.67 (148.61) cm^3. Mean total intracranial volume for male and female were 1439.14 (142.49) cm^3 and 1322.12 (133.12) cm^3 respectively. There were significant differences in the total intracranial volume between male and female subjects (P = 0.002). There were good correlation between the TIV obtained from the alternative measurement methods and that from the standard method (ICCs [0.977 to 0.981] and Cronbach's Alpha [0.991]).

Conclusion: The study had shown comparable alternative measurement methods for total intracranial volume without significant loss of the accuracy and reliability of these methods as compared to the standard measurement method. This study also revealed that the male subjects had significantly larger total intracranial volume as compared to female subjects.

Supervisor:
Dr Mohd Shafie Abdullah
Co-supervisor:
Dr Win Mar @ Salmah Jalaludin

UNIVERSAL AND RISK FACTOR BASED SCREENING FOR GESTATIONAL DIABETES IN HOSPITAL RAJA PERMAISURI BAINUN: A PROSPECTIVE COHORT STUDY

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Introduction: Diabetes mellitus is major public health and economic problem of global significance, responsible for significant mortality and morbidity among general population. Prevalence of diabetes continues to rise and increasingly affects individuals of all ages, including young adults, children and women of childbearing age that who are at increased risk of diabetes during pregnancy and the rate is expected to go higher in the foreseeable future. The World Health Organization (WHO) has estimated that in 2030, Malaysia would have a total number of 3 million diabetics compare to 0.94 million in 2000. In concordance with this, the prevalence of gestational diabetes mellitus is (GDM) increasing as well. The mean prevalence of GDM lies between 3% and 5% with an upper boundary of 14%. GDM represents the most common metabolic complication of pregnancy, and is associated with maternal (pre-eclampsia, hypertension and cesarean section) and fetal morbidity (macrosomia, birth trauma, hypoglycemia, hyperbilirubinemia, hypocalcemia and respiratory distress syndrome).

Objectives: The aim of the study is to determine the fetomaternal outcomes in GDM mothers (antenatally, intrapartum and postpartum) and to compare the adverse outcome between glucose challenge test (GCT) negative, GCT false positive and GDM mothers.

Methods: This is a prospective cohort study carried out in the Obstetrics and Gynaecology Department, Hospital Ipoh from June 2009 to January 2010. All pregnant women attending antenatal clinic at Hospital Permaisuri Bainun were included into the study once they fulfill the inclusion criteria. Once enrolled the progress of the pregnancy was followed up until delivery. All the recruited mother were subjected to 50 g oral glucose challenge test (OGCT) regardless to fasting state. 1-h venous plasma glucose concentration of > 7.2 mmol/l was arbitrarily considered as a positive screening result. Patients with a positive OGCT subsequently underwent a 75 g 2 h OGTT, which was considered as the actual diagnostic test for GDM. In addition, women with risk factors (negative GCT) for GDM also underwent a 75 g OGTT regardless of the result of OGCT. In this study, GDM was diagnosed if either or both of fasting plasma glucose is ≥ 5.6 mmol/L or 2 hour plasma glucose is ≥ 7.8 mmol according to WHO guideline. The various maternal and fetal outcomes were compiled with the help of a questionnaire. All the data entry and analysis were carried out using the SPSS version 12 (SPSS Inc., Chicago, IL). A P-value of less than 0.05 was considered statistically significant.

Results: Number of patients enrolled in this study was 992. The main bulk of the study population were Malays (46%), but when analysed individually the highest prevalence of GDM was seen among Chinese (25%). Majority of the study group in GDM category were multiparous (88.8%) and moderate obesity (BMI range 26–29). There were strong association between obesity and incidence of GDM (P < 0.001). Using a multivariate analysis even after adjusted for the possible confounders the following conditions were significantly associated with GDM mother (odds ratio [OR], 95% confidence interval [CI], incidence of polyhydramnious) (OR: 4.21, 95% CI, 2.43–7.31), incidence of PPROM (OR: 3.21, 95% CI, 1.89–5.47), incidence of preterm labour (OR: 3.99, 95% CI, 2.53–6.30), incidence of gestational hypertension (OR: 2.09, 95% CI, 1.31–3.34), incidence of caesarean delivery

(OR: 3.80, 95% CI, 2.63–5.49), incidence of instrumental delivery (OR: 3.49, 95% CI, 1.69–7.20), incidence of macrosomic baby (OR: 1.80, 95% CI, 1.02 –3.19), incidence of shoulder dystocia (OR: 5.60, 95% CI, 1.67–18.77), incidence of extended perineal tears (OR: 3.60, 95% CI, 1.32–9.78). Where else among the GCT false posive mothers: Incidence of PPROM (OR: 2.03, 95% CI, 1.08–3.84), incidence of caesarean delivery (OR: 3.74, 95% CI, 2.51–5.58), incidence of macrosomic babies (OR: 2.15, 95% CI, 1.19–3.88), extended perineal tears (OR: 5.82, 95% CI, 2.22–15.27). There were no significant differences were noted in following aspects like pre-eclampsia, babies born with low APGAR score (< 6 in 5 minutes), cord blood pH and delayed discharge from ward following LSCS. There were also noted trends of adverse fetomaternal outcome among the patients with false positive GCT.

Conclusion: Gestational diabetes mellitus is an independent risk factor for a number of adverse obstetric outcomes; in our population 50 g OGCT appears to identify a higher number of GDM than risk factor based screening. Combined with risk factor screening a few more cases of GDM would be found. GCT false positive mothers had an increased likehood of an adverse pregnancy outcome as well.

THE RELATIONSHIP OF LENS THICKNESS AND ANTERIOR CHAMBER DEPTH WITH INTRAOCULAR PRESSURE DURING HEMODIALYSIS

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Introduction: Hemodialysis is a common renal replacement therapy in the end-stage renal failure. Fluctuation of intraocular pressure occurred during hemodialysis. Individuals with compromised aqueous outflow facility have increased risk of symptomatic elevation of intraocular pressure. Lens thickness changes may result in alteration of anterior chamber depth that can further compromise aqueous drainage. Early detection of the lens thickness changes during hemodialysis can prevent elevation of intraocular pressure and visual loss. Thus, evaluation of the lens thickness and anterior chamber depth with intraocular pressure changes during hemodialysis are essential.

Objectives: To determine the mean lens thickness and the relationship between lens thickness and anterior chamber depth, between anterior chamber depth and intraocular pressure as well as between lens thickness and intraocular pressure during hemodialysis.

Methods: 70 eyes from 70 study subjects were recruited from Hemodialysis Unit, Queen Elizabeth Hospital. Lens thickness, anterior chamber depth and intraocular pressure were measured at 0 hour, 2 hour, and 4 hour of hemodialysis. The mean lens thickness, anterior chamber depth and intraocular pressure changes based on time effect of hemodialysis were analysed with repeated measures ANOVA and multiple paired samples T-test with bonferonni correction (P = 0.017). The relationship between study variables were evaluated with correlation analysis.

Result: There were significant increased mean lens thickness and intraocular pressure among all study subjects by 0.21 ± 0.69 mm (P = 0.015) and 1.26 ± 3.02 mmHg (P = 0.001) in the first 2 hours of hemodialysis. The anterior chamber depth changes was insignificant. The mean lens thickness and intraocular pressure were increased more in diabetic and older age group in the first 2 hours of hemodialysis but significant for intraocular pressure changes only. At 2 hours of hemodialysis, there were inverse correlation between lens thickness and anterior chamber depth, inverse correlation between anterior chamber and intraocular pressure and linear correlation between lens thickness and intraocular pressure but not significant. At 4 hour of hemodialysis, there was a significant fair inverse correlation between lens thickness and anterior chamber depth (r = -0.286, P = 0.016) but the correlation between other variables were not significant.

Conclusion: In the first 2 hours of hemodialysis, there were significant increased mean lens thickness and intraocular pressure but no significant correlation between study variables suggested other mechanisms of raised intraocular pressure were involved rather than due to lens thickness changes only. A significant inverse relationship between lens thickness and anterior chamber depth was established at 4 hours of hemodialysis but it did not lead to significant raised intraocular pressure in normal eyes. Intraocular pressure rise may become significant if individuals have compromised aqueous drainage. Diabetes mellitus and age had significant influence on intraocular pressure but not on lens thickness and anterior chamber depth during hemodialysis.

Supervisor:
Associate Professor Dr Mohtar Ibrahim
Co-supervisor:
Dr Azhany Yaakub

THE ASSOCIATION OF BODY MASS INDEX (BMI) WITH CLINICAL OUTCOMES IN PATIENTS WITH PULMONARY TUBERCULOSIS

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Introduction: It is accounted for the top 10 leading cause of death especially in the middle income countries. Globally, according to World Health Organization (WHO),

there were an estimated 9.4 million new cases of pulmonary tuberculosis (TB), in 2008 with 140 new cases per 100 000 population. Several studies showed that patients with active TB are more likely to have low body mass index (BMI = wt [kg]/ht [m^2]) compared to healthy individuals.

Objectives: The aim of this study is to identified the use of BMI to predicts clinical outcomes of TB, so that this relatively simple measurement can be used for clinical benefit especially in resource limited setting. With this objective in mind, the present study was aimed at clarifying the association of the BMI with the clinical outcomes of TB patients and subsequently help in improving the treatment outcomes among TB patients.

Methods: During the study period, a total of 127 patients were recruited for this study. The total of estimated sample size ($n = 156$) cannot be recruited due to time constraint. The mean age of presentation was 44.74 ± 17.38 years. The study population had male predominant (53.1%) and Malay's ethnic contributed to the highest proportion of the study subjects (96.9%). A quarter (26.6%) of patients did not have formal education level and 36.7% had either primary or secondary education's level. Other than that, patient had background of college or university level, 25.0% and 10.9% respectively.

Results: The study shows no significant association between the variables (body mass index [BMI], age, gender, co-morbidities and smoking) with the sputum conversion rate ($P > 0.05$). No multivariate analysis was performed since all $P > 0.10$. Study also shows significant association between the smoking status with the weight gain ($P = 0.015$). Aside from that, there is no significant association between the variables with the adverse drug reactions ($P > 0.05$).

Conclusion: Between 64%–100% of smear positive sputum patients had sputum conversion irrespective of the initial BMI. Between 74%–100% of patients had weight gain irrespective of the initial BMI. 12% of patients developed allergic drug reactions and mostly in lower BMI groups.

A COMPARISON BETWEEN THE EFFECTIVENESS OF LYCRA AND SILON PRESSURE GARMENTS FOR TREATMENT OF HYPERTROPHIC SCAR IN BURNS

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Introduction: Hypertrophic scarring after burns remains a major challenge for burn care providers. Pressure garments and silicone sheets have been the mainstay of hypertrophic scar treatment. This study was to compare the effectiveness of the traditional Lycra pressure garment and the silicone incorporated pressure garment (Silon) and also to determine patients' satisfaction with pressure garment among burns patients in Hospital Universiti Sains Malaysia.

Methods: This is was a 2-phased study. Phase I was a retrospective study, which involved patients who were treated with the Lycra pressure garments from June 2007 until Jun 2009. Meanwhile, phase II was a prospective study, involving patients who were treated with the Silon pressure garments from June 2008 until June 2010. Demographic details collected included age, type and depth of burn, total burn surface area (TBSA) and cause of injury. The effectiveness of the treatment was determined based on the Vancouver Scar Scale score. Patients' scars were assessed 2 weeks after complete wound healing and every 4 months, for up to 1 year.

Result: Repeated measures ANOVA showed significant improvement in terms of scar vascularity, itch, and pain within each study group ($P < 0.05$). However, there was no statistical difference between the 2 pressure garment groups ($P > 0.05$). Meanwhile, there was no significant difference within and between the 2 study groups in terms of scar height, pigmentation and pliability. Majority of the patient complained of itch, sweating, discomfort and tightness upon wearing the pressure garments. In addition to interfering with their daily activities, they also reported no improvement of their scar appearance. Nevertheless, they still believe that compliance with the treatment is of great importance in order to gain optimal result.

Conclusion: We cannot conclude that the combined pressure garment and silicone therapy (Silon) was more effective than the traditional pressure garment (Lycra). Hypertrophic scars following burns injuries can take up to 2 years to reach maturity. Thus, it is recommended that scars should be monitored and pressure garment treatment should be carried out for at least 2 years.

Supervisor:
Dr Ananda Dorai

THREE DIMENSIONAL HIGH RESOLUTION MRI MYELOGRAPHY OF CERVICAL SPINE IN PATIENTS WITH CERVICAL SPONDYLOTIC RADICULOPATHY USING MODERATELY T2 WEIGHTED 3D TSE-FS SEQUENCE

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Introduction: Neck pain is the most frequent cause of consultation in primary care worldwide. The most common cause of neck pain in adult more than 50 years of age is cervical spondylosis. These degenerative changes causing impingement of the nerve root that exit from the foramina producing the patient's clinical symptoms. MRI myelogram is a non-invasive radiation free procedure. Its special sequence is a new technique that complement conventional MRI in

making diagnosis by detecting nerve root impingement. The advantage of this new technique over the conventional MRI is still under investigation. The agreement of the findings between these procedures can give an additional information in the process of making MR myelography as an effective screening tool in the future.

Objectives: The objective of this study is to prospectively associate the clinical variables with nerve root impingement in both conventional MRI and MRI myelogram, to determine the agreement of findings (demonstration of foraminal nerve root impingement in cervical spondylotic radiculopathy) between these 2 procedures and to determine the interobserver variability between the 2 observers in depicting the nerve root impingement.

Methods: A randomised cross-sectional prospective study to depict the nerve root impingement in patients with clinical diagnosis of cervical spondylotic radiculopathy using both conventional MRI and MRI myelogram of the cervical spine. Images from both 2 imaging findings of each patient were reviewed by 2 experienced radiologists. They interpretation of the images were done independently without knowing the symptoms and clinical findings of the involved patients. The agreement of findings between the observers were compared.

Result: Cervical spondylotic radiculopathy affects mainly of high productivity age group. There was significant correlation between clinical symptoms and signs with nerve root compression in both imaging techniques. There were moderate agreement of findings between MRI myelogram with conventional MRI and there were moderate agreement of findings between 2 observers in depicting nerve root impingement.

Conclusion: MRI myelogram altered the interpretation of nerve root impingement in 22 cases out of 47 nerve roots (approximately 50% of the cases). This value is very significant that MRI myelogram can be used as a complementary test to the conventional MRI in detecting nerve root impingement in patient with cervical spondylotic radiculopathy. MRI myelogram gave additional information (8 nerve roots) that appeared to impinge on MRI myelogram but did not appear on conventional MRI. Even though this value is minimal to make MRI myelogram as an independent imaging technique, it gives a big value to the patients.

Supervisor:
Ass Prof Dr Mohd Ezane b. Aziz
Co-supervisor:
Dr Elinah bt. Ali

A STUDY ON KNOWLEDGE, ATTITUDE AND PRACTICE ON COLORECTAL CANCER SCREENING AMONG AVERAGE RISK MALAY PATIENTS ATTENDING SELISING HEALTH CLINIC

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Introduction: Colorectal cancer (CRC) is rapidly increasing in Asia. Despite the rising trend in incidence and mortality, colorectal cancer screening rates are still low in most Asian countries. The acceptability of CRC screening is influenced by people's knowledge and attitude. This study was conducted to evaluate the knowledge, attitude and practice of Malay people toward CRC screening.

Objectives: The objectives of the study are to determine the level of knowledge, attitude, practice and their associated factors on CRC screening among average risk Malay patients. It also to determine the relationship between knowledge and attitude score and knowledge and practice score on colorectal cancer screening.

Methods: It was a cross sectional study conducted from October 2009 to December 2009 at Selising Health Clinic. The study used a self-administered questionnaire which involved 262 Malay participants aged 50 years and above. The questionnaire consisted of 3 parts, which dealt with knowledge, attitude and practice on colorectal cancer and screening.

Result: There were only 6.1% respondents had good knowledge and 31.7% of the respondents had good attitudes on colorectal cancer screening. Consequently, colorectal cancer screening uptake was extremely poor with only 2 out of 262 of the respondents had CRC screening. There was moderate to good positive correlation between knowledge and attitude score. In addition, the results show male gender, low education level and non-professional group are the associated factors for low level of knowledge on CRC screening.

Conclusion: These findings indicate that average risk Malay patients had inadequate knowledge, poor attitude on colorectal cancer screening together with extremely poor practice on colorectal cancer prevention. This study also concluded that increasing knowledge on colorectal cancer screening may encourage less negative attitudes about colorectal cancer screening. Other than that, educational level appears to be the major determinant on the level of knowledge and attitudes. While, type of occupation affects the level of knowledge and practice on colorectal cancer screening.

Supervisor:
Dr Harmy Mohd Yusoff
Co-supervisor:
Dr Norwati Daud

A RANDOMISED CONTROLLED TRIAL COMPARING THE EFFECTS OF HONEY VERSUS SUCROSE AS AN ANALGESIA DURING ROUTINE VENEPUNCTURE IN NEWBORNS

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Objectives: To determine the effectiveness and short term side effects of honey as analgesia in comparison to sucrose during routine venepuncture in newborn.

Methods: A total of 78 term neonates were recruited from the Neonatal Intensive Care Unit and Special Care Nursery of Hospital Universiti Sains Malaysia. These neonates were randomised into 2 equal sized group receiving either 2 ml of oral 24% sucrose or 2 ml of Tualang honey 2 minutes prior to venepuncture. The whole procedure was videotaped. The degree of pain score using PIPP and duration of crying time were determined twice by 2 independent observer. The Mann-Whitney U test was used to compare the pain scores and duration of cry between the study groups while the Wilcoxon signed-rank test was used to compare differences within each group.

Result: The result showed no significant differences in the demographic characteristics of the neonates. The median values of PIPP at 30 seconds and 150 seconds were comparable (P = 0.871) between both groups (median PIPP sucrose = 5, 3 median PIPP for honey = 5, 2 respectively). The median PIPP score within each group was significantly higher (P = 0.00) at 30 seconds (median = 5) compared to at 150 seconds (median = 2.5). The duration of audible cry after venepuncture was not statistically significant (P = 0.803) in neonates receiving honey (median = 5.5 seconds) compared to neonates receiving 24% sucrose (median = 4 seconds). No neonates developed hyperglycemia, diarrhea or glycosuria in this study.

Conclusion: In conclusion, this study strongly suggests that Tualang honey is not more effective than sucrose for procedure related analgesia in neonates. The absence of adverse effects following the administration of small amounts of honey to neonates may facilitate further studies using different doses or different types of honey.

Supervisor:
Dr Nor Rosidah Ibrahim

EFFECT OF SEDATION PROPOFOL WITH TARGET CONTROLLED INFUSION ON COGNITIVE FUNCTIONS ON PATIENTS UNDERGOING OPERATIVE PROCEDURES UNDER LOCAL ANAESTHESIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Introduction: Surgical procedures are increasingly being performed under local anesthesia alone but most patients prefer to be sedated. Sedation combined with local anesthesia is a safe alternative to GA as spontaneous respiration, protective reflexes, and patient co-operation are retained while fear and apprehensions are reduced. The changes in cognitive function frequently complicate the post-operative course of patients undergoing non-cardiac surgery. Some patients are at a greater risk than the others of cognitive impairment and what doses of drugs? If yes, then for how long? Hence, the need for experimental study to answer these questions.

Objectives: The aim of this study was to evaluate the cognitive changes after propofol sedation via TCI as monitored anesthetic care and factors influencing it were explored.

Methods: This was a prospective randomised controlled trial. Study subjects were placed in either arm as per double block randomisation pre-operative after fulfilling inclusion criteria. Standard monitoring was done during intra-operative and post-operative period. 104 consenting ASA physical status I and II patients scheduled to undergo elective surgical procedures with local infilteration were assigned, to receive either sedation propofol infusion or only local infiltration (without propofol sedation) intra-operatively, by the researcher. Upon arrival in pre-operative holding area, patients were to undergo 2 cognitive function tests (MMSE and SOMCT) beside the demographic data as baseline. These tests were carried out by blinded investigator to avoid bias. The patients were then taken into operating rooms and standard monitoring was applied. After intravenous line was secured, local infiltration of operative area was done by surgeon. Interventional group received sedation propofol via marsh model target control infusion targeting plasma concentration level of 0.5 ug/ml, and those in control group received local infiltration only. Propofol infusion was stopped at the end of surgery. Patients were brought to post-anesthetic care unit (PACU) and monitored continuously. Cognitive function tests were repeated at 20 and 60 minutes post-operatively for both the groups by blinded investigator. Standard clinical discharge criteria were used to discharge patients from recovery room.

Results: Demographic data were comparable in both groups. Cognitive status was improved at the end of 60 minutes in both the study groups but slower response was observed in experimental group as compared to control group. Analysis of co-variable demonstrated that males showed more marked cognitive decline as compared to females in the experimental group, whereas males of control group had no observed cognitive drop. Similar changes were observed with other co-variables like race, age, smoking habits and subjects with history of previous general anesthesia. Duration of infused sedation seems to have effect on psychomotor functions as longer operative procedures (> 30 minutes) had loss of recovery pattern. Subjects who had higher education and employed had better performance of cognitive tests but still slower recovery as compared to control group. Also the assessment of both the cognitive tests were done and MMSE was found to be more sensitive in detecting the cognitive changes as compared to SOMCT, while SOMCT was more specific.

Conclusion: Based on our study results, we can conclude that as propofol is sedative which explain the improvement of cognitive scores with time but a slow recovery pattern had been noted in experimental group as compare to control group. Hence, we conclude that there is no significant cognitive function deficit noted after propofol TCI sedation but the trend of slower recovery has been shown when compared to control. Other co-variables may have an influence on post-operative cognitive decline.

Supervisor:
Assoc Prof Dr Wan Aasim Wan Adnan
Co-supervisor:
Dr Rhendra Hardy Mohamad Zaini

DIAGNOSTIC VALUE OF SONOGRAPHY IN IDENTIFYING AXILLARY LYMPH NODE METASTASIS IN BREAST CANCER PATIENT

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Introduction: Axillary lymph node status has been the single most important factor predictive of survival in breast cancer. Axillary lymph node dissection is performed as part of surgical treatment of breast cancer, mainly for staging and planning of systemic adjuvant therapy. However, axillary lymph node dissection is associated with substantial cost and morbidity. Many pre-operative non invasive imaging methods to obtain accurate diagnosis and assess extent of disease has been utilized. Axillary ultrasound has been proven to have demonstrated superior diagnostic accuracy. It is relatively cheap and without ionising radiation involved. Axillary lymph nodes have specific ultrasound characteristics to be differentiated between metastatic and non-metastatic nodes. This study was done to determine the diagnostic value and usefulness of identifying axillary lymph node metastasis in breast cancer patient and improvise the ultrasound technique in providing staging information and determining prognosis in woman with breast cancer metastasis. This study aimed to minimise complications for patients undergoing axillary clearance surgery as the parameters which are pre-operatively observed and evaluated in sonographic lymph nodes criteria will help the managing surgeons to justify the indication and benefits of undergoing axillary clearance surgery.

Objectives: To evaluate the sonographic characteristics of axillary lymph node in breast cancer patient.

Methods: This was a cross-sectional study to evaluate the sonographic characteristics of axillary lymph node in breast cancer patient. The study period was from June 2009 to March 2011. The age of the patients ranged from 45- to 67-years-old. A total of 18 female patients were included. Ultrasound of axilla was performed using a Siemens SONOLINE® Elegra ultrasound machine. High frequency linear probe 13.7 MHz was used. The grey scale morphology of axillary lymph node was evaluated. The presence of nodal vascularity was assessed using colour Doppler sonography. The spectral Doppler indexes (resistive index and pulsatility indexes) were evaluated using ultrasound software.

Result: The relationship between afferent resistive index value to metastastic and non-metastatic axillary lymph node was significant (P = 0.010). The presence of round shape (76.7%) heterogenous cortical echogenicity (78.6%), cortical thickness more than 2 mm (77.8%), eccentric cortex morphology (84.6%), hypoechoic mediastinum (80.0%), lost of hilum (76.9%), presence of no calcification (76.9%) and peripheral colour Doppler vascularity pattern showed high positive predictive value percentage. However there were no significant relationship between grey scale morphology and axillary lymph node histopathological findings. The sensitivity and specificity in this ultrasound study were fairly low.

Conclusion: This study has proven that spectral Doppler resistive index value of the afferent lymph node vessel is useful in differentiating metastatic axillary lymph node. However the grey scale criterias in differentiating nodal malignancy is not statistically significant. This study demonstrated reasonably high grey scale morphology positive predictive value with low sensitivity and specificity.

Supervisor:
Dr Nik Munirah Nik Mahd
Co-supervisor:
Dr Salwah binti Hashim

RANDOMISE CONTROL STUDY USING VITAMIN D IN PREVENTING POST TOTAL THYROIDECTOMY TRANSIENT HYPOCALCEMIA

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Introduction: Total thyroidectomy is a common surgical procedure for thyroid disease. The common complication of thyroid operation is bleeding, injury to the superior and recurrent laryngeal nerve, thyroid storm, hypothyroidism, transient hypocalcemia and infection. With the recent advanced technology and surgical skill, thyroid operation is very safe and most can be done as a day care procedure. However, the risk for transient hypocalcemia still remain high. Without doubt, this problem causing discomfort to the patient and also prolonged the needs to stay in the hospital.

Objectives: The aim of our open label randomised control study was to determine the incidence of transient hypocalcemia developing post-total thyroidectomy in Malaysia and the benefit of pre-operative treatment using oral vitamin D in total thyroidectomy.

Methods: This is a randomised control study which recruits a total of 74 patients from Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II. The study was carried out over 1 year duration since 5th May 2009 until 30th April 2010. The ethnical approval was obtained from The Research Ethnical Committee (Human), Universiti Sains Malaysia and Ethnical Board Clinical Research Center (CRC), Ministry of Health. Sample size was calculated using Power and Sample Size (PS) calculation software (PS software, 1997). 74 patients underwent total thyroidectomy were randomised into 2 groups. For study group; 37 patients treated with oral vitamin D (calcitriol) 1.5 ug/day for 2 days duration before operation followed by 1.0 ug/day plus oral calcium lactate 1800 mg/day for 7 days after operation. While for control group; 37 patients did not receive oral Vitamin D. All the patient were assessed either clinically or biochemically for hypocalcemia. All data were entered and analysed using SPSS software version 12.0. Studied parameters analysed using frequency and percentage, univariate and multivariate logistic regression and repeated measure ancova.

Result: There was not significant difference between the study and control group in terms of demographic distribution of age, sex, diagnosis, surgeon, operating duration, parathyroid gland autotransplant and baseline level of serum calcium, phosphate and intact PTH. The incidence of post-total thyroidectomy transient hypocalcemia in the study group is about 16.7% compared with control group of 75%. Among the cases, 50.0% in study group and 64.3% in control group are symptomatic. The incidence of permanent hypoparathyroidism is 2.7%. There was significant difference in term of incidence of asymptomatic hypocalcemia and symptomatic hypocalcemia between these 2 groups. There was also significant difference between control and study group with regards to the trend of post-operative serum calcium changes. However, there was no significant difference in the risk of developing permanent hypoparathyroidism. The post-operative stay is significantly longer in control group, 4.59 days compared with study group, 3.92 days.

Conclusion: The administration of oral vitamin D had significantly reduced the incidence of transient hypocalcemia post total thyroidectomy.

Supervisor:
Dr Zaidi Zakaria
Co-supervisors:
Dr Zainal Mahmood
Dr Imisairi Haji Abdul Hadi

EVALUATION OF RESULT OF CIRCUMCISION DONE IN HOSPITAL RAJA PEREMPUAN ZAINAB II AND CIRCUMCISION DONE IN THE COMMUNITY SETTING.

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I***ntroduction:*** Circumcision is an important medical and ritual procedure that already performed for thousand of years. Nowadays, circumcision is practised in hospital, in the community setting under clean but non-sterile environment and also in the traditional way. The hazards of traditional circumcision is clearly documented, however the result of circumcision done in the community was not objectively studied. This raises the question whether such practice is safe or other recommendation should be made to improve the outcome of this important procedure.

Objectives: This study aims to evaluate the difference in the incidence of bleeding and infection complication of circumcision done inside and outside hospital.

Methods: This is a prospective study reviewing 75 circumcisions done in Hospital Raja Perempuan Zainab II and 84 circumcisions done outside hospital in Kota Bharu and Pasir Mas area. The study period is between 1st November 2009 and 31st December 2009. Patients were followed-up 1 hour, 3 days and 7 days after the circumcision. Incidence of bleeding and wound infection was recorded. Data analysis was done using SPSS software version 18.0.

Result: The incidence of wound infection of outside hospital group is higher than inside hospital group (22.6% vs 9.3%, P = 0.024) with relative risk of 2.42. The incidence of bleeding is no different between outside hospital and inside hospital group (4.8% vs 6.7%, P = 0.736).

Conclusion: This study proves that circumcision performed outside hospital has more risk of developing wound infection compared to circumcision done in the hospital. However the bleeding complication is identical in between these 2 groups.

Supervisor:
Dr Mehboob Alam Pasha
Co-supervisor:
Dr Mohd Tarmizi Mohd Nor

OPEN RESECTION (OR) VERSUS LAPAROSCOPIC ASSISTED RESECTION (LAR) IN PATIENTS WITH COLORECTAL CANCER AT HOSPITAL TAIPING. A RETROSPECTIVE STUDY

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Introduction: Carcinoma of the colon and rectum was previously considered a disease of the western population. It was uncommon in southern Asia and equatorial Africa, fairly common in the middle of Europe and very common in north-western Europe, the United States, Canada and New Zealand (WHO, 1981). This trend have changed now due to changing polarisation in world development and economy, as the incidence of the disease is very much related to the degree of development of country (Soybel, Bliss Jr et al. 1987). Malaysia, being rapidly developing nation is probably witnessing an increasing trend in colorectal cancers. In the past decades, there were tremendous changes in the lifestyles of Malaysians including dietary habits, which have become westernised. As a country with multiracial population, the incidence of certain diseases among various races of Malaysians might vary from one to the other. It was noted the incidence and the mortality of colorectal cancers was much higher in the Chinese population compared to that of the Malay population in Singapore (Foong and Lee). This variation among racial groups may be true for this country as well. Thus, in this study the epidemiological aspect of colorectal carcinomas is looked into, in addition to the clinical and therapeutic aspects of this disease. This dissertation is a retrospective study of patients with colorectal cancers who had underwent curative surgical resection by either Open Resection (OR) or Laparoscopic Assisted Resection (LAR) method in Hospital Taiping, Perak from January 2005 till December 2009. The foray to LAR for colorectal malignancy was started in early 2004 by Dr Vimal Vasuedavan and Dr Umasangar in their capacity as consultant general surgeon at this hospital. Both of them had performed at least 20 laparoscopic resections for benign disease as the learning curve recommended by American Society of Colon and Rectal Surgeons (SAGES), by the end of 2004 before embarking on LAR for colorectal cancers.

Objectives: To study the epidemiology of colorectal carcinoma in the Larut, Matang and Selama district. The primary objective was to evaluate short-term benefits of laparoscopic assisted resection compared to open resection in colorectal malignancy and the feasibility of undertaking this at a district hospital. As the scope of this topic is too wide, the purpose of this study has been limited to compare the outcome of the 2 modalities of treatment as outlined in the specific objectives. To review and compare: (1) Length of hospital stay post surgery (number of days), (2) Length of operative time (time in minutes), (3) Early post-operative complications (4) Surgical free margin.

Methods: This is a retrospective study of all colorectal cancer cases who underwent resection either OR or LAR, from January 2005 till December 2009 at Hospital Taiping which is 607 bedded hospital, with 105 surgical bed. There are 4 general surgeons and 2 of them have special interest in minimal invasive technique and about 30–35 cases of colorectal carcinoma diagnosed yearly. All cases were identified by retrospective review of the colorectal cancer from oncology book, ward admission book and the operation register book in operation theatre from January 2005 to December 2008 at Hospital Taiping. Patients diagnosed with colorectal cancer within this period of study but refused surgical intervention, inoperable due to advance disease or patients with incomplete records are excluded from this study. Patient's medical record, Computerized Operating Theatre Documentation System (COTDS) notes and histopathology report were traced and reviewed. Information needed entered in the performa. Data will be entered and analysed through SPSS version 18, descriptive statistics like frequency, means and their standard deviation will be calculated. For comparison between OR and LAR, Chi-square test will be applied for categorical variables and independent *t*-test applied for numerical variables. *P*-value of less than 0.05 will be considered as significant.

Results: A total number of 193 patients were studied for 5 years period ranging from January 2005 till December 2009. The ratio of patients underwent open resection compared to laparoscopy was 2:1. There was almost equal sex distribution in each group. Majority of patients are Malay followed by Chinese and Indian. The average age at presentation was 62 in OR and 58 in LAR. Almost all patients requiring emergency surgery underwent OR to safeguard oncologic resection which had resulted to favourable patient selection for the LAR group. The duration of surgery in LAR group was longer compared to OR group. The post-operative stay in LAR group was significantly shorter compared to OR group. The post-operative complications was lesser in LAR group but not statistically significant. The surgical free margin from the resected specimen showed no significant association between surgical methods and margin.

Conclusion: LAR confers short term advantage compare to OR and a prospective randomised multicenter trial with at least 5 year follow-up should be conducted, to gauge

the long term outcome of LAR in colorectal malignancy.

Supervisor:
Dr Syed Hassan Syed Abdul Aziz
Co-supervisor:
Dr Vimal Vasudeavan

A STUDY OF BODY COMPOSITION AND ITS ASSOCIATION WITH DISEASE SEVERITY IN STABLE CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS IN HUSM

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Introduction: Chronic obstructive pulmonary disease (COPD) is not just a disease of the lungs alone; it has systemic manifestations due to the underlying pathogenesis of inflammatory reaction. Systemic manifestations in term of reduction in body composition (body mass index [BMI] and fat free mass index [FFMI]) has been shown to be an independent risk factor for disease severity and mortality in COPD.

Objectives: The objective of this study is to determine the association of body composition with disease severity in stable COPD patients (patients who had no exacerbation in the past 3 months).

Methods: We evaluated 38 stable COPD patients attending Respiratory Clinic in HUSM and calculated their BMI and FFMI and determined their 6 minutes walking distance and serum CRP-values.

Results: There was no satisfactory significant difference between body composition and disease severity in COPD patients noted in this study ($P > 0.05$).

Conclusion: Body composition (BMI and FFMI) is not suitable for assessment of disease severity in stable COPD patients.

Supervisor:
Dr Shaharudin Abdullah
Co-supervisors:
Dr Hamid Jan
Dr Rosediani

RAPID PLEURODESIS USING SMALL BORE PIGTAIL CATHETER AND BLEOMYCIN IN MALIGNANT PLEURAL EFFUSIONS: A CASE SERIES

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Introduction: Pleural drainage is the treatment of choice for patients presented with symptomatic malignant pleural effusion. The conventional method of treatment is insertion of large bore thoracostomy tube (chest tube) before proceeding to chemical pleurodesis.

Objectives: The aim of this preliminary prospective study was to investigate the success rate of performing pleurodesis using a small bore pigtail catheter (Mar Flow® CH12) in patients with malignant pleural effusion. Pleurodesis was performed within 24 hours after insertion of pigtail catheter with bleomycin as sclerosing agent. Patients were follow-up at 4 weeks post pleurodesis with chest radiography. The intervention was scored as "successful" if no radiographic evidence of fluid reaccumulation was noted at 4 weeks. A "partial success" score indicated accumulation of fluid that did not produce symptoms and did not require repeat pleural drainage of any sort. All other outcomes were scored as "unsuccessful". 5 patients with malignant pleural effusion from Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II were included in this study with mean age of 53.6 year old. The primary diseases include breast, lung, ovarian, and colon cancers. The mean time of pleurodesis was 9.5 hours. Of the 5 pleurodesis performed, a complete response ("successful") was seen in 3 patients (60%), a partial response ("partial success") was seen in 1 patient (20%) and 1 patient (20%) did not respond to rapid pleurodesis. In conclusion, pleurodesis in patients with malignant pleurodesis can be achieved rapidly using small bore pigtail catheter and bleomycin.

Supervisors:
Assoc Prof Dr Ziyadi Hj Ghazali
Dr Zulkarnain Hasan

A COMPARISON BETWEEN THE GLIDESCOPE AND THE MCCOY LARYNGOSCOPE IN MANIKIN MODEL WITH MANUAL IN-LINE STABILIZATION TECHNIQUE

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Introduction: Intubation of the trachea in patients with cervical spine injury is a challenging situation. Such acute trauma that requires direct laryngoscopy is accomplished with a standard manoeuvre of manual in-line stabilisation technique. Unfortunately this technique creates unnecessary cause of difficult airway. Ideally intubation should be easy, fast, and cause minimal cervical spine movement in cases of head and neck injury.

Obejctives: The objective of the study is to compare the GlideScope with the McCoy laryngoscopes in manual in line stabilization (MILS) technique in manikins. There is a hope of indirect laryngoscopy with the GlideScope to achieve

these goals.

Methods: This prospective and cross over study involved a total number of 47 participants who were anesthetic resident. Following a brief didactic instruction on the GlideScope and the McCoy each participant took turn performing laryngoscopy and intubation with each device. They were evaluated for each device on their success rate of intubation, mean intubation time, glottic score improvement and their preferences of laryngoscopy.

Result: We found that the success rate of intubation was 91.5% among the McCoy laryngoscope and 87.2% among the GlideScope users. Statistically these figures were not significant with *P*-value of 0.727. The McCoy laryngoscope intubations were faster than the GlideScope. The mean times of intubation were 24.4 seconds ± 15.97 and 35.3 seconds ± 17.56, respectively. The *P*-value was significant ($P < 0.001$). The modified Cormack Lehane Score (CLS) in class I and II were greater with the GlideScope (72.3%) than the McCoy (46.8%). The CLS at moderate class of glottis IIIb to IIIa was improved for 60% and class IIIa to II for 73%. Among the participants, their preference of laryngoscope was almost the same where 53.2% had chosen the McCoy while another 46.8% of them favoured the GlideScope.

Conclusion: In this study using manikins, mean intubation time was significantly faster in the McCoy group. On the other hand, the glottic score and dental trauma complications were found to be improved significantly in the GlideScope users. There was no significant difference in the success rate and easiness of intubation. Both laryngoscopes were being equally preferred among the participants. Overall, the GlideScope performance has comparable efficacy with the McCoy in this difficult airway, except it conferred greater improvement in the glottis score view. Unfortunately this did not facilitate intubation faster and easier than the McCoy. The GlideScope may be a good alternative for managing the difficult airway but clinical trials evaluating its use on patients with an actual difficult airway are needed.

Supervisor:
Assoc Prof Dr Shamsul Kamalrujan Hassan

CARBAPENEM RESISTANT ACINETOBACTER INFECTION: A RETROSPECTIVE COHORT STUDY IN INTENSIVE CARE UNIT HOSPITAL UNIVERSITI SAINS MALAYSIA

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Objectives: This study aims to determine the incidence, risk factors and the outcome of patients with carbapenem-resistant Acinetobacter infection in ICU (HUSM).

Methodology: This was a retrospective cohort study from January 2008 until December 2009. List of the patients were obtained from Infection Surveillances unit and ICU record. The details of the patients were retrospectively reviewed from their medical records in the Record Unit of HUSM. A total of 92 patients were reviewed and only 54 were analysed.

Result: The incidence of carbapenem-resistant Acinetobacter infection in ICU (HUSM) was 7.3%. Age was the only significant risk factor associated with carbapenem-resistant Acinetobacter infections in ICU (HUSM), (adjusted OR = 1.045, 95% CI: 1.010, 1.081, $P = 0.011$). There were no significant association of other risk factors such as gender, APACHE II score, multi organ failure, co-morbidities, previous hospital and ICU stay. Mortality rate of this infection was 50%. Age was significantly different between survived and non-survived group; (43.1 ± 21.1 and 57.1 ± 14.3) with *P*-value = 0.006. There were no significant differences between the 2 groups in other factors.

Conclusion Mortality rate of carbapenem-resistant Acinetobacter infections in ICU (HUSM) was 50% and age was a significant risk factor for the mortality.

Supervisor:
Dr Wan Mohd Nazaruddin b Wan Hassan

BACTEREMIA IN MINOR TRAUMATIC WOUNDS–AN EXPLORATIVE STUDY

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Introduction: Patient with minor traumatic wound can be treated in the Alternative Medical Treatment Site (AMTS) or Emergency Department. However, there was no evidence to prove that these patients are safe to be discharge without any risk of bacteremia after getting early treatment. We postulated that the risk of bacteremia in those with minor traumatic wound are low but can cause mortality. Therefore, we carried out research using the blood culture to find out the incident of bacteremia and to determine characteristic of patient and wound that prone to develop bacteremia.

Methods: This was a cross sectional study with alternate patient selection. The study involved 50 consented adult with minor traumatic wound from 1st January 2010 until 31st December 2010 in Emergency Department, Hospital Universiti Sains Malaysia. Blood Culture and Sensitivity (BC&S) were taken on arrival then repeated 30 minutes after wound management. The primary outcome in this study was the bacteremia.

Result: Median age of the participant was 24-year-old. Of these 50 patient, 4 had chronic illness (Hypertension, Diabetes Mellitus, Epilepsy and G6PD

deficiency). Most of the injuries was due to motor vehicle accident (82%). Medium time of arrival was 2 hours. Main complaint was injury to the hand due to abrasion wound followed by laceration wound and incised wound. Foreign body present in the wound less than 10%. 5 patients had increase in the white blood cell count more than 15 000 /mmP3P. The mean Random Blood Sugar (RBS) was 5.1 mmol/L ± 2.1. One patient had RBS more than 10 mmol/L and none had RBS less than 1.1 mmol/L. There was no patient in this study had increase CRP level and positive blood culture.

Conclusion: This study suggested that, there was no bacteremia in minor traumatic wound. The patient can be directly been treated at the site of incident. However, the wound should be frequently inspect and properly cared until fully healed.

Supervisor:
Dr Nik Arif Nik Mohamed
Co-supervisors:
Assoc Prof Dr Rashidi Ahmad
Assoc Prof Dr Habsah Hassan

THE EFFECT OF TUALANG HONEY INGESTION ON REDUCTION OF SYMPTOMS SCORE AND SPECIFIC IgE LEVEL IN ALLERGIC RHINITIS PATIENTS

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Introduction: Allergic rhinitis (AR) is a symptomatic disorder of the nose induced by an IgE mediated inflammation after allergen exposure of the membranes of the nose, characterised by one or more of the following symptoms including nasal itchiness, nasal blockage, running nose and sneezing. Skin prick test is a known conventional method and is widely used to diagnose allergic rhinitis. However, with the emerging of new in vitro technology methods to measure IgE level, it may help further in diagnosis and management of allergic rhinitis. There are a standardised set pharmacological treatments of allergic rhinitis with the strong held believed of alternative medicines include herbs and honey. In this study, we were looking for any effect of our local Tualang honey ingestion on specific IgE level and patients symptom score.

Objectives: The objectives of this study were to determine the magnitude of allergic rhinitis symptoms improvement with honey treatment and to determine magnitude of specific IgE reduction after honey treatment.

Methods: An open label prospective randomised controlled clinical trial was carried out in Otorhinolaryngology clinic HUSM from July 2009 till April 2010. 40 patients with history suggestive of allergic rhinitis were recruited in this study. They were divided into control and case group. The patients particulars and history takings were recorded and compiled. Selected patients were examined by using nasal speculum for anterior rhinoscopy and findings were recorded. Patients then undergone skin prick test and blood taken for serum specific IgE. The allergen included in this study was cat (*Felis Domesticus*), wheat flour, house dust mite (*Blomia tropicalis*) and peanut. Symptoms scores and serum specific IgE were recorded at initial, day 14 and day 28. The control group was given oral antihistamine while the case group was given oral antihistamine and Tualang honey 20 mg per kg body weight in divided doses.

Result: The highest prevalence of positive skin prick test among studied patients was house dust mite (97.5%) and the lowest prevalence was wheat flour (72.5%). The highest prevalence of positive serum specific IgE among studied patient was also house dust mite (65%) and the lowest prevalence was cat (5%). There were significant differences in overall symptoms score observed in both groups between initial week 0, week 2 and week 4. However, the case group showed a progressive improvement in their symptoms score as compared to control group between the comparison weeks. Nevertheless, there were no significant differences elicited in specific IgE level in either group between initial, week 2 and week 4.

Conclusion: Tualang honey had significant effect in improving the overall symptoms in allergic rhinitis patient as compared to those who are receiving conventional antihistamine alone. However, no effect of Tualang honey in reduction of specific IgE was elicited. By these observations, honey is found to be beneficial and may prove the held believed to improve the patient symptoms. However, perhaps with a standard and appropriate allergen manufactory in this Asia tropical region, we might be able see the effect of honey in reduction of specific IgE in future as it does in animal study.

Supervisor:
Dr Wan Shah Jihan Wan Din
Co-supervisor:
Dr Che Maraina Che Hussin

ASSESSMENT OF KNOWLEDGE AMONG INTENSIVE CARE NURSES TOWARDS THE EVIDENCE-BASED GUIDELINES FOR THE PREVENTION OF VENTILATOR ASSOCIATED PNEUMONIA IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Introduction: Ventilator associated pneumonia (VAP) leads to a considerable excess in morbidity, mortality and contribute to a significant economic burden. An evidence-based guidelines has been established for prevention of VAP.

Objective: This study aimed to determine intensive

care nurses knowledge evidence-based recommendations for VAP prevention.

Methodology: This was a self-reported survey (questionnaires) conducted on 115 GICU, NeuroICU and CCU nurses in HUSM regarding the non-pharmacological guidelines for VAP prevention, conducted in March 2011.

Result: The intensive care nurses mean knowledge score were 54.0% (SD, 17.2%). Nurses who work in GICU have a better score than other ICU setting ($P < 0.001$). Male nurses has a better knowledge compared to the female ($P < 0.001$). There were no correlation on other demographic with their knowledge.

Conclusion: HUSM intensive care nurses knowledge regarding recommendations for VAP prevention was still lacking and need further improvement. GICU nurses and male nurses were more knowledgeable on the VAP prevention evidence-based guidelines.

Supervisor:
Professor Dr Nik Abdullah Nik Mohammed

REVIEW OF OESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA IN HOSPITAL SULTANAH BAHIYAH, ALOR STAR 2000–2009

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Introduction: Esophageal atresia (EA) and tracheoesophageal fistula (TEF) are one of the congenital anomaly occurring in the newborns with the incidence of 1 in 2, 500 births seen worldwide.

Objectives: The aim of this study is to determine the association of birth weight, time taken for surgical intervention, presence of congenital anomaly and pneumonia with the outcome of surgery.

Methods: This is a cross sectional study with retrospective record review among babies with TEF and EA in Hospital Sultanah Bahiyah (HSB) from January 2000 to December 2009. It was conducted in the Paediatric Surgical Unit, Department of Surgery, Hospital Sultanah Bahiyah, Alor Star.

Result: There were 47 patients with esophageal atresia admitted to HSB from January 2000 to December 2009, out of which 26 (55%) were males and 21 (45%) females. The distribution of patients by race were 34 Malays (72%), 9 Chinese (19%) and 4 Indians (9%). Out of 47 babies with TEF and EA, 36% of them had polyhdromnios in the antenatal evaluation. There were only 3 types of EA/TEF seen; Type A (9%), Type C (87%) and Type E (4%). The birth weight of the babies range from 0.8 kg to 4.0 kg. The smallest surviving baby weighing 1.1 kg. There was a significant association with the outcome of the surgery ($P < 0.05$). Most of the babies (20) were operated within 24 hours of presentation. There were no significant association between time of surgical intervention and outcome ($P > 0.05$). 23 (49%) of them were born with congenital malformation and there was a significant association with the outcome of the surgery ($P < 0.05$). Based on the chest roentgenogram, 20 (43%) of them had pneumonia with significant association with the outcome ($P < 0.05$). The mortality rate is 23% and the causes of death were severe pneumonia (36%), severe renal failure (18%), severe cardiac malformation (18%) and multiple congenital malformations (28%).

Conclusion: In conclusion, the outcome of EA and TEF is determined mainly by birth weight, congenital malformations, and presence of preoperative pneumonia. Bremen classification is most suitable in determining the prognosis of the babies with TEF and EA in Hospital Sultanah Bahiyah, Alor Star.

Supervisor:
Dr Syed Hassan Syed Abdul Aziz
Co-supervisor:
Dato' Mr Mohan Nallusamy

THE PREVALENCE OF FUNCTIONAL DYSPEPSIA USING ROME III QUESTIONNAIRE AMONG ADULT PATIENTS ATTENDING KLINIK RAWATAN KELUARGA, HOSPITAL UNIVERSITI SAINS MALAYSIA

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MMed (Family Medicine)

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Introduction: Functional dyspepsia (FD) is one of the functional gastrointestinal disease in which there is no specific organic and pathological cause can be identified. It's prevalence is sparse as it requires an endoscopic examination and also due to the different criteria used in different studies. Objectives: The aims of this study were to determine the prevalence of FD and its associated factors.

Methods: This cross-sectional study was conducted at Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia (HUSM). The study period started on 1st December 2009 till 31st March 2010. Self-administered Bahasa Malaysia version of Rome III questionnaire was used. Endoscopic examination was performed in order to exclude the organic cause of dyspepsia among patients who fulfill the criteria for FD. The diagnosis of FD was made based on the normal endoscopic finding.

Result: A total of 192 patients were recruited and 32 who did not complete the questionnaires and refused endoscopy were excluded. Out of 160 patients, the prevalence of FD was 10% ($n = 16$). About 68% of the FD patients ($n = 11$) had Epigastric Pain syndrome (EPS) and 32% of

them (n = 5) were those who had mix symptoms of post-prandial distress syndrome and EPS. There were significant association between overweight (BMI 28 vs 25 kg/m^2, P < 0.05), being married (P < 0.05) and also having psychosocial symptoms (P < 0.05) with FD in univariate analysis. Multivariate analysis showed psychosocial symptoms (OR: 3.76, 95% CI, 1.01–13.99) and currently married (OR: 8.08, 95% CI, 1.03–63.51) were predictive of FD.

Conclusion: This study supported that psychosocial symptoms were related with FD. As most of the patients who had FD were married, this could have attributed the significant association between marital status and FD.

Supervisor:
Dr Juwita Shaaban
Co-supervisors:
Dr Nazri Mustaffa
Dr Norwati Daud

THE VALIDATION OF THE MALAY TRANSLATED SLEEP APNEA QUALITY OF LIFE INDEX (SAQLI) IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA

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Introduction: The Sleep Apnea Quality of Life Index (SAQLI) is a disease specific instrument developed to record the key elements of obstructive sleep apnea syndrome disorder that are important to patients and act as an outcome as well as an evaluative measure in clinical trials.

Objectives: The objectives of this study were to translate SAQLI into the Malay language and to determine the feasibility, validity and reliability of the Malay version of SAQLI.

Methods: This was a cross sectional study conducted at Sleep and General ORL-HNS Clinic, Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan. 82 respondents were involved. The Malay translated SAQLI and a previously Malay translated and validated Short Form 36 (SF-36) were administered by interviewer. The translation used forward, backward and respondent testing and has been reviewed for face and content validity. The Malay translated SAQLI were administered again at 2 to 4 weeks interval. Analysis included the determination of the scaling assumptions, feasibility, reliability and validity.

Result: All subjects completed the questionnaire successfully. The Malay version of SAQLI has no floor or ceiling effects. The 4 domains of the Malay SAQLI have means ranging from 3.59 to 4.82 and standard deviation, SD ranging from 0.846 to 0.945. The Cronbach's alpha were very high, more than 0.95 for all domains; domain daily functioning: 0.966, domain social interaction: 0.981 and domain emotional functioning: 0.971 suggested items redundancy. The standard of test-retest reliability was also fulfilled with intraclass correlation coefficients were excellent ranging from 0.796 to 0.984. The Pearson's item-scale correlation between item and its hypothesised scale was 0.4 or above, thus item-scale convergent and discriminant validity were satisfied. Factor analysis showed items in the 3 domains all loaded on the hypothesised scales. Known group validity showed no significant correlations between SAQLI and AHI (P > 0.05). Criterion validity was confirmed by significant correlations with SF-36 subscale scores.

Conclusion: The translation of the Malay version of SAQLI was acceptable. The feasibility is present and the scaling assumptions met. The internal consistency and intraclass correlation coefficients were excellent. The content validity has been established with evidence of acceptable construct and criterion validity. The Malay version of SAQLI should be used in the management and studies involving OSAS patients and a shorter version of SAQLI is recommended.

A STUDY ON FEASIBILITY OF LAPAROSCOPIC INGUINAL HERNIA REPAIR IN A DISTRICT HOSPITAL (HOSPITAL SULTAN ABDUL HALIM, SUNGAI PETANI)

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Introduction: Even though hernia repair is a very common general surgical procedure, repairing bilateral and recurrent inguinal hernia always give problems to the surgeon. The operation performed have higher tendency towards cost increment and morbidity. With the relatively higher capital cost but good outcomes, we decided to study the feasibility of performing laparoscopic inguinal hernia repair in a district hospital setting.

Objectives: The study objective is to compare the cost effectiveness of laparoscopic versus open inguinal hernia surgery. Besides that, we would like to determine the duration of post-operative hospital stay and operative time usage of laparoscopic surgery. In addition, we would like to identify the complications of both operative techniques.

Methods: Retrospective analysis of laparoscopic and open technique in bilateral and recurrent inguinal hernia.

Result: The total numbers of patients were 155. Laparoscopic surgery consisted of 84 patients. 53 cases were bilateral, 19 cases were right recurrent and 12 cases were left recurrent. TEP was performed in 53 cases and 31 cases of TAPP. In open technique, 48 cases were bilateral, 15 cases were right recurrent and 8 were left recurrent. Only 3 female noted and Malay were predominant (73 %). The mean

duration of post-operative hospital stay was 34 hours in open and 25 hours in laparoscopic surgery (P = 0.002). The mean hospitalisation cost of open (RM 194.50) is cheaper than laparoscopy (RM 417.35). The difference was significant as P < 0.000. The mean operative time is longer in open repair (P = 0.034). The conversion of laparoscopy to open was 6.45 %. Conversion of TEP to TAPP was 4 % only. No major complications noted.

Conclusion: It is feasible to perform laparoscopic surgery for recurrent and bilateral inguinal hernia in district or non referral centre. However, well-designed study is indicated.

Supervisor:
Dr Syed Hassan

THE PREVALENCE OF RELAPSE AND ITS ASSOCIATED FACTORS AMONG SMOKERS ATTENDING KLINIK RAWATAN KELUARGA, HOSPITAL UNIVERSITI SAINS MALAYSIA

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Objectives: To determine the prevalence of relapse and its associated factors among smokers at Klinik Rawatan Keluarga, HUSM.

Methods: This is a cross-sectional study. 294 respondents agreed to participate in the study from June until August 2010. The socio-demographic and associated risk factors were recorded in the data questionnaires.

Result: A total of 283 respondents managed to complete the questionnaires. There was 96.3% response rate. The proportion of smokers who relapsed was 59.4% (n = 168). The significant associated factors to relapse were age less than 40-years-old, marital status , Fagerstrom score, duration of smoking and stressful life event.

Conclusion: The prevalence of relapsed is high which is comparative to many other studies. For smokers who are attending quit smoking clinics, special attention should be given to those with the associated factors to make the process to quit smoking clinic more successful.

Supervisor:
Dr Harmy Mohd Yusoff
Co-supervisor:
Dr Adibah Hanim Ismail

A TWO YEAR RETROSPECTIVE REVIEW OF LAPAROSCOPIC VERSUS OPEN APPENDICECTOMY IN PERFORATED APPENDIX IN HOSPITAL IPOH (JUNE 2006–MAY 2008)

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Introduction: One of the most common general surgical procedures that is performed in the surgical department is appendicectomy. The open approach has become the standard surgical intervention for appendicitis, remaining virtually unchanged for 100 years owing to its proven efficacy and safety (McBurney et al., 1894).

The optimal approach for appendicectomy is still under debate although laparoscopic appendicectomy has been performed since 1980 (Lityinski, 1999). The longer operating time, similar duration of hospital stay and increased incidence of intra-abdominal collection or post-operative ileus with laparoscopic appendicectomy outweighed any improvement in wound complication, recovery time or cosmesis. Current studies however present evidence of reduction in operating time, faster recovery and lower wound complication rates, with the reversal in the risk of developing ileus in favour of laparoscopy (Golub et al., 1998).

Objectives: The aim of this study is to compare laparoscopic and open appendicectomy in the management of perforated appendicitis to review and compare length of hospital stay (number of days of admission), length of operative time (time in minutes), duration of ileus (number of days the patients is not able to tolerate orally), days for temperature to settle (in number of days), post-operative complications-(readmission, surgical site infection) and analgesia (total amount of IV analgesia in milligrams used while in the ward).

Methods: All cases of perforated appendicitis that were admitted to the surgical ward in Hospital Permaisuri Bainun Ipoh from 1st June 2006 till 31st May 2008 were included in the study unless they did not fulfill the inclusion criteria. The duration of the data collection was for 24 months. The names of all the patients perforated appendicitis were collected from the COTDS (Computerised Operating Theatre Documentation System) and the operating theatre log books and their case notes were traced from the records office. The relevant details were reviewed and documented according to the proforma (Appendice 1).

Result: 205 patients with perforated appendicitis were reviewed. 56 patients had laparoscopic appendicectomy and 149 patients had open appendicectomy. The median age in the laparoscopic group was 28 and the open group was 30. The difference in the median age groups was not statistically significant. The P-value is 0.310. The mean (SD) operating time for laparoscopic appendicectomy was 69 ± 29 minutes.

The mean operating time for the open group was 63 ± 28 minutes. This study showed that there was no significant difference in the mean length of operating time between the 2 methods. The *P*-value is 0.669. The mean (SD) length of hospital stay for the patients in the laparoscopic group was 3.5 ± 1.6 days. In the open group the mean length of hospital stay was 3.1 ± 1.9 days. This was statistically not significant (P = 0.382). There was also no statistical significance in the duration the patients took to tolerate orally and for the temperature to settle in both the groups. There were a total of 6 patients with the surgical site infection and 7 who had readmission. Although all 6 patients with surgical site infection were from the open group and none in the laparoscopic group this was not statiscally significant (P = 1.000). 5 patients in the laparoscopic group and 2 in the open group were readmitted within a week of their respective surgeries for ileus. This difference was also not statistically significant with a *P*-value of 1.000. The mean (SD) amount of analgesia used in laparoscopic appendicectomy was 387.5 ± 259.4 mg. The mean (SD) for the use of analgesia in the open group was 274.5 ± 204.3 mg for the open group. This was statistically significant where P = 0.006.

Conclusion: The laparoscopic appendicectomy is a safe and suitable procedure for surgical training and will ensure that large numbers of surgical trainees can proceed to more advanced laparoscopic techniques during their training programme. Perforated appendicitis is now routinely managed laparoscopically in some hospitals and developments in surgical training will allow this approach to become standard practice in the near future.

FUNCTIONAL OUTCOME OF MICROSURGICAL CLIPPING COMPARED TO ENDOVASCULAR COILING

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Introduction: Nontraumatic subarachnoid hemorrhage is the second most frequent cause of hemorrhagic stroke and accounts for 3%–5% of all strokes. In more than 85% of cases, it is caused by a ruptured intracranial aneurysm with incidence of at 6–8 cases per 100 000 population. The treatment options available for ruptured aneurysms includes microsurgical and endovascular means. In recent years endovascular coiling has been used increasingly as an alternative to microsurgical clipping for treating subarachnoid hemorrhage secondary to aneurysm rupture.

Objectives: The purpose of this study was to compare functional outcomes in terms of modified rankining scale, morbidity and mortality at 6 months after treatment of post-subarachnoid hemorrhage secondary to cerebral aneurysm rupture in subjects who were either microsurgically clipped or endovascularly coiled. In addition, the present study aims to identify the predictors in the clinical course of primary subarachnoid hemorrhage.

Methods: A retrospective case review on the treatment methods of aneurysm rupture in Hospital Kuala Lumpur over the period of 5 years (2005–2009). A total of 268 patients who fulfilled the inclusion criteria were included in this study. These patients were broadly categorised into 2 groups based on their treatment mode for ruptured aneurysm. The case notes, CT brain films reports and angiography reports were analyzed with respect to their clinical, radiological, surgical clipping or endovascular coiling treatments and outcome data. Statistical analysis was determined using Chi-Square tests to study these associations.

Results: There was a female predominance with male-to-female ratio 1:1.4. The mean age was 50.9-years-old in this series. 50 patients were less than 40 years (18.7%) and 218 patients were more than 40-years-old (81.3%). 37 patients (74%) in age group less than 40-years-old had significant good outcome as compared to 125 (57.3%) patients above 40-years-old (P = 0.03). 181 patients (67.5%) presented with good WFNS (WFNS1-2) and 87 patients (32.5%) presented with poor WFNS (WFNS 3-5) prior to intervention. 162 patients (60.4%) had good functional outcome (mRS grade 0-2) as compared to 106 patients (39.6%) who had poor mRS outcome (MRS 3–6) while 50 patients died (18.7%) during our follow-up to 6 months . When we analysed the WFNS group with functional outcome (mRS), there was significant association (P < 0.01). In good WFNS, 143 (79%) had good outcome and in poor WFNS, 68 patients (78.2%) had poor mRS outcome. There were 204 (76.1%) patients in clipping group and 64 (23.9%) patients in coiling group. Patients who underwent coiling, initially showed a better mRS outcome with 47 patients (73.4%) than, 115 patients (56.4%) in clipping. Further comparison showed that 89 (43.6%) patients in clipping group had poor functional (MRS) outcome as compared to 17 patients (26.6%) coiling, which was significant (P = 0.015). However when we controlled the WFNS grade of presentation in the treatment groups, we obtained a different result. In good WFNS group, it was noted that 98 patients (76%) out of 129 patients in clipping group had a good MRS outcome while, 45 patients (86.5%) out of 52 patients in coiling group had good mRS outcome (P = 0.114). In poor WFNS presentation, it was noted that in clipping group, 58 patients (77.3%) out of 75 had poor mRS outcome. Similarly with poor WFNS presentation, 10 (83.3%) out of 12 patient in coiling group had poor outcome (P = 1.00). Hence, when we control the WFNS group, there was no significant association between treatment group (clipping and coiling) and mRS outcome at 6 months. Further we noted that age less than 40 and Fisher grade of 1–2 have better outcome while patients with EVD, CSF infection and pneumonia have poorer outcome. Using multiple logistic regression analysis we have determined that good mRS outcome is associated with good WFNS and absence of EVD.

Conclusion: Clinical severity of the SAH (WFNS grade) was the most significant predictor of functional outcome (mRS) at 6 months. Therefore the decision regarding treatment option needs to be individualised based on the presentation of the patient.

Supervisor:
Dr Ramesh Narenthiranathan
Co-supervisor:
Associate Professor Dr Hillol Kanti Pol

COMPARATIVE STUDY OF DYDROGESTERONE DOSAGE OF THE DUPHASTON 40 MG DAILY AND DUPHASTON 20 MG DAILY IN THE OUTCOME OF PREGNANCY WITH THREATENED MISCARRIAGE IN HUSM

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Objectives: To evaluate the effectiveness and the adverse effect of Duphaston 40 mg daily and Duphaston 20 mg daily in threatened miscarriage.

Methods: This is a prospective randomized controlled trial conducted at Hospital Universiti Sains Malaysia (HUSM), Kubang Kerian, Kelantan from 1st of March 2009 until 30th March 2010. A total of 130 patients were studied, 65 patients in group A for those who is taking Duphaston 20 mg daily and the other 65 patients in group B on Duphaston 40 mg daily. Besides the effectiveness, the side effect of the 2 different dosage of Duphaston is also evaluated. The successful of the pregnancy is measured by continuity of the pregnancy beyond 20 weeks of gestation. Result was analysed with Chi-square and Fisher's Exact tests to determine the statistical significant. The tests considered significant if *P*-value < 0.05.

Results: There were higher successful pregnancy in Group B (Duphaston 40 mg daily) compared to Group A (Duphaston 20 mg daily) (86.7% versus 81.7%). But this is not statistically significant as the *P*-value in multivariate analysis is 0.50 ($P > 0.05$). There were no significant differences in adverse effect of the 2 different dosage of Duphaston.

Conclusion: Duphaston 40 mg daily was not associated with higher chances of successful pregnancy in threatened miscarriage ($P = 0.50$ in multivariate analysis). There were also no significant differences of adverse effect of the drugs in between the 2 groups.

COMPARISON BETWEEN TRIAMCINOLONE INJECTION AND HYDROCORTISONE INJECTION IN TREATMENT OF TRIGGER FINGER: A PROSPECTIVE SINGLE-BLINDED RANDOMIZED CONTROLLED STUDY

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Introduction: Trigger finger is a term for stenosing tenovaginitis affecting the excursion of the long flexor of the hand at the area of zone II of the digit. Steroid injection is one of the treatment option. Triamcinolone is the steroid mainly used for trigger finger treatment. Hydrocortisone is used only in peditric trigger finger. Therefore result and outcome of hydrocortisone in treatment of adult trigger finger still not establish.

Objectives: This study was designed to test the null hypothesis that there is no difference in resolution of trigger finger in term of pain, tenderness and triggering/locking in 3 months after injection with triamcinolone, a depot form of potent steroid or hydrocortisone, a highly soluble form but less potent steroid.

Methods: Seventy patients were enrolled in a prospective randomised controlled study comparing triamcinolone and hydrocortisone injection for idiopathic trigger finger. They were randomised into 2 groups; triamcinolone group and hydrocortisone group. All patients required to answer Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire, give Visual Analog Scale (VAS) score and evaluated for triggering/locking and tenderness at A1 pulley before injection, immediately after injection and 3 months after injection. 59 patients completed the 3 months follow-up (28 triamcinolone arm, 31 dexamethasone arm). Outcome measures included the DASH questionnaire, presence/ absence of triggering/locking finger, presence/ absence of A1 pulley tenderness and pains severity base on visual analog scale. A Chi-square test and student *t*-test were used to compare both groups.

Result: Immediately after injection, absence of triggering was documented in 24 of 34 patients (70.6%) in the triamcinolone group and in 28 of 36 patients (77.8%) in the hydrocortisone group. The rates of resolution of triggering 3 months after injection were 22 of 28 (78.6%) in the triamcinolone group and 26 of 31 (83.9%) in the hydrocortisone group. In term of tenderness of A1 pulley, immediately after injection, absence of tenderness was documented in 26 of 34 patients (76.5%) in the triamcinolone group and in 28 of 36 patients (77.8%) in the hydrocortisone group. The rates of resolution of tenderness 3 months after injection were 18 of 28 (64.3%) in the triamcinolone group and 22 of 31 (71%) in the hydrocortisone group. There were

no significant differences between DASH scores and VAS score for pain immediately after injection and the 3-month follow-up. After the close of the study, there was no complication in both treatment groups.

Conclusion: There is no significant different in term of resolutionof tenderness over A1 pulley, resolution triggering/locking, pain and physical disabilities score improvement between the 2 types of steroid injection.

Supervisor:
Dr Abdul Nawfar Sadagatullah

IN VITRO AND IN VIVO COMPARISON OF DIFFERENT GRADES OF CHITOSAN WITH COMMON SURGICAL HEMOSTATS

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Introduction: The most common cause of significant intra-operative bleeding is inadequate surgical hemostasis. Nearly all reviews of intra-operative and early post-operative bleeding point that 75% to 90% of all bleeding is technical in nature. Whatever the cause, uncontrolled bleeding can lead to a combination of factors which may further exacerbate the problem of a vicious bloody circle. Dilutional thrombocytopenia, platelet dysfunction and consumption of clotting factors present a difficult problem to address as continual blood loss continue to compound the problem while blood component replacement therapy attempts to correct the deficiency.

Objectives: Our study aims to compare hemostatic efficacy of different grades of chitosan compared to the common hemostatic surgical hemostats. We hypothesise that chitosan based hemostats are superior to the common surgical hemostats in inducing platelet aggregation, affecting Prothrombin Time (PT) and Partial Thromboplastin Time (PTT) and red cell aggregation.

Methods: There were 2 parts to the study. In the in vitro study blood sample was obtained from the blood bank. Blood sample was collected utilizing the CP2D/AS-3 systems with additive solution (AS-3, Nutricel®) to maintain red blood cell viability. Collected whole blood was separated into 4 separate components (whole blood, heparinised whole blood, platelet rich and platelet poor plasma). In the platelet aggregation test, stirred citrated PRP was contacted with 3.5 mg of each hemostatic agent premoistened with 100 micro liter of phosphate-buffered saline (PBS) in a test tube (as would be used in traditional platelet aggregometry). Aliquots of supernatant (100 micro liter) were removed every 5 minute for a total of 15 minutes and the platelet count was measured in triplicate utilizing an electronic cell counter (XT2000i Sysmax Analyzer, Sysmex America Inc., Mundelein, IL); platelet counts from each experimental aliquot were normalized using counts from unreacted PRP. For each hemostatic agent 3 independent sets of experiments were performed. A similar set of platelet aggregation experiments was performed using the hemostatic sponge agents (3 different grades of Chitosan, Lyostypt® and Surgicel®) premoistened with PBS. In the PT/PTT test, each hemostatic agent was reacted with platelet rich and platelet poor plasma. The serum was centrifuged to remove possible deposition. 6 parallel experiments were conducted to measure PT and APTT of the serum using a hemostasis analyzer (Stago STA Compact Haemostatic Analyzer, Diamond Diagnostics, MA. USA) In the red cell aggregation test, each haemostatic agent was reacted with whole blood, heparinized blood and platelet poor blood. The blood with hemostatic agents were left to stand and the erythrocyte sedimentation rate was measured with the Sedy 400 sedimentation analyzer. In the animal experiment, 36 Sprague-Dawley rats were utilised. Under general aesthesia, via a midline laparotomy the right and left kidneys were isolated. Heminephrectomies were carried out and hemostats were applied to the cut surface and time taken to hemostasis was tabulated.

Result: In the platelet aggregation test, no definite trend in platelet aggregation was observed. NoCMC 36 3% showed the lowest platelet count of all hemostatic agents at 5 minutes. Lyostypt® and Surgicel® were superior compared to chitosan hemostats at 10 minutes of contact. In the coagulation test (PT/PTT) mean prothrombin time for Chitosan (NoCMC 8%) was the shortest in platelet rich plasma. Mean partial thromboplastin time was the shortest for Chitosan (NoCMC 3%) in platelet rich plasma. In platelet poor plasma, the shortest prothrombin time was seen in both the Chitosan hemostats (NoCMC 3% and NoCMC 8%). Partial thromboplastin time was shortest for Chitosan (NoCMC 3%) hemostat. In the red cell aggregation test, Chitosan hemostat (NoCMC 3%) demonstrated the highest erythrocyte sedimentation ratio in platelet poor blood as well as heparinised blood specimens. Chitosan hemostat (NoCMC 8%) demonstrated the highest erythrocyte sedimentation ratio in heparinised whole blood.

Conclusion: In the animal experiment, there was no statistical difference between the hemostats in arresting bleeding from heminephrectomy specimens. The Chitosan hemostat (NoCMC 36 3%) however demonstrated the shortest time to hemostasis compared to the other hemostats. From the study we concluded that Chitosan hemostats causes platelet to aggregate the earliest compared to other hemostats. They shorten prothrombin and partial thromboplastin time. They have been also found to aggregate red blood cells the most compared to other hemostatic agents.

Supervisor:
Professor Dr Ahmad Sukari Halim

KNOWLEDGE, ATTITUDE AND PRACTICE ON CARDIOVASCULAR DISEASE AMONG WOMEN ATTENDING PRIMARY HEALTH CARE FACILITIES IN KELANTAN

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Introduction: Although coronary heart disease causes more than 455 000 deaths in women each year, much of the research on coronary heart disease in the last 20 years has either excluded women or include very few women since cardiovascular was perceived as a disease which primarily affected men. This resulted in less women being exposed to the information regarding heart disease.

Objectives: To study the knowledge, attitude and practice on cardiovascular disease among women attending health care facilities in Kelantan.

Methods: This is a cross-sectional study involving 448 patients, age between 25 to 65 years old attending health care facilities in Kelantan from Jun till December 2010. The sampling method using multistage random sampling which was only 7 clinics were selected using simple random sampling and 64 patients from each clinic were selected using systematic random sampling 1:2. Self-administrated structured questionnaire was given for data collection.

Result: All 448 patients complete the entire questionnaire that make the response rate of 100%. The data were analysis using descriptive statistic for knowledge, attitude, and practice level. The mean (SD) knowledge score was 70.6 ± 13.76. Only 55.6% had good knowledge score. For the attitude score, median (IQR) was 88.2 ± 14.71. Good attitude score consists of 55.1% of respondents. The mean (SD) for practice score was 63.7 ± 13.59. About half of respondents (51.1%) had good practice score. General linear regression showed a significant (P < 0.001) association between attitude and knowledge, practice and knowledge and practice and attitude after controlling for age, ethnic, marital status, occupation, education level, household income, medical illness and family history of medical illness .

Conclusion: The knowledge, attitude and practice level are equal between good and poor score among Kelantanese women. So a better structured educational programmed on cardiovascular disease should be enforced that specially target women since they are the pillars for the family.

Supervisor:
Dr Rosediani Muhamad
Co-supervisor:
Dr Harmy Mohd Yusoff

THE INFLUENCE OF ORAL AND TOPICAL CHANNA STRIATUS ON TENSILE STRENGTH, EPITHELIAZATION, FIBROBLAST COUNT AND HYDROXYPROLINE ASSAY IN LAPAROTOMY WOUND HEALING OF MALNOURISHED RATS

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Introduction: *Channa striatus* has been used in traditional medicine for centuries to accelerate wound healing. Recently several scientific studies have shown the healing properties of *Channa striatus*. However study yet to be done on its healing effect on laparotomy wound healing which has greater morbidity and mortality in the event of laparotomy wound failure. There is also no study on its healing effect in malnourished patient whom may benefit the most.

Objectives: The aim of the study is to evaluate the effect of Channa striatus on tensile strength, epitheliasation, fibroblast count and hydroxyprolene level in the healing of laparotomy wound in malnourished rat.

Methods: 40 malnourished wistar rat underwent laparotomy and the wound closed primarily. The rats were divided into 2 groups by block randomization. Group 1 is the control group. Group 2 received oral and topical *Channa striatus* daily. The rats were euthanised and full thickness strips of the wound were subjected to tensile strength measurement, histopathological examination for epitheliasation and fibroblast counts. Hydroxyprolene assays was not done due to technical problem.

Result: The results demonstrates that the group treated with oral and topical *Channa striatus* were significantly higher in tensile strength, epithelial and fibroblast cell counts (P-value < 0.001).

Conclusion: This study suggests that oral and topical *Channa striatus* enhances laparotomy wound healing in malnourished rat by increasing the tensile strength, epithelialisation and fibroblast count.

Supervisor:
Dr Syed Hassan Syed Abd Aziz

RETROSPECTIVE SEVEN YEARS ANALYSIS OF DEXAMETHASONE THERAPY IN PRETERM PREGNANCY ADMITTED TO HOSPITAL UNIVERSITY SAINS MALAYSIA FROM THE YEAR 2003 TO 2009

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Introduction: Prematurity is the main cause of neonatal morbidity and mortality. Antenatal corticosteroid therapy has been shown to markedly reduced complications of prematurity. A complete course of antenatal corticosteroid treatment is recommended to prevent pulmonary complications of preterm infants. Repeating courses of antenatal corticosteroid in mothers who are at risk of preterm delivery is still debatable.

Objectives: The primary objective of the study is to examine the association between different doses of antenatal intramuscular (IM) dexamethasone therapy and fetal respiratory outcomes.

Methods: Retrospective study on case records of patients who delivered preterm and received antenatal IM dexamethasone therapy in HUSM from the year 2003 to 2009. Those who received IM dexamethasone 12.5 mg upon admission or diagnosis, followed by another dose of IM dexamethasone 12.5 mg, 12 hours later (total of 25 mg per day), is defined to receive a complete course of IM dexamethasone. Those who did not complete 2 doses of IM dexamethasone 12.5 mg, 12 hours apart is defined to receive incomplete course of IM dexamethasone. Those who were given another dose of IM dexamethasone after 1 week or more of the first course, is defined to receive repeat course of IM dexamethasone. Their babies' case records were reviewed to assess the fetal respiratory outcomes.

Result: We reviewed 927 case records of mothers who delivered preterm in HUSM from the year 2003 to 2009, and 980 case records of their newborns. There were 407 of mothers received incomplete, 484 received complete and 36 received repeat course of IM dexamethasone. Then, 435 infants exposed to incomplete, 503 infants exposed to complete and 42 infants exposed to repeated courses of antenatal IM dexamethasone for analysis. There were 61 infants delivered at 24 to 28 completed weeks, 515 infants delivered at more than 28 to 34 completed weeks and 404 infants delivered at more than 34 to less than 37 completed weeks. In the group of infants who were delivered at more than 28 to 34 completed weeks gestation, a complete course of antenatal IM dexamethasone is significantly associated with better respiratory outcomes compared to those infants who were exposed to an incomplete course of antenatal IM dexamethasone. However, in the group of infants who were delivered at 24 to 28 completed weeks gestation as well as those delivered at more than 34 to less than 37 completed weeks period of gestation, there was no significant association between complete or incomplete course of antenatal IM dexamethasone and the respiratory outcomes.

Conclusions: A complete course of antenatal IM dexamethasone therapy significantly reduces the respiratory complications in the preterm infants delivered at more than 28 to 34 completed weeks period of gestation compared to those who were exposed to incomplete course of antenatal IM dexamethasone.

Supervisor:
Assoc Prof Dr Shah Reza Johan Nor
Co-supervisor:
Dr Mohd Ismail Ibrahim

PREVALENCE OF SEXUAL DYSFUNCTION AND ASSOCIATED FACTORS AMONG ESSENTIAL HYPERTENSIVE WOMEN ATTENDING HYPERTENSIVE AND OUT-PATIENT CLINICS, HUSM

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Introduction: Hypertension is one of the chronic diseases that has become a global public health care concern. In Malaysia, prevalence increases over the year and female predominate from age 40-years-old with the Malay women predominate in terms of race. Hypertension does not only affect the brain, heart and kidneys, but it also will affect sexual function of the person. Even though the prevalence of female sexual dysfunction was high, not much attention has been paid on it and most of the theories and belief about female sexuality are still inconclusive (2).

Objectives: The aim of this study is to determine the prevalence of sexual dysfunction and associated risk factors in hypertensive women. Research design and methods data was collected from 348 hypertensive women in the Hypertensive and Out Patient Clinic of Hospital Universiti Sains Malaysia (HUSM) using Malay Version of Female Sexual Function Index. Socio-demographics, marital profiles, obstetric and gynecological problems, presence of hypertension, presence of other medical illness, and husband chronic illness were recorded.

Results: The prevalence of sexual dysfunction among hypertensive women was 21.3% (95% CI, 17.00, 25.60). Desire disorder was reported as the highest percentage (42.8%), followed by lubrication disorder (24.1%), arousal disorder (22.7%), satisfaction and sexual pain disorder (19.0%) and orgasm disorder (14.1%). Less frequent sexual intercourse, lack of satisfaction with husband's sexual performance, unhappy marriage, having urinary incontinence and ACE I administration were significant associated factors for sexual dysfunction in hypertensive women.

Conclusion: The result showed that almost 1 in 5 hypertensive women suffered from sexual dysfunction. This indicates that sexual dysfunction is a major public health concern and health care providers should be more serious in evaluating this issue.

Supervisor:
Dr Rosediani Muhammad
Co-supervisor:
Professor Dr Hatta Sidi

A STUDY TO DETERMINE THE ASSOCIATION BETWEEN PATTERN OF CALCIFICATION IN CT SCAN AND STAGING OF RETINOBLASTOMA IN HOSPITAL UNIVERSITY SCIENCE MALAYSIA (HUSM)

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Introduction: Retinoblastoma is one of the most common intraocular malignancy in children under 15-years-old. About 80% of cases occurs in patients under 3-years-old. The incidence varies form countries to countries. In United States of America, it occurs in 1 of every 15 000 live birth. Most incidence of retinoblastoma is unilateral, bilateral involvement is seen in approximately 30% of cases and it is detected earlier. Physical and radiological examination helps in diagnosing retinoblastoma. CT scan of the orbit is one of the important tools in diagnosing retinoblastoma. Intraocular calcification can be detected in about 80% of the CT scan of orbit. Many researches have been performed since 1980s to determine association between intraocular calcification in retinoblastoma with prognosis and size of the tumour.

Objectives: To determine frequency of intraocular calcification in retinoblastoma and association between the pattern of calcification with histopathological examination, clinical data and staging.

Methods: This was a retrospective descriptive study. All patients had undergone pre-treatment CT scan of the orbit and enucleation. Characteristic of calcification on CT scan images which were presence of calcification, size, site and Hounsfield Unit of calcification were recorded. CT scan images were reviewed via GE Centricity PACS- IW (Intregrated web) version 3.71. Histological findings which were presence of calcification, size, site of tumour and optic nerve involvement were recorded. History of presenting illness, family history, demographic data and clinical classification were sought form medical record and recorded. Association between characteristic of calcification and histological findings, clinical data and staging were determined.

Result: There was 95% intraocular CT calcification seen in retinoblastoma in this study. There was significant association between presence of calcification on CT and presence of calcification on HPE (P = 0.042). There was also significant association between presence of HPE calcification and CT calcification site (P = 0.016). Significant association noted between CT calcification size, and strabismus (P = 0.035). However, there was no significant association between the patterns of calcification on CT with staging of retinoblastoma.

Conclusion: Although presence of calcification on CT scan was used as a criteria to diagnosed retinoblastoma, there is no significant association between patterns of the calcification with staging in retinoblastoma.

Supervisor:
Assoc Prof Noreen Nurfaraheen Lee Abdullah

THE EFFECTS OF HORMONE REPLACEMENT THERAPY ON MAMMOGRAPHIC DENSITY AMONG POST-MENOPAUSAL WOMEN IN HOSPITAL RAJA PEREMPUAN ZAINAB II, KOTA BHARU, KELANTAN

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Introduction: Hormone replacement therapy (HRT) is commonly prescribed to post-menopausal women to improve their post-menopausal symptoms. Post-menopausal hormone use is associated with increase in mammographic density and increased incidence of breast pain. Mammographic density is an independent risk factor for breast cancer.

Objectives: The purpose was to evaluate the effects of HRT on mammographic density in post-menopausal women in Kota Bharu, Kelantan, Malaysia.

Methods: An observational study was conducted for a period of 18 months. A total of 33 post-menopausal women who received combined HRT (containing estrogen and progesterone) were included as study subjects. Mammograms were performed at baseline and after 12 months of receiving HRT. Mammographic density was evaluated according to BIRADS classification of breast density. During follow-up, patients were also enquired about breast pain and they were asked to classify according to a specified scale.

Result: The categorical assessments showed that there was a significant shift in categorical classification as assessed by BIRADS categories among the post-menopausal women receiving HRT. Amongst these women, 30.3% had increased mammographic density after treatment with HRT. There was also significant association between breast pain and increase in mammographic density. Amongst the study population, 33.3% complained of breast pain after HRT. We also concluded that the study factors (grade, age, parity, BMI, duration of menopause and age at menopause) did not significantly influence change in mammographic density.

Conclusion: HRT significantly affects the mammographic density and increased mammographic density was associated with breast pain in women receiving hormonal therapy.

Supervisor:
Assoc Prof Dr Noreen Norfaraheen Lee
Co-supervisor:
Dr Md Ariff Abas

A STUDY TO INVESTIGATE THE EFFECT OF HORMONE REPLACEMENT THERAPY (HRT) ON PLATELET ACTIVATION MARKERS (CD62P & PAC-1) DETERMINED BY FLOW CYTOMETRY IN HEALTHY POSTMENOPAUSAL WOMEN

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Introduction: In healthy post-menopausal women increased platelet activation has been associated with the adverse cardiovascular events including unstable angina, myocardial infarction, stroke and other thrombotic states. There is much debate about the relationship between platelet function and serum estradiol levels in such post-menopausal women. It is postulated that estrogen may result in decreased platelet activation.

Objectives: The aim of the study was to determine the effect of HRT on the platelet activation markers (CD62P & PAC-1) in healthy post-menopausal women and to determine the correlation between platelet activation markers and serum estradiol, BMI and age of post- menopausal women.

Methods: A prospective case control study on 48 post-menopausal women was conducted at Hospital Universiti Sains Malaysia (HUSM). Group A consisted of 48 women not on hormone replacement therapy (HRT) (Control Group) and group B comprised of same 48 women who were given HRT (conjugated equine estrogen 0.625 mg orally once daily) for 2 weeks (study group). Platelet activation was evaluated at baseline and after 2 weeks of treatment by flow cytometric analysis using CD62P and PAC1 as activation markers. Comparisons within groups (before and after HRT) were analyzed using the paired *t*-tests.

Results: The expressions of CD62P and PAC1 showed a decreased platelet activation status in postmenopausal women who were given HRT. Platelet activation markers (CD62P & PAC-1) among healthy post-menopausal women in the group A were 7.00% ± 5.91 (CD62P) and 41.75% ± 26.85 (PAC-1) respectively (increased platelet activation in this group) which were reduced to 3.05% ± 2.47 (CD62P) and 20.86% ± 19.02 (PAC-1) respectively in the group B after 2 weeks of HRT administration (*P*-value < 0.001).

Conclusion: HRT decreases the platelet activation markers (CD62P & PAC-1) in healthy post menopausal women. Platelet activation markers (CD62P & PAC-1) are found to be increased in healthy post-menopausal women as compared to the post-menopausal women who were treated with HRT. There is a significant negative fair correlation between estradiol andmplatelet activation markers (CD62P & PAC-1). However, there was no significant relation among BMI, age and platelet activation markers. It is concluded that short term use of HRT has a favorable effect on reduction of platelet activity in post-menopausal women and thus it is postulated to be cardio protective. Further study on the long-term effect of HRT on platelets is needed.

Supervisor:
Professor Dr Nik Mohamed Zaki Nik Mahmood
Co-Supervisor:
Assoc Prof Shah Reza Johan Noor
Dr Tariq Mahmood Roshan

ANTHROPOMETRIC MEASUREMENT OF THE LIP-NOSE COMPLEX AMONG YOUNG ADULTS IN KUALA LUMPUR, MALAYSIA

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Introduction: The lip-nose complex is an important aesthetic subunit of the mid and lower face. To date, there is no published data on lip-nose complex anthropometry for the Malaysian population.

Objectives: This cross-sectional descriptive study aims to establish the norms of the lip-nose complex among Malaysian Malays, Chinese, and Indians and to compare the transgender and transethnic variation between them.

Methods: 7 parameters of the lip-nose complex namely mouth width, cupids bow width, columellar width, nasal width, lip height, columellar height and dome height were measured using standard anthropometric measurement tools. 316 students were randomly selected from 3 schools in Kuala Lumpur, with equal gender and ethnic distribution.

Result: All 7 parameters the lip-nose complex in Malay, Chinese, and Indian males were consistently larger than their respective female counterparts ($P < 0.05$). The difference in lip-nose complex measurements for mouth width, nasal width, lip height and dome height were statistically different between Malays, Chinese, and Indians. Mouth width and nasal width were widest among Malays. Lip height was highest amongst Indians. Dome height was highest amongst the Chinese. The cupids bow distance, columellar width and height showed minimal difference within the 3 races ($P > 0.05$). Malays and Chinese differed in all parameters except cupids bow width. Malays and Indians only differed in mouth width and nasal width. Chinese and Indians differed in lip height and dome height.

Conclusion: Malays and Chinese show differences in their lip-nose complex profile despite having originated from the East Asian continent. Malays and Indians differed in width measures, while the Chinese and Indians differed in height measures. The variation of anthropological measurements among the 3 ethnic groups reinforces the need to have individualised norms. These findings form a baseline for future studies that are age based which would then serve

as an invaluable guide to the reconstructive surgeon especially when dealing with unilateral and bilateral cleft lip repairs.

Supervisor:
Prof Dr Ahmad Sukari Halim
Co-supervisor:
Dr Normala Hj Basiron

KNOWLEDGE REGARDING MANAGEMENT OF DIABETIC NEPHROPATHY AMONG MEDICAL OFFICERS (MO) AT HUSM AND ITS ASSOCIATION WITH MO PROFILES

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Introduction: Many studies had assessed the knowledge and practices among the physicians in the management of chronic kidney disease (CKD) but no specific study to assess the knowledge of medical officers (MOs) regarding the management of diabetic nephropathy. Many patient with diabetic nephropathy are seen by MOs level, who are less experienced than nephrologists to offer optimal care. It is not known whether knowledge regarding management of diabetic nephropathy among MOs are adequate in care of diabetic nephropathy patient and whether characteristics of medical officer are associated with having adequate knowledge.

Methods: Self-administered questionnaire to medical officers at 2 medical based department HUSM (n = 102) with distribution of 51 Internal Medicine and 51 Family Medicine in April 2011. The questionnaire consist of 4 knowledge domains regarding management of diabetic nephropathy and had established validation.

Result: Total 102 out of 108 (94%) eligible medical officers returned a completed survey. Overall, 49% of MOs have adequate level of knowledge. All MOs have managed diabetic nephropathy cases but even so, only 78% of them have attended seminars/talks or workshops regarding diabetic nephropathy. Overall, no relationship between level of knowledge and MO specialties (Internal Medicine Vs Family Medicine department). There were also no significant relationship between level of knowledge and status of MOs (service MO or master MO). There were significant relationship between level of knowledge and the year of master (P = 0.016) and year 4 masters MO had more than 7 fold greater odds of showing a adequate level of knowledge compared with MO who are not yet joining master (95% CI, 1.44, 36.20, P = 0.016).

Conclusion: We found that medical officers have significant gaps in their knowledge regarding management of diabetic nephropathy that might require further improvement for better future patient care. Master training may offer the best opportunity to improve the awareness and knowledge of diabetic nephropathy guidelines through more focused educational efforts.

A PROSPECTIVE STUDY OF RELATIONSHIP OF VASCULAR PEDICLE WIDTH AND CARDIOTHORACIC RATIO IN ADULT PULMONARY OEDEMA PATIENTS DURING TREATMENT IN ICU

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Introduction: Determination of intravascular volume status in critically ill patient is very important. Traditionally, invasive hemodynamic pressure measurements have been used to assess the volume status in this group of patients. However, the information available from vascular pedicle width (VPW) in portable supine chest radiographs are least costly and least invasive of determining volume status in critically ill patient. The true utility of VPW reflecting intravascular volume status seen in few studies from portable supine chest radiographs especially in monitoring patients who have volume overload and are receiving treatment.

Objectives: To determine the relationship of VPW, cardiothoracic ratio (CTR) and net fluid balance by using serial portable supine chest radiograph in adult pulmonary oedema patients during treatment in Intensive Care Unit (ICU) in Hospital Universiti Sains Malaysia (HUSM).

Methods: A prospective study was done from Jun 2008 until Jun 2009 involving 51 patients who had been diagnosed to have pulmonary oedema in ICU and Neuroscience ICU, HUSM. Serial supine portable chest radiographs were taken from day 1 of the onset of pulmonary oedema in ICU until day 3 consecutively. First chest radiograph was taken before starting treatment. Subsequent chest radiographs were taken about 24 hours apart. 3 consecutive 24 hours net fluid balance data were taken from ICU monitoring chart according to the day of CXRs. Computed chest radiograph is used for evaluation of the VPW and CTR. The VPW and CTR were measured by researcher in separated occasion without clinical data related to patient available.

Result: 51 patient involved in this study with the mean age of 54.43. Total of 39 patients (76.5%) received intravenous (IV) Frusemide and 12 patients (23.5%) received IV Frusemide in combination with dialysis as treatment of pulmonary oedema. There was a weak but not significant correlation between VPW and CTR in each day from day 1 (r1 = 0.10, P = 0.34), day 2 (r2 = -0.01, p = 0.92) and day 3 (r3 = 0.02, P = 0.91). Similar findings of a weak but not significant correlation was also seen between VPW and net fluid balance on day 1 (r1 = 0.10, P = 0.47), on day 2 (r2 = -0.05, P = 0.73)

and on day 3 (r3 = -0.05, *P* = 0.74). However, by using paired *t*-test significant mean changes of VPW between day 1 to day 2 and between day 2 to day 3 (*P* < 0.001). Significant mean changes of net fluid balance were also seen between day 1 to day 2 and between day 2 to day 3 (*P* < 0.001). No significant mean changes of CTR seen between day 1 to day 2 and between day 2 to day 3 (*P* = 0.58). In addition, there were daily reduction of the mean of VPW and net fluid balance in 3 days duration with IV Frusemide and combination treatment. However, no significant difference between both treatments with the mean of VPW (*P* = 0.099) and net fluid balance (*P* = 0.162) in 3 days period.

Conclusion: This study showed that there was strong significant mean changes of VPW and net fluid balance between day 1 to day 2 as well as day 2 to day 3. However, no significant mean changes of CTR between day 1 to day 2 and day 2 to day 3.

Supervisors :
Dr Nik Munirah Nik Mahdi
Dr Mohd Shafie Abdullah
Co-supervisors:
Dr Mohd Ariff Abas
Dr Mahamarowi Omar

STONE FREE RATE OF EXTRACORPOREAL SHOCKWAVE LITHOTRIPSY (ESWL) FOR TREATMENT OF RENAL STONES

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Introduction: Renal stones or renal calculi is a common disease encountered in the population worldwide. The cause of renal stones in majority of the cases are idiopathic. Management of renal stones has changed over the years. Before 1980s, open surgery was the treatment of choice. However, minimally invasive intervention has replaced open surgery in the treatment of most renal stones. This included extracorporeal shockwave lithotripsy (ESWL).

ESWL used shock waves to break the stone into small pieces or fragments which can be passed through the urinary tract. Therefore, it is more preferred method for treatment of renal stones and several ureteral stones. It has favourable clinical outcome, low complications rate and few absolute contraindications.

Objectives: The objective of this study is to obtain an epidemiological data of patients with renal stones who underwent ESWL in Hospital Universiti Sains Malaysia (HUSM). We also would like to review the outcome of this treatment in terms of stone clearance including the factors that may influences its success rate in our center.

Methods: A retrospective cohort study had been done involving patients with renal stones who underwent ESWL for their treatment in Urology Unit, Department of Surgery, HUSM. This study was done in 18 months duration, from 1st May 2007 until 30th October 2008. All patients were treated with ESWL machine SONOLITH® Vision. The radio-opaque stone was localised with X-rays. Patient's medical record and KUB X-rays before and after the treatment were reviewed. Data was analysed using SPSS version 12 with *P*-value of less than 0.05 was considered significant.

Result: During the study period from May 2007 till October 2008, 104 patients were involved. In this study, 56 (53.8%) patients were male and 48 (46.2%) were female with male: female ratio 1.1:1. The mean age was 50.8-years-old (range 16–83 years old). Majority of the patients were from Malay ethnics (97.1%) followed by Chinese (1.9%) and other ethnic groups (1.0%). The mean stone size was 13.07 mm with 42 (40.4%) stones measuring 10 mm or less and 62 (59.6%) more than 10 mm but not more than 20 mm. Most of renal stones were located at the middle calyx (32.7%), followed by lower calyx (28.9%), upper calyx (23.1%) and renal pelvis (17.3%). 78 point eight percent (78.8%) had single stone while another 21.2% had multiple stones. Our overall stone clearance rate was 53.8%. However in our study, stone size, location of the stones and numbers of stone did not affect overall stone clearance.

Conclusion: In conclusion, ESWL was a good treatment for renal stones measuring less than 20 mm. However, we need to select patients that is going to benefits from this treatment and have a regular or proper follow-up in order to have a better outcome.

Supervisor:
Dr Mohd Nor Gohar Rahman
Co-supervisors:
Dr Mohamed Ashraf Mohamed Daud
Dr Mossadeq A

A STUDY ON THE EFFECTS OF ANDROGRAPHIS PANICULATA (HEMPEDU BUMI) ON SERUM PROTEIN C, PROTEIN S ACTIVITY AND FASTING BLOOD GLUCOSE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Introduction: Patients with type 2 diabetes mellitus (DM2) show enhanced activation of the blood coagulation system and decrease level of natural anticoagulant such as protein C and protein S. This is believed to contribute to the high incidence of premature atherosclerosis attributable to

myocardial infarction, cardiovascular disease, and peripheral vascular disease in diabetic patients. *Andrographis paniculata* (Hempedu bumi) has been well known to have blood sugar lowering properties in diabetes patients and has been used by local Malaysians as an alternative to current oral hypoglycaemic agents. With the benefit of its blood sugar lowering properties it is hoped that *Andrographis paniculata* may also increases level serum protein C and protein S in diabetic patients, thus reducing the risk of atherosclerotic disease.

Objectives: This study was conducted to determine the changes in fasting blood sugar levels and to assess the changes in serum protein C and protein S activity following oral administration of *Andrographis paniculata* among DM2 patients in Hospital Universiti Sains Malaysia (HUSM) Diabetic Medical Clinic.

Methods: This is an open-labelled, randomised treatment versus control study which was conducted among DM2 patient on follow up at HUSM Diabetic Medical Clinic from August 2010 till November 2010. A total of 34 subjects were recruited in this study. Of this, 17 were randomly given the study medication; 2 tablets each containing 250 mg of *Andrographis paniculata* for 2 weeks duration while the other 17 patients were allowed to continue with their previous medication without any alteration. Blood samples containing fasting blood glucose (FBG), serum protein C and protein S were taken at baseline and after 2 weeks intervention for both groups.

Result: A total number of 34 patients were involved in this study. The mean age was 55.2 ± 9.8 years. The baseline HbA1c was 9.2% ± 2.4 % in both groups. The mean fasting blood sugar during pre-intervention in the control group was 8.6 mmol/L ± 3.7 while in treatment group is 9.1 mmol/L ± 5.0 and post-treatment, the mean fasting blood sugar was 8.3 mmol/L ± 2.9 and 9.3 mmol/L ± 4.0, respectively. The mean of protein C in the pre-intervention for control group was 117.2% ± 17.3 and in the treatment group was 125.1% ± 21.3. Post-intervention mean protein C in the control group was 121.1% ± 25.4 and in the treatment group is 125.9% ± 18.9. The mean protein S in the pre-intervention for control group was 202.4% ± 128.0 and for treatment group is 135.4% ± 30.1 while in the post-intervention mean for control group was 208.3% ± 129.5 and in the treatment group 134.1% ± 25.3. The mean difference of fasting blood sugar, protein C and protein S between pre- and post-intervention for both groups were statistically not significant.

Conclusion: Our study demonstrated that generally the blood sugar control among DM2 patients is still poor with mean HbA1c of 9.2 % ± 2.4. There were no significant changes in mean serum fasting blood glucose, protein C and protein S for pre- and post-treatment of oral administration of 500 mg of *Andrographis paniculata* for 2 weeks duration in the treatment group when compared to control group. These findings were probably related to inadequate dose of *Andrographis paniculata* since there was no study of bioequivalence in this study and also inadequate study duration to produce desirable effects in this study.

A CLINICOPATHOLOGIC STUDY ON TRIPLE-NEGATIVE BREAST CANCER PATIENTS: HUSM EXPERIENCE

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Introduction: Breast cancer is the most common cancer among Malaysian women. There are many prognostic factors contributing to the disease and the outcome of the patients. Triple negative breast cancers are defined by a lack of expression of oestrogen, progesterone, and c erbB-2 receptors. They tend to have a higher grade with a poorer outcome compared to non-triple negative breast cancers.

Objectives: The study was carried out aiming to observe the association of triple negative; (oestrogen receptor [ER], progesterone receptor [PR] and c erbB-2) breast cancer patients to the pathological (histological subtype, tumour grade, tumour size, and lymph node involvement) and non-pathological parameters (patient's age and ethnicity).

Methods: Retrospective review of histopathology reports in Hospital Universiti Sains Malaysia from 1st January 2002 to 31st December 2004. 23 cases of triple negative breast cancer among 115 cases of breast cancer diagnosed in 3 years (2002 to 2004) were reviewed. They represented 20.0% of total breast cancer patients.

Result: There were significant association between triple negative breast cancer with tumour size, lymph node involvement, and lymphovascular invasion. However, age, race, histological subtype and histological grade did not show significant association.

Conclusion: From these findings, we conclude that tumour size is the strongest factor associated with the triple negative breast cancer. Besides that, lymph node involvement is also associated with triple negative breast cancer. However, lymph vascular invasion is not associated with triple negative vascular breast cancer.

Supervisor
Dr Venkatesh R Naik

COMPARISON OF ANXIETY AND DEPRESSION BETWEEN PATIENT WITH AND WITHOUT FIXED AIRFLOW LIMITATION IN SEVERE ASTHMATICS IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM) AND HOSPITAL RAJA PEREMPUAN ZAINAB II (HRPZ II)

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Introduction: Asthma is a common chronic disease worldwide. Despite important advances in diagnosis and treatment, asthma has become a public health problem for all countries. Poorly controlled asthma exerts a high cost for both patients and society. Fixed airflow limitation can develop in patients with severe asthma. Anxiety and depression were significantly more common among asthmatic patients and psychiatric co-morbidity is associated with poor asthma outcome.

Objectives: To compare the prevalence of anxiety and depression between patients with and without fixed airflow limitation among severe asthmatic patients and to determine the association between anxiety and depression with airflow limitation in severe asthmatic patients.

Methods: This was a comparative cross-sectional study among 158 severe asthmatic patients attending the chest clinic follow-up in Klinik Pakar Perubatan HUSM and HRPZ II from 15 August 2009 till 15 April 2010. Each patient was interviewed and their medical notes were reviewed to assess their medications as well as their asthma severity. Spirometry test was performed to determine the presence of fixed airflow limitation. They were then given 2 sets of self- administered questionnaires; (1) the socio-demographic questionnaire and (2) the Malay HADS questionnaire.

Result: There were 81 patients in the fixed airflow limitation group with mean age (SD) of 54.1 ± 9.8 and 77 patients in the group without fixed airflow limitation with mean age of 50.1 ± 12.3. The prevalence of anxiety and depression in the fixed airflow limitation group was both 29.6% whereas in the group without fixed airflow limitation were 24.7% and 18.2% respectively. Simple and multiple logistic regressions found no significant relationship between anxiety or depression and presence of fixed airflow limitation.

Conclusion: The prevalence of anxiety and depression in severe asthmatic patients with fixed airflow limitations is similar to those without fixed airflow limitation. There is no increased risk of developing anxiety or depression associated with having fixed airflow limitation in severe asthmatics.

Supervisor:
Dr Norwati Daud

A PILOT STUDY OF INTRASTROMAL INJECTION OF AMPHOTERICIN B 0.0005% IN FUNGAL KERATITIS

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Introduction: Fungal keratitis is an important infectious keratitis in developing countries such as Malaysia. It is difficult to diagnose and treat. The current available antifungal agents have poor ocular penetration. New method of drug delivery which was the intrastromal injection of amphotericin B was evaluated to see its effectiveness in the treatment of fungal keratitis.

Objectives: The objective of this study is to determine the effectiveness of intrastromal amphotericin B 0.0005% injection in human fungal keratitis.

Methods: This was a pilot study involving 20 subjects. 10 subjects received intrastromal injection of amphotericin B and 10 subjects were in the control group in which they received the standard topical antifungal therapy.

Result: About 30% of patients with very poor visual acuity had improved vision to good visual acuity in the intervention group. Complete re-epithelialisation was seen in 30% of patients in the intervention group compared to 20% in the control group. Resolution of stromal abscess and reduction in the level of stromal infiltrate were seen earlier in the intervention group. 40% of subjects in the intervention group showed complete healing of the stromal compared to 10% in control group.

Conclusion: Intrastromal injection of amphotericin B 0.0005% (5 µg/ml) was found to be effective in treating fungal keratitis in human.

Supervisor:
Associate Prof Mohtar Ibrahim
Co-supervisor:
Dr Adil Hussein
Dr Noram Azlan Ramli

PREVALENCE OF EOSINOPHILIC NASAL POLYPS AND ANALYSIS OF THEIR PRESENTATION IN HUSM KUBANG KERIAN, KELANTAN

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I***ntroduction:*** Nasal polyp pathogeneses and etiology is still unknown, but now it is regarded as one form of the chronic inflammatory reaction of the sinonasal mucosa which eosinophiles are mainly involved in the mechanism of its formation. It is quite common disease affecting 1%–2% of the adult population and has the potential for high recurrence. Clinically most of the patients are complaining of nasal blockage and reduce sense of smell. The easy accessibility to the nasal polyp facilitates histological examination of it and broadly divided them into 2 histological subtypes the eosinophilic and non-eosinophilic types.

Objectives: The aim of the study was to determine the percentage of each histological subtype of the nasal polyp and to study the association of the clinical presentation of each type.

Methods: 62 patients with nasal polyp underwent functional endoscopic sinus surgery (FESS) in HUSM over the period of 4 years extending from 2004 to 2008 were included in the study and their histopathological reports were reviewed and their clinical presentation was studied in relation to the symptoms and the findings were written in specifically prepared form for this purpose.

Result: 87% of the sample had eosinophilic type of nasal polyp and 13% had non-eosinophilic.There was no statistically significant difference in the clinical presentation in relation to nasal blockage or loss of smell between the 2 histological subtypes. High recurrence rates was noted among our subjects compared to published figures for the same surgical intervention (FESS).

Conclusion: The study showed that the incidence of histological subtypes of nasal polyp is almost the same as that found in other parts of the world (Europe and North America) which will reduce the possibility of racial or geographical influence on the pathogenesis of the nasal polyp. Clinical symptoms and presentation alone are not enough to differentiate the type of the nasal polyp without the histological studies.

Supervisor:
Dr Ramiza Ramza bin Ramli
Co-supervisor:
Dr Irfan Mohammed

PREMATURE CORONARY ARTERY DISEASE AMONG ANGIOGRAPHICALLY PROVEN ATHEROSCLEROTIC CAD IN HUSM

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Objectives: To determine the proportion of premature coronary artery disease (CAD) among angiographically positive CAD patients in Hospital Universiti Sains Malaysia (HUSM) and to identify its risk factors.

Methods: This is a cross-sectional study. 350 medical records of patients undergoing coronary angiogram due to CAD from October 2002 till 2004 were reviewed. The socio-demographic, associated risk factors and angiographic findings were recorded in a data questionnaire.

Result: A total of 165 cases were included, which 55% (n = 91) were premature CAD and 45% (n = 74) were older CAD. The mean age of premature CAD was 49.7 years of male and 51.4 years for female and male gender was predominant by 80%. The significant factors associated with premature CAD were family history of heart disease 38.5% ($P < 0.05$) and low HDL level 1.2 ± 0.30 ($P < 0.05$). Compared with older patients, younger patient had pre-ponderance of double-vessel disease.

Conclusion: There was a high prevalence of premature CAD patients among angiographically proven atherosclerotic CAD. Family history of heart disease and low HDL level are associated with premature CAD. Thus early cardiovascular screening in family member of patient with heart disease and aggressive treatment to increase HDL level are the first step for prevention of CAD in young age.

Supervisor:
Assoc Prof Dr Zurkurnai Yusof
Co-supervisor:
Dr Azidah Abd Kadir

Abstracts

Abstracts of Theses Approved for the MSc and PhD at the School of Health Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia

CONSTRUCTION AND EVALUATION OF MULTIGENE MUTANTS OF VIBRIO CHOLERAE 0139 AS VACCINE CANDIDATES

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Introduction: Cholera is a major health issue, affecting millions of lives annually. In light of the recurrent outbreaks of cholera, there is a pressing need for the development of vaccines that allow rapid mass vaccination.

Objectives: In this study, genetically modified vaccine candidates, VCUSM21P and VCUSM22P, were designed. VCUSM2lP is a prototrophic vaccine which encodes non-toxic cholera toxin A (ctxA) subunit immunogen and has accessory cholera enterotoxin (ace), zonula occludens toxin (zot), and repeats-in-toxin CIA (rtxC/A) mutations. On the other hand, VCUSM22P is ace, zot, ctxA, rtxCIA, and hemagglutinin/protease (hap) mutant. Both mutants were found not to disassemble the actin of HEp2 cells.

Methods: Mouse colonisation assay was used to determine VCUSM21P and VCUSM22P colonization ability in-vivo. Rabbit ileal loop assay was performed to evaluate the reactogenicity caused by them. The immune responses provoked by the 2 vaccine candidates and their protective function against cholera were evaluated in a rabbit model. The mutants were found to be good colonizer of the mouse intestine. In the ileal loop assay using non-immunised rabbits, fluid accumulation was found in loops injected with 1 × l06 and 1 × l08 colony forming unit (CFU) of wild Type (WT) V. cholerae. Unlike the WT V. cholerae challenge, 1 × l06 and 1 × CFU of the mutants did not cause any reactogenicity in-non immunised rabbits. Immunisation using 1 × l010 CFU of the mutants induced both IgA and IgG antibodies production against cholera toxin (CT) and 139 lipopolysaccharides (LPS), as well as elevated vibriocidal antibody.

Result: The reactogenicity caused by the WT V. cholerae in rabbits immunised with 1 × 1010 CFU of the mutants was found to be reduced as evidenced by the absence of fluid in loops administered with 1 × l02 - 1 × l07 CFU of WT V. cholerae. In the Removable Intestinal Tie Adult Rabbit Diarrhoea (RIT ARD) experiment, the non-immunised rabbits were found unprotected against a lethal challenge with 1 × 109 CFU WT V. cholerae. However, 100% of rabbits immunised with the mutants survived the WT V. cholerae challenge.

Conclusion: Immunohistochemical, histopathological, and ultrastructural examination of non-immunised rabbit's ileum challenged with WT V. cholerae revealed severe ileal damages. But less severe damages were noted following the WT V. cholerae challenge in the ileum of rabbits immunized with VCUSM21P and VCUSM22P. The multigene mutants could be used for vaccination against potentially fatal V. cholerae 0139.

Supervisor:
Prof Dr Lalitha P
Co-supervisor:
Dr Shyamoli Mustafa

THE RELATIONSHIP BETWEEN PROTEIN AND MRNA EXPRESSION OF TRANSCRIPTION REPRESSOR DREAM, C-FOS AND PRODYNORPHIN IN MODULATING PAIN RESPONSES INDUCED BY FORMALIN IN THE RAT SPINAL CORD

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Introduction: Downstream Regulatory Element Antagonist Modulator (DREAM) protein acts as a transcription repressor for c-Fos and prodynorphin gene which is involved in modulating pain processes.

Objectives: This study was conducted to investigate the relationship between DREAM, c-Fos, prodynorphin protein and mRNA expression through opioid and non-opioid receptors in the modulation of pain responses induced by formalin in the rat spinal cord.

Methods: Male Sprague Dawley rats weighing between 250–300 g were divided into 5 major groups. Group 1 consisted of rats treated with pre-emptive administration of ketamine (anaesthetic drug) (5 mg/kg body weight) intraperitoneally (i.p) and given formalin injection (K + F group) (n = 36) after 30 minutes. Group 2 consisted of rats treated with preemptive administration of norbinaltorphimine dihydrochloride (norBNI) (kappa opioid receptor antagonist) (2 mg/kg body weight) (i.p) and given formalin injection (N + F group) (n = 36) after 24 hours. Rats in group 3 were treated with preemptive administration of both ketamine and norBNI (i.p) and given formalin injection (NK + F group) (n = 36). Rats in group 4 were only treated with normal saline and given formalin injection (F group) (n = 36) while rats in

group 5 were not given any treatment and considered as a control group (C group) (n = 18). Each experimental group except the control group was further divided into subgroups (n = 6) consists of rats that were sacrificed at 2 and 4 hours after formalin injection. 50 µl of formalin 5% (1.85% formaldehyde solution), was subcutaneously injected into the plantar surface of the left hind paw of the rat. The pain behaviour responses were recorded for 1 hour for rats in the C, F, K + F, N + F, and NK+F groups. The rats were then sacrificed 2 and 4 hours after formalin injection and the lumbar L4/L5 segments of spinal cords were removed for immunohistochemistry, Western blot, and real-time PCR analysis. Noxious stimuli (formalin injection) in this study increased the total number of FLI and PLI neurons, consistent with an increase in relative c-Fos and prodynorphin mRNA levels at 2 hours after formalin injection on the ipsilateral side. The mean relative DREAM protein in the nuclear extract and relative DREAM mRNA levels were also increased at the same time. These effects probably contributed to increase in pain behaviour responses during the tonic phase of the formalin test. However, pre-emptive administration of ketamine prevented the increase of total number of FLI and PLI neurons and relative c-Fos and prodynorphin mRNA level at 2 hours after formalin injection on the ipsilateral side. At the same time, this study found that the relative DREAM mRNA level was decreased but the mean relative DREAM protein level in the nuclear extract was increased at this time. These effects may reduce pain behavior responses during the tonic phase of the formalin test in this group. Pre-emptive administration of norBNI (kappa opioid receptor antagonist) increased the total number of FLI and PLI neurons, consistent with the relative c-Fos and prodynorphin mRNA level at 2 hours after formalin injection on the ipsilateral side. These resulting in decreased mean relative DREAM protein level in the nuclear extract and relative DREAM mRNA level at this time. Furthermore, pre-emptive administration of norBNI enhanced pain behaviour responses during the tonic phase of the formalin test. Pre-emptive administration of both ketamine and norBNI eliminated some of the effects of pre-emptive administration of ketamine and norBNI. These findings suggest that both NMDA and kappa opioid receptors are involved in modulating acute pain responses in this study. However, the changes in c-Fos and DREAM mRNA and protein expression at 2 hours are not prolonged and reverse to the basal state at 4 hours except for the changes in prodynorphin mRNA and protein expression.

Result: These findings suggest that prodynorphin mRNA and protein expression are important in persistent pain mechanisms. In addition, the mean relative DREAM protein in the cytoplasm extract was unaffected in each of the experimental groups in this study after 2 and 4 hours following formalin injection.

Conclusion: In conclusion, this study shows that DREAM protein acts as a transcription repressor for c-Fos and prodynorphin gene, and can be modulated by NMDA and kappa opioid receptor action during acute pain. The modulation is achieved through changes in the localization of DREAM protein in the nucleus or cytoplasm of neurons. This is an important mechanism which permits the upregulation and downregulation of c-Fos and prodynorphin gene and its protein expression in the rat spinal cord during acute pain processes.

Supervisor:
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PREVALENCE AND MICROSCOPIC STUDY OF THE HERBS USED IN PREGNANCY

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Introduction: The use of herbal medicine is common in Malaysia including its use during pregnancy. However, there have been very few formal studies of herbal consumption in pregnancy and even fewer looking at ultra-structural features and trace elements of herbal medicine.

Objectives: This study was to determine the prevalence of use and to identify possible chemical properties and morphological structure of herbal medicine found to be popularly used among the Kelantanese Malay women during the pregnancy period.

Methods: A study was conducted among 460 Kelantanese Malay women at antenatal and postnatal ward Hospital USM from September to December 2007 using structured close-ended questionnaires. The surface morphology and the microstructure of *Anastatica Hierochuntica L.* were captured by Supra 50 VPSE-SEM LEO and Olympus SZ40 stereo microscope with image analyzer. Elemental analysis was done by using Energy Dispersive X-Ray (EDX). Of these 460 women, 55.7% were housewives, 61% had attended secondary education, 85% were aged between 21–40 years and 57.2% were para 2 to 5. Herbal medicine used during pregnancy was 34.3% while 73% utilized herbal in labor because in the belief that it can shorten labor and makes labor easier. The most commonly used herbal medicine in pregnancy was *Anastatica Hierochuntica L.* (Sanggul Fatimah) (60.1%), followed by coconut oil (35.4%), and herbs prepared by traditional midwives (6.3%). The majority of women (89.2%) used only 1 type of herbal medicine and took it when necessary (53.2%) with 1 capsule/glass (38%) per day. Herbal medicines used by pregnant women were commonly unsupervised (81%), with most women getting information from their parents (60.7%) and buying the products directly from traditional midwifes (32.2%) and 77% agreed upon its efficacy and safety. *Anastatica Hierochuntica L.* structures

were viewed under VPSEM and were discussed.

Result: Micro diffraction analysis of the herb revealed inert significant presence of useful mineral such as magnesium, aluminium, potassium, zinc, iron, and calcium as well as elements like carbon, oxygen, and silica.

Conclusion: Herbal medicine is still being commonly used among the Malay Kelantanese women communities. A detailed study is therefore needed to establish among others, the efficacy and safety of these herbs where the well-being of mother and fetus are of paramount.

Supervisor:
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Co-supervisors:
Dr Soon Lean Keng

SINGLE NUCLEOTIDE POLYMORPHISMS (SNPs) OF ADIPONECTIN GENE AND ITS ASSOCIATION WITH SERUM ADIPONECTIN CONCENTRATION AND METABOLIC SYNDROME RISK FACTORS AMONG MALAY ADULTS

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Introduction: Metabolic syndrome is a cluster of risk factors that include central obesity, hypertriglyceridaemia, reduced HDL cholesterol, hypertension, and hyperglycemia. Accumulating evidences support the hypothesis that hypoadiponectinemia, a type of adipokine, confer increased risk for metabolic diseases. Of interest, some of the common polymorphisms in the promoter region, exon and intron 2 of the human adiponectin gene are associated with risk factors of metabolic syndrome.

Objectives: The present study aims to investigate the association of several single nucleotide polymorphisms in the adiponectin gene with serum adiponectin concentration and metabolic syndrome risk factors among Malay adults.

Methods: A total of 298 Malay adults were recruited in this study. Measurements for waist circumference and blood pressure were taken-before drawing an overnight fasting blood. Biochemical tests for triglycerides, HDL cholesterol, and glucose were carried out by using commercially available kits. Plasma adiponectin concentration was measured using Human Adiponectin ELISA kit. A total of 5 sites of single nucleotide polymorphisms in adiponectin gene (SNPs -11426, -11391, and -11377 at proximal promoter and SNPs +276 and +45 at exon 2 regions) were screened using mini sequencing method.

Result: Findings from this study showed that the adiponectin concentration in the subjects with MS was significantly lower than those without MS ($P < 0.05$). The adiponectin concentration was also significantly associated with only hypertriglyceridemia ($P < 0.001$) and reduced HDL cholesterol ($P < 0.001$). None of the studied SNPs or haplotypes showed any significant association with the adiponectin concentration. Moreover, only SNP -11426 was significantly associated with MS ($P < 0.05$), while SNP +276 was associated with hypertriglyceridemia ($P < 0.05$), and haplotype -11426/-11377 was associated with hyperglycemia ($P < 0.05$). Overall, there was no statistically significant interaction between the status of MS and SNPs or haplotypes with respect to the adiponectin concentration. However, there was a significant association between the adiponectin concentration and the status of reduced HDL cholesterol with SNP-11426 ($P < 0.05$). Besides, a significant association was also observed in the adiponectin concentration and hypertriglyceridemia with haplotype 11426/+45 ($P < 0.05$).

Conclusion: In conclusion, hypoadiponectinemia and SNPs and haplotypes of adiponectin gene may contribute to the development of metabolic syndrome and its risk factors, via unknown mechanisms in Malay population.

Supervisor:
Dr Hamid Jan Jan Mohamed
Co-supervisor:
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'ULAM': CONSUMPTION AMONGST KELANTANESE MALAY FROM SELECTED DISTRICTS AND THEIR ANTIOXIDANT PROPERTIES

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Introduction: Eating styles have been shown to exert a major impact on the quality of life and this can be shown in the health status of the individual. So the saying "We are what we eat".

Objectives: The present study was carried out to evaluate the consumption of 'ulam' amongst Kelantanese Malay who are synonyms with the famous Kelantanese cuisine of nasi kerabu and nasi ulam.

Methods: 168 participants, 67 male and 101 female had agreed to participate in this survey. They were residents from the districts of Batu Mengkebang, Salor and Tawang, aged 18 years old and above. The result showed 32.8% of male and 32.7% of female participants took 'ulam' daily. Meanwhile, participants who aged 40–59 years old contributed the major percentage in practicing daily intake of 'ulam'. The study shows the relationship between income and 'ulam' intake in each district. The result also revealed that 83 .6% of male and 74.3% of female participants combined various type of 'ulams' at one sitting. Most of them took 2 type of 'ulams' during

meal time. Majority of participants agreed that 'ulams' can increase appetite and are safe to consume. Topography of the area of study and availability of 'ulam' in the vicinity possibly influenced the type of 'ulam' consumed in each district. In conclusion, there was similarity between the genders in practice of 'ulam' intake. It is hoped that this study will provide relevant information pertaining to the consumption and properties of various 'ulam' that are being consumed in society, especially those 'ulam' that are edible wild plants available in Kelantan. Methanolic extract of 10 'ulam' were investigated for their antioxidants properties. Antioxidant activity of the methanolic extracts of *Luffa acutangula* (Petola segi), *Oroxylum indicum* (Buah beko), *Jenerih* (no scientific name available as yet), *Leucaena leucocephala* (Petai belalang), *Emilia Sonchifolia* (Bayam peraksi), *Acrostichum aureum* (Piai), *Garcinia xanthochymus* (Asam kandis), *Syzygium inophylla* (Gelam tikus), *Curcuma longa* (Bunga kunyit) and *Moringa Oleifera* (Merungai) were screened by using DPPH radical Scavenging (0.5 mg mL-1) and Ferric thiocyanate assay (1 mg mL-1).

Result: Out of the 10 'ulam'; *Syzygium inophylla, Curcuma longa, Emilia Sonchifolia, Moringa Oleifera* and *Oroxylum indicum* showed significantly higher in antioxidant activity (> 90%) detected by both assay.

Conclusion: In conclusion, the outcome of the study may help in contribution towards the development of dietary control or production of neutraceutical for chronic diseases. This study assisted in increasing the available information regarding 'ulam' that used among Malaysian and it can also help in identification of potent sources of natural antioxidant.

Supervisor:
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Co-supervisor:
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DETERMINATION OF MACRONUTRIENTS IN SELECTED FOODS FOUND IN KELANTAN

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Objectives: The present study was conducted to determine the nutrient composition of selected prepared foods popularly consumed among the people of Kelantan state of Malaysia. The outcome of this study is vital in establishing reliable data on the nutrient composition of foods consumed by the community

Methods: 100 types of foods that are prepared and served in Kelantan had been chosen in this study. Food samples for analyse were purchased from 3 places. Macronutrients such as calorie, carbohydrate, moisture, protein, fat, and ash were analyzed using the standard methods of AOAC (1995). Range of carbohydrate foods analyzed was between 4.71–96.49 g per 100g, protein, between 0.11–31.99 g per 100 g and fat between 0.23–26.81 g per 100 g.

Result: The results show that the foods analysed generally high in carbohydrate content. Foods that were high in carbohydrate, which is more than 70 g per 100 g is 'dodol', 'pengat pisang' dan 'gelembung buaya'. Even though these foods are high in carbohydrate, the Kelantanese communities still able to consume them by controlling the amount of food intake.

Conclusion: These results will be used in the estimation of nutrient intake related to the study of diet and health relationship for Kelantan.

Supervisor:
Dr Sakinah Harith
Co-supervisors:
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En Nor Azmi Zainal

THE ROLE OF DREAM IN THE REGULATION OF FORMALIN INDUCED PAIN IN RAPID EYE MOVEMENT (REM) SLEEP DEPRIVED RATS

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Introduction: Rapid eye movement (REM) sleep deprivation has been shown to decrease pain threshold after various pain stimulis. Down regulatory antagonist modulator (DREAM) is a transcriptional repressor of prodynorphin gene.
Objectives: This study evaluates the effect on DREAM in relation to REM sleep deprivation, formalin induced pain, or combination of both; and its relationship to the formalin induced pain behavioural responses.

Methods: Male Sprague Dawley rats (250-300 g) were divided into 4 major treatments; free moving control (n = 36), REM sleep deprivation (n = 36), tank control (n = 36), and sleep recovery (n = 36). REM sleep deprivation was elicited for 72 hours using the inverted flower pot technique. Each group was further divided into 2 groups which consisted of rats that were either injected with 2.5% formalin or not. Food consumption and body weight gain were measured before and after the treatment. The formalin induced pain behavioural responses were recorded for 1 hour for rats that subjected to formalin injection. The ventrobasal thalamic complex of brain (VB) were removed from each group for immunohistochemistry (n = 6), Western blot (n = 6) and real-time PCR analysis (n = 6) separately. The ' inverted flower' pot technique was confirmed to induce REM sleep deprivation in the REM sleep deprived, and sleep recovered rats by the classic pattern of hyperphagia with converse loss of body weight. There is a marked hypoalgesia demonstrated in the second phase of formalin induced pain in the REM sleep deprived

rats REM sleep deprivation per se did induce morphological change and reduced the number of DREAM positive neurons (DPN) bilaterally. There was an increase in nuclear DREAM extraction bilaterally. After 72 hours sleep recovery, the morphological changes still persisted with reduction of the DREAM mRNA bilaterally. Formalin induced pain reduced the number of DPN bilaterally and increased the nuclear DREAM extraction contralateral to formalin injected site. Interestingly, REM sleep deprivation with formalin test increased the number of DPN, cytoplasmic, and nuclear DREAM extraction bilaterally which was more on the contralateral side except for nuclear extraction.

Result: There was a significant decrease of DREAM mRNA ipsilaterally. However the changes seem to be reversible as no change is seen in DPN, DREAM extractions, and mRNA in sleep recovery group with formalin induced pain.

Conclusion: In conclusion, REM sleep deprivation and formalin induced pain per se generated their own distinct effects on DREAM. Nevertheless, the combination of both treatments resulted in dynamic intracellular changes which reflected the survival ability of neuronal cells, at least by preserving its basic functions. As DREAM is a transcriptional regulator of prodynorphin, the functional survivability of the neuronal cells was reflected behaviourally by the significant hypoalgesia after both REM sleep deprivation and formalin induced pain.

Supervisor:
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Co-supervisors:
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FRACTURE PHENOMENA IN SODA LIME SILICA GLASS CAUSED BY BULLET IMPACTS

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Objectives: A series of studies was performed under controlled experimental conditions to investigate the fracture patterns produced in static loading (ball dropping experiments) and also the impacts of bullets of different calibres and nose shapes, fired from different weapons, onto soda lime silica glass of different dimensions and thicknesses.

Methods: The results obtained in static loading experiments confirmed the earlier findings reported in the literature. In the bullet induced glass fracture experiments, all the bullets were fully metal jacketed except 0.38 Special ones that had exposed lead. Nose types varied from round nose and flat nose to hollow point. The velocity of the bullets varied from 220–1020 m/s. 2 chronographs, 1 placed in front of the glass target and the other immediately behind it, measured the striking and remaining velocities of the bullets. The bullets after penetration of the glass were recovered using a bullet catch. The resulting crack patterns on glass were studied for their characteristics and surface markings. Some of them were also analysed quantitatively using the concept of fractal dimension that measured the complexity of irregular patterns. Observations revealed substantial differences in the behavior of the bullets to produce fracture patterns in the glass. These patterns were much different from those produced during static loading tests. Each bullet of a specific calibre and type produced a unique pattern by which it can be identified. Further, the same calibre bullets (9 mm round nose and flat nose and 5.56 mm rifle calibre) discharged from 2 different weapons (pistol and sub machine gun for 9 mm calibre/ and rifle and Carbine for 5.56 mm calibre) produced distinguishable patterns according to each weapon. The bullets deformed by mushrooming and shearing of its tip confirming the ductile nature of the projectiles at high velocities. The percentage of bullet deformation showed linear relationship to the complexity of the resulting fracture pattern: the greater the percentage the more complicated the patterns that were formed. The velocity loss for a specific calibre for a given thickness of glass was almost same irrespective of the striking velocity.

Result: Significantly, the fractal dimensions of the patterns varied linearly with the kinetic energy lost to glass during the penetration of the bullet. It was found that the dimension of the glass target had an influence in the fracture patterns caused. The larger dimensional glass had less cracking patterns and the characteristics were confined mostly to the regions close to the hole and the crater. The smaller dimensional glass had the patterns spread throughout the glass. This can be understood qualitatively. The waves that were setup in the glass by the impact of the bullet, responsible for the fracture pattern, were influenced by the boundary conditions obtained at the glass frame. These boundary conditions obviously affected the propagation of the waves created more when the boundary is near to the point of bullet impact than when it is far away.

Conclusion: A quantitative study of the influence of glass dimensions on the fracture patterns should be worthwhile. The data and analysis presented in the thesis demonstrated that they can be used in real crime scene reconstructions involving shooting incidents including those in which bullets have passed through intermediate glass targets. Soda lime silica glass finds extensive use in the windows of buildings and it is also an important glass component in laminated and bullet proof glass. The current study might also help the material scientists to understand better the behaviour of this type of glass subjected to high velocity bullet impacts so that better bullet proof glass constructions could be conceived.

Supervisor:
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Co-supervisors:
Assoc Prof Dr Sharifah Mastura Syed Mohamad
Dr Mohamad Hadzri Yaacob

TOTAL SULFATED GLYCOSAMINOGLYCAN (GAG) OF MALAYSIAN SEA CUCUMBERS STICHOPUS HERMANNI AND STICHOPUS VASTUS AND ITS EFFECTS ON WOUND HEALING IN RATS

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Introduction: Sea cucumbers have long been exploited as a source of medicinal compounds due to the presence of sulfated glycosaminoglycans (GAGs).

Objectives: The aim of this study was to investigate the occurrence of total sulfated GAG from the integument body wall, the visceral internal organs, and the coelomic fluid of Malaysian sea cucumbers; *Stichopus hermanni* and *Stichopus vastus* and evaluate the effect of total sulfated GAG on wound healing in rats using macroscopic and microscopic evaluations.

Methods: In both species, the integument body wall was the highest source of total, O- and N-sulfated GAGs followed by the visceral internal organs and the coelomic fluid. There was more O-sulfated GAGs compared to N-sulfated GAGs for percentage (%) division in both species. In the full-thickness excisional wound model using 47 female Sprague-dawley rats, 20 µl of 1 µg/ml concentration of total sulfated GAG from each anatomical part of each sea cucumber species were applied to the wound area (6 mm diameter) from Day 0 to Day 12, while phosphate buffered saline (PBS) was applied to control group. The progress of healing was assessed through macroscopic examination and analysis of epithelization, inflammatory cells, fibroblasts proliferation, new vessels formation and collagen fibers organisation using light microscope (LM), transmission electron microscope (TEM), and scanning electron microscope (SEM).

Result: Macroscopic examination revealed significantly (P < 0.0167) wound contraction percentage (%) on each observation occurred in sulfated GAGs treated group from *S.vastus coelomic fluid* (day 1 [8 .33, IqR 9.38], day 6 [33.33, IqR 6.25], and day 12 [75.00, IqR 2.08]) as compared to control group (day 1 [0.00, IqR 0.00], day 6 [8.33, IqR 9.38], and day 12 [54.17, IqR 18.75]). The epithelisation progress of *S. vastus* integument body wall and coelomic fluid sulfated GAGs treated groups was significantly (P < 0.0167) greater compared to control group. LM and SEM evaluations showed that all treatment groups have fully bridged the excised wound on the 12th day of observations. LM and TEM evaluations showed enhanced fibroblasts proliferation with significant (P < 0.0167) finding occurred in sulfated GAGs treated group from *S. vastus* coelomic fluid compared to control group. For new vessels formation, LM and TEM showed a significant (P < 0.05) increase in the sulfated GAGs treated group from *S. vastus* anatomical parts compared to control group. LM, TEM, and SEM evaluations showed that sulfated GAGs from *S. vastus* anatomical parts stimulate dense organisation of collagen fibers on the 12th day of observation, significantly (P < 0.05) compared to control group.

Conclusion: This study strongly indicate that sulfated GAGs in particularly from S.vastus coelomic fluid, seems to hasten the wound healing event through positive effect on acceleration of wound contraction percentage (%), enhance epithelization migration, fibroblast proliferation, angiogenesis process, and collagen organization.

Supervisor:
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Co-supervisors:
Assoc Prof Dr K. N. S. Sirajudeen

ASSOCIATION OF MITOCHONDRIAL DNA 10398 POLYMORPHISM WITH BREAST CANCER AND APOPTOSIS IN MALAY POPULATION

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Introduction: The mitochondrial DNA 10398 polymorphism has been observed to associate with breast cancer in several populations.

Objectives: In this study, mitochondrial DNA 10398 polymorphism was screened in 101 Malay female patients with invasive breast cancer and 90 age-matched healthy female controls using minisequencing method.

Methods: The results showed a statistically significant difference with P-value of P = 0.007 (OR, 2.29; 95% CI, 1.252–4.200) with the proportion of G variant was higher (73%) than A variant in patients (27%) as well as in controls (G = 54%, A = 46%). The breast cancer tissues were then analyzed using immunohistochemistry method to investigate the relation of this polymorphism in affecting apoptotic level in breast cancer.

Result: No significant difference was observed between the expression of pro (Bax) and anti-apoptotic (Bcl-2) proteins among patients carrying A variant (P = 0.48). However, significant difference was observed in patients with G variant (P = 0.016).

Conclusion: These results indicate that mtDNA 10398 polymorphism may be useful as a breast cancer risk marker in this population.

Supervisor:
Assoc Prof Dr Zafarina Zainuddin
Co-supervisors:
Dr Rapeah Suppian

DEVELOPMENT OF FLUORESCING METIDCILLIN RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) AS A TOOL FOR SCREENING OF ANTmACTERIAL PROPERTIES OF MIMUSOPS ELENGI LINN

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Introduction: Staphylococcus aureus is a gram-positive bacterium that can cause abscesses, various pyogenic infections (e.g., endocarditis and osteomyelitis), food poisoning, and toxic-shock syndrome. It is also one of the most common causes of nosocomial infection (pneumoniae, septicaemia, and surgical-wound infections). The Methicillin Resistant Staphylococcus aureus (MRSA) is a strain that is resistant to β-lactam antibiotic by virtue of changes in the penicillin-binding protein within their cell membrane. Consequently, all antibiotics that has β-lactam ring like penicillin group and cephalosporin group are unable to inhibit the growth of this organism.

Green fluorescent protein (GFP) is a protein of unknown function found in the jellyfish, Aequorea victoria. This GFP-fusion protein shows a punctuate pattern when localises in the cytoplasm.

Objectives: The present study focused on the development of a fluorescing MRSA by the construction of MRSA vector carrying GFP gene with the intention of determining whether the fluorescing MRSA strain can be used as a tool for the rapid screening of antibacterial properties of natural product.

Methods: The natural products that had been used were aqueous and several organic solvents extracts from the bark of plant *Mimusops elengi Linn*, known locally as 'Bunga Tanjung' plant. This plant has been reported to contain a potent antibacterial component. In this study, phytochemical investigation of aqueous, ethanolic and ethyl acetate extracts of *M elengi Linn*. Studies revealed the presence of alkaloids, flavonoids, and tannin compounds. Whereas, the diethyl ether and petroleum ether extracts revealed the presence of alkaloids only but absence of flavonoids and tannin compounds. These secondary metabolites are known to be synthesized in response to microbial infection.

Result: The present study is, therefore, designed to assess the antibacterial potency of different solvent extracts (aqueous, diethyl ether, ethyl acetate, ethanolic, and petroleum ether) of the bark of *M elengi Linn*. on MRSA. The antibacterial activity of each extract was tested for their minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) which can inhibit the growth of at least 99.9 % of the bacterial colonies.

Conclusion: The aqueous, diethyl ether, and ethyl acetate extracts had recorded the same results of MI.C (16 µg/ml) and MBC (32 µg/ml) against MRSA. Whereas, the ethanolic and petroleum ether extracts had recorded higher results of MIC and MBC (i.e., 32 µg/ml and 64 µg/ml) against MRSA. These results showed that all aqueous and organic solvents extracts had antibacterial activities against MRSA.

Supervisor:
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Co-supervisors:
Dr Few Ling Ling

Abstracts of Theses Approved for the MSc at the School of Dental Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia

EFFECT OF CARBONATED BEVERAGE AND FLUORIDE MOUTH RINSES ON ENAMEL SURFACE AND SHEAR BOND STRENGTH OF CONVENTIONAL RESIN BASED ORTHODONTIC ADHESIVE COMPOSITE

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Introduction: Carbonated beverages contains high amount of sugar and acids that can affect oral health negatively. There were some indications about the erosive effect of mouth rinses on enamel surface.

Objectives: This study was conducted to determine the long term consumption of carbonated beverage and the use of fluoride mouth rinses on enamel surface and shear bond strength of conventional resin based orthodontic adhesive composite.

Methods: An in-vitro study was done on 180 extracted human teeth. The brackets were bonded on the teeth with Transbond XT orthodontic adhesive. The teeth were divided randomly and equally into 6 groups. 25 days exposure cycles were done for all groups as following: group 1 control (distilled water), group 2 (Coca Cola), group 3 (Colgate mouth rinse), group 4 (Oral-B mouth rinse), group 5 (Coca Cola plus Colgate mouth rinse), and group 6 (Coca Cola plus Oral-B mouth rinse). Image analyzer was used and the percentage of enamel decalcification surface area was calculated. Universal test machine was used to determine the shear bond strength. Image analyzer was also used for calculating adhesive remnant index on enamel surface after debonding. Data were entered in PASW version 18 (SPSS Inc., Chicago, IL). Kruskal-Wallis and Mann-Whitney tests were used to compare the percentage of the enamel decalcification surface area between groups.

Result: It was found that all groups have enamel decalcification greater than control group with different degrees. One-way ANOVA test and Scheffe multiple comparisons test were used to compare significant differences of shear bond strength between study groups. There was significant difference between control group 1/group 2 (P = 0.001) and 5 (P = 0.047). There was no significant difference between group 1/group 3 (P = 0.983), 4 (P = 0.480), and 6 (P = 0.670). Moreover, Kruskal-Wallis and Mann Whitney tests were used to compare significant differences of adhesive remnant index among study groups. There was no significant difference among study groups.

Conclusion: This study concluded that the long period consumption of carbonated beverage caused enamel decalcification, reducing shear bond strength of the orthodontic adhesive, and cause debonding failure site at enamel-adhesive interface. The long use of acidic fluoride mouth rinses can cause enamel decalcification and debonding failure site at enamel-adhesive interface However, it will not affect the shear bond strength. The use of fluoride mouth rinses after carbonated beverage consumption has limited effect on shear bond strength except for Oral-B mouth rinse, enamel decalcification, and failure site.

Supervisor:
Assoc Prof Dr Normastura Abd Rahman

IN VITRO EVALUATION OF THE FERRULE EFFECT AND POST MATERIAL ON FAILURE LOAD AND MODE IN ENDODONTICALLY TREATED TEETH

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Introduction: There are still controversy regarding the ferrule effect and a better bonded pre-fabricated posts on strength of endodontically treated teeth.

Objectives: The aim of this study was to compare the effect of ferrule and 2 types of bonded post materials on failure load and failure mode of restored endodontically treated teeth.

Methods: 68 extracted maxillary central incisors were sectioned 15 ± 0.1 mm coronal to the root apex using hard tissue cutter (Exakt, DE) and high speed handpiece. Then, they were endodontically instrumented using step-back technique with master apical file size 45 and obturated with gutta-percha (Meta Dental Co. Ltd, KR) and sealed with AH 26 (Dentsply Maillefer, DE) using lateral condensation technique. Post spaces were then prepared using Gates-Glidden rotary instrument to remove gutta-percha leaving 5 mm from the apex, followed by Tenax drills (Coltene Whaledent, US) up to size 1.3 mm in diameter to enlarge the canals. Samples were randomly divided into 4 groups of 17 where group A was placed with titanium post (Tenax post, Coltene Whaledent, US) without ferrule preparation, group B placed with titanium post and 2 mm ferrule preparation, group C placed with glass fiber reinforced composite post (Tenax fiber white post, Coltene Whaledent, US) without ferrule preparation, and group D placed with glass fiber reinforced composite post and 2mm ferrule preparation. All posts were cemented using

Panavia F (Kuraray Medical Inc., JP) before the core was built with Paracore (Coltene Whaledent, US) and standardise the size using paraform coreformer #1. Then, crowns fabricated using Ni-Cr where the length of each sample with the crown in place was 23 ± 0.1 mm, checked using a digital calliper. Crowns were cemented using Ketac-Cem (3M ESPE, DE). 4 metal blocks were used to hold the specimens during mechanical testing. Each block had a drilled cylindrical hole with a different diameter (5.5 mm, 6.5 mm, 7.5 mm, and 8.5 mm) to accommodate to different specimens' widths with rubber silicon impression material injected to simulate the periodontal ligament.

Result: A universal testing machine (Instron 3366, US) was used for the mechanical testing by applying a compressive load at a crosshead speed of 1 mm/min at an angle of 135° to the long axis of the sample until failure. The medians of failure load for groups A, B, C, and D were 253.10 N (76.6), 265.40 N (279.7), 203.10 N (68.7), and 251.75 N (69.2), respectively. Kruskal-Wallis test indicated that the medians of failure load were not statistically significant across the 4 groups ($P > 0.05$). Failure mode was classified as either favorable failure (failure of the restoration only) or unfavorable failure (failure of the restoration and the supporting tooth structure). Group C had the highest frequency of favorable failures (87.5% favorable and 12.5% unfavorable failures). Group A had (37.5% favorable and 62.5% unfavorable failures). Group B and D had (0% favorable and 100% unfavorable failures. Chi-square test for independence indicated a significant difference in failure mode between the groups ($P < 0.05$).

Conclusion: The ferrule effect and post material did not significantly affect the failure load of endodontically treated teeth, but those restored with glass fiber reinforced composite posts had a more favorable failure mode than those restored with titanium posts when the ferrule effect was not present.

Supervisors:
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FABRICATION AND CHARACTERIZATION OF EXPERIMENTAL NANOCOMPOSITES FOR DENTAL RESTORATION

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Introduction: Currently, restorative dental composites have become preferred among patients due to their esthetic characteristic and also their durability. The high costs of composites, as well as the rising demand by patients have lead researchers to produce a local product with equivalent standard as compared to the commercially available dental composites. Recently, monodispersed, spherical silica nanofillers with a size range of 10–20 nm were successfully synthesised via a sol-gel process and have a great potential to be used in fabrication of dental composites.

Objectives: This present study was carried out to fabricate and characterize the experimental dental nanocomposite from the synthesised nanosilica fillers.

Methods: Dental composites, namely experimental nanocomposite 1 (ENC1) and experimental nanocomposite 2 (ENC2) with 2 different filler content, 30 and 35 wt% respectively were fabricated, molded, and polymerized with a light curing unit for 40 seconds. The properties that were tested including their flexural strength, modulus, compressive strength, micro hardness, degree of conversion, volumetric shrinkage, water sorption, solubility, surface roughness as well as filler distribution. The data obtained were statistically analysed with one-way ANOVA with the level of significance $P = 0.05$. Various type of commercial composites such as FiltekTM Z350 (nanocomposite), Spectrum® TPH®3 (microhybrid), Z100TM (hybrid), and Durafill® VS (microfilled) were chosen to compare their properties with the experimental nanocomposites. The properties of composites were also referred to the ISO and ANSI/ADA No. 27 requirements.

Result: From the results obtained, it can be summarised that the experimental nanocomposites and commercial composites comply with the ISO and ANSI/ADA No. 27 requirements. Similar properties can be found between experimental nanocomposites and Durafill® VS (microfilled composite) regarding their flexural strength, modulus, compressive strength, hardness, and also surface roughness. These properties are sufficient to be applied for the anterior restoration. However, the properties of the experimental nanocomposites were still inferior compared with the posterior restorative composites (FiltekTM Z350, Spectrum® TPH®3, and Z100TM) particularly in flexural strength, modulus, hardness, shrinkage, and water sorption. Comparing both of the experimental nanocomposites, ENC2 seems to have better properties compared with ENC1 except for the compressive strength.

Conclusion: Overall, the main factor that contributes to the properties of dental composites is inorganic fillers including their filler content, size, morphology, and distribution. Highly filled composites exhibited excellent properties than the composites with low filler content. The synthesised nanosilica might be an option to be used for making a dental composite. However, concerns also arise regarding dental composites problem of achieving the high filler loading, which limit their application only for making anterior composite.

Supervisor:
Dr Dasmawati Mohamad
Co-supervisor:
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