THE MALAYSIAN JOURNAL OF MedicalSciences

Volume 18, No. 2, 2011
ISSN 13-94-195X | e-ISSN 2180-4303

PENERBIT USM
Penerbit Universiti Sains Malaysia

Abstracts are indexed in:

refine your research SCOPUS™ ELSEVIER INDEX COPERNICUS INTERNATIONAL
EBSCO HOST Bioline International BRITISH LIBRARY

and 21 other international and Malaysian database

Editorial

Published by
PENERBIT UNIVERSITI SAINS MALAYSIA
Bangunan D34, Universiti Sains Malaysia
11800 USM, Pulau Pinang, Malaysia

Printed by
SINARAN BROS SDN BHD
389, Lebuh Chulia
10200, Pulau Pinang, Malaysia

Contents

Editorial

Original Article

Brief Communication

Case Report

Editorial

For an International Decade of the Mind

James L Olds

Submitted: 12 Oct 2010
Accepted: 13 Oct 2010

Krasnow Institute for Advanced Study, 4400 University Drive, Mail Stop 2A1, George Mason University, Fairfax, Virginia 22030, United States of America

Abstract

The International Decade of the Mind Project seeks to harness science across multiple disciplines to discover how human "mind" emerges from the biological activity of human brains. Given the complexity of the human brain, with approximately 10^{11} neurons each with 10^4 connections, the effort will be daunting and require resources and expertise from many nations. The Decade of the Mind Project began as a United States initiative in 2007 and expanded to Europe in 2009 and then Asia in 2010. Here we advocate for a team-based approach to the Decade of the Mind initiative, where each nation contributes to the overall scientific effort with its own indigenous scientific expertise.

Keywords: *brain research, cognition, conferences, mental processes, Asia*

The recent conclusion of the Sixth Decade of the Mind (DOM) Symposium in Singapore presents a welcome opportunity to laud the accomplishments to date and to chart the course ahead for the DOM Project, now in its third year of planning. The DOM initiative arose out of a conference convened by the Krasnow Institute for Advanced Study at George Mason University in May 2007. The meeting brought together science leaders across an array of disciplines, spanning robotics to neuroscience, with the stated goal of gaining US government support for research aimed at explaining how mind and behavior arise from the activity of human and animal brains. A further goal of the original 2007 meeting was to prepare a manifesto in support of the Project, which might be published in a high-impact journal.

The initial May conference was successful and the resultant manifesto was published in Science (1). The Manifesto was essentially a road map for the project that had the aim of catching the imagination of US decision-makers, scientists, and the lay public. The key message was that the science in a constellation of disciplines had matured to the point where, given sustained new US research and development support, decoding how mind emerges from brain would be practicable.

In October 2007, a second, much smaller conference was held at George Mason University. At this second conference, high-level US civil servant decision-makers were asked to respond to the Manifesto. Multiple US agencies were represented, including the National Institutes of Health, the National Science Foundation, and the Department of Defense. What emerged at the second conference was the notion of different agencies pulling off different pieces of the overall DOM project in accordance with their specific missions.

The third DOM meeting was designed to build support for the project at the grassroots level, in the American heartland, during the general election campaign of 2008. Hence, DOM III (as the meetings began to be named) was held in Des Moines, Iowa, on the campus of the Great Apes Trust, and it focused on animal mind, especially the minds of the primates, such as the orangutans and bonobos. The meeting was a great success and attracted the attention of both local and national media.

Just after the election of President Obama, DOM IV was held in Tamaya, New Mexico. This meeting was organized by Sandia National Laboratories and the US Department of Energy. In contrast to the previous DOM conferences, DOM IV focused on reverse-engineering the human brain to facilitate the development of advanced artifacts and applications, such as robots. It was at the DOM IV conference that the first beginnings

of internationalization began. Representatives of the government of Singapore attended DOM IV, and a paper was published in Europe urging that the DOM Project take place across the entire globe (2).

As a result of the international interest, DOM V was held in Berlin, Germany, in September 2009. The intellectual centerpiece of this conference was on how a DOM project might impact education. Conferees reported on studies at the intersection of neuroscience and education, with the notion that one of the key benefits of the Project might be in the area of improved educational outcomes, particularly in the areas of science, technology, engineering, and mathematics. The DOM V conference was organized by Professor Manfred Spitzer from the University of Ulm, Germany.

The most recent conference in Singapore was organized by the Singapore Ministry of Defense in collaboration with several other organizations. As with the New Mexico meeting (DOM IV), the focus was on taking what we can learn from human minds and applying that knowledge, both in machines and in augmented cognition for human beings. DOM VI was an extremely successful conference, both from the standpoint of the overall Project and from the science presented.

All of the above begs the question: where do we go from here? The answer is complex. The global economic crisis has put in jeopardy the original goal of significant new US research and development investment. As the economic storm in the US abated, the European Union is now facing serious challenges to sovereign wealth and the Euro. Only Asia has continued to show a sustained economic growth, which might support the scale of resources necessary to crack the problem of mind (3). At the same time, the nations of North America and Europe continue to have critical mass in terms of academic centers, patents, and publications, which are also necessary to make progress.

In the original idea for a DOM, one key notion was for different and diverse US agencies to pull out mission-appropriate pieces of the overall project as part of a "team" approach. Perhaps the proper evolution of this original idea is for different nations to apply their own expertise and indigenous resources towards the Problem—for an overall international "team" approach.

Correspondence

Professor Dr James L Olds
PhD Neuroscience (University of Michigan)
Krasnow Institute for Advanced Study
4400 University Drive, Mail Stop 2A1
George Mason University
Fairfax, Virginia 22030
United States of America
Tel: +1 703 993 4333
Fax: +1 703 993 4325
Email: jolds@gmu.edu

References

1. Albus JS, Bekey GA, Holland JH, Kanwisher NG, Krichmar JL, Mishkin M, et al. A proposal for a Decade of the Mind initiative. Science. 2007;**317(5843)**:1321.

2. Spitzer M. Decade of the Mind. Philos Ethics Humanit Med. 2008;**3**:7.

3. Abdullah JM. *The Decade of the Mind 2010 to 2020: How Malaysian neuroscientists can create knowledge, skills and innovative research to drive the 10th and 11th Malaysia Plan within the New Economic Model*. Kuala Lumpur: Akademi Sains Malaysia; 2010.

Original Article

Brain Activation during Addition and Subtraction Tasks In-Noise and In-Quiet

Aini Ismafairus Abd Hamid[1], Ahmad Nazlim Yusoff[1], Siti Zamratol-Mai Sarah Mukari[2], Mazlyfarina Mohamad[1]

Submitted: 9 Jun 2010
Accepted: 16 Feb 2011

[1] *Functional Image Processing Laboratory, Diagnostic Imaging and Radiotherapy Programme, Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia*

[2] *Department of Audiology and Speech Sciences, Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda Abdul Aziz, 50300 Kuala Lumpur, Malaysia*

Abstract

***Background*: In spite of extensive research conducted to study how human brain works, little is known about a special function of the brain that stores and manipulates information—the working memory—and how noise influences this special ability. In this study, Functional magnetic resonance imaging (fMRI) was used to investigate brain responses to arithmetic problems solved in noisy and quiet backgrounds.**

***Methods:* Eighteen healthy young males performed simple arithmetic operations of addition and subtraction with in-quiet and in-noise backgrounds. The MATLAB-based Statistical Parametric Mapping (SPM8) was implemented on the fMRI datasets to generate and analyse the activated brain regions.**

***Results*: Group results showed that addition and subtraction operations evoked extended activation in the left inferior parietal lobe, left precentral gyrus, left superior parietal lobe, left supramarginal gyrus, and left middle temporal gyrus. This supported the hypothesis that the human brain relatively activates its left hemisphere more compared with the right hemisphere when solving arithmetic problems. The insula, middle cingulate cortex, and middle frontal gyrus, however, showed more extended right hemispheric activation, potentially due to the involvement of attention, executive processes, and working memory. For addition operations, there was extensive left hemispheric activation in the superior temporal gyrus, inferior frontal gyrus, and thalamus. In contrast, subtraction tasks evoked a greater activation of similar brain structures in the right hemisphere. For both addition and subtraction operations, the total number of activated voxels was higher for in-noise than in-quiet conditions.**

***Conclusion*: These findings suggest that when arithmetic operations were delivered auditorily, the auditory, attention, and working memory functions were required to accomplish the executive processing of the mathematical calculation. The respective brain activation patterns appear to be modulated by the noisy background condition.**

Keywords: *brain mapping, fMRI, functional laterality, mathematics, memory and cognition, noise*

Introduction

Arithmetic is a branch of mathematics involving problem solving and processing of numbers, such as in addition and subtraction (1). Problem solving in mathematics incorporates various cognitive processes and strategies. Three mental operations (i.e., information storage, data organisation, and executive control) are necessary in solving arithmetic problems (2).

Different brain regions are responsible for the different functions executed during arithmetic problem solving. Evidence from brain-imaging studies indicates that parietal lobe areas are central in calculating and processing of numbers (1,3), while frontal lobe areas are involved in recalling numerical knowledge and working memory (3,4).

Working memory is a comprehensive function of the brain normally used in processing and storing information temporarily and is very important for many cognitive actions (5). Several functional imaging studies (6,7) found that the frontal lobe areas are activated in tasks involving executive function and working memory. It has been suggested that frontal lobe areas such as

inferior frontal gyrus (IFG), superior frontal gyrus (SFG), and medial frontal gyrus support working memory demand during arithmetic operations (6–10). A previous study on the laterality of brain areas associated with arithmetic calculation (11) revealed greater activation in the right hemisphere IFG than in the left hemisphere. However, different modes of task presentation produce different hemispheric dominance in the frontal region. For example, visually presented tasks tend to produce bilateral frontal region activation (12), whereas tasks presented auditorily trigger a relatively larger activation in the right frontal regions (13). It has also been suggested that the laterality index (LI), which measures the hemispheric dominance of IFG, increases with task difficulty (11). Thus, a complex task is expected to produce a greater number of activated voxels in the left compared with the right hemisphere. Gruber et al. (14) and Fehr et al. (12,13) demonstrated that bilateral frontal regions were differently involved during simple and complex arithmetic tasks in different operations (i.e., addition, subtraction, multiplication, and division), from which complex arithmetic tasks required working memory involvement, whereas simple tasks only required arithmetic facts retrieval (12). In addition to frontal lobe areas, parietal lobe areas are also important in mental calculation, specifically for representing and manipulating quantitative information (4). Number processing and calculation have been shown to activate the inferior parietal lobe regions, including intraparietal sulcus (IPS), angular gyrus (AG), and supramarginal gyrus (SMG) (4). These areas are involved in addition, subtraction, and multiplication tasks (4). The LI of the inferior parietal lobule decreases with increasing task difficulty (11). It is also important to note that the inferior parietal cortex is the region specifically activated in response to increasing arithmetic complexity (10,11). In relation to that, SMG has also been identified as the region that deals with calculation difficulty (4,10), such as listening to spoken words in a noisy background.

However, knowledge of how the human brain processes arithmetic operations in different environments is still lacking, as verbal communication often occurs in the presence of an interfering background, such as noise. The superior temporal gyrus (STG) plays a central role in the perception of speech (15–19) and non-speech stimuli (20). Listening to speech in noisy conditions resulted in the engagement of attention and cognitive networks (18). Other regions involved in attention are the cingulate gyrus, medial frontal gyrus, basal ganglia, and thalamus (19).

In the present study, brain activations involved in arithmetic processing (addition and subtraction) in the human brain for in-quiet and in-noise were explored using a functional magnetic resonance imaging (fMRI) technique and statistical parametric mapping (SPM). The objectives of the study were (1) to identify the areas of activation, and (2) to determine the LI of the areas activated when the participants performed arithmetic working memory tasks for in-quiet and in-noise backgrounds. To achieve a quiet condition, a silent fMRI imaging paradigm (21) with a long silent interval was applied during stimulus presentation; this avoided the effects of scanner sound on the functional images (22).

Subjects and Methods

This study was approved by the Universiti Kebangsaan Malaysia (UKM) Ethics Committee (IEC) (NN-049-2009), and informed consent was obtained from all study subjects prior to testing.

Participants

Eighteen native, Malay-speaking, male adults with an average age of 23.2 (SD 2.5) years (range of 20–28 years) participated in the present study. All participants were screened by means of the Sijil Pelajaran Malaysia (Malaysian Certificate of Education) to obtain a group of participants able to perform simple mathematical operations; only those who passed their mathematics papers were enrolled in this study. Participants' handedness was determined using the Edinburgh Handedness Inventory (23).

fMRI data acquisition

The fMRI scans were conducted in the Department of Radiology, UKM Medical Centre. Functional images were acquired using a 1.5-T magnetic resonance imaging (MRI) system (Siemens Avanto, Erlangen, Germany) equipped with blood oxygenation level-dependent imaging protocol, echo-planar imaging capabilities, and radiofrequency head coil used for signal transmission and reception. Gradient-echo echo-planar imaging pulse sequence with the following parameters was used: repetition time (TR) = 16000 ms, acquisition time (TA) = 5000 ms (interscan interval = 16000 ms – 5000 ms = 11000 ms), echo time (TE) = 50 ms, field of view (FOV) = 192 × 192 mm, flip angle = 90°, matrix size = 128 × 128, and slice thickness = 3 mm. In addition, high resolution anatomical images of the entire brain

were obtained using a T1-weighted multiplanar reconstruction (MPR) spin-echo pulse sequence with the following parameters: TR = 1620 ms, FOV = 250 × 250 mm, flip angle = 90°, matrix size = 128 × 128, and slice thickness = 1 mm.

Tasks

The experimental tasks consisted of simple arithmetic calculations involving addition and subtraction, presented auditorily for in-quiet and in-noise backgrounds. For in-noise conditions, the 83-dB stimuli were embedded in 80-dB white noise. Prior to the scanning, all participants were given detailed instructions on how to respond to the stimuli. The participants were instructed to listen to a series of simple arithmetic operations (e.g., 1 + 2 + 3 + 4) presented binaurally via headphones (transmission of sound through air) and were required to perform the calculations. The participants were also instructed not to move their head during the scan as head movements can cause signal intensity changes over time from any one voxel and present a serious confound in fMRI studies. To minimise head movement, immobilising devices were used together with the head coil. A training session was carried out prior to the scanning session, to ensure that participants understood the task.

A silent fMRI-imaging paradigm was used to eliminate the effects of the scanner sound on the MRI images. The stimuli were presented during the silent gaps between volume acquisitions so that they did not overlap with the sound arising from the scanner. This paradigm is commonly used in auditory studies using fMRI (21,24). Each participant was subjected to 2 scanning sessions, which were exclusively carried out for addition and subtraction operations. Each session consisted of 2 different conditions, which were scanning in-quiet and in-noise. Thus, the 4 test conditions were addition in-quiet, addition in-noise, subtraction in-quiet, and subtraction in-noise. A schematic representation of the paradigm used in this study is shown in Figure 1. In the first scan, single-digit addition problems were used as stimuli (e.g., 1 + 2 + 3 + 4). Each set of digits that consisted of numbers 1–9 were randomly presented auditorily, without visual presentation, to the participants. In the second scan, single-digit subtractions were used as stimuli (e.g., 9 – 4 – 3 – 1). In this task, the minuend was always larger than the subtrahend, so that the answer to the problem was always positive. The participants were required to provide an answer verbally to each addition and subtraction task in order to evoke responses in the respective brain areas, and to ensure that the participants remained alert and focused throughout the scanning session.

Each functional scan consisted of 120 series of trials (or measurements); 30 trials each for both in-quiet conditions (i.e., addition in-quiet and subtraction in-quiet), 30 trials each for both in-noise conditions (i.e., addition in-noise and subtraction in-noise), and 60 trials for baseline (stimulus not given). A long (11 s) inter-measurement interval was used to allow for the haemodynamic response to decline after each given stimulus. The acquisition time was 5 s, with each functional measurement producing 35 axial slices in the 5-s duration (1 image slice per 143 ms). The measurement started with the active state. The imaging time for each session was 32 minutes, which produced 120 × 35 = 4200 images in total.

Post-processing

All the functional (T2*-weighted) and structural (T1-weighted) images were processed in the Functional Image Processing Laboratory, Diagnostic Imaging & Radiotherapy Programme, Faculty of Allied Health Sciences, UKM, Kuala Lumpur. Image analyses were performed using a personal computer using the software MATLAB 7.6 R2008a (Mathworks Inc., Natick, MA, USA) and Statistical Parametric Mapping (SPM8) (Functional Imaging Laboratory, Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College of London). The raw data in DICOM (.dcm) format were transformed into Analyze (.hdr, .img) format using SPM8. Functional images for each measurement were realigned using the 6-parameter affine transformation in translational (x, y, and z) and rotational (pitch, roll, and yaw) directions to reduce artefacts from subject movement and to make within- and between-subject comparisons meaningful (25). After realignment, a mean image of the series was used to estimate some warping parameters that mapped it onto a template that conformed to a standard anatomical space, i.e., EPI template (26) provided by the Montreal Neurological Institute (MNI). The normalisation procedure used a 12-parameter affine transformation, where the parameters constituted a spatial transformation matrix. The images were then smoothed using a 6-mm full-width-at-half-maximum Gaussian kernel. The activated voxels were identified by the general linear model approach by estimating the parameters of the model and deriving the appropriate test statistic (*t* statistic) for every voxel. Statistical inferences were finally obtained on the basis of the general linear model and Gaussian random field theory (27).

Group analyses

The participants' activation maps were defined using the WFU Pick Atlas software (28). For group random effects (RFX) analysis, significant statistical inference was made at $\alpha = 0.001$, uncorrected for multiple comparisons. The laterality of the functional areas was evaluated using LI for each participant for all regions of interest (ROIs). Here, laterality is defined as the hemispheric dominance or preference between left and right hemispheres of functional activation (29). The chosen ROIs for the analysis of LI were based on the activations obtained from single subject analysis, group analysis, and from those reported in previous studies (29,30). The LI for any one ROI was calculated using the formula $LI = (V_L - V_R) / (V_L + V_R)$, in which V_L is the number of the activated voxels in the left hemisphere, and VR is the number of the activated voxels in the right hemisphere (11). The LI values ranged from –1 to 1, with the range –1 to 0 indicating right-hemisphere dominance and range 0 to 1, left-hemisphere dominance.

Analysis of the main effects and interaction

The two-way repeated measures ANOVA was used to investigate the interaction between tasks (addition and subtraction) and conditions (in-quiet and in-noise) and to make inferences concerning the effects of tasks and conditions. The level of significance was set at uncorrected $\alpha = 0.05$.

Results

Brain activation

The brain activation obtained from RFX for (a) addition in-quiet, (b) addition in-noise, (c) subtraction in-quiet, and (d) subtraction in-noise, overlaid onto a 3-dimensional MNI-template for brain structure is shown in Figure 1. The corresponding activated regions, together with their number of activated voxels (NOV) at $\alpha = 0.001$, coordinates of maximum intensity, and the respective *t* values were tabulated in Tables 1 and 2 . All the addition and subtraction operations in-quiet and in-noise evoked bilateral activation in Heschl's gyrus (HG), STG, IFG, SMG, precentral gyrus (PCG), superior parietal lobe (SPL), insula lobe, thalamus, and middle temporal gyrus (MTG). However, for MFG and middle cingulate cortex (MCC), there was brain activation only in the right hemisphere in all test conditions. For the inferior parietal lobe (IPL), there was bilateral activation during addition in-quiet and in-noise, whereas during subtraction in-quiet and in-noise, only the left IPL was activated. The total number of activated voxels summed for all ROIs ($\alpha = 0.001$) were 5516 during addition in-quiet and 5731 during addition in-noise, while for subtraction in-quiet and in-noise, there were 2025 and 3162 activated voxels, respectively (Tables 1 and 2). A greater activation was observed in-noise compared with in-quiet for both addition and subtraction operations. The addition operation activated a relatively larger area of the whole brain than subtraction for both in-quiet and in-noise conditions.

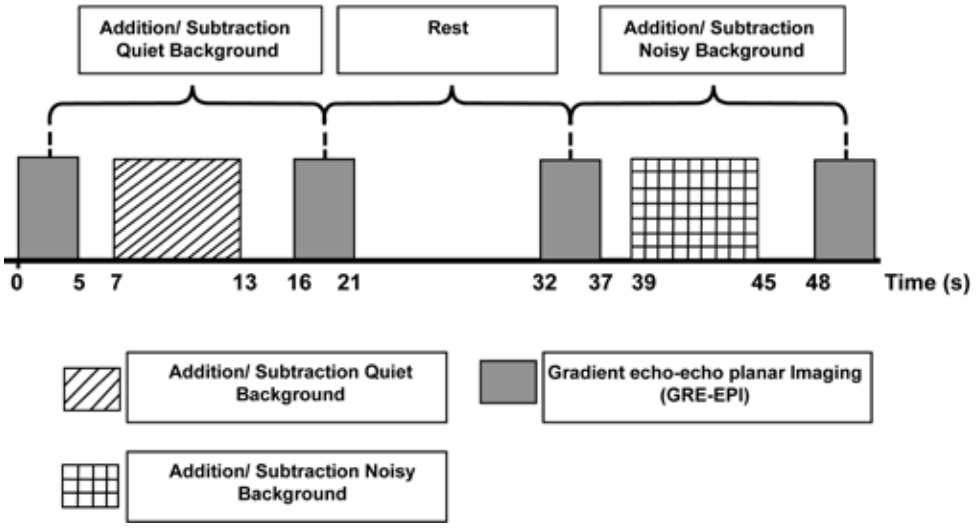

Figure 1: The study paradigm

Table 1: Number of activated voxels (NOV), coordinates of maximum intensity (x,y,z), and the t value obtained from brain activation of group random effects analysis shown in Figures 2 (a) and (b) for addition task

Condition		AIQ				AIN				
Region	**Hemisphere**	**NOV**	**x, y, z**			***t***	**NOV**	**x, y, z**		***t***
HG	L	154	-38,	-28,	10	6.66	149	-42,	-24,	10	7.46
	R	119	40,	-26,	8	5.83	146	48,	-20,	8	7.47
STG	L	1608	-46,	-20,	4	11.69	1562	-52,	-4,	0	10.84
	R	1236	46,	-14,	4	7.68	1326	58,	-24,	-4	8.32
IFG	L	15	-48,	16,	-6	5.83	23	-48,	16,	-6	6.09
	R	34	52,	18,	-8	7.55	40	52,	18,	-8	6.81
IPL	L	27	-42,	-48,	52	3.92	51	-42,	-46,	48	4.42
	R	76	52,	-40,	52	6.12	42	50,	-38,	50	5.49
SG	L	138	-64,	-38,	24	4.95	127	-52,	-42,	28	5.17
	R	27	68,	-40,	26	5.03	10	68,	-40,	24	3.19
Insula	L	213	-46,	8,	-6	6.66	299	-46,	6,	-4	7.11
	R	287	46,	2,	-8	5.74	294	50,	12,	-6	6.73
Thalamus	L	123	-2,	-24,	8	7.10	121	-2,	-24,	8	7.44
	R	170	8,	-24,	10	7.96	144	4,	-22,	8	8.22
MCC	L	-		-		-	-		-		-
	R	148	6,	-22,	32	7.12	71	4,	22,	32	
PG	L	269	-52,	-4,	24	8.29	308	-48,	-8,	46	7.56
	R	130	50,	-6,	40	7.74	160	50,	-6,	38	7.88
MTG	L	432	-60,	-30,	6	7.03	445	-56,	-20,	0	8.68
	R	298	60,	-24,	-4	8.59	399	60,	-24,	-4	8.11
MFG	L	-		-		-	-		-		-
	R	2	32,	6,	60	3.71	10	32,	6,	58	4.03
SPL	L	-		-		-	4	-28,	-66,	50	4.15
	R	10	54,	-38,	58	4.20	-		-		-

Abbreviations: AIQ = addition in-quiet, AIN = addition in-noise, HG = Heschl's gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, IPL = inferior parietal lobe, SG = supramarginal gyrus, MCC = middle cingulate cortex, PG = pre-central gyrus, MTG = middle temporal gyrus, MFG = middle frontal gyrus, SPL = superior parietal lobe

Laterality

The laterality of the brain regions in relation to addition and subtraction operations was evaluated by LI as previously described (Table 3). Addition and subtraction produced asymmetrical activation in the IPL, PCG, and SPL that favoured the left hemisphere, in both in-quiet and in-noise conditions (i.e., LI > 0). In contrast, the areas of activation for the insula and MCC were more extended in the right hemisphere for all addition and subtraction in-quiet and in-noise (i.e., LI < 0). The STG, IFG, and thalamus indicated a left lateralisation with a small increase in activation for addition (i.e., LI > 0), while subtraction produced reversed lateralization (i.e., LI < 0). For HG, addition and subtraction evoked the right hemisphere region more extensively, except for addition in-quiet, which showed left-hemispheric preference. For MFG, subtraction in-quiet produced a left-hemispheric preference, whereas other tasks increased right-hemisphere activation. For MTG, there was extensive activation in the left hemisphere for all tasks except for subtraction in-noise, which had a right-hemispheric preference. Generally, there was relatively larger activation in the left hemisphere for both arithmetic tasks either for in-quiet or in-noise conditions.

Table 2: Number of activated voxels (NOV), coordinates of maximum intensity (x,y,z), and the t value obtained from brain activation from group random effects analysis shown in Figure 2 (c) and (d) for subtraction task

Condition		SIQ			SIN			
Region	Hemisphere	NOV	x, y, z	*t*	NOV	x, y, z	*t*
HG	L	30	-46, -14, 4	4.24	84	-40, -24, 6	5.56
	R	27	52, -16, 10	3.97	32	48, -12, 6	4.42
STG	L	372	-52, 0, 3	6.47	602	-40, -28, 6	8.38
	R	602	60, -26, 2	5.91	795	64, -20, 0	6.66
IFG	L	33	-38, 22, -4	6.14	39	-38, 22, -4	6.22
	R	34	52, 18, -6	5.03	52	52, 18, -6	5.43
IPL	L	9	-44, -38, 44	4.04	38	-44, -36, 46	4.93
	R	-	-	-	-	38, -44, 46	3.42
SG	L	37	-50, -40, 28	4.27	72	-62, -24, 16	4.85
	R	24	62, -42, 24	4.79	21	64, -42, 24	4.38
Insula	L	53	-36, 22, -4	5.64	146	-38, 20, -4	6.21
	R	73	48, 4, -3	7.18	163	48, 8, -8	8.55
Thalamus	L	90	-4, -18, 8	5.70	364	-6, -22, 8	9.41
	R	91	6, -22, 8	4.04	3	6, -20, 6	9.06
MCC	L	-	-	-	-	-	-
	R	15	6, 24, 32	3.78	103	4, 12, 44	6.50
PG	L	332	-50, -6, 22	6.90	307	-54, -4, 24	6.82
	R	116	48, -6, 28	6.30	117	44, -10, 36	8.43
MTG	L	11	-58, -22, 0	4.12	56	-60, -26, 2	4.63
	R	49	58, -28, 0	5.60	135	58, -28, 0	5.86
MFG	L	12	-30, 50, 20	4.41	19	-32, 50, 20	4.30
	R	15	32, 6, 60	5.11	14	36, 6, 56	4.53
SPL	L	-	-	-	-	-	-
	R	-	-	-	-	-	-

Abbreviations: SIQ = substraction in-quiet, SIN = substraction in-noise, HG = Heschl's gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, IPL = inferior parietal lobe, SG = supramarginal gyrus, MCC = middle cingulate cortex, PG = pre-central gyrus, MTG = middle temporal gyrus, MFG = middle frontal gyrus, SPL = superior parietal lobe.

Main effects and interaction

The two-way repeated measures ANOVA revealed a significant main effect of arithmetic operations (addition versus subtraction) on brain responses (uncorrected $P < 0.05$) for bilateral STG, IFG, IPL, MCC, insula lobe, thalamus, PCG, MTG, SFG, and SPL, including left HG and right SMG (Table 4). The comparison between the addition and subtraction operations (addition in-quiet > subtraction in-quiet, and addition in-noise > subtraction in-noise) revealed that the left HG, left STG, left insula lobe, right MCC, bilateral MTG and bilateral MFG were significantly activated according to *t* values (Table 5). The reverse contrast (subtraction in-quiet > addition in-quiet, and subtraction in-noise > addition in-noise) showed that bilateral hemispheres IPL, SMG, PCG, SPL, and SFG were activated but with a higher number of activated voxels for subtraction compared with addition (Table 6).

However, there was no significant main effect of background conditions (i.e., in-quiet and in-noise) and their interaction with operations (i.e., addition and subtraction) in any brain region.

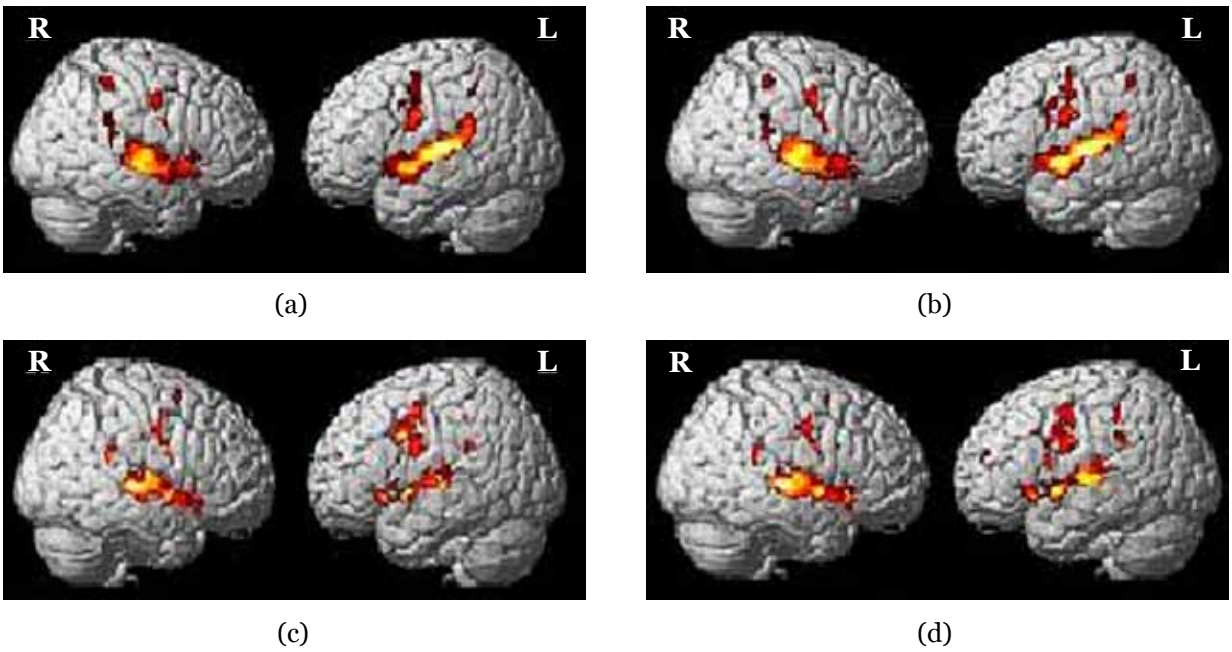

Figure 2: Brain activation from group random effect analysis for addition in-quite, (b) addition in-noise, (c) subtraction in-quite, and (d) subtraction in-noise thresholded at α = 0.001 uncorrected for multiple comparisons. R denotes the right side of the brain, while L denotes the left side.

Table 3: The laterality index for all regions computed from all different tasks and conditions averaged over 18 participants

Region	AIQ	AIN	SIQ	SIN
HG	0.05 (0.66)	-0.06 (0.65)	-0.01 (0.55)	-0.07 (0.59)
STG	0.13 (0.31)	0.01 (0.38)	-0.05 (0.38)	-0.10 (0.35)
IFG	0.08 (0.50)	0.10 (0.50)	-0.08 (0.52)	-0.13 (0.60)
IPL	0.50 (0.52)	0.30 (0.66)	0.33 (0.56)	0.33 (0.49)
SG	0.27 (0.61)	0.18 (0.61)	-0.09 (0.55)	0.16 (0.39)
Insula	-0.29 (0.40)	-0.19 (0.36)	-0.16 (0.55)	-0.37 (0.49)
Thalamus	0.09 (0.37)	0.09 (0.39)	-0.18 (0.52)	-0.10 (0.53)
MCC	-0.19 (0.52)	-0.26 (0.67)	-0.17 (0.49)	-0.29 (0.43)
PG	0.19 (0.57)	0.28 (0.45)	0.26 (0.38)	0.18 (0.40)
MTG	0.14 (0.43)	0.10 (0.40)	0.01 (0.48)	-0.09 (0.43)
MFG	- 0.16 (0.45)	-0.25 (0.49)	-0.03 (0.57)	0.00 (0.61)
SPL	0.08 (0.73)	0.03 (0.68)	0.22 (0.59)	0.05 (0.70)

Data are expressed in mean (SD).
Abbreviations: AIQ = addition in-quiet, AIN = addition in-noise, SIQ = substraction in-quiet, SIN = substraction in-noise, HG = Heschl's gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, IPL = inferior parietal lobe, SG = supramarginal gyrus, MCC = middle cingulate cortex, PG = precentral gyrus, MTG = middle temporal gyrus, MFG = middle frontal gyrus, SPL = superior parietal lobe.

Table 4: Activated brain region during the main effects of arithmetic stimulus typeat uncorrected $P < 0.05$

Region	Hemisphere	NOV	x, y, z	*F* value	*P* value
HG	L	35	-40, -20, 2	6.90	0.005
STG	L	487	-58, -36, 12	15.56	0.000
	R	25	50, -10, -6	4.49	0.008
IFG	L	14	-28, 24, -24	9.15	0.003
	R	7	52, 26, -8	4.84	0.031
IPL	L	80	-44, -30, 44	9.25	0.003
	R	184	30, -44, 50	9.45	0.003
SG	R	92	60, -16, 28	9.09	0.004
Insula	L	126	-34, 18, 14	12.38	0.001
	R	10	42, -4, -8	4.52	0.036
Thalamus	L	23	-12, -32, 0	7.63	0.007
MCC	L	27	-8, 2, 40	5.68	0.020
	R	73	0, 18, 32	7.94	0.006
PG	L	74	-20, -24, 70	11.98	0.001
	R	79	50, -14, 54	9.18	0.003
MTG	L	404	-58, -26, -6	11.37	0.001
	R	217	48, -76, 20	16.77	0.000
MFG	L	220	-24, 0, 48	17.38	0.000
	R	184	34, 54, 0	11.07	0.001
SFG	L	71	-22, 0, 48	18.05	0.000
	R	59	22, 0, 62	9.71	0.003
SPL	L	116	-16, -58, 50	6.70	0.012
	R	264	24, -66, 48	14.12	0.000

Abbreviations: NOV = number of activated voxels, HG = Heschl's gyrus, STG = superior temporal gyrus, IFG = inferior frontal gyrus, IPL = inferior parietal lobe, SG = supramarginal gyrus, MCC = middle cingulate cortex, PG = precentral gyrus, MTG = middle temporal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, SPL = superior parietal lobe.

Discussion

This study identified the activated areas in the brain and their laterality during simple addition and subtraction operations for in-quiet and in-noise backgrounds. In addition, it also examined the differential effect of background noise on the task-related activation during the aforementioned operations.

SPM analyses indicated that performing subtraction or addition in-quiet as well as in-noise resulted in a different spatial extent of activation in several brain regions. Group results showed that addition and subtraction operations evoked brain activation in the HG, STG, IFG, IPL, SMG, PCG, MTG, MFG, SPL, MCC, insula, and thalamus. In general, NOV was higher during addition than subtraction, for both in-quiet and in-noise. NOV was also modulated by background condition, where in-noise produced higher NOV in both addition and subtraction operations compared with in-quiet conditions. The differences in NOV for different mathematical operations and background conditions were possibly due to the difference in task demand and participants' efforts in accomplishing the tasks. These results were similar to those of other studies on speech perception in-noise (19,31) that found increased activation in some regions, especially in superior temporal activation, due to increased effort in extracting the speech signal in-noise.

Table 5: Activated brain regions during addition greater than subtraction in the quiet and noise conditions at uncorrected $P < 0.05$

Region	Hemisphere	AIQ > SIQ					AIN > SIN				
		NOV	x, y, z			*t*	NOV	x, y, z			*t*
HG	L	24	-40,	-20,	4	1.81	5	-40,	-20,	2	1.96
STG	L	322	-58,	-36,	12	3.12	251	-46,	-14,	-10	2.64
	R	9	50,	-24,	12	1.77	-		-		-
MTG	L	225	-40,	6,	-28	2.88	253	-58,	-24,	-6	2.72
	R	58	56,	-14,	-18	2.13	51	58,	-16,	-18	2.14
Insula	L	40	-34,	18,	14	2.44	31	-34,	18,	14	2.53
MCC	R	28	4,	-24,	44	1.87	12	4,	-24,	44	1.77
SFG	R	6	18,	56,	30	2.05	11	-20,	52,	32	2.30
MFG	L	-		-		-	6		-		-
	R	14	34,	60,	-2	2.20	18	40,	12,	42	2.10

Abbreviations: AIQ = addition in-quiet, AIN = addition in-noise, SIQ = substraction in-quiet, SIN = substraction in-noise, NOV = number of activated voxels, HG = Heschl's gyrus, STG = superior temporal gyrus, MTG = middle temporal gyrus, MCC = middle cingulate cortex, SFG = superior frontal gyrus, MFG = middle frontal gyrus.

Table 6: Activated brain regions during subtraction greater than addition in the quiet and noise conditions at uncorrected $P < 0.05$

Region	Hemisphere	SIQ > AIQ					AIN > SIN				
		NOV	x, y, z			*t*	NOV	x, y, z			*t*
IPL	L	14	-58,	-40,	38	1.94	70	-44,	-30,	44	2.58
	R	121	34,	-42,	54	2.44	30	30,	-44,	50	1.99
SPL	L	6	-24,	-56,	58	1.74	41	-16,	-58,	50	2.11
	R	152	16,	-56,	58	2.61	126	24,	-66,	48	2.77
SG	L	4	-58,	-40,	36	1.53			-		
	R	88	60,	-16,	28	2.33	16	60,	-16,	28	1.95
SFG	L	54	-22,	0,	48	2.87	31	-22,	0,	48	3.13
	R	59	22,	24,	58	2.32	12	20,	2,	60	1.90
PG	L	34	-20,	-24,	70	2.33	27	-20,	-24,	70	2.56
	R	49	18,	-26,	72	2.16	47	50,	-14,	54	2.37

Abbreviations: AIQ = addition in-quiet, AIN = addition in-noise, SIQ = substraction in-quiet, SIN = substraction in-noise, IPL = inferior parietal lobe, SPL = superior parietal lobe, SG = supramarginal gyrus, SFG = superior frontal gyrus, PG = precentral gyrus.

An extended spread of activation in bilateral HG and STG was observed in-noise compared with in-quiet for both addition and subtraction operations, similar to that found in a study of speech perception, where greater activation was found during speech perception in-noise than in-quiet (19). Bilateral activation of HG and STG was expected due to their respective functions in processing auditory stimuli (18–20,32). The HG, together with the posterior area of STG, is known to be the primary auditory area and is associated to BA41 in Brodmann classification (33). In the present study, HG and parts of STG were assumed to act as the input centre for auditory processing, where auditory signals from sub-cortical areas were received before transmission to other cortical areas involved in processing of arithmetic stimuli. Verbal stimuli (e.g., speech or word numbers) caused an extended activation in the left auditory compared with the right auditory

area (34). However, the right auditory area has been shown to be more sensitive to tonality or non-verbal stimuli, such as pure tones and noises. For example, listening to white noise has been found to produce a larger number of activated voxels in the right HG compared with the left HG (32). These findings by Tervaniemia et al. (34) and Yusoff et al. (32) indicate that HG responds differently to verbal and non-verbal stimuli. However, the present study showed that the right HG triggered a relatively wider area of activation (LI < 0) compared with the left HG for all tasks except for addition in-quiet, which evoked a relatively wider extent of activation in the left hemisphere (LI > 0). This right hemispheric dominance is potentially due to the change in the processing strategy for HG when dealing with simple arithmetic operations. For STG, there was an extended activation area in the left hemisphere (LI > 0) for addition in-quiet and in-noise; in contrast, subtraction in-quiet and in-noise showed a wider extent of activation in the right hemisphere (LI < 0). However, the LI values obtained from the analyses were small, reflecting small differences in NOV between the left and right STG during addition and subtraction operation in-quiet and in-noise. These findings suggest that both left and right STG play equal roles in processing mathematical input presented auditorily (19,35).

The present study also found that addition and subtraction operations resulted in extended activation in the frontal and parietal lobes, 2 regions known to be involved in mental calculations (36). In the frontal lobes, there was significant activation in bilateral IFG, SFG, and MFG–regions related to working memory and executive functions (7,8). The present study also revealed that addition and subtraction operations resulted in bilateral activations in the IFG and SFG, suggesting that they may play a role in supporting the processes of arithmetic working memory. The IFG results indicate that the left hemisphere IFG has extended activation compared with the right IFG in addition operations both in-quiet and in-noise (i.e., LI > 0). In contrast, subtraction operations both in-quiet and in-noise resulted in a greater activation in the right hemisphere (LI < 0). In a previous study on simple calculation, complex calculation, and proximity judgement (11), the right IFG exhibited a wider extent of activation than the left IFG, suggesting that the right IFG was associated with the executive function of arithmetic operations. The MFG activation pattern showed a slightly extended activation in the right hemisphere (LI < 0) during addition in-quiet and in-noise, as well as subtraction in-quiet, but not for subtraction in-noise (LI > 0). In addition, a wider spread of bilateral activation in MFG during addition and subtraction tasks may indicate that MFG is the central region in working memory processes dedicated to numerical processing (37). These findings suggest that (1) addition and subtraction operations require working memory for arithmetic facts retrieval, and (2) addition and subtraction in-quiet and in-noise conditions produced different hemispheric laterality patterns in the frontal regions.

The parietal regions are commonly activated in tasks that involve number operations. The activated regions include the IPL (4,10), SPL, and SMG (4,10,11), all regions that play important roles in processing and manipulating numbers. Processing of numbers appears to be important especially in differentiating the arithmetic stimulus type, i.e., addition and subtraction. Furthermore, the IPL, SPL, and SMG seemed to have a wider extent of activation for addition task. For both SMG and IPL, there was LI > 0, and these 2 regions seemed to have a wider extent of activation in the left hemisphere, except for SMG for subtraction in-quiet that was otherwise. Rueckert et al. (38) and Dehaene et al. (39), found bilateral activation in IPL. However, it is well known that the left IPL plays an important role in arithmetic operations as retrieval of arithmetic information involves the left Broca areas (40). Menon et al. (10) identified the IPL region as specifically activated in response to increasing arithmetic complexity. They also suggested that SMG was activated due to increased difficulty of the arithmetic operation. The wider extent of activation in the IPL during addition operations revealed from the present study showed that addition was relatively difficult to solve compared with subtraction.

Interestingly, the right MCC revealed activation during all combinations of operations and conditions. The right MCC also exhibited a wider extent of activation during addition compared with subtraction. In Cowel et al. (40), the activation found in cingulate cortex was associated to cognitive requirements of attention, working memory, and decision making. Based on the results given above, performing addition for in-noise conditions needed higher attention and executive function of working memory compared with subtraction. Thus, the involvement of MCC in this study can be associated with attention when the participants were trying to solve the addition and subtraction operations.

The motor system in the bilateral PCG has also been found to be activated during addition and subtraction in this study. Besides, a wider activation in the left PCG was observed as the LI > 0 during addition and subtraction for both in-noise and in-quiet (43). The motor areas may be activated due to imagery finger movement when the participants were trying to solve numerical processing such as counting (41,42). Both the left and right PCG showed greater activation during subtraction compared with addition. Counting in numerical processing would appear to be most important to differentiate between addition and subtraction (12). Subtraction seemed to promote a relatively larger imagery finger movement in processing numerical quantities to solve problems compared with addition (44).

We also observed other brain areas that were significantly activated ($P < 0.001$), e.g., the insula lobe and thalamus. The activation in these areas was more extensive in the right compared with the left hemisphere, except for activation in the thalamus for subtraction in-noise that was otherwise. These areas have been suggested to be components of working memory and attention (32).

The results of the present study should be interpreted carefully while considering at least 2 possible limitations: (1) The statistical thresholds used for the whole brain data analyses were rather moderate, and (2) perisylvian activation patterns in relation to arithmetic processing might be over-interpreted due to the underlying contrasts, including a verbal comprehension versus a nonverbal baseline condition. Nevertheless, interaction analyses between modalities and tasks provide valuable information for the presented differential discussion.

Conclusion

The results showed that addition and subtraction tasks evoked extended activation in the left inferior parietal lobe, left precentral gyrus, left superior parietal lobe, left supramarginal gyrus, and left middle temporal gyrus. This was due to the hypothesis that the human brain activates its left hemisphere when working on logical thinking. However, brain areas in the insula, MCC, and MFG showed extended activation in the right hemisphere. For superior temporal gyrus, inferior frontal gyrus, and thalamus, there was extensive left-hemispheric activation for addition tasks but not for subtraction tasks. The bilateral activation in parietal regions promotes arithmetic problem solving, but the involvement of frontal brain regions for mental calculation are for executive processes and working memory in mathematical calculations. The results of the present study suggest that addition (compared with subtraction) and in-noise (compared with in-quiet) conditions promoted higher cognitive processes in working memory and attention. The left hemisphere of the brain showed apparent extended activation in regard to attention, executive processes and working memory.

Acknowledgement

The authors would like to thank Sa'adon Samian from the Department of Radiology, UKM Medical Centre for conducting the fMRI scans. This work was supported by the UKM research grant GUP-SUK-SK-07-20-205.

Authors' Contributions

Conception and design: AIAH, ANY, SZSM, MM
Provision of study materials or patients, collection, assembly, analysis, and interpretation of the data, drafting of the article: AIAH, ANY
Obtaining of funding, statistical expertise, critical revision and final approval of the article, administrative, technical, or logistic support: ANY

Correspondence

Miss Aini Ismafairus Abd Hamid
BASc (Hons) Medical Physics (USM)
Functional Image Processing Laboratory
Diagnostic Imaging and Radiotherapy Programme
Faculty of Allied Health Sciences
Universiti Kebangsaan Malaysia
Jalan Raja Muda Abdul Aziz
50300 Kuala Lumpur
Malaysia
Tel: +603-9289 7682
Fax: +603-9289 7915
Email: aini_ismafairus@yahoo.com.my

References

1. Dahaene S, Piazza M, Pinel P, Cohen L. Three parietal circuits for number processing. *Cogn Neuropsychol*. 2003;**20(3)**:487–506.

2. Fayol M, Abdi H, Gombert JE. Arithmetic problems formulation and working memory load. *Cognition Instruct*. 1987;**4(3)**:187–202.

3. Dehaene S. Varieties of numerical abilities. *Cognition*. 1992;**44(1–2)**:1–42.

4. Wu SS, Chang TT, Majid A, Caspers S, Eikhoff SB, Menon V. Functional heterogeneity of inferior parietal cortex during mathematical cognition assessed with cytoarchitectonic probability maps. *Cereb Cortex*. 2009; **19(12)**:2930–2945.

5. Constantinidis C, Procyk E. The primate working memory networks. *Cogn Affect Behav Ne*. 2004;**4(4)**:444–465.

6. Kazui H, Kitagi H, Mori E. Cortical activation during retrieval of arithmetical facts and actual calculation: A functional magnetic resonance imaging study. *Psychiat Clin Neuros*. 2000;**54**:479–485.

7. Delazer M, Domahs F, Bartha L, Brenneis, Lochy A, Trieb T, et al. Learning complex arithmetic—An fMRI study. *Cognitive Brain Res*. 2003;**18(1)**:76–88.

8. Ranganath C, Johnson MK, D'Esposito M. Prefrontal activity associated with working memory and episodic long-term memory. *Neuropsychologia*. 2003;**41(3)**:378–389.

9. Rickard C, Romero SG, Basso G, Wharton C, Flitman S, Grafman J. The calculating brain: An fMRI study. *Neuropsychologia*. 2000;**38(3)**:325–335.

10. Menon V, Rivera SM, White CD, Glover GH, Reiss AL. Dissociating prefrontal and parietal cortex activation during arithmetic processing. *NeuroImage*. 2000;**12(4)**:357–365.

11. Zhang YT, Zhang Q, Zhang J, Wei L. Laterality of brain areas associated with arithmetic calculations revealed by functional magnetic resonance imaging. *Chinese Med J-Peking*. 2005;**118(8)**:633–638.

12. Fehr T, Code C, Herrmann M. Common brain regions underlying different arithmetic operations as revealed by conjunct fMRI-BOLD activation. *Brain Res*. 2007;**1172(3)**:93–102.

13. Fehr T, Code C, Herrmann M. Auditory task presentation reveals predominantly right hemispheric fMRI activation patterns during mental calculation. *Neurosci Lett*. 2008;**431(1)**:39–44.

14. Gruber O, Indefrey P, Steinmetz H, Kleinschmidt A. Dissociating neural correlates of cognitive components in mental calculation. *Cereb Cortex*. 2001:**11(4)**;350–359.

15. Liebenthal E, Binder JR, Spritzer SM, Possing ET, Medler DA. Neural substrates of phonemic perception. *Cereb Cortex*. 2005;**15(10)**:1621–1631.

16. Scoot SK, Wise RJS. The functional neuroanatomy of prelexical processing in speech perception. *Cognition*. 2004;**92(1–2)**:13–45.

17. Wong PCM, Nusbaum HC, Small SL. Neural bases of talker normalization. *J Cognitive Neurosci*. 2004;**16(7)**:1173–1184.

18. Scott SK, Rosen S, Wickham L, Wise RJ. A positron emission tomography study of the neural basis of informational and energetic masking efforts in speech perception. *J Acoust Soc Am*. 2004;**115(2)**:813–821.

19. Wong PCM, Uppunda AK, Parish TB, Dhar S. Cortical mechanisms of speech perception in noise. *J Speech Lang Hear Res*. 2008;**51**:1026–1041.

20. Hall DA, Johnsrude IS, Haggard MP, Palmer AR, Akeroyd MA, Summerfield AQ. Spectral and temporal processing in human auditory cortex. *Cereb Cortex*. 2002;**12(2)**:140–149.

21. Hall DA, Haggard MP, Akeroyd MA, Palmer AR, Summerfield AQ, Elliott MP, et al. "Sparse" temporal sampling in auditory fMRI. *Hum Brain Mapp*. 1999;**7(3)**:213–223.

22. Tomasi D, Caparelli EC, Chang L, Ernst T. fMRI-acoustic noise alters brain activation during working memory tasks. *NeuroImage*. 2005;**27(2)**:377–386.

23. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;**9(1)**:97–113.

24. Binder JR, Liebenthal, E, Possing ET, Medler DA, Ward BD. Neural correlates of sensory and decision processes in auditory object identification. *Nat Neuro*. 2004;**7(3)**:295–301.

25. Ashburner J, Good CD. Spatial registration of images. In: Tofts P, editor. *Qualitative MRI of the brain: Measuring changes caused by disease*. Chichester, UK: John Wiley & Sons Ltd; 2003. p. 503–531.

26. Ashburner J, Friston KJ. Computational neuroanatomy. In: Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Price CJ, Zeki S, et al., editors. *Human brain function*. Amsterdam: Elsevier Academic Press; 2004. p. 655–672.

27. Friston KJ. Experimental design and statistical parametric mapping. In: Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Price CJ, Zeki S, et al., editors. *Human brain function*. Amsterdam: Elsevier Academic Press; 2004. p. 599 – 632.

28. Maldijan JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *NeuroImage*. 2003;**19(3)**:1233–1239.

29. Seghier ML. Laterality index in functional MRI: Methodological issues. *Mag Reson Imaging*. 2008;**26(5)**:594–601.

30. Pinel P, Dehaene S. Beyond hemispheric dominance: brain regions underlying the joint lateralization of language and arithmetic to the left hemisphere. *J Cognitive Neurosci*. 2010;**22(1)**:48–66.

31. Wong PC, Jin JX, Gunasekera GM, Abel R, Lee ER, Dhar S. Aging and cortical mechanisms of speech perception in noise. *Neuropsychologia*. 2009;**47(3)**:693–703.

32. Yusoff AN, Abdul Hamid K, Mohamad M, Abd Hamid AI. The acquisition, analyses and interpretation of fMRI data: A study on functional specialization in primary auditory cortex. *Med Health*. 2008;**3(2)**:131–148.

33. Upadhyay J, Silver A, Knaus TA, Lindgren KA, Ducros M, Kim DS, et al. Effective and structural connectivity in the human auditory cortex. *J Neurosci*. 2008;**28(13)**:3341–3349.

34. Tervaniemia M, Hugdahl K. Lateralization of auditory-cortex functions. *Brain Res Rev*. 2003;**43(3)**:231–246.

35. Munoz-Lopez MM, Mohedano-Mariano A, Insausti R. Anatomical pathways for auditory memory in primates. *Front Neuroanat*. 2010;**4(129)**:1–13.

36. Davis N, Cannistraci CJ, Rogers BP, Gatenby JC, Fuchs LS, Anderson AW, et al. The neural correlates of calculation ability in children: An fMRI study. *Magn Reson Imaging*. 2009;**27(9)**:1187–1197.

37. Burbaud P, Degreze P, Lafon P, Franconi JM, Bouligand B, Bioulac B, et al. Lateralization of prefrontal activation during internal mental calculation. *J Neurophysiol*. 1995;**74(5)**:2194–2200.

38. Rueckert L, Lange N, Paetiot A, Appollonio I, Litvan I, Bihan SDL, et al. Visualizing cortical activation during mental calculation with functional MRI. *NeuroImage*. 1996;**3(2)**:97–103.

39. Dehaene S, Cohen L. Towards an anatomical and functional model of number processing. *Math Cogn*. 1995;**1(1)**:83 –120.

40. Cowel SF, Egan GF, Code SC, Harasty J, Watson JDG. The functional neuroanatomy of simple calculation and number repetition: A parametric PET activation study. *NeuroImage*. 2000;**12(5)**:565–573.

41. Hanakawa T, Immisch I, Toma K, Dimyan MA, van Gelderen P, Hallet M. Functional properties of brain areas associated with motor execution and imagery. *J Neurophysiol*. 2003;**89(2)**:989–1002.

42. Lacourse MG, Orr ELR, Cramer SC, Cohen MJ. Brain activation during execution and motor imagery of novel and skilled sequential hand movements. *NeuroImage*. 2005;**27(3)**:505–519.

43. Yusoff AN, Mohamad M, Ayob MM, Hashim MH. Brain activations evoked by passive and active listening: A preliminary study on multiple subjects. *Malaysian J Health Sci*. 2008;**6(1)**:35–36.

44. Cohen L, Dehaene S, Chochon F, Lehericy S, Naccache L. Language and calculation within the parietal lobe: A combined cognitive, anatomical and fMRI study. *Neuropsychologia*. 2000; **38(10)**:1426–1440.

Original Article

Ergonomic Training Reduces Musculoskeletal Disorders among Office Workers: Results from the 6-Month Follow-Up

Norashikin Mahmud[1], Dianna Theadora Kenny[2], Raemy Md Zein[3], Siti Nurani Hassan[3]

Submitted: 2 Jun 2010
Accepted: 19 Aug 2010

[1] *Program of Industrial and Organizational Psychology, Faculty of Management and Human Resource Development, Universiti Teknologi Malaysia, 81310 Skudai, Johor, Malaysia*

[2] *Disciplines of Behavioural and Social Sciences in Health, Faculty of Health Sciences, University of Sydney, 75 East St, Lidcombe NSW 2141, Australia*

[3] *National Institutes of Occupational Safety and Health, Lot 1, Jalan 15/1, Section 15, 43650, Bandar Baru Bangi, Selangor, Malaysia*

Abstract

Background: **Musculoskeletal disorders are commonly reported among computer users. This study explored whether these disorders can be reduced by the provision of ergonomics education.**

Methods: **A cluster randomised controlled trial was conducted in which 3 units were randomised for intervention and received training, and 3 units were given a leaflet. The effect of intervention on workstation habits, musculoskeletal disorders, days and episodes of sick leave, and psychological well-being were assessed.**

Results**: A significant improvement in workstation habits was found, and the differences remained significant at the follow-up time point for keyboard, mouse, chair, and desk use. The largest reduction in the percentage of musculoskeletal disorders was in the neck region (-42.2%, 95% CI -60.0 to -24.4). After adjusting for baseline values, significant differences were found at the follow-up time point in the neck, right shoulder, right and left upper limbs, lower back, and right and left lower limbs. No significant differences were found for the days and episodes of sick leave or the psychological well-being among workers after the intervention.**

Conclusion**: Consistent reductions were observed for all musculoskeletal disorders at the follow-up time point, although the difference was not statistically significant for the upper back. The improvements in the musculoskeletal disorders did not translate into fewer days lost from work or improved psychological well-being.**

Keywords: *adult, ergonomics, musculoskeletal diseases, occupational health, training*

Introduction

Musculoskeletal disorders (MSDs) are commonly reported by office workers worldwide, and these disorders can have detrimental effects on workers' health and productivity (1,2). Factors that predict the risk of developing MSDs can be divided into individual (3–5), ergonomic (6–11), and psychosocial factors (12–15). The risk of developing MSDs is higher among workers who have a high work strain, longer mouse and keyboard use, perceived high muscle tension, and previous MSDs in the neck and shoulder; these risk factors were reported in several longitudinal studies with a follow-up ranging from 3 months to 5.4 years (16–23).

Awareness and knowledge of the relationship between computer usage and MSDs are essential for preventing MSDs from becoming more severe. A study conducted by a French company reported that office and blue collar workers had a higher risk of sickness absence because of upper limb disorders compared with managers and professionals (24). A population-based study in Sweden also found that respondents who reported concurrent low back pain and neck-shoulder disorders were at high risk for short- and long-term sickness absences from work (25).

In a work setting, ergonomics education/training is the best initial strategy to educate computer users about office ergonomics (26). Training may also educate individuals from different managerial levels in the organisation

about office safety, which may simultaneously promote increased levels of safety in the organisation. Previous studies conducted on the effectiveness of office ergonomic training reported improvements in knowledge and workstation habits and a reduction in MSDs. One study used various educational interventions, including posters, emails, pictures of stretching and stress relief activities, workshops, and informational booklets. These interventions increased the workers' knowledge of cumulative trauma disorders and resulted in changes in the hand/wrist and neck/shoulder posture when using computers (27). The other study conducted on workers in a petrochemical research and development facility reported improvements in workstation posture and symptom severity, but they did not report any reduction in symptoms (28). Studies using different methods of ergonomics training have reported positive results. For example, those who received education programs, such as participatory training (an active learning session involving discussions and problem-solving exercises) and traditional training (lectures and handouts), reported less pain/discomfort and a positive perception of psychosocial work stress compared with those who did not receive training (29). Another study demonstrated that both instructor-directed and self-directed learning were effective in causing positive changes in ergonomic habits among workers (30). However, a study reported that training alone did not reduce MSD symptoms among respondents (31). The researchers suggested that knowledge derived from training would not be effective unless workers were provided with the appropriate equipment to implement it.

Recent studies on office ergonomics by Robertson et al. (32,33) also found positive results. One study looked at the effect of 3 interventions, office ergonomics training, a flexible workstation, and training with a flexible workstation, on an individual's psychological work environment, musculoskeletal disorders, and work effectiveness. In the study, flexible workstation was architecturally designed to create a sense of openness, provide natural lighting throughout the workspace, and enhance auditory and visual privacy. The layout of the individual workstations was a soft U-shape, with each workstation having adjustable storage and paper management tools. Each workstation was equipped with a highly adjustable ergonomic chair. Regarding MSDs, they showed a significant reduction in MSDs in the training with a flexible workstation group (32). Another study aimed to investigate the effects of training and training with an adjustable chair on musculoskeletal risk, knowledge, and behavioural change. An improvement in the observed computing body postures for the right and left side of the body with the training and training with a chair groups. Regarding behavioural changes, only the training group reported a significant improvement in the workstation changes at the time of the follow-up session (33).

The aim of the current study was to evaluate the effects of office ergonomics training, compared with no training, on MSDs and psychological well-being in university-based office workers. A cross-sectional survey that assessed their awareness of office ergonomics and the prevalence of MSDs had been previously conducted among the target group of the Universiti Teknologi Malaysia (UTM) office workers. The findings reported a low level of office ergonomics awareness and high 12-month prevalence rates of MSDs in the shoulder (51.6%), neck (48.2%), and back (42.2%) (34). Results from the study suggested that UTM staff were in need of office ergonomics training because they had not previously received any formal training. Two hypotheses were drawn: (1) office ergonomics training reduces musculoskeletal disorders among office workers; and (2) office ergonomics training can improve the psychological well-being among office workers.

Subjects and Methods

Study design

Ethical approval to conduct the study was obtained from the University of Sydney Human Research Ethics Committee. This study was designed as a two-armed cluster randomised controlled trial. The experimental group received office ergonomic training, and the control group was asked to conduct "business as usual" (no ergonomic training); 3 units were randomly assigned to the experimental group, and 3 were assigned to the control group using a random number table. The random number was set at 6. The minimum value was set at 1 (experimental group) and maximum value at 2 (control group). The researchers were aware of the allocation of the groups. Respondents were aware of the study, but they did not know whether they belonged to the experimental or control group. The study flow chart is presented in Figure 1.

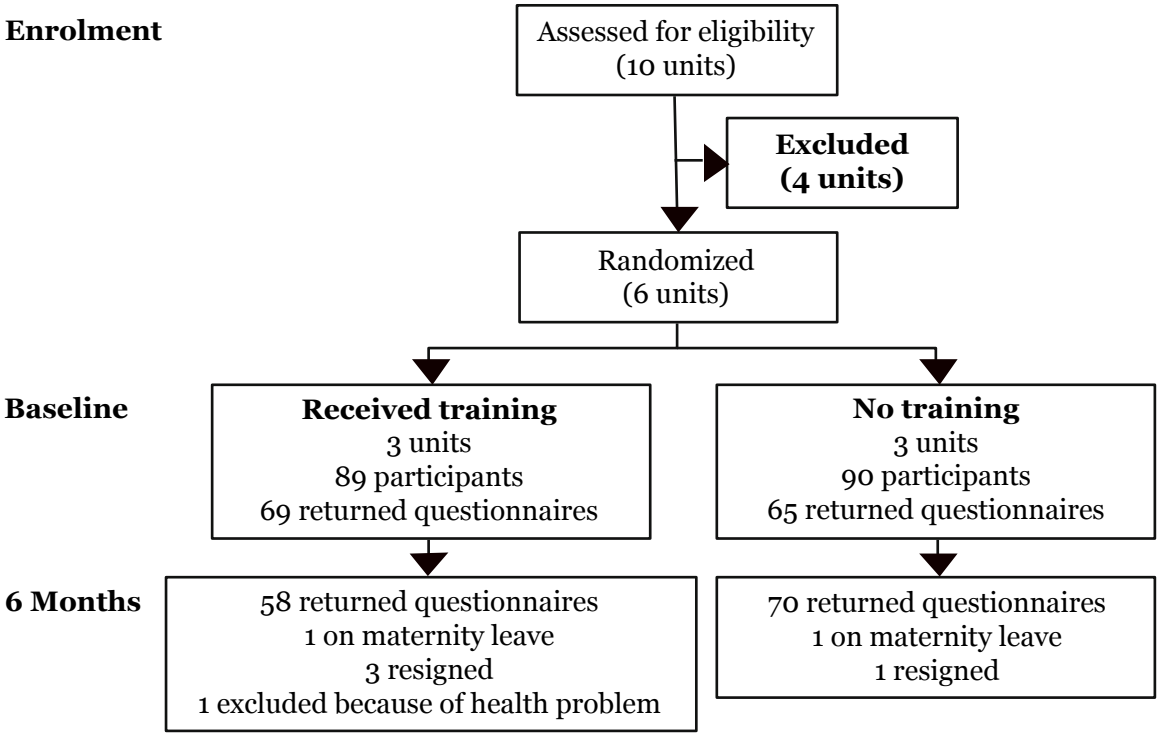

Figure 1: Study flow diagram

Participants and setting

Office workers from 6 units were invited to participate in the study. The 6 units were Bursary, Registry, Library, Research Management Centre, Professional and Continuing Education, and Centre of Information and Communication Technology. The inclusion criteria were people who worked with computers for at least 3 hours per day, in either permanent or contract employment. The exclusion criteria were people who had any previous illness and/or injuries that may have contributed to MSDs. The majority of the office workers sat in cubicles; the size of the cubicle was standardised, but it may have been smaller for several of the workstations due to space constraints. Each worker had his/her own designated desk equipped with a monitor (traditional or flat screen), a keyboard (traditional), and a mouse (without a wrist rest). The majority of workers working in a cubicle had a keyboard tray (without a mouse tray), which was attached to the desk. Some, but not all, workers who were not working in a cubicle had desks with a keyboard tray. Workers who did not have a keyboard tray placed their keyboard on their desk. Most staff had their own telephone; however, a small number of participants shared a telephone with co-workers (1:2). Chairs and desks were adjustable, and the staff had flexibility with respect to the movement of their keyboard and mouse. Workstation layouts were generally consistent across units. No serious efforts had been made by management to ergonomically upgrade these workstations. The initial awareness of office ergonomics was low (34).

Intervention

Respondents from the intervention groups received office ergonomics training. The in-house ergonomics training was conducted by trainers from the National Institute of Safety and Health (NIOSH). The training took place over a period of 1 day, divided into 2 sessions; the first session consisted of lectures on office ergonomics, understanding the relationship between office ergonomics and the development of MSDs, ergonomic improvements and adjustments of workstations, and stretching exercises. The second session focused on the practical aspects of the training; trainers visited the participants' workstations and provided assistance to them on how to adjust workstations effectively. We encouraged respondents to stay at their workstation so that the trainers could help them readjust their workstation if necessary. Trainers made suggestions on how to improve workstation practices, but these were restricted to different arrangements of the workstation furniture

without compromising the space available. Respondents were also encouraged to participate in their workstation adjustments. Under some circumstances, further suggestions were made on how to adjust the workstation and/or space. These suggested changes would have required support from management; for example, trainers suggested buying new furniture or allocating more space.

Respondents from the control groups received a leaflet that consisted of an ergonomic office diagram, tips on how to take a break, tips on how to reduce their workload, and stretching exercises. The leaflet was based on a comprehensive literature search from the National Institute of Occupational of Safety and Health and other health and safety websites related to office ergonomics issues or problems. The experimental group also received the same leaflet in addition to the ergonomic training.

Outcome measures

We assessed outcomes at the 6-month time point after training. The primary outcome measure was self-reported MSDs. Respondents were asked if they had experienced any MSDs at any time during the previous 6 months. Musculoskeletal disorders were measured based on 9 categories: neck, right and left shoulder, upper and lower back, right and left upper limbs (upper arm, elbow, lower arm, wrist, and fingers), and right and left lower limbs (thigh/hip, knee, and feet). Data concerning the prevalence of MSDs were gathered using the modified Nordic Questionnaire (35).

Workstation habits, psychological well-being, and sick leave were the secondary outcome measures. A sample of the respondents' workstation habits was randomly selected for observation in each of the 6 units at both baseline and follow-up time points. The observations were conducted by 4 people from the NIOSH. Trial observations were conducted prior to actual observation of 2 office workers to make sure that trainers had a clear understanding of the workstation specification checklist (Table 1) and would use it reliably. The rating was either yes (if the respondents had the desired workstation habits) or no (undesired workstation habits). A strong inter-rater reliability was found between the 4 observers (Cronbach's alpha 0.844). The checklist included items related to the use of the monitor (5 items), keyboard (7 items), mouse (2 items), chair (7 items), and desk (2 items); for example, some items were as follows: if the monitor is at arm's length away from the user, if the keyboard is at the right height (elbow height), and if the mouse is placed near the keyboard and within reach.

Psychological well-being was measured using the Depression Anxiety Stress Scale (DASS)-21 questionnaire (36). Respondents were asked to evaluate their psychological well-being based on a 4-point scale (0 = did not apply to me at all; 1 = applied to me to some degree or some of the time; 2 = applied to me a considerable degree or a good part of the time; and 3 = applied to me very much or most of the time). Sick leave was assessed by 2 items: "in the last 6 months, how many days (approximately) in total have you had off work due to work-related musculoskeletal discomfort?" and "in the last 6 months, how many separate times have you had time off work due to work-related musculoskeletal discomfort?"

Statistical analysis

We conducted an intention-to-treat analysis in which respondents were considered for the intervention that was assigned to them, i.e., training and workstation adjustments. Respondents who provided data at baseline and post-intervention time points were included in the analysis. We measured the effect of short-term behavioural changes at 2 weeks post-intervention. The between-group differences for workstation habits were calculated by examining the differences in the mean scores of correct ergonomic habits for the monitor, keyboard, mouse, chair, and desk; an independent *t* test analysis was used to analyse significant differences between the groups at follow-up. The between-group differences for the rates of MSDs were calculated using percent differences with 95% confidence intervals. Chi-square analysis was used to analyse the significant differences between groups. We then adjusted the *P* value for the baseline values using logistic regression. We calculated the number needed to treat (NNT) to determine the number of individuals that need to receive the intervention to reduce MSDs. For the analysis of the effect of intervention on sick leave, a Mann–Whitney U analysis was used to determine post-intervention significant differences between groups. An independent *t* test was used to calculate the mean differences between post-intervention and pre-intervention of psychological well-being scores and significant differences between groups. We used an analysis of co-variance (general linear model) to adjust follow-up values for baseline values for sick leave and psychological well-being.

Table 1: Workstation observation checklist

Monitor	Finding (Circle one)	
Monitor is at arm's length away from user	**Yes** 1	**No** 0
Top of the monitor at eye level or slightly below	**Yes** 1	**No** 0
Centre of monitor place directly in line with middle of body, spacebar, and keyboard	**Yes** 1	**No** 0
Glare is minimized	**Yes** 1	**No** 0
Head in neutral position without straining forward and backward	**Yes** 1	**No** 0
Keyboard		
Keyboard at the right height (elbow height)	**Yes** 1	**No** 0
Keyboard positioned in front of user	**Yes** 1	**No** 0
Elbow at side and angle about 90° to 110°	**Yes** 1	**No** 0
Forearms parallel to floor	**Yes** 1	**No** 0
Wrist are straight (without flexing up or down) and flat	**Yes** 1	**No** 0
Upper hands and elbows close to the body when hands on the keyboard	**Yes** 1	**No** 0
Shoulders relax when hands on the keyboard	**Yes** 1	**No** 0
Mouse		
Mouse is placed close to keyboard and within reach (at elbow height)	**Yes** 1	**No** 0
Wrist in a straight or neutral position	**Yes** 1	**No** 0
Chairs		
Adequate back support	**Yes** 1	**No** 0
Back posture 90° to 110°	**Yes** 1	**No** 0
Feet touching supported by the floor or footrest	**Yes** 1	**No** 0
Thigh parallel with the floor	**Yes** 1	**No** 0
Upper body straight	**Yes** 1	**No** 0
Knee are about the same height as the hip with the feet slightly forward	**Yes** 1	**No** 0
Allow special clearance to move knee and less under the desk or keyboard tray	**Yes** 1	**No** 0
Desks		
There is enough room for legs to comfortably fit under the desk or table	**Yes** 1	**No** 0
Item used most often are within arm length of reach	**Yes** 1	**No** 0

Results

Baseline results for demographic and occupational characteristics

The demographic and occupational characteristics of the study population are presented in Table 2. The baseline characteristics between the 2 groups were similar for age, gender distribution, body mass index, psychological well-being, and workplace characteristics. However, a greater number of respondents in the control group completed higher education and exercised less than the experimental group. Respondents who provided data at baseline and post-intervention were included in the analysis. In total, data from 43 respondents in the experimental group and 55 in the control group were analysed (for primary and secondary measures).

Table 2: Demographics and occupational characteristics of study population

Personal characteristics	INT (n =43)		CON (n = 55)	
Age	34.6	(10.4)	34.2	(8.4)
Gender				
Male	30.2%		20%	
Female	69.8%		80%	
BMI				
Male	23.8	(3.0)	25.9	(5.8)
Female	22.9	(4.7)	22.9	(3.6)
Education				
High school (SRP/SPM)	58.1%		29.1%	
Technical certificate/diploma	23.3%		32.7%	
Degree (bachelor/post-degree)	9.3%		30.9%	
Other	9.3%		7.3%	
Hand used to operate computer				
Right	90.7%		92.7%	
Left	9.3%		7.3%	
Exercise every week				
No	30.2%		58.2%	
Yes	69.8%		41.8%	
DASS stress	5.4	(3.9)	4.3	(3.2)
DASS anxiety	4.2	(2.9)	3.6	(3.3)
DASS depression	3.4	(3.4)	3.2	(2.8)
Years of working using computer	10.4	(6.9)	11.2	(6.8)
Hours sitting while using computer	6.6	(1.6)	6.9	(1.4)
Hours typing	5.1	(1.9)	5.2	(1.9)
Sick leave (days)	0.26	(0.6)	0.78	(1.6)
Sick episode	0.26	(0.6)	0.58	(1.4)

Data are expressed in mean (SD) or percentage.
Abbreviations:Abbreviations: INT = intervention, CON = control, BMI = body mass index, SRP = Sijil Rendah Pelajaran (Lower Certificate of Education), SPM = Sijil Pelajaran Malaysia (Malaysian Certificate of Education), DASS = Depression Anxiety Stress Scale.

Workstation observations

Short-term improvements were observed with intervention in workstation habits in the intervention groups (Table 3); specifically, these improvements were seen with the use of the monitor (mean score = 3.8), keyboard (mean score = 5.4), mouse (mean score = 1.2), chair (mean score = 5.7), and desk (mean score = 1.8) at the follow-up time point. The differences between groups were significant for the keyboard (P = 0.005), mouse (P = 0.042), chair (P <0.0001), and desk (P = 0.033). A marginally significant difference for monitor use was observed (P = 0.063). Conversely, only 1 significant difference for the improvement of workstation habits was recorded in the control group, and it was related to the space needed for the participant's legs to comfortably fit under the desk and the placement of items on the desk (P = 0.025).

Self-reported musculoskeletal disorders

Summaries of MSDs are given in Table 4. The results show that the percentage of MSDs in the intervention groups was consistently reduced for all outcomes at the follow-up time point

and ranged from -10.3% to -44.2%. The largest reduction percentage was for the neck region (-42.2%, 95% CI -60.0 to -24.4), followed by the left upper limb (-29.6%, 95% CI 46.31 to -12.89) and left lower limb (-28.1%, 95% CI -41.99 to -14.21). The lowest reported reduction percentage was for the upper back (-10.3%, 95% CI -28.9 to 8.3), left shoulder (-19.9%, 95% CI -38.4 to 1.4), and right upper limb (-19.9%, 95% CI -39.45 to -0.35). The unadjusted effects for baseline values showed statistically significant lower discomforts in the neck, right shoulder, right and left upper limbs, lower back, and right and left lower limbs. For these regions, NNT was in the range of 2 to 5, which indicated that 2 to 5 people needed to receive the intervention for 1 person to benefit from a reduced musculoskeletal problem. The results on the left shoulder were marginally significant, but the differences between the groups were clinically important and greater than 19%. No statistically significant benefits were observed for the upper back, and the NNT was much higher (10).

Table 3: Workstation habits differences between groups at baseline and 2 weeks post-intervention

Outcome	Intervention			Control		
	Baseline (n = 30)	2 weeks (n = 25)	*P* value	Baseline (n = 30)	2 weeks (n = 23)	*P* value
Monitor	3.3 (1.0)	3.8 (1.0)	0.063	2.6 (1.3)	2.7 (0.9)	0.614
Keyboard	3.9 (2.2)	5.4 (1.6)	0.005	3.7 (1.9)	3.2 (1.5)	0.342
Mouse	0.8 (0.8)	1.2 (0.8)	0.042	0.8 (0.7)	0.5 (0.6)	0.079
Chair	3.8 (1.4)	5.7 (1.3)	<0.0001	3.9 (1.9)	3.9 (1.7)	0.962
Desk	1.5 (0.6)	1.8 (0.4)	0.033	1.4 (0.6)	1.7 (0.4)	0.025

Data are expressed in mean score (SD).

Table 4: Musculoskeletal disorders at a 6-month follow-up time point (unadjusted and adjusted for baseline) assessed using the modified Nordic Questionnaires

Outcome	Baseline[a]		6 months[a]		Difference[b]	NNT	*P* value
	INT (n = 43)	CON (n = 55)	INT (n = 43)	CON (n = 55)			
Neck	22 (51.2%)	35 (63.6%)	10 (23.3%)	36 (65.5%)	-42.2 (-60.0 to -24.4)	2	U: <0.001 A: <0.001
Right shoulder	21 (48.8%)	32 (58.2%)	13 (30.2%)	31 (56.4%)	-26.2 (-45.1 to -7.2)	4	U: 0.017 A: 0.017
Left shoulder	13 (30.2%)	22 (40%)	11 (25.6%)	25 (45.5%)	-19.9 (-38.4 to -1.4)	5	U: 0.070 A: 0.058
Upper back	15 (34.9%)	23 (41.8%)	12 (27.9%)	21 (38.2%)	-10.3 (-28.9 to 8.3)	10	U: 0.394 A: 0.381
Right upper limb	15 (34.9%)	29 (52.7%)	18 (41.9%)	34 (61.8%)	-19.9 (-39.45 to -0.35)	5	U: 0.049 A: <0.001
Left upper limb	7 (16.3%)	20 (36.4%)	6 (14%)	24 (43.6%)	-29.6 (-46.31 to -12.89)	3	U: 0.002 A: 0.002
Lower back	11 (25.6%)	18 (32.7%)	7 (16.3%)	21 (38.2%)	-21.9 (-38.8 to -4.9)	5	U: 0.031 A: 0.015
Right lower limb	10 (23.3%)	19 (34.5%)	3 (6.9%)	18 (32.7%)	-25.8 (-40.33 to -11.27)	4	U: 0.002 A: 0.001
Left lower limb	8 (18.6%)	17 (31%)	2 (4.6%)	18 (32.7%)	-28.1 (-41.99 to -14.21)	4	U: 0.001 A: 0.001

[a]Data are expressed in number of subjects (percentage). [b]Difference between 6 months of INT and CON in percentage (95% CI). Abbreviations: INT = intervention, CON = control, NNT = number needed to treat, U = unadjusted *P* value, A = *P* value adjusted for baseline.

Number of days and episodes of sick leave and psychological well-being

The unadjusted and adjusted effects of the intervention showed no significant differences between groups for the number and episodes of sick day outcomes (Table 5). Although mean score differences were found between the 2 groups for stress (-0.593, 95% CI -1.7 to 0.5), anxiety (-0.018, 95% CI -1.1 to 1.1), and depression (-0.431, 95% CI -1.5 to 0.7) during the follow-up, these effects were not statistically significant (Table 6).

Discussion

The findings of this study suggest that training improved workstation habits with respect to how workers used their monitor, keyboard, mouse, chair, and desk in the intervention group at 2 weeks post-intervention. The largest improvements were found in the workers' body posture in the back region, thighs, knees, and feet while sitting. Significant improvements were also found regarding the position of the keyboard, workers' body posture for the elbow, forearms, upper arms, wrists, and shoulders when typing. The differences between groups during the follow-up period were significant for the keyboard, mouse, chair, and desk. Only 1 significant improvement for workstations was found in the control group (i.e., monitor use, space for legs under the desk, and location of items on desk). Our findings are consistent with other studies that have found that ergonomics training improved workstation habits (30,37,38).

The intervention group scored consistently lower values for all outcomes during the follow-up, although the difference was not statistically significant for the upper back. The largest percentage reduction was found for the neck, followed by the left upper and lower limbs. This outcome is in agreement with the findings of other studies that reported reductions in MSDs among computer users after attending training (32,38). It was also supported by the fact that the respondents had positive improvements on workstation habits, especially in how they sat and used keyboards, which may reduce the risk of developing neck, back, and other upper extremity disorders.

Table 5: Number of days and episodes of sick leave

Outcome	Baseline[a]		6 months[a]		*P* value	
	INT (n = 43)	CON (n = 55)	INT (n = 43)	CON (n = 55)		
Sick leave (days)	0.26 (0.6; 0–2)	0.78 (1.6; 0–9)	0.44 (1.6; 0–10)	0.71 (1.6; 0–8)	U: A:	0.239 0.642
Episodes of sick leave	0.26 (0.6; 0–2)	0.58 (1.4; 0–9)	0.42 (1.6; 0–10)	0.47 (1.1; 0–6)	U: A:	0.445 0.977

Data are expressed in mean (SD; range).
Abbreviations: INT = intervention, CON = control, U= unadjusted *P* value, A = *P* value adjusted for baseline.

Table 6: Psychological well-being (stress, anxiety, and depression) as assessed using DASS-21

Outcome	Baseline[a]		6 months[a]		Mean difference[b]	*P* value	
	INT (n = 43)	CON (n = 55)	INT (n = 43)	CON (n = 55)			
Stress	5.4 (3.9; 0–13)	4.3 (3.2; 0–14)	3.0 (2.7; 0–10)	3.6 (2.4; 0–9)	- 0.593 (-1.7 to 0.5)	U: A:	0.266 0.148
Anxiety	4.2 (2.9; 0–11)	3.6 (3.1; 0–14)	3.1 (3.1; 0–10)	3.1 (2.3; 0–9)	- 0.018 (-1.1 to 1.1)	U: A:	0.976 0.337
Depression	3.4 (3.4; 0–16)	3.2 (2.8; 0–9)	2.1 (2.6; 0–9)	2.5 (2.7; 0–11)	-0.431 (-1.5 to 0.7)	U: A:	0.437 0.773

[a]Data are expressed in mean score (SD; range). [b]Difference between 6 months of INT and CON in mean score (95% CI).
Abbreviations: DASS = Depression Anxiety Stress Scale, INT = intervention, CON = control, U= unadjusted *P* value, A = *P* value adjusted for baseline.

The improvements in MSDs did not translate into fewer days lost from work. We are not sure whether the reduction of MSDs had an effect on the number and episodes of sick leave among workers. We measured a reduction in the symptoms' frequency but not the severity and duration of pain among respondents. Therefore, it was unclear whether training reduced MSDs and resulted in fewer sick days among respondents. Similarly, intervention had no effect on workers' psychological well-being. The lack of significant changes on depression, anxiety, and stress, assessed by the DASS-21 questionnaire, may have been due to a floor effect. As a whole, the samples did not demonstrate a significant level of depression, anxiety, and stress at the baseline, and this did not change over the course of the study. Our findings did not agree with the results of Bohr (29), who reported that training improved the health status and reduced the respondents' psychosocial work stress perceptions among those who received the education programs. The researcher was not sure whether the decrease of psychosocial work stress was caused by the improvement in the work area configuration or the improvement in the worker's posture.

The present study provided evidence that training had a positive impact on the workers' musculoskeletal disorders at a 6-month follow-up. Several studies conducted on the effectiveness of office ergonomic training on MSDs included a follow-up at 12th month. These studies provided evidence of a long-term positive effect of training on MSDs. The current researchers are also interested in conducting a follow-up at 12th months to determine the impact of training on musculoskeletal disorders, number of days and episodes of sick leave, and psychological well-being.

Contamination between individuals from the same clusters may influence the outcome effect. In addition, transfer of knowledge between clusters might occur during social interactions or from workers who were from the same geographical area but in different locations (i.e., buildings). We did not adjust for confounding effects, such as age, years of working with computers, or hours spent typing, in the analysis of the effects of the intervention. Although these confounding effects might influence the outcome, they were fairly well balanced at baseline by the randomisation process. The strength of our study was the randomisation of groups for intervention and control, which is the most efficient way to control for the effects of known and unknown confounding effects. However, blinding the respondents and the researchers could have helped reduced the responder and observer biases.

Conclusion

The current study was a preliminary report to determine the effectiveness of office ergonomic training to reduce MSDs in UTM. We found that office ergonomic training improved workstation habits and reduced MSDs among office workers. We hope that the results will benefit the UTM staff because they demonstrate to the management that inexpensive ergonomic training had a positive impact on the safety and health of office workers. University management can actively participate in both training and investing in adjustable furniture for office workers. Further research that combines training and the use of adjustable furniture in UTM is recommended in the future.

Acknowledgements

The authors thank each member of units who participated in the study, and also the Director of Occupational Health and Safety Unit, UTM, who supported our study. We also would like to thank trainers from NIOSH who conducted workstation observations.

Authors' Contributions

Conception and design, analysis and interpretation of the data: NM, DK
Collection and assembly of the data: NM, DK, RMZ, SNH
Drafting of the article: NM
Critical revision of the article: DK

Correspondence

Dr Norashikin Mahmud
PhD Health Sciences (University of Sydney)
Program of Industrial and Organizational Psychology
Faculty of Management and Human Resource Development
Universiti Teknologi Malaysia
81310 Skudai, Johor
Malaysia
Tel: +607-553 6442
Fax: +607-556 6911
Email: norashikin@fppsm.utm.my

References

1. Halford V, Cohen HH. Technology use and psychosocial factors in the self-reporting of musculoskeletal disorder symptoms in call center workers. *J Safety Res*. 2003;**34(2)**:167–173.
2. Sillanpaa J, Huikko S, Nyberg M, Kivi P, Laippala P, Uitti J. Effect of work with visual display units on musculo-skeletal disorders in the office environment. *Occup Med*. 2003;**53(7)**:443–451.
3. Ekman A, Andersson A, Hagberg M, Hjelm EW. Gender differences in musculoskeletal health of computer and mouse users in the Swedish workforce. *Occup Med*. 2000;**50(8)**:608–613.
4. Johnston V, Souvlis T, Jimmieson NL, Jull G. Associations between individual and workplace risk factors for self-reported neck pain and disability among female office workers. *Appl Ergon*. 2008;**39(2)**:171–182.
5. Spyropoulos P, Papathanasiou G, Georgoudis G, Chronopoulos E, Koutis H, Koumoutsou F. Prevalence of low back pain in Greek public office workers. *Pain Physician*. 2007;**10(5)**:651–660.
6. Demure B, Luippold RS, Bigelow C, Ali D, Mundt KA, Liese B. Video display terminal workstation improvement program: I. Baseline associations between musculoskeletal discomfort and ergonomic features of workstations. *J Occup Environ Med*. 2000;**42(8)**:783–791.
7. Nakazawa T, Okubo Y, Suwazono Y, Kobayashi E, Komine S, Kato N, et al. Association between duration of daily VDT use and subjective symptoms. *Am J Ind Med*. 2002;**42(5)**:421–426.
8. Ortiz-Hernandez L, Tamez-Gonzalez S, Martinez-Alcantara S, Mendez-Ramirez I. Computer use increases the risk of musculoskeletal disorders among newspaper office workers. *Arch Med Res*. 2003;**34(4)**:331–342.
9. Ye Z, Abe Y, Kusano Y, Takamura N, Eida K, Takemoto T, et al. The influence of visual display terminal use on the physical and mental conditions of administrative staff in Japan. *J Physiol Anthropol*. 2007;**26(2)**: 69–73.
10. Palmer KT, Cooper C, Walker-Bone K, Syddall H, Coggon D. Use of keyboards and symptoms in the neck and arm: Evidence from a national survey. *Occup Med*. 2001;**51(6)**:392–395.
11. Klussmann A, Gebhardt H, Liebers F, Rieger MA. Musculoskeletal symptoms of the upper extremities and the neck: A cross-sectional study on prevalence and symptom-predicting factors at visual display terminal (VDT) workstations. *BMC Musculoskelet Disord*. 2008;**9**:96.
12. Faucett J, Rempel D. VDT-related musculoskeletal symptoms: Interactions between work posture and psychosocial work factors. *Am J Ind Med*. 1994;**26(5)**:597–612.
13. Hanse J. The impact of VDU use and psychosocial factors at work on musculoskeletal shoulder symptoms among white-collar workers. *Work Stress*. 2002;**16(2)**:121–126.
14. Polanyi MF, Cole DC, Beaton DE, Chung J, Wells R, Abdolell M, et al. Upper limb work-related musculoskeletal disorders among newspaper employees: Cross-sectional survey results. *Am J Ind Med*. 1997;**32(6)**:620–628.
15. Haufler AJ, Feuerstein M, Huang GD. Job stress, upper extremity pain and functional limitations in symptomatic computer users. *Am J Ind Med*. 2000;**38(5)**:507–515.
16. Hannan LM, Monteilh CP, Gerr F, Kleinbaum DG, Marcus M. Job strain and risk of musculoskeletal symptoms among a prospective cohort of occupational computer users. *Scand J Work Environ Health*. 2005;**31(5)**:375–386.
17. Hush JM, Michaleff Z, Maher CG, Refshauge K. Individual, physical and psychological risk factors for neck pain in Australian office workers: A 1-year longitudinal study. *Eur Spine J*. 2009;**18(10)**:1532–1540.
18. Kryger AI, Andersen JH, Lassen CF, Brandt LP, Vilstrup I, Overgaard E, et al. Does computer use pose an occupational hazard for forearm pain; from the NUDATA study. *Occup Environ Med*. 2003;**60(11)**:14.
19. Smith L, Louw Q, Crous L, Grimmer-Somers K. Prevalence of neck pain and headaches: Impact of computer use and other associative factors. *Cephalalgia*. 2009;**29(2)**:250–257.
20. Werner RA, Franzblau A, Gell N, Ulin SS, Armstrong TJ. A longitudinal study of industrial and clerical workers: Predictors of upper extremity tendonitis. *J Occup Rehabil*. 2005;**15(1)**:37–46.
21. Juul-Kristensen B, Sogaard K, Stroyer J, Jensen C. Computer users' risk factors for developing shoulder, elbow and back symptoms. *Scand J Work Environ Health*. 2004;**30(5)**:390–398.
22. Brandt LP, Andersen JH, Lassen CF, Kryger A, Overgaard E, Vilstrup I, et al. Neck and shoulder symptoms and disorders among Danish computer workers. *Scand J Work Environ Health*. 2004;**30(5)**:399–409.
23. Nicholas RA, Feuerstein M, Suchday S. Workstyle and upper-extremity symptoms: A biobehavioral perspective. *J Occup Environ Med*. 2005;**47(4)**: 352–361.
24. Wilson d'Almeida K, Godard C, Leclerc A, Lahon G. Sickness absence for upper limb disorders in a French company. *Occup Med*. 2008;**58(7)**:506–508.
25. Nyman T, Grooten WJA, Wiktorin C, Liwing J, Norrman L. Sickness absence and concurrent low back and neck-shoulder pain: results from the MUSIC-Norrtalje study. *Eur Spine J*. 2007;**16(5)**:631–638.

26. Westgaard RH, Winkel J. Ergonomic intervention research for improved musculoskeletal health: A critical review. *Int J Ind Ergonom*. 1997;**20(6)**: 463–500.

27. Marcoux BC, Krause V, Nieuwenhuijsen ER. Effectiveness of an educational intervention to increase knowledge and reduce use of risky behaviors associated with cumulative trauma in office workers. *Work*. 2000;**14(2)**:127–135.

28. Lewis RJ, Fogleman M, Deeb J, Crandall E, Agopsowicz D. Effectiveness of a VDT ergonomics training program. *Int J Ind Ergon*. 2001;**27(2)**:119–131.

29. Bohr PC. Office ergonomics education: A comparison of traditional and participatory methods. *Work*. 2002;**19(2)**:185–191.

30. Rizzo TH, Pelletier KR, Serxner S, Chikamoto Y. Reducing risk factors for cumulative trauma disorders (CTDs): The impact of preventive ergonomic training on knowledge, intentions, and practices related to computer use. *Am J Health Promot*. 1997;**11(4)**:250–253.

31. Amick BC 3rd, Robertson MM, DeRango K, Bazzani L, Moore A, Rooney T, et al. Effect of office ergonomics intervention on reducing musculoskeletal symptoms. *Spine*. 2003;**28(24)**:2706–2711.

32. Robertson MM, Huang YH, O'Neill MJ, Schleifer LM. Flexible workspace design and ergonomics training: Impacts on the psychosocial work environment, musculoskeletal health, and work effectiveness among knowledge workers. *Appl Ergon*. 2008;**39(4)**:482–494.

33. Robertson M, Amick BC 3rd, DeRango K, Rooney T, Bazzani L, Harrist R, et al. The effects of an office ergonomics training and chair intervention on worker knowledge, behavior and musculoskeletal risk. *Appl Ergon*. 2009;**40(1)**:124–135.

34. Mahmud N, Kenny DT, Heard R. Office ergonomics awareness and prevalence of musculoskeletal disorders among office workers in the Universiti Teknologi Malaysia: A cross sectional study. *Malaysian J Med Health Sci*. Forthcoming.

35. Kuorinka I, Jonsson B, Kilbom A, Vinterberg H, Biering-Sorensen F, Andersson G, et al. Standardised Nordic questionnaires for the analysis of musculoskeletal symptoms. *Appl Ergon*. 1987;**18(3)**:233–237.

36. Lovibond SH, Lovibond PF. *Manual for the Depression Anxiety Stress Scales*. 2nd ed. Sydney: Psychology Foundation; 1995.

37. Greene BL, DeJoy DM, Olejnik S. Effects of an active ergonomics training program on risk exposure, worker beliefs, and symptoms in computer users. *Work*. 2005;**24(1)**:41–52.

38. Harrington SS, Walker BL. The effects of ergonomics training on the knowledge, attitudes, and practices of teleworkers. *J Safety Res*. 2004;**35(1)**:13–22.

Original Article

Microbiology of Lower Respiratory Tract Infections in Benin City, Nigeria

Christopher Aye Egbe[1], Casimir Ndiokwere[1], Richard Omoregie[1,2]

Submitted: 2 Oct 2010
Accepted: 21 Dec 2010

[1] *Department of Medical Microbiology, University of Benin Teaching Hospital, PMB 1111, Benin City, Edo State, Nigeria*

[2] *School of Medical Laboratory Science, University of Benin Teaching Hospital, PMB 1111, Benin City, Edo State, Nigeria*

Abstract

Background: **Lower respiratory tract infections are among the most common infectious diseases of humans worldwide and continue to be a major cause of morbidity in Nigeria. This study focused on determining the microbial agents of lower respiratory tract infections, the effect of age and gender on its prevalence, and the susceptibility profile of bacterial isolates.**

Methods: **Sputum specimens were collected from 1539 patients with symptoms of lower respiratory tract infections. The sputum specimens were processed to recover microbial aetiologic agents and susceptibility profiles of bacterial isolates were determined using standard techniques.**

Results**: An overall prevalence of 18.91% of lower respiratory tract infections was observed in this study. There is no difference in the prevalence of lower respiratory tract infection between the genders (*P* = 0.649). The prevalence of lower respiratory tract infections increases significantly with age (*P* < 0.001), with patients 71 years and older having the highest prevalence. *Klebsiella pneumoniae* was the most predominant isolate causing lower respiratory tract infection while *Acinetobacter* species were the least predominant isolate. The fluoroquinolones, β-lactams, and gentamicin showed moderate to high activity.**

Conclusion**: Gender did not affect the prevalence, but age did. β-lactams, fluoroquinolones, and gentamicin were the most active antibacterial agents and, therefore, the drugs of choice in treating lower respiratory tract infections in our setting.**

Keywords: *aetiology, antibacterial agents, clinical microbiology, Nigeria, prevalence, respiratory tract infections*

Introduction

Lower respiratory tract infections (LRTIs) are among the most common infectious diseases affecting humans worldwide (1). They are important causes of morbidity and mortality for all age groups, and each year approximately 7 million people die as a direct consequence of acute and chronic respiratory infections (2). In Nigeria, LRTIs continue to be the major cause of morbidity (3). Age, gender, and season are factors that have been implicated to affect the prevalence of LRTIs (4).

The aetiologic agents of LRTIs vary from area to area (2,5), so the susceptibility profile will also differ between geographical locations. Knowing the local susceptibility profile is important, as antimicrobial therapies for LRTIs are frequently empirical and presumptive (2). Current knowledge of the organisms that cause LRTIs and their antibiotic susceptibility profiles are therefore necessary for the prescription of appropriate therapy. This study was conducted to determine the microbial agents of human respiratory tract infections, the effect of age and gender on the prevalence of LRTIs, and the susceptibility pattern of bacterial isolates.

Subjects and Methods

Study population

A retrospective laboratory record review was undertaken. This study recruited a total of 1539 patients with symptoms of LRTIs who visited the chest clinic of the University of Benin Teaching Hospital, Benin City, Nigeria, between 1 February 2007 and 30 July 2010; 841 patients were men and 698, women. The age range of the patients was between 2 and 98 years. Exclusion criteria included antibiotic usage within 1 week prior to clinic visit, positive for HIV, or sputum smear positive for acid-fast bacilli. Verbal

informed consent was obtained from each patient or their parents/guardians (for children) prior to specimen collection. The Ethical Committee of University of Benin Teaching Hospital approved this study.

Specimen collection and processing

Early morning sputum specimens, or for children, transtracheal aspirates, were collected from each patient into wide-mouthed sterile containers and transported to the laboratory. Films were made from the sputum specimens and stained by Gram's method. The presence of numerous pus cells confirms true sputum and only such specimens were cultured. Each sputum sample was inoculated on chocolate, blood, and MacConkey agar plates. The plates were incubated at 37 °C for 24–48 hours. Emergent colonies were identified using standard methods (6). Susceptibility tests were performed on significant bacterial isolates using the British Society for Antimicrobial Chemotherapy (BSAC) standardized disc susceptibility testing method (7).

Statistical analysis

The data obtained were analyzed with chi-square (χ^2) test using the INSTAT® statistical software (GraphPad Software Inc, San Diego, CA, USA).

Result

A total of 291 (18.91%) out of 1539 sputum samples yielded significant growth. There were no significant differences in the prevalence of LRTIs (P = 0.649) and mixed infections (P = 0.196) between men and women (Table 1). The prevalence of LRTIs increased significantly (P < 0.001) with age, with the age group of 71 years and older having the highest prevalence, 48.57% (Table 2). Generally, *Klebsiella pneumoniae* (30.16%) was the predominant isolate recovered, followed by *Haemophilus influenzae* (17.05%), *Staphylococcus aureus* (15.41%), and *Acinetobacter species* (0.66%). *K. pneumoniae* was also the predominant isolate in both genders. *S. aureus* was the second most predominant isolate in women, whereas

Table 1: Effect of gender on the prevalence of lower respiratory tract infections

Gender	No. tested	No. positive growth (%)	No. with mixed growth (%)
Male	841	163 (19.38)	5 (3.07)
Female	698	128 (18.34)	9 (7.03)
Total	**1539**	**291 (18.91)**	**14 (4.81)**

Gender versus positive growth: χ^2= 0.207, P= 0.649
Gender versus mixed growth: χ^2= 1.670, P= 0.196

Table 2: Effect of age on the prevalence of lower respiratory tract infections

Age (years)	Male		Female		Total	
	No. tested	No. positive growth (%)	No. tested	No. positive growth (%)	No. tested	No. positive growth (%)
1–10	38	5 (13.16)	34	9 (26.49)	72	14 (19.44)
11–20	77	3 (3.90)	38	6 (15.79)	115	9 (7.88)
21-30	233	43 (18.45)	220	26 (11.82)	453	69 (15.23)
31-40	265	58 (21.89)	206	35 (16.99)	471	93 (19.75)
41-50	88	27 (30.68)	82	14 (17.07)	170	41 (24.12)
51-60	81	17 (20.99)	71	16 (22.54)	152	33 (21.71)
61–70	41	4 (9.76)	30	11 (36.67)	71	15 (21.13)
≥ 71	18	6 (33.33)	17	11 (64.71)	35	17 (48.57)

Age versus positive growth: χ2= 37.484, P < 0.001

Table 3: Aetiologic agents in lower respiratory tract infections

Organisms	Males (%)		Females (%)		Total (%)	
Escherichia coli	6	(3.60)	7	(5.12)	13	(4.26)
Klebsiella pneumoniae	47	(27.98)	45	(32.85)	92	(30.16)
Citrobacter species	5	(2.98)	4	(2.92)	9	(2.95)
Enterobacter species	2	(1.19)	1	(0.73)	3	(0.98)
Proteus species	18	(10.71)	5	(3.65)	23	(7.54)
Providencia species	5	(2.98)	5	(3.65)	10	(3.29)
Acinetobacter species	1	(0.60)	1	(0.73)	2	(0.66)
Alcaligenes species	6	(3.60)	6	(4.38)	12	(3.93)
Pseudomonas aeruginosa	9	(5.36)	5	(3.65)	14	(4.59)
Haemophilus influenza	31	(18.45)	21	(15.33)	52	(17.05)
Staphylococcus aureus	24	(14.29)	23	(16.79)	47	(15.41)
Streptococcus pneumoniae	1	(0.60)	5	(3.65)	6	(1.97)
Candida albicans	13	(7.74)	9	(6.57)	22	(7.21)
Total	**168**	**(55.08)**	**137**	**(44.92)**	**305**	**(100)**

H. influenzae was the second most predominant isolate in men (Table 3). *K. pneumoniae* and *Candida albicans* were isolated from 5 patients, making them the highest combination of mixed infection, while the followings were isolated from 1 patient each: *Proteus* species and *K. pneumoniae, K. pneumoniae* and *Enterobacter* species, *K. pneumoniae* and *Providencia* species, *Escherichia coli* and *C. albicans*, *E. coli* and *Proteus* species, *Citrobacter* species and *Alcaligenes* species, *Citrobacter* species and *Proteus* species, *H. influenzae* and *C. albicans*, and *H. influenzae* and *S. aureus*.

The susceptibility profile of bacterial isolates is shown in Table 4. The fluoroquinolones (ofloxacin, ciprofloxacin), β-lactams (amoxicillin-clavulanate, cefuroxime, cetazidime, ceftriaxone), and gentamicin showed moderate to high activity. Sulfamethoxazole-trimetroprim, tetracycline, erythromycin, and cloxacillin showed no activity against any bacterial isolates.

Discussion

The aetiologic agents of LRTIs vary from area to area, and the bacterial aetiology as well as their susceptibility pattern will be useful in the management of this infection. This study focused on determining the prevalence of microbial aetiology of LRTIs and their susceptibility profile.

A total of 291 (18.91%) of the 1539 sputum specimens yielded clinically significant pathogens. This prevalence is lower than the figures in previous reports: 59.4% (2), 47.2% (3), and 27.0% (8). Among children with diarrhea, prevalence of the infection varied with geographical locations, regions within the same country, and even over time in the same location and population (9). Indeed, the Ozyilmaz et al.'s study (2) was conducted in Turkey, the Egbagbe and Mordi's study (3) was conducted in University of Benin Teaching Hospital, Benin City, Nigeria, while the Okesola and Ige's study (8) was conducted in Ibadan in Nigeria.

Previous reports had also indicated higher prevalence of LRTIs in women than in men (3,8). However, in this study the prevalence of LRTIs did not differ significantly between men and women. The prevalence of LRTIs was significantly higher in patients 71 years and older. People within this age group may have lower immunity due to age (10) or other ailments that may compromise the immune system, which may explain the high prevalence observed in this study.

K. pneumoniae was the most predominant isolate recovered from patients with LRTIs. This is in agreement with previous studies (3,8); however, another study (2) reported *H. influenzae* as the most prevalent. *Acinetobacter* species have been associated with hospital-acquired pneumonia (1), but as our subjects were outpatients, the *Acinetobacter* species recovered

Table 4: Susceptibility profiles of bacterial agents of lower respiratory tract infections

Organisms	Antibacterial agents (µg/disc)											
	OFX (5)	CIP (5)	CN (10)	AUG (30)	SXT (25)	OB (5)	TE (10)	CXM (30)	C (10)	E (5)	CRO (30)	CAZ (30)
Escherichia coli (*n* = 13)	13 (100.0)	13 (100.0)	13 (100.0)	13 (100.0)	0 (0.0)	ND	0 (0.0)	11 (84.6)	0 (0.0)	ND	12 (92.3)	11 (84.6)
Klebsiella pneumonia (*n* = 92)	88 (95.6)	86 (93.5)	79 (85.9)	86 (95.6)	0 (0.0)	ND	0 (0.0)	86 (93.5)	0 (0.0)	ND	84 (91.3)	81 (88.0)
Citrobacter species (*n* = 9)	9 (100.0)	9 (100.0)	6 (66.7)	0 (0.0)	0 (0.0)	ND	0 (0.0)	9 (100.0)	0 (0.0)	ND	7 (77.8)	5 (55.6)
Enterobacter species (*n* = 3)	3 (100.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	ND	0 (0.0)	3 (100.0)	0 (0.0)	ND	3 (100.0)	3 (100.0)
Proteus species (*n* = 23)	23 (100.0)	19 (82.6)	17 (73.9)	19 (82.6)	0 (0.0)	ND	0 (0.0)	19 (82.6)	0 (0.0)	ND	10 (43.5)	10 (43.5)
Providencia species (*n* = 10)	10 (100.0)	8 (80.0)	6 (60.0)	10 (100.0)	0 (0.0)	ND	0 (0.0)	8 (80.0)	3 (30.0)	ND	6 (60.0)	6 (60.0)
Acinetobacter species (*n* = 2)	2 (100.0)	2 (100.0)	1 (50.0)	10 (100.0)	0 (0.0)	ND	0 (0.0)	1 (50.0)	0 (0.0)	ND	1 (50.0)	0 (0.0)
Alcaligenes species (*n* = 12)	10 (83.3)	8 (66.7)	7 (58.3)	10 (83.3)	0 (0.0)	ND	0 (0.0)	8 (66.7)	0 (0.0)	ND	8 (66.7)	7 (58.3)
Pseudomonas aeruginosa (*n* = 14)	14 (100.0)	2 (85.7)	10 (71.4)	6 (42.9)	0 (0.0)	ND	0 (0.0)	0 (0.0)	0 (0.0)	ND	9 (64.3)	6 (42z.9)
Haemophilus influenzae (*n* = 52)	52 (100.0)	50 (96.2)	50 (96.2)	47 (90.3)	0 (0.0)	ND	0 (0.0)	45 (86.5)	0 (0.0)	ND	48 (92.3)	47 (90.4)
Staphylococcus aureus (*n* = 47)	47 (100.0)	43 (91.45)	39 (83.0)	41 (67.2)	0 (0.0)	0 (0.0)	0 (0.0)	44 (93.6)	0 (0.0)	0 (0.0)	43 (91.5)	40 (85.1)
Streptococcus pneumoniae (*n* = 6)	6 (100.0)	6 (100.0)	0 (0.0)	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (83.3)	0 (0.0)	0 (0.0)	5 (83.3)	5 (83.3)

Data are expressed in number of susceptible isolates (percentage susceptibility).
Abbreviations: OFX = ofloxacin, CIP = ciprofloxacin, CN = gentamicin, AUG = amoxycillin/clavulanate, SXT = cotrimoxazole, OB = cloxacillin, TE = tetracycline, CXM = cefuroxime, ND = not done, C = chloramphenicol, E = erythromycin, CRO = ceftriaxone, CAZ = ceftazidime.

in this study may be associated with community-acquired LRTIs. Further investigation is required to verify this result, as many patients come to our centre after visiting either public hospitals or primary and secondary care hospitals. Other microbial agents recovered in this study have been reported to be associated with LRTIs (1–3,8).

The susceptibility pattern of the bacterial isolates revealed that β-lactams, gentamicin, and flouroquinolones were very active against the bacterial isolates. This is surprising as sales of antibiotics without prescriptions are rife in Nigeria (11,12). However, sulfamethoxazole-trimetroprim, tetracycline, cloxacillin, and

erythromycin were not active against any bacterial isolate, while only 30% of *Providencia* species were susceptible to chloramphenicol. This may indicate resistance has evolved due to long-term use of these quite affordable antibacterial agents in the community. The fluoroquinolones are contraindicated in children and pregnant women, while ceftriaxone, ceftazidime, and cefuroxine are very expensive. Gentamicin has toxic side effect in patients with renal impairment, so amoxicillin/clavulanate appears to be the drug of choice, depending on the bacterial isolates.

Conclusion

An overall prevalence of 18.91% of LRTIs was observed in this study. Gender did not affect the prevalence of LRTIs. Patients of 71 years and older have a significantly higher prevalence of LRTI compared with other age groups. *K. pneumoniae* is the most predominant bacteria isolates. β-lactams, fluoroquinolones, and gentamicin were the most active antibacterial agents. This study highlights the aetiology of LRTIs and the bacteria susceptibility profiles may be helpful for empiric therapy.

Correspondence

Mr Christopher Aye Egbe
MSc Medical Microbiology (Ambrose Alli University)
Department of Medical Microbiology
University of Benin Teaching Hospital
PMB 1111, Benin City
Edo State, Nigeria
Tel: +2348055963431
Email: egbeaye@yahoo.com

References

1. Carroll KC. Laboratory diagnosis of lower respiratory tract infections: Controversy and conundrums. *J Clin Microbiol*. 2002;**40(9)**:3115–3120.

2. Ozyilmaz E, Akan OA, Gulhan M, Ahmed K, Nagatake T. Major bacteria of community-acquired respiratory tract infections in Turkey. *J Infect Dis*. 2005;**58(1)**: 50–52.

3. Egbagbe EE, Mordi RM. Aetiology of lower respiratory tract infection in Benin City, Nigeria. *J Med Biomed Res*. 2006;**5(2)**:22–27.

4. Erling V, Jalil F, Hanson LA, Zaman S. The impact of climate on the prevalence of respiratory tract infection in early childhood in Lahore, Pakistan. *J Pub Health*. 1999;**21(3)**:331–339.

5. Liebowitz LD, Slabbert M, Huisamen A. National surveillance programme on susceptibility patterns of respiratory pathogens in South Africa: Moxifloxacin compared with eight other antimicrobial agents. *J Clin Path*. 2003;**56(5)**:3444–3447.

6. Barrow GI, Feltham RKA. *Cowan and Steel's manual for the identification of medical bacteria*. 3rd ed. Cambridge (UK): Cambridge University Press; 2003.

7. Andrews JM. BSAC standardized disc susceptibility testing method (version 8). *J Antimicrob Chemother*. 2009;**64(3)**:454–489.

8. Okesola AO, Ige OM. Trends in bacterial pathogens of lower respiratory tract infections. *Indian J Chest Dis Allied Sci*. 2007;**50(3)**:270–272.

9. Petri WA Jr, Miller M, Brinder HJ, Levine MM, Dillingham R, Guerrant RL. Enteric infections, diarrhea, and their impact on function and development. *J Clin Invest*. 2008;**118(4)**:1277–1290.

10. Hakim FT, Gress RE. Immunosenescence: Deficits in adaptive immunity in the elderly. *Tissue Antigens*. 2007;**70(3)**:179–189.

11. Okeke IN, Lamikara A, Edelman R. Socio-economic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerg Infect Dis*. 1999;**5(1)**:18–27.

12. Omoregie R, Eghafona NO. Urinary tract infection among asymptomatic HIV patients in Benin City, Nigeria. *Br J Biomed Sci*. 2009;**66(4)**:190–193.

Original Article

The Changes of Tear Status after Conventional and Wavefront-Guided IntraLASIK

Say Kiang Foo[1], Sharanjeet-Kaur[2], Faudziah Abd Manan[2], Aloysius Joseph Low[3]

Submitted: 19 Oct 2010
Accepted: 9 Dec 2010

[1] *Faculty of Optometry & Vision Sciences, SEGi University College, No. 9, Jalan Teknologi, Kota Damansara, 47810 Petaling Jaya, Selangor, Malaysia*

[2] *Department of Optometry, Faculty of Allied Health Sciences, Universiti Kebangsaan Malaysia, Jalan Raja Muda, 50300 Kuala Lumpur, Malaysia*

[3] *Vista Laser Eye Center Sdn Bhd, Unit 228, The Curve, Mutiara Damansara, 47800 Petaling Jaya, Selangor, Malaysia*

Abstract

Background: **IntraLASIK is a LASIK surgery that involved IntraLase femtosecond laser for the corneal flap creating. The objective of this research was to investigate and compare the changes in tear status at 1 and 3 months after undergoing conventional IntraLASIK with Bausch & Lomb PlanoScan (PS) algorithm, Bausch & Lomb Zyoptix Tissue Saving (ZTS) algorithm, and wavefront-guided (WG) IntraLASIK with VISX CustomVue.**

Methods: **Tear status of 36 patients who were divided into 3 groups depending on the type of IntraLASIK they underwent (PS, *n* = 13; ZTS, *n* = 9; WG, *n* = 14) was evaluated. Tear status was determined by classifying the category of the thickness of pre-corneal tear lipid layer, non-invasive tear break-up time, and tear meniscus height. Repeated measures analysis of variance (ANOVA) and one way ANOVA were used for the statistical analyses.**

Results**: The category of the thickness of tear lipid layer, non-invasive tear break up time and tear meniscus height were neither significantly changed after IntraLASIK for all groups nor showed significant difference among groups at 1 and 3 months post-IntraLASIK (*P* > 0.05). Blinking rate and palpebral aperture also had no significant changed after IntraLASIK.**

Conclusion**: Both conventional (PS and ZTS) and WG IntraLASIK did not affect tear status up to 3 months post-IntraLASIK. WG IntraLASIK did not show superiority in preserving tear status 1 and 3 months post-surgery compared with conventional IntraLASIK.**

Keywords: *laser, LASIK, ophthalmology, refractive surgery, side effects, tear*

Introduction

Laser in situ keratomileusis (LASIK) has provided patients with fast and relatively painless recovery of vision, lower probability of regression of refractive correction, and absence of subepithelial haze (1). However, LASIK has been shown to affect the health of the ocular surface by decreasing corneal sensation (2), tear secretion, tear quality, corneal and conjunctival epithelial integrity, and conjunctival goblet cell density (3). As a consequence, these alterations decrease tear film stability (4), which may lead to dry eye symptom during the first 6 months post-surgery (1,2,5,6). Asians have been reported to be more prone to having dry eyes after LASIK surgery compared with Caucasians (7). The prevalence of myopia is much higher in Asians than in Caucasians (8,9) and appears to be increasing in urbanised Asian communities (10). Presently, LASIK continues to be the dominant refractive surgery procedure for myopia (11), and therefore it is likely that an increasing number of myopic Asians will opt for LASIK for refractive correction. Advancement of the technology in refractive surgery, such as the improvements in machine features and the introduction of IntraLase femtosecond laser and wavefront-guided LASIK, can minimise the risk of having dry eye symptom after LASIK surgery.

Wavefront-guided (WG) LASIK uses customized laser ablation with the help of aberrometer to treat visual problems, including higher-order aberrations. This method provides better vision quality than conventional LASIK (12,13). With the availability of various ablation sizes, WG laser is able to save more corneal tissue compared with several conventional LASIK procedures. Both Bausch & Lomb PlanoScan (PS) algorithm and Zyoptix Tissue Saving (ZTS) algorithm are examples of conventional LASIK procedures, which treat defocus and astigmatism measured from subjective refraction method. ZTS have been shown to reduced ablation depth (14) with availability of smaller ablation size and truncated Gaussian laser beam compared with PS. The lower ablation depth minimized the injury to the corneal layer during the surgery and reduced the risk of post-LASIK dry eye.

As such, a study was conducted in Vista Laser Eye Center, Petaling Jaya, Malaysia, where the demand of the LASIK surgery is increasing in recent years. In this study, the tear characteristics before and after LASIK surgery in which IntraLase femtosecond laser was used to create the corneal flap (IntraLASIK) was assessed. The aim of this study was to investigate the changes of tear status and compare the tear status among 3 IntraLASIK procedures at 1 and 3 months post-IntraLASIK. The study also aimed to find out whether the improvement of the methods or techniques could minimize the complications caused by LASIK.

Subjects and Methods

A total of 36 patients who gave written informed consent were recruited in this prospective, longitudinal, and non-randomized study. The study was approved by Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee (UKM 1.5.3.5/244/SPP2, 24 July 2006) and was conducted according to the tenets of Declaration of Helsinki.

The eligibility criteria were as follows:

- age between 20 and 35 years;
- no autoimmune, metabolic, or uncontrolled systemic disease;
- no active disease of the external eye or adnexae;
- no intraocular disease;
- no degenerative or neurotrophic corneal disease;
- no pre- or post-operative use of topical medications other than those prescribed;
- no previous ocular surgery or trauma;
- not pregnant, expecting to become pregnant within 6 months following the LASIK procedure, or breastfeeding;
- stable refraction for at least 12 months within ± 0.50 D prior to LASIK;
- refractive error within -1.00 DS and -12.00 DS and maximum astigmatism of -4.00 D;
- stable keratometry and pachymetry following cessation of contact lens wear;
- no lenticular opacities identified before or after surgery that were deemed to have a significant effect on the refractive outcome; and
- compliant with prescribed tear film and ocular surface management before and after surgery.

Patients who failed to attend all the visits and undergo all the clinical examinations required were excluded from this study.

All LASIK procedures were performed by two ophthalmologists in Vista Eye Laser Center, and the clinical examinations were performed by an optometrist who was blinded to what type of LASIK surgery patients underwent. The patients were divided into 3 groups depending on the type of LASIK surgery they underwent: conventional LASIK with PS or ZTS, and WG LASIK with VISX CustomVue. IntraLase femtosecond laser (FS30) was used to create the corneal flap for all the patients. The decision on the type of IntraLASIK to be performed on each subject was based on the ophthalmologist's recommendation, which depended on subject's refractive error, corneal layer thickness, pupil size, and subject's individual expectation of the surgery outcome. If the subject was eligible for all 3 procedures, the decision would depend on subject's preference and the procedure's affordability.

The excimer laser platform used for PS and ZTS was Bausch & Lomb Technolas 217z; for WG, VISX STAR S4™. A 6.0-, 6.5-, or 7.0-mm ablation zone was selected based on the available corneal stroma thickness and pupil size. Corneal flap with 100- or 110-µm thickness and 90° superior hinge was created by IntraLase femtosecond laser. After surgery, all patients were given dexamethasone (0.1%) every 2 hours on the first day and 2 times daily for a week, moxifloxacin hydrochloride (5.45 mg) every 4 hours on the first day and 4 times daily for a week, and artificial tear every hour on the first day and 4 times or more daily for a month. All subjects had finished their medication with a minimum of 1 day before their 1-month post-IntraLASIK visit.

The tear status of the patients was assessed 1 week pre-surgery (baseline) as well as 1 and 3 months post-surgery. The clinical examination of tear status included classifying the category of thickness of pre-corneal tear lipid layer, non-invasive tear break-up time (NITBUT), and tear meniscus height (TMH). Blinking rate and palpebral aperture of patients were also measured at every visit.

Keeler Tearscope Plus was used to determine the category of the thickness of the pre-corneal tear lipid layer. The thickness of the tear lipid layer was divided into 5 categories based on the overall interference pattern on the tear lipid layer: (1) no lipid layer, (2) open/closed meshwork (up to 50 nm), (3) wave/flow (50 to 80 nm), (4) amorphous (80 to 90 nm), and (5) colour fringes (more than 90 nm). NITBUT was also measured by using Keeler Tearscope plus by observing the grid image on patient's eye. NITBUT was recorded as the interval between the last complete blink and the first appearance of a distortion on the grid image. Three readings were recorded; each new reading was taken after the patients had closed their eyes for 1 minute. TMH was measured using slit lamp biomicroscope; 25 times magnification and 0.3 mm slit height were used to guide the measurement. Only 1 reading was taken for each eye as the light from the slit lamp can cause tear stimulation, which will affect the study result. Blinking rate was taken while the patient was reading a distance chart for 1 minute, and palpebral aperture was measured using a ruler.

Statistical analyses were performed with SPSS 12.0 (SPSS Inc., Chicago, IL). Distributions of the data was determined first by using Shapiro–Wilk test and the skewness of the data; repeated measures analysis of variance (ANOVA) was used on the results with normally distributed data while Friedman test was used on non-normally distributed data or results with categorical variables to determine the significance of the changes in tear status after IntraLASIK. In order to determine the significance of the differences among the 3 groups, one way ANOVA was used for normally distributed data while Kruskal–Wallis test was used for non-normally distributed data.

Results

All 36 patients underwent bilateral IntraLASIK: 13 patients underwent conventional LASIK with PS, 9 patients underwent conventional LASIK with ZTS, and 14 patients underwent WG LASIK with VISX CustomVue. Only the result for the right eye was taken for this study. There were no intra- or post-operative complications up to 3 months of examination in this series of 36 eyes. The means of age and spherical equivalent for each group are shown in Table 1. There was no significant age difference among the 3 groups ($F(2, 33) = 0.345$, $P = 0.711$), but the PS group had significantly lower spherical equivalent refraction before LASIK compared with the other 2 groups (one-way ANOVA, $P = 0.045$). All patients attended their 1- and 3-month post-IntraLASIK visits.

There were no statistically significant differences among all 3 visits for all the parameters measured for the PS group, as shown in Table 2. NITBUT showed some increment at 1 and 3 months post-IntraLASIK, but the difference is not statistically significant. Blinking rate and palpebral aperture also did not change significantly at 1 and 3 months post-IntraLASIK. The ZTS group and WG group also showed no statistically significant changes at 1 and 3 months post-IntraLASIK in NITBUT, TMH, category of the thickness of tear lipid layer, blinking rate, and palpebral aperture, as shown in Table 3 and 4.

A comparison among the 3 groups at 1 month post-IntraLASIK shows no statistically significant differences for all the tear-related parameters measured, as shown in Table 5. All groups also showed no statistically significant differences at 3 months post-IntraLASIK (shown in Table 5), although PS group had significantly lower spherical equivalent refraction before surgery compared with the other 2 groups.

There were no differences among the medians of the lipid thickness category of all groups at 1 and 3 months post-IntraLASIK. However, based on the distribution of tear lipid layer thickness categories, there were increments in the subject number in thinner categories (less than 50 nm) for PS group (at 1 and 3 months post-IntraLASIK) and ZTS group (at 3 months post-IntraLASIK), as shown in Figure 1; such increment was not seen in WG group. On the other hand, WG group had an increment in the subject number in thicker categories (more than 80 nm) after IntraLASIK, and such increment was not seen in PS and ZTS groups.

Table 1: Means of age and spherical equivalent of subjects

Type of LASIK	*n*	Age (year)		Spherical Equivalent (D)		Range	
		Mean (SD)	Range	Mean (SD)	Range	Sphere (D)	Cylinder (-)(D)
PS	13	27.6 (3.9)	22–35	-4.43 (2.36)	-10.38 to -1.88	-8.75 to -1.75	0.00 to 3.25
ZTS	9	27.7 (4.7)	22–35	-6.24 (1.93)	-9.38 to -4.25	-9.00 to -4.00	0.00 to 2.00
WG	14	28.9 (4.4)	21– 35	-6.73 (3.13)	-12.50 to -2.75	-11.50 to -2.50	0.00 to 2.00
P value*		0.711		0.045			

* One-way ANOVA
Abbreviations: PS = PlanoScan algorithm, ZTS = Zyoptix Tissue Saving algorithm, WG = wavefront-guided.

Table 2: Tear status outcomes for PlanoScan (PS) group at baseline, 1 month, and 3 months post-IntraLASIK

Type of test	*n*	Baseline		Post-IntraLASIK				*P* value
				1 month		3 months		
NITBUT (s)	13	14.55	(9.05)	17.99	(5.84)	22.59	(13.38)	0.152 [b]
TMH (mm)	13	0.22	(0.06)	0.20	(0.06)	0.20	(0.06)	0.679 [b]
Lipid thickness (category)[a]	13	3	(2 to 5)	3	(2 to 4)	3	(2 to 5)	0.446 [c]
Blinking rate (no./ min)	13	12.85	(9.53)	14.46	(10.71)	15.69	(11.39)	0.511 [b]
Palpebral aperture (mm)	13	10.00	(0.65)	9.69	(0.95)	9.73	(1.15)	0.455 [b]

Data are expressed in mean (SD) with exception of [a] lipid thickness, in median (range). [b] Repeated measures ANOVA and [c] Friedman test were conducted.

Table 3: Tear status outcomes for Zyoptix Tissue Saving (ZTS) group at baseline, 1 month, and 3 months post-IntraLASIK

Type of test	*n*	Baseline		Post-IntraLASIK				*P* value
				1 month		3 months		
NITBUT (s)	9	14.82	(5.22)	12.87	(8.40)	15.44	(9.18)	0.781 [b]
TMH (mm)	9	0.19	(0.07)	0.15	(0.03)	0.18	(0.04)	0.189 [b]
Lipid thickness (category)[a]	9	3	(2 to 4)	3	(2 to 3)	3	(2 to 3)	0.472 [c]
Blinking rate (no./ min)	9	15.33	(8.70)	14.22	(8.23)	18.56	(8.76)	0.283 [b]
Palpebral aperture (mm)	9	10.17	(0.71)	9.56	(0.58)	9.56	(0.68)	0.054 [b]

Data are expressed in mean (SD) with exception of [a] lipid thickness, in median (range). [b] Repeated measures ANOVA and [c] Friedman test were conducted.

Table 4: Tear status outcomes for wavefront-guided (WG) group at baseline, 1 month, and 3 months post-IntraLASIK

Type of test	*n*	Baseline		Post-IntraLASIK				*P* value
				1 month		3 months		
NITBUT (s)	14	17.46	(9.19)	16.43	(11.84)	15.00	(10.21)	0.622 [b]
TMH (mm)	14	0.26	(0.22)	0.20	(0.09)	0.20	(0.08)	0.195 [b]
Lipid thickness (category)[a]	14	3	(2 to 5)	3	(2 to 5)	3	(2 to 5)	0.846 [c]
Blinking rate (no./ min)	14	15.93	(8.94)	14.86	(8.16)	16.71	(6.43)	0.565 [b]
Palpebral aperture (mm)	14	10.14	(1.31)	9.96	(1.39)	10.25	(1.45)	0.404 [b]

Data are expressed in mean (SD) with exception of [a] lipid thickness, in median (range). [b] Repeated measures ANOVA and [c] Friedman test were conducted.

Table 5: *P* values in the comparison of tear status assessments among PS, ZTS, and WG groups at baseline, 1 month, and 3 months post-IntraLASIK

Type of test	Baseline	Post-IntraLASIK	
		1 month	3 months
NITBUT (s)	0.620 [a]	0.442 [a]	0.180 [a]
TMH (mm)	0.575 [a]	0.167 [a]	0.726 [a]
Lipid thickness (category)	0.203 [b]	0.478 [b]	0.430 [b]
Blinking rate (no./ min))	0.661 [a]	0.986 [a]	0.767 [a]
Palpebral aperture (mm)	0.902 [a]	0.651 [a]	0.342 [a]

[a] One-way ANOVA and [b] Kruskal–Wallis test were conducted.

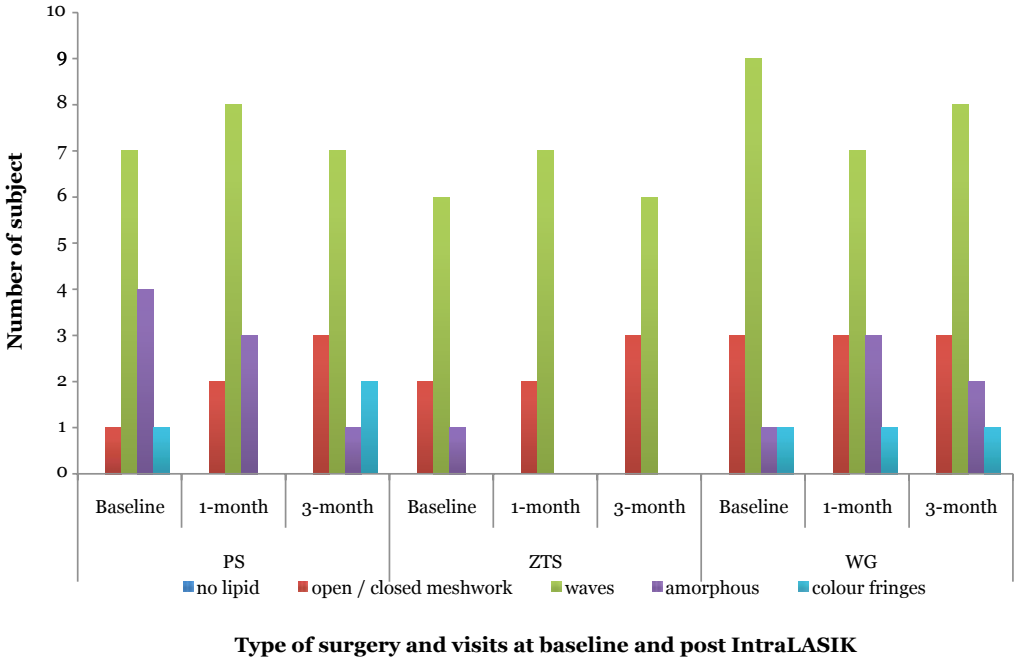

Figure 1: Frequency distribution of tear lipid layer thickness categories

Discussion

All assessments involved in this research were non-invasive as the cornea layer needs minimal disruption during its healing process. NITBUT and tear lipid layer thickness were used to check the tear quality and stability, and TMH was used to monitor the tear quantity. This study assessed the tear parameters at 3 visits (i.e., 1 week pre-IntraLASIK, 1 and 3 months post-IntraLASIK) to determine the effects of the IntraLASIK on patients' tear status.

Subjects who underwent conventional LASIK with PS showed no significant changes 1 and 3 months post-LASIK in TMH, NITBUT, and category of tear lipid layer thickness. There was a study that reported subjects having dry eye 1 month post-LASIK surgery (1), but the research used more invasive test, such as fluorescein tear break-up time and Schirmer test. Yu et al. (15) also showed lower tear break-up time after LASIK that was caused by operative trauma on cornea epithelium. In LASIK, the major corneal nerve trunks are severed by the microkeratome, and the anterior stromal nerves are disrupted by photoablation (16). Both processes damage the corneal innervation. The reduction in corneal neuronal feedback to the brain stem reduces brain stem innervation of the lacrimal glands, thus diminishing tear production. Corneal nerves regenerates post-operatively and corneal sensation returns to normal level within 3 to 6 months (1,17–19). However, another study reported that both sub-basal and stromal corneal nerves in LASIK flaps recovered slowly and did not return to pre-operative densities by 3 years post-LASIK (20). Kato et al. (21) also reported that the corneal recovery process took up to 9 months, while Benitez-del-Castillo et al. (22) reported that the tear secretion took up to 9 months for recovery after surgery.

All these studies were conducted before 2007, and technology in LASIK surgery has improved since then. One of the new technologies introduced in the recent years is the IntraLase femtosecond laser. Femtosecond laser is said to reduce the intra-operative risk in LASIK surgery and minimize damage to the corneal layer (23). This was seen in the present study as there was no significant changes in tear status after IntraLASIK for PS group. The IntraLase femtosecond laser may play an important role in maintaining the tear status after LASIK surgery.

Although the mean spherical equivalent before surgery for PS group was lower than the other 2 groups and thus less laser ablation was needed, there was no significant difference among the groups in terms of their tear quality and quantity.

ZTS group also showed no significant changes in NITBUT and TMH after surgery. This group had higher pre-operative mean spherical equivalent compared with PS group; however, with the introduction of IntraLase and availability of smaller laser beam size, the damage caused by more laser ablation on cornea could be minimized.

Based on data from Yu et al. (15), 59.4% of subjects who underwent LASIK surgery had dry eye symptoms 1 month post-surgery. The reasons given were injury to corneal epithelium caused by the surgery, toxicity from prescribed eye-drop, inflamatory responses to the surgery with the release of cytokines and immune mediator, reduction of corneal sensation that caused lower blinking rate, and the changes of corneal contour where flatter central corneal surface affects the distribution of the tear. However, in the current study, the blinking rates were not reduced after IntraLASIK in all groups. In fact, there was an increment in blinking rate 3 months post-IntraLASIK for all 3 groups; this could be a reaction to reduce the dryness of the eyes.

IntraLase femtosecond laser was used in this study for creating the corneal flap. A consistent and thinner corneal flap was created with IntraLase (24). The damage to the corneal layer could be reduced using this technology. IntraLase femtosecond laser also uses disposable suction ring, which causes less damages to the conjunctiva compared with microkeratome. This may reduce the possibility of the changes to the mucin layer in tear film, which is produced by conjuctival goblet cells. Salomao et al. (25) showed that eyes with femtosecond flaps had a lower incidence of LASIK-associated dry eye and required less treatment for the disorder compared with microkeratome.

WG group had the highest mean pre-operative spherical equivalent compared with the other 2 groups. With the advancement of the technology and improvement of the features, WG LASIK with VISX CustomVue uses variable laser spot size, which could minimize the damage to corneal layer caused by laser ablation. This can help to preserve the tear quality and quantity. From this study, WG group showed no significant changes in NITBUT, TMH, and category of tear lipid layer thickness, but they also showed no difference compared with PS group and ZTS group 1 and 3 months post-IntraLASIK. The advantage of wavefront-guided LASIK in preserving tear quality and quantity could not be shown in this study.

In a study by Patel et al. (26), it was seen that the tear lipid layer thickness was reduced after LASIK surgery. Although a similar method of evaluation of tear lipid layer thickness was used in this study, no significant change in categories of tear lipid layer thickness after IntraLASIK was seen in any group. PS and ZTS group, which used conventional LASIK as Patel's research, showed some increments in the number of subject under the categories of less than 50 nm tear lipid layer thickness after surgery, but not the WG group. On the contrary, WG group showed an increment in thicker categories, and the increment was not seen in PS and ZTS groups. The flatter corneal contour after surgery could affect the distribution of the tear lipid layer; however, this was not evident in this study. Combination IntraLase and improved technology could minimize the damage in the corneal layer; this could be the reason the results of this study are different from the results of Patel et al.'s (26). However, Durrie et al. (27) did show that there was no difference in corneal sensation recovery between IntraLase and microkeratome.

Conclusion

Tear status of the subjects who underwent IntraLASIK were not affected at 1 and 3 months post-IntraLASIK. Conventional and WG IntraLASIK did not show differences in preserving tear quality and quantity after surgery. Therefore, this study showed that the tear stability and tear quantity were maintained 1 and 3 months post-IntraLASIK.

Authors' Contributions

Conception and design: SKF, SK, AJL
Obtaining of funding: SK, FAM, AJL
Provision of study materials or patients: AJL
Collection and assembly of the data: SKF
Analysis and interpretation of the data, drafting of the article: SKF, SK
Criticle revision of the article, final approval of the article: SK, FAM

Correspondence

Associate Professor Dr Sharanjeet-Kaur
SmOptom (UKM), PhD (UMIST)
Department of Optometry
Faculty of Allied Health Sciences
Universiti Kebangsaan Malaysia
Jalan Raja Muda
50300 Kuala Lumpur
Malaysia
Tel: +603-9289 7629
Fax: +603-2691 0488
Email: sharan@medic.ukm.my

References

1. Toda I, Asano-Kato N, Komai-Hori Y, Tsubota K. Dry eye after laser in situ keratomileusis. *Am J Ophthalmol*. 2001;**132(1)**:1–7.

2. Perez-Santonja JJ, Sakla HF, Cardona C, Chipont E, Alio JL. Corneal sensitivity after photorefractive keratectomy and laser in situ keratomileusis for low myopia. *Am J Ophthalmol*. 1999;**127(5)**:497–504.

3. Albietz JM, Lenton LM. Management of the ocular surface and tear film before, during, and after laser in situ keratomileusis. *J Refract Surg*. 2004;**20(1)**: 62–71.

4. Goto T, Zheng X, Klyce SD, Kataoka H, Uno T, Yamaguchi M, et al. Evaluation of the tear film stability after laser in situ keratomileusis using the tear film stability analysis system. *Am J Ophthalmol*. 2004;**137(1)**:116–120.

5. Albietz J, Lenton L, McLennan S. The effect of tear film and ocular surface management on myopic LASIK outcomes. *Adv Exp Med Biol*. 2002;**506(Pt A)**:711–717.

6. Albietz JM, Lenton LM, McLennan SG. Chronic dry eye and regression after laser in situ keratomileusis for myopia. *J Cataract Refract Surg*. 2004;**30(3)**: 675– 684.

7. Albietz JM, Lenton LM, McLennan SG. Dry eye after LASIK: Comparison of outcomes for Asian and Caucasian eyes. *Clin Exp Optom*. 2005;**88(2)**:89–96.

8. Kleinstein RN, Jones LA, Hullett S, Kwon S, Lee RJ, Friedman NE, et al. Refractive error and ethnicity in children. *Arch Ophthalmol*. 2003;**121(8)**:1141–1147.

9. Voo I, Lee DA, Oelrich FO. Prevalence of ocular conditions among Hispanic, white, Asian, and black immigrant students examined by the UCLA Mobile Eye Clinic. *J Am Optom Assoc*. 1998;**69(4)**:255–261.

10. Lin LL, Shih YF, Hsiao CK, Chen CJ, Lee LA, Hung PT. Epidemiologic study of the prevalence and severity of myopia among school children in Taiwan in 2000. *J Formos Med Assoc*. 2001;**100(10)**:684–691.

11. Duffey RJ, Leaming D. US trends in refractive surgery: 2002 ISRS survey. *J Refract Surg*. 2003;**19(3)**: 357–363.

12. MacRae SM, Subbaram MV. Customized corneal treatments for refractive errors. In: Kohnen T, Koch DD, editors. *Cataract and refractive surgery*. Heidelberg: Springer; 2006. p. 49–63.

13. Holladay JT. Wavefront-guided laser vision correction reduces higher-order aberrations. Congress report: XXVI Congress of the ESCRS. Berlin, Germany. September 2008. *ESCRS Eurotimes*. 2008 Sep;**Suppl**:3.

14. McGrath D. Tissue-saving algorithm boosts Zyotix results. *EuroTimes*. 2007;**12(9)**:20.

15. Yu EY, Leung A, Rao S, Lam DS. Effect of laser in situ keratomileusis on tear stability. *Ophthalmology*. 2000;**107(12)**:2131–2135.

16. Solomon R, Donnenfeld ED, Perry HD. Etiology, prevention and management of dry eye following LASIK. In: Pandey SK, editor. *Dry eye and ocular surface disorders*. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2006. p. 115–126.

17. Linna TU, Vesaluoma MH, Perez-Santonja JJ, Petroll WM, Alio JL, Tervo TM. Effect of myopic LASIK on corneal sensitivity and morphology of sub-basal nerves. *Invest Ophthalmol Vis Sci*. 2000;**41(2)**: 393–397.

18. Michaeli A, Slomovic AR, Sakhichand K, Rootman DS. Effect of laser in situ keratomileusis on tear secretion and corneal sensitivity. *J Refract Surg*. 2004;**20(4)**:379–383.

19. Lee SJ, Kim JK, Seo KY, Kim EK, Lee HK. Comparison of corneal nerve regeneration and sensitivity between LASIK and laser epithelial keratomileusis (LASEK). *Am J Ophthalmol*. 2006;**141(6)**:1009–1015.

20. Carvillo MP, McLaren JW, Hodge DO, Bourne WM. Corneal reinnervation after LASIK: Prospective 3-year longitudinal study. *Invest Ophthalmol Vis Sci*. 2004;**45(11)**:3991–3996.

21. Kato T, Nakayasu K, Hosoda Y, Watanabe Y, Kanai A. Corneal wound healing following laser in situ keratomileusis (LASIK): A histopathological study in rabbits. *Br J Ophthalmol*. 1999;**83(11)**:1302–1305.

22. Benitez-del-Castillo JM, del Rio T, Iradier T, Hernandez JL, Castillo A, Garcia-Sanchez J. Decrease in tear secretion and corneal sensitivity after laser in situ keratomileusis. *Cornea*. 2001;**20(1)**:30–32.

23. Will B, Kurtz RM. IntraLase is best. In: Probst LE, editor. LASIK: Advances, controversies, and custom. Thorofare, NJ: SLACK Inc; 2004. p. 397–402.

24. Binder PS. The femtosecond difference. Congress report: XXVI Congress of the ESCRS. Berlin, Germany. September 2008. *ESCRS Eurotimes*. 2008 Sep;**Suppl**:4.

25. Salomao MQ, Ambrosio R Jr, Wilson SE. Dry eye associated with laser in situ keratomileusis: Mechanical microkeratome versus femtosecond laser. *J Cataract Refract Surg*. 2009;**35(10)**:1756–1760.

26. Patel S, Perez-Santonja JJ, Alio JL, Murphy PJ. Corneal sensitivity and some properties of the tear film after laser in-situ keratomileusis. *J Refract Surg*. 2001;**17(1)**:17–24.

27. Durrie DS, Kezirian GM. Femtosecond laser versus mechanical keratome flaps in wavefront-guided laser in situ keratomileusis: Prospective contralateral eye study. *J Cataract Refract Surg*. 2005;**31(1)**:120–126.

Original Article

Influence of Sitting and Prone Lying Positions on Proprioceptive Knee Assessment Score in Early Knee Osteoarthritis

Vijay Batra[1], Vijai Prakash Sharma[1], Meenakshi Batra[1], Girdhar Gopal Agarwal[2], Vineet Sharma[3]

Submitted: 9 Mar 2010
Accepted: 28 Aug 2010

[1] *Department of Physical Medicine and Rehabilitation, Rehabilitation and Artificial Limb Centre, Chhatrapati Shahuji Maharaj Medical University (Formerly King George Medical University), Dali Ganj Bridge, Nabiullah Road, Lucknow: 226018, Uttar Pradesh, India*

[2] *Department of Statistics, Lucknow University, Lucknow:226 007, India*

[3] *Department of Orthopaedics, Chhatrapati Shahuji Maharaj Medical University (Formerly King George Medical University), Dali Ganj Bridge, Nabiullah Road, Lucknow: 226018, Uttar Pradesh, India*

Abstract

Background: **Knee proprioception is compromised in knee osteoarthritis. There are several ways of measuring proprioceptive acuity, but there is lack of consensus over the ideal testing position. The study aimed to evaluate the influence of 2 testing positions (sitting versus prone lying) on proprioceptive knee assessment score in patients with early knee osteoarthritis.**

Methods: **The study included 70 subjects who came to the Out-Patient Department with a diagnosis of early knee osteoarthritis. The subjects were assessed for their proprioceptive acuity scores in both the test positions at 30° and 60° of knee flexion using proprioceptive knee assessment device. They were asked to perform 5 trials in both testing positions with appropriate rest intervals. After initial assessment, the subjects were randomly allocated among group 1 and group 2. Treatment implementation was done for 8 weeks followed by re-evaluation: group 1 received context-specific proprioceptive retraining along with multijoint coupling strategies and group 2, conventional treatment.**

Results: **The subjects were compared using difference of pre- and post-treatment proprioceptive acuity scores. The difference of proprioceptive acuity impairment scores of the left knee at 30° and 60°, and the right knee at 60° in prone lying position were statistically significant, with *P* value ranging from less than 0.001 to 0.028.**

Conclusion: **It was found that the prone lying testing position was more sensitive than sitting position for assessing proprioceptive acuity for knee osteoarthritis.**

Keywords: *adaptive behavior, knee, patient positioning, proprioception, osteoarthritis*

Introduction

Proprioception is the sense of position and movement of the limbs, and it is the result of sensory inputs arising from muscle, skin, and joint structures (1). It can also be defined as the conscious and unconscious awareness of body position, movement, and forces acting on the body, for which accurate sensory input and central integration from peripheral proprioceptors are a must (2). Proprioception contributes to the development of the motor control and plays a major role in the reflex protection of joints against potentially harmful forces (1). The proprioceptive acuity impairment significantly affects neuromusculoskeletal integrity, contributing to pain and functional disability (2–4). Knee proprioception has consistently been reported to be compromised in individuals with knee osteoarthritis (3,5–11). This neuromuscular deficit has been suggested as the major contributing factor to the disease process (7,10–13). However, studies have shown that the impairment of proprioceptive acuity is not exclusively a local result of the disease, and there is a need to study its importance in the development and progression of knee osteoarthritis (10,11).

There are several ways of measuring proprioceptive acuity; one of them is the threshold detection of passive movement. However, passive movements do not reflect real life movement or function; proprioceptive functions in healthy and pathological joints are quite variable and there is a lack of correlation between different measurements of proprioception in the knee (14–17). Active assessments by asking the patient to replicate limb position, using active movement, with vision occluded (16) or by reproducing lower limb static loads (15) have been suggested. Generally, proprioceptive assessment of the knee is done in sitting position (16). However, the ideal testing position for proprioceptive assessment of the knee is still debatable. One of the reasons could be that, during assessment, the subject may exhibit an adaptive behaviour to compensate for the loss of proprioceptive acuity by using vision or not relaxing the muscles completely before attempting to replicate limb position. The purpose of the present study was to evaluate the influence of 2 testing positions (sitting and prone lying) on proprioceptive acuity scores (17) in the assessment of early knee osteoarthritis.

Subjects and Methods

The study involved 70 subjects (22 males and 48 females) with history of knee pain and clinical diagnosis of early knee osteoarthritis, with radiological findings of grade I (33 subjects) and grade II (37 subjects) according to the Kellgren and Lawrence Classification System (18). All patients were between 40 and 60 years of age. Subjects with traumatic knee injury, inflammatory arthritis, metabolic disorder, as well as cardiovascular and psychiatric illnesses were excluded from the study.

The ethical approval was obtained from The Human Ethical Committee of Chhatrapati Shahuji Maharaj Medical University (formerly King George Medical College), Lucknow. Informed consent was obtained from the patient or the accompanying family member.

The baseline evaluation of all the subjects was done in 2 testing positions (sitting and prone lying) for proprioceptive acuity score (17) using proprioceptive knee assessment device. The device comprises a goniometer attached with a static bar and a movable set of 5 bars that are fixed, with respect to each other, at 10° interval. The central bar of the movable set of 5 bars is longer than the other 4 bars (2 on each side). The central mechanical axis of the goniometer coincides with the anatomical axis of knee joint.

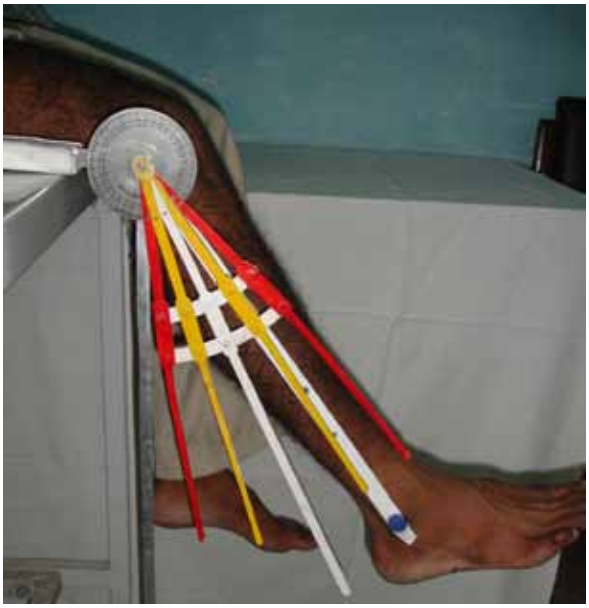

Figure 1: Proprioceptive assessment device.

The static bar corresponds to the 90° of knee flexion, perpendicular to the ground. The central bar was positioned at the desired angles, i.e., 30° and 60° of knee flexion (Figure 1). Any deviation from the central bar was treated as an error.

With vision occluded, each subject was asked to perform 30° and 60° flexion of each knee for 5 times, with intermittent rest intervals of at least 10–15 seconds. Proprioceptive impairment was calculated by adding the proprioceptive acuity scores of all the 5 attempts for each knee (Table 1).

Our main objective is to compare the 2 test positions; thus, to rule out the possibility of results being influenced by certain treatments, the subjects were randomly allocated among 2 intervention groups (group 1 and group 2) with 35 subjects in each arm. The mean age was not significantly different between the 2 groups; the mean age for group 1 was 50.14 years (SD 5.49), while for group 2, it was 51.15 years (SD 5.9). In group 1, context-specific proprioceptive retraining along with multijoint coupling strategies (17) was used, while for group 2, conventional treatment was used. Test position 1 (sitting) was considered as control while test position 2 (prone lying) was considered as experimental.

The context-specific proprioceptive retraining technique incorporated both neurophysiological and biomechanical procedures and techniques to influence neuromusculoskeletal integrity (12,18–21) within functional context using facilitatory and inhibitory procedures, sensorimotor experiences, procedures to enhance dynamic adjustment

Table 1: Proprioceptive knee assessment scoring system

Score	Description
1	Normal
2	Patient overshoots or undershoots the target by more than 10° but can acquire the target position
3	Patient overshoots or undershoots the target by more than 30° but can acquire the target position
4	Patient overshoots or undershoots the target by more than 10° and cannot acquire the target position
5	Patient overshoots or undershoots the target by more than 30° and cannot acquire the target position
6	Impaired

range, coupled motions of knee, hip, and ankle joints, and multijoint coupling strategies (17). The conventional treatment incorporated joint reproducibility with and without vision occluded, quadriceps strengthening using isometric and isotonic exercises, physical agent modalities, manual therapy, mobilization, and manipulation.

The subjects in each group received intervention 3 times per week for 30 minutes per session. At the end of 8 weeks of intervention, each subject's proprioceptive acuity was reassessed in both knees at each angle in both testing positions (17).

Test position 1 (sitting)

Each subject was asked to sit over the plinth with hip at 90° of flexion and knee relaxed and suspended off the plinth in gravity-dependent position. Both knees were assessed separately. Initially, the subject was asked to relax for 5 minutes. Then, the knee was passively positioned by a therapist using proprioceptive assessment device in 30° of flexion, and the subject was instructed to replicate the same knee position. The subject was asked to perform 5 trials with intermittent rest intervals of 10 to 15 seconds each. The other knee was also assessed by using the same procedure. The similar sequence was followed, for each knee separately, at 60° of flexion.

Test position 2 (prone lying)

The subject was asked to lie in prone position while keeping both the hip and knees neutral (i.e., hip in 0° of flexion or extension, 0° of abduction or adduction, and 0° of internal or external rotation; knee in full extension). The testing procedure was same as the procedure for position 1 (sitting).

Statistical analysis

In order to adjust for the discrepancies in baseline characteristics, the differences of pre- and post-proprioceptive acuity scores were used for analysis. Some of these differences were negative and skewed. Therefore, a logarithmic transformation of the form ln (x + c) was used, where c is a suitably chosen positive constant. Student's *t* test was performed on the transformed data. For asymmetrically distributed variables, non-parametric Mann–Whitney U test was used. *P* value of less than 0.05 was considered as statistically significant.

Results

All 70 subjects, irrespective of the treatment, were analyzed for their various acuity scores in the 2 testing positions.

Between-group analysis

Student's *t* test was used for the analysis of proprioceptive acuity scores of the left knee at 30° and 60°, and the right knee at 60°; Mann–Whitney U test was used for the right knee at 30°. The mean for sitting position for the left knee at 30° and 60°, and the right knee at 60° were 1.498 (SD 0.062), 1.515 (SD 0.075), and 1.509 (SD 0.072), respectively. The mean for prone lying position for the left knee at 30° and 60°, and the right knee at 60° were 1.534 (SD 0.059), 1.549 (SD 0.069), and 1.55 (SD 0.066), respectively. The median and interquartile range in sitting position for the right knee at 30° was 1.491 and 0.063, and for prone lying position, 1.505 and 0.071, respectively. The *P* values at 95 % confidence interval for the change in proprioceptive acuity scores of the left knee at 30° ($P < 0.001$), the

left knee at 60° (P = 0.007), and the right knee at 60° (P < 0.001) were found to be statistically significant (Table 2).

Between-group analysis

The subgroup analyses were also done to rule out the treatment effect. Student's t test was used for the analysis of proprioceptive acuity scores of the left knee at 30° and 60°, and the right knee at 60°; Mann–Whitney U test was used for the right knee at 30°.

The mean proprioceptive acuity score for sitting position (group 1) for the left knee at 30° and 60°, and the right knee at 60° were 1.532 (SD 0.049), 1.564 (SD 0.043), and 1.554 (SD 0.041), respectively. In prone lying position, the values were 1.568 (SD 0.051), 1.598 (SD 0.043), and 1.598 (SD 0.040), respectively. The median and interquartile range in sitting position for the right knee at 30° was 1.519 and 0.039; for prone lying position, they were 1.531 and 0.051, respectively (Table 3). The changes in proprioceptive acuity scores of the left knee at 30° (P = 0.004), the left knee at 60° (P = 0.002), and the right knee at 60° (P < 0.001) were statistically significant, whereas no significant difference was observed for the right knee at 30° (P = 0.068) (Table 3).

The mean proprioceptive acuity score for sitting position (group 2) for the left knee at 30° and 60°, and right knee at 60° were 1.464 (SD 0.055), 1.467 (SD 0.069), and 1.464 (SD 0.068); for prone lying position, the mean values were 1.501 (SD 0.047), 1.500 (SD 0.052), and 1.502 (SD 0.051), respectively. The median and interquartile range in sitting position for the right knee at 30° was 1.462 and 0.076; for prone lying position, they were 1.477 and 0.044, respectively.The changes in proprioceptive acuity scores of the left knee at 30° (P = 0.004), the left knee at 60° (P = 0.028), and the right knee at 60° (P = 0.009) were statistically significant, whereas no significant difference was observed for the right knee at 30° (P = 0.162) (Table 4).

Discussion

Based on the analyses, null hypothesis stating that both sitting and prone lying positions are equally effective for assessing proprioceptive acuity impairment in knee osteoarthritis can be rejected; the prone lying test position was found to be more sensitive than the sitting position in most of the components. The results can be explained based on the neurophysiological mechanism of neuromuscular control system.

In early knee osteoarthritis, the knee joint complex is richly innervated with mechanoreceptors, such as receptors in the joint, skin, and muscle (22,23). The combination of both muscle and joint receptors forms an integral component of a complex sensorimotor system that plays a major role in the proprioceptive mechanism (24,25). Mechanoreceptors can be quick-adapting and slow-adapting, and they have different shapes, threshold levels, locations, and adaptive properties based on their response to stimuli (23,25–27). Quick-adapting mechanoreceptors mediate the sensation of joint motion, whereas the slow-adapting mechanoreceptors mediate the sensation and change in joint position (22,23). The proprioceptive mechanism, which is initiated by activation of these mechanoreceptors, has direct implication over proprioceptive acuity score of the knee. Since proprioceptive acuity score of each knee has a combined effect over the functional status, in the present study, proprioceptive impairment of each knee was assessed separately to identify the ideal test position.

Statistical analysis showed mixed results, but the prone lying position was found to be more sensitive for assessing proprioceptive acuity status than the sitting position. In prone lying, the knee arc of motion starts from extension to flexion, with both knees and hip in neutral; the direct influence of gravity and the effect of diarthodial muscles are nullified, and the length feedback is controlled in a better manner. As a result, mechanoreceptors (especially slow-adapting) do not get stimulated, and the knees can be fully relaxed. On the other hand, in sitting position, the hip and the knees are in 90° of flexion, and the knee arc of motion starts from 90° knee flexion to extension. In addition, the muscles around knee, being diarthodial, are under the direct influence of gravity, and the muscle stretch reflex activity may get stimulated. The proprioceptive acuity scores obtained in sitting position may not represent the actual proprioceptive acuity status of each knee.

Motor control relies on inputs from proprioceptors, visual receptors (telereceptors), and vestibular receptors. When knee proprioceptive acuity gets impaired, the subject may exhibit adaptive behaviours (23,25,26) to accommodate proprioceptive deficit by relying on vision or not allowing the muscles to get relaxed before attempting to replicate limb position. In the present, study this adaptive behaviour was drastically minimized by occluding the vision and incorporating intermittent rest intervals. However, in prone lying position, the reliance on vision and muscle tension as well as the effect

Table 2: Comparison of the changes in proprioceptive acuity scores (pre- and post-intervention between sitting and prone lying positions

Proprioceptive Acuity	Left Knee				Right Knee			
	30° [a]		60° [a]		30° [b]		60° [a]	
Sitting position	1.498	(0.062)	1.515	(0.043)	1.491	(0.063)	1.509	(0.072)
Prone lying position	1.534	(0.059)	1.549	(0.685)	1.505	(0.071)	1.550	(0.066)
Test statistics (df)	-3.525	(138)	-2.741	(138)	-1.576		-3.532	(138)
P value	<0.001		0.007		0.115		<0.001	

Statistical analyses were conducted using [a] *t* test and [b] *Z* test. Data are expressed in [a] mean (standard deviation) and [b] median (interquartile range).

Table 3: Comparison of the changes in proprioceptive acuity scores (pre- and post-intervention) between sitting and prone lying positions in group 1

Proprioceptive Acuity	Left Knee				Right Knee			
	30° [a]		60° [a]		30° [b]		60° [a]	
Sitting position	1.532	(0.049)	1.564	(0.043)	1.519	(0.039)	1.554	(0.041)
Prone lying position	1.568	(0.051)	1.548	(0.043)	1.531	(0.051)	1.598	(0.04)
Test statistics (df)	-3.012	(68)	-3.291	(68)	-4.549		-1.828	(68)
P value	0.004		0.007		0.068		<0.001	

Statistical analyses were conducted using [a] *t* test and [b] *Z* test. Data are expressed in [a] mean (standard deviation) and [b] median (interquartile range).

Table 2: Comparison of the changes in proprioceptive acuity scores (pre- and post-intervention) between sitting and prone lying positions in group 2

Proprioceptive Acuity	Left Knee				Right Knee			
	30° [a]		60° [a]		30° [b]		60° [a]	
Sitting position	1.464	(0.055)	1.467	(0.069)	1.462	(0.076)	1.464	(0.068)
Prone lying position	1.501	(0.047)	1.5	(0.052)	1.477	(0.044)	1.502	(0.051)
Test statistics (df)	-2.965	(68)	-2.244	(68)	-1.4		-2.684	(68)
P value	0.004		0.028		0.162		0.009	

Statistical analyses were conducted using [a] t test and [b] Z test. Data are expressed in [a] mean (standard deviation) and [b] median (interquartile range).

of diarthodial muscles on the proprioceptive acuity could be ruled out. Both test positions were equally sensitive in the assessment of proprioceptive acuity for the right knee at 30°. Therefore, each test position is useful in different methods of assessment. Since onset of knee osteoarthritis is usually unilateral and may later progress bilaterally, the proprioceptive acuity scores of each knee can guide the treatment process. Hence, the null hypothesis was rejected.

Conclusion

The prone lying position is more sensitive than the sitting position in assessing proprioceptive acuity of each knee and identifying the actual proprioceptive impairment status. Prone lying position could serve as an effective evaluation tool to guide the treatment process in patients with early knee osteoarthritis.

Acknowledgements

We are thankful to the Indian Council for Medical Research for their financial support.

Authors' Contributions

Conception and design, collection and assembly of the data: VB, MB
Drafting and final approval of the article: VB, VPS, MB, VS
Statistical expertise: GGA

Correspondence

Dr Vijay Batra
PhD Occupational Therapy (Chhatrapati Shahuji Maharaj Medical University)
Department of Physical Medicine & Rehabilitation
Rehabilitation and Artificial Limb Centre
Chhatrapati Shahuji Maharaj Medical University
(Formerly King George Medical University)
Dali Ganj Bridge, Nabiullah Road
Lucknow: 226018
Uttar Pradesh, India
Tel: +91-9868019077, +91-9044467434
Email: vijaybatra@yahoo.com,
vijaybatras@gmail.com

References

1. Gandevia SC. Kinesthesia: Roles for afferent signals and motor commands. In: Rowell LB, Shepard JT, editors. *Handbook on integration of motor, circulatory, respiratory and metabolic control during exercise*. Bethesda, MD: American Physiological Society; 1996. p. 128–172.

2. Riemann BL, Lephart SM. The sensorimotor system, part I: The physiologic basis of functional joint stability. *J Athl Train*. 2002;**37(1)**:71–79.

3. Felson DT, Gross KD, Nevitt MC, Yang M, Lane NE, Torner JC, et al. The effects of impaired joint position sense on the development and progression of pain and structural damage in knee osteoarthritis. *Arthritis Rheum*. 2009;**61(8)**:1070–1076.

4. Bennell KL, Hinman RS, Metcalf BR, Crossley KM, Buchbinder R, Smith M, et al. Relationship of knee joint proprioception to pain and disability in individuals with knee osteoarthritis. *J Orthop Res*. 2003:**21(5)**:792–797.

5. Barrett DS, Cobb AG, Bently G. Joint proprioception in normal, osteoarthritic and replaced knees. *J Bone Joint Surg*. 1991;**73(1)**:53–56.

6. Garsden LR, Bullock-Saxton JE. Joint reposition sense in subjects with unilateral osteoarthritis of the knee. *Clin Rehabil*. 1999;**13(2)**:148–155.

7. Hurley MV, Scott DL, Rees J, Newham DJ. Sensorimotor changes and functional performance in patients with knee osteoarthritis. *Ann Rheum Dis*. 1997:**56(11)**:641–648.

8. Marks R. Further evidence of impaired position sense in knee osteoarthritis. *Physiother Res Int*. 1996;**1(2)**:127–136.

9. Pai YC, Rymer WZ, Chang RW, Sharma L. Effect of age and osteoarthritis on knee proprioception. *Arthritis Rheum*. 1997;**40(12)**:2260–2265.

10. Sharma L, Pai YC. Impaired proprioception and osteoarthritis. *Curr Opin Rheumatol*. 1997;**9(3)**: 253–258.

11. Sharma L, Pai YC, Holtkamp K, Rymer WZ. Is knee joint proprioception worse in the arthritic knee versus the unaffected knee in unilateral knee osteoarthritis? *Arthritis Rheum*. 1997;**40(8)**:1518–1525.

12. Hurley MV, Scott DL. Improvement in quadriceps sensorimotor function and disability of patients with knee osteoarthritis following a clinically practicable exercise regime. *Br J Rheumatol*. 1998:**37(11)**: 1181–1187.

13. Salo P. The role of joint innervation in the pathogenesis of arthritis. *Can J Surg*. 1999;**42(2)**:91–100.

14. Grob KR, Kuster MS, Higgins SA, Lloyed DG, Yata H. Lack of correlation between different measurements of proprioception in the knee. *J Bone Joint Surg Br*. 2002:**84(4)**:614–618.

15. Murtaugh K, Costigan PA, Evaluating the proprioception of lower extremity loads. *Winter*. 2003:**6(2)**:15–19.

16. Olson L, Lund H, Henriksen M, Rogind H, Bliddal H, Danneskiold-Samsoe B. Test–retest reliability of a knee joint position sense measurement method in sitting and prone position. *Adv Physiother*. 2004;**6(1)**:37–47.

17. Batra V, Sharma VP, Batra M, Agarwal GG, Sharma V. Multi-joint coupling strategies to enhance functional recovery in knee osteoarthritis. *Ind J Phys Occ Ther*. Forthcoming.

18. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. American College of Rheumatology. *Arthritis Rheum*. 1995;**38(11)**:1535–1540.

19. Hurley MV. Muscle dysfunction and effective rehabilitation of knee osteoarthritis: What we know and what we need to find out. *Arthritis Rheum*. 2003;**49(3)**:444–452.

20. Farina D, Arendt-Nielsen L, Graven-Nielsen T. Experimental muscle pain reduces initial motor unit discharge rates during sustained sub maximal contractions. *J Appl Physiol*. 2005;**98(3)**:999–1005.

21. Smania N, Picelli A, Romano M, Negrini S. Neurophysiological basis of rehabilitation of adolescent idiopathic scoliosis. *Disabil Rehabil*. 2008;**30(10)**:763–771.

22. Sekir U, Gur H. A multi-station proprioceptive exercise program in patients with bilateral knee osteoarthrosis: Functional capacity, pain and sensorimotor function. A randomized controlled trial. *J Sports Sci Med*. 2005:**4**:590–603.

23. Williams GN, Chmielewski T, Rudolph K, Buchanan TS, Snyder-Mackler L. Dynamic knee stability: Current theory and implications for clinicians and scientists. *J Orthop Sports Phys Ther*. 2001;**31(10)**:546–566.

24. Dixon J, Howe TE. Quadriceps force generation in patients with osteoarthritis of the knee and asymptomatic participants during patellar tendon reflex reactions: An exploratory cross-sectional study. *BMC Musculoskelet Disord*. 2005:**6**:46.

25. Houk JC. Regulation of stiffness by skeletomotor reflexes. *Annu Rev Physiol*. 1979:**41**:99–114.

26. Houk JC, Rymer WZ. Neural control of muscle length and tension. In: Brooks VB, editor. *Handbook of physiology: Section I. The nervous system. Volume 2: Motor control*. Bethesda, MD: American Physiological Society; 1981. p. 257–323.

27. Nichols TR, Cope TC, Abelew TA. Rapid spinal mechanisms of motor coordination. *Exerc Sport Sci Rev*. 1999:**27**:255–284.

Original Article

Chemical Composition of Gallstones from Al-Jouf Province of Saudi Arabia

Bashir M Jarrar, Meshref A Al-Rowaili

Submitted: 26 Aug 2010
Accepted: 23 Jan 2011

Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Al-Jouf University, PO Box 2014, Saudi Arabia

Abstract

Background: **It is essential to understand the aetiopathogenesis of gallstone disease. This study was undertaken to determine the chemical composition of gallstones from patients living in Al-Jouf Province of Saudi Arabia.**

Methods: **This was a descriptive study where 46 gallstones from Al-Jouf Province of Saudi Arabia were analysed by semiquantitative titrimetric and colourimetric methods. The proportion of different types of gallstones was described using 95% confidence interval based on exact method.**

Results**: Gallstones were found more frequently in female patients (60.9%) than males (39.1%), and these stones were composed of pure cholesterol (54.3%), pure bilirubin (2.2%), or mixed stones (43.5%). The most common chemical constituent was cholesterol (82.6%), while bilirubin was seen in 26.1% of the stones. Calcium was present in 32.6% of the stones in the form of calcium salts of bilirubin and carbonate. Bilirubin-containing stones were slightly more frequent in males than in females, while cholesterol-containing stones were less frequent in males.**

Conclusion**: The findings indicate that gallstones in the Al-Jouf Province develop more frequently in the age group of the third decade of life, with more risk among females than males, and are predominated by cholesterol together with calcium bilirubinate and calcium carbonate.**

Keywords: *bilirubin, calcium bilirubinate, cholesterol, clinical chemistry, gallstones, Saudi Arabia*

Introduction

Gallstones have been known to humans for many years and have been found in the gallbladders of Egyptian mummies dating back to 1000 BC (1). Gallstone is one of the diseases prevalent in developed nations, but it is less prevalent in the developing populations that still consume traditional diets (2,3). Gallstones are more common in North America, Europe, and Australia, and are less prevalent in Africa, India, China, Japan, Kashmir, and Egypt, with variable frequency, such as 4.1% in Tunisia, 4.7% in Iran, 5.4% in Bangladesh, 5.4% in Peru, 7.8% in Germany, 20.8% in New Zealand, and 15% in the USA (4–6).

Epidemiological studies show that gallstones formation is a complex multifactorial disease associated with dietary habits, overweight, sex, and family history of gallstone disease, with no evidence of racial or climatological factors resulting in the increase in cholelithiasis (3,7,8). The chemical composition and location of the biliary calculi differ in various parts of the world and change over time because of nutritional, socio-economic, and demographic factors (9).

Gallstone chemical analysis gives important evidences for the origin, aetiology, and the metabolic basis of its formation, and helps in the identification of risk factors that predispose certain individuals to the calculi formation. Few scattered reports on gallstone disease are available from different parts of Saudi Arabia; the disease prevalence at the country level is increasing, but no thorough study has been conducted (2,8,10–15). Few, if any, reports are available about the chemical composition and the aetiopathogenesis of gallstones in Saudi Arabia. The present study was done to determine the chemical composition of gallstones removed from patients receiving treatment in Al-Jouf Province of Saudi Arabia, and their incidences, as well as to find the association of gallstones with age distribution and lifestyle in an attempt to understand the pathogenesis of cholelithiasis in Saudi Arabia.

Subjects and Methods

Chemical analyses were conducted on 46 gallstones from patients in Al-Jouf Province of Saudi Arabia. These stones were removed surgically from January 2007 to January 2008 in the hospitals of Al-Jouf Province. Analyses were carried out at the central laboratory of the Department of Clinical Laboratory Sciences, Al-Jouf University. The relevant patients' information, namely, age, sex, number of calculi, estrogen therapy, number of childbirths, and family history of cholelithiasis, were obtained from hospitals' records. The physical parameters of the calculi, such as colour, number, shape, texture, and cross section, were noted. The size was determined by measuring the largest diameter of solitary stones and deducing the average for the multiple stones. The calculi were powdered in a mortar and were analysed chemically by semiquantitative titrimetric and colourimetric methods (16,17). Powdered stones were analysed for cholesterol, bilirubin, triglyceride, calcium, and carbonate. Test solutions were prepared by dissolving 30 mg of powdered stone in 3 mL of chloroform, and the solutions were kept in a water bath at 100 °C for 2 minutes. These stone solutions were used for the determination of total cholesterol and total bilirubin by colourimetric methods (17). In a separate preparation, 30 mg of powdered stone was dissolved in 3 mL of 1 N hydrochloric acid; distilled water was then added to a final volume of 10 mL. The test solutions were kept in boiling water for 60 minutes. These solutions were used for the determination of triglyceride, calcium, and carbonate by titrimetric and colourimetric methods (16). Organic and inorganic nature of the gallstones was identified by flame and burning tests (18). The dissolved stone solutions were stored at 2–6 °C when not in use.

The incidence of gallstone was analysed using the number of specific gallstones as the numerator and the number of gallstones extracted (n = 46) as the denominator. The exact confidence interval was calculated using a web-based calculator (http://www.measuringusability.com/Exact.htm). One sample-one tailed Z test was used for comparison of statistical significance, which was defined as $P < 0.05$ (19,20).

Results

Out of 46 gallstones of 46 patients , 28 (60.9%) stones belonged to females while 18 (39.1%) belonged to males , giving a male to female ratio of 1:1.6. The age of the patients ranged 19– 75 years, while 19 (41.3 %) patients were in their third decade of life (Figure 1). The hospitals' records indicated that 38 (82.6%) patients suffered from cholecystitis while 25 (54.3%) had family history of cholelithiasis. Out of 28 female patients, 13 (46.4%) had multiple parity.

There were 18 (39.1%) patients with multiple stones, while the rest had solitary stones. Cholesterol stones were soft with smooth surface and showed central radiations on cross sections (Figure 2). Bilirubin stones were soft and amorphous with rough surface, while the mixed stones had rough surface with laminated cross sections (Figure 3). The size of the tested stones varied in diameter (4–62 mm), where 21 (45.7%) of these gallstones measured 25 mm and above. Pure cholesterol stones were bigger in size in comparison with pure bilirubin and mixed stones and were mainly green yellowish, with a few stones that were whitish yellow.

The result of the chemical analyses revealed that 56.5% of the stones were pure stones (cholesterol or bilirubin), while 43.5% contained more than one chemical. Table 1 shows the distribution of the types of stones according to the chemical analyses.

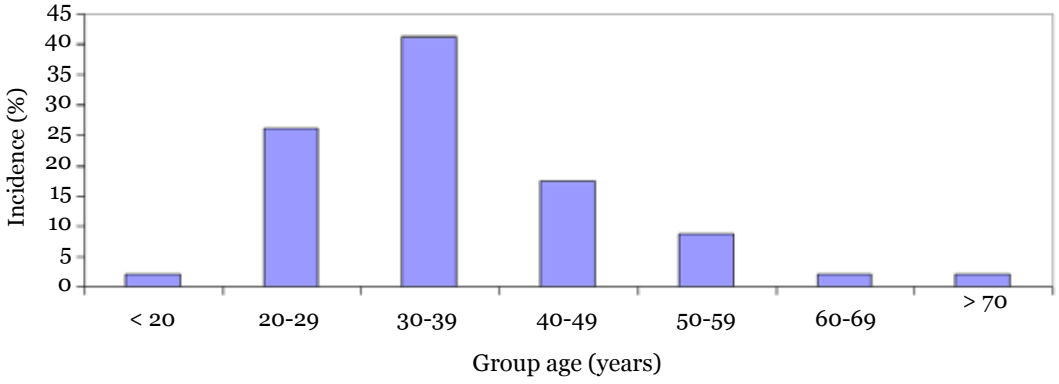

Figure 1: Distribution of calculi according to age.

Figure 2: Cholesterol gallstone.

Figure 3: Mixed gallstone.

Cholesterol was present in 38 (82.6%) stones; it was more frequent in females (n = 24, 63.2%, 95% CI 46.0–78.2) than in males (P < 0.001). The incidence of bilirubin-containing stones (n = 12, 26.1%) was slightly higher in males (n = 7, 58.3%) than in females (n = 5, 41.7%). However, this was not statistically significant (P = 0.240). The triglycerides were seen only in cholesterol and bilirubin mixed calculi.

Calcium was seen in 15 (32.6%) of the calculi, and it accompanied cholesterol stones more than bilirubin stones (P < 0.001). Carbonate accompanied calcium in only 7 (15.2%) of the stones, where calcium carbonate was seen mainly in the cholesterol mixed calculi, with 2 (4.3%) stones containing calcium and bilirubin only.

Discussion

Gallstones represent a major problem in many countries, including Saudi Arabia (21,22). Reports from different parts of the world indicate that the incidence of gallstones is correlated with socio-economic conditions and dietary factors (9,23); other risk factors are marked obesity, family history of gallstone disease, high energy intake, aging, multiple parity, cholecystitis, and sedentary lifestyle (15,24–27). Gallstones are more frequent among patients with certain conditions, such as Crohn's disease and liver cirrhosis (25).

Studies in Saudi Arabia showed changes in dietary habits; the average daily individual consumption of the total calories, including fat and sugar, increased, while consumption of high-fibre grain fell (13). This might contribute to an increase in the frequency of cholelithiasis, as cholecystectomy in Saudi Arabia became one of the most common major abdominal surgeries in the Kingdom (13). Consumption of simple sugars and saturated fat has been mostly associated to a higher risk of cholelithiasis (27).

Table 1: Distribution of stones according to the chemical groups

Type of stone	Number of stones	Frequency (%)	95% confidence interval*
Pure stones	26	56.5	0.41 – 0.71
Pure cholesterol	25	54.3	0.39 – 0.69
Pure bilirubin	1	2.2	0.0006 – 0.12
Mixed stones	20	43.5	0.29 – 0.59
Mixed cholesterol	13	28.3	0.16 – 0.43
Mixed bilirubinate	11	24.0	0.13 – 0.39
Mixed triglycerides	3	6.5	0.01 – 0.18
Mixed calcium	15	32.6	0.20 – 0.48
Calcium bilirubinate	2	4.3	0.005 – 0.15
Calcium carbonate	7	15.2	0.06 – 0.29
Calcium bilirubinate and cholesterol	6	13.0	0.05 – 0.26
Cholesterol, bilirubin, and triglycerides	3	6.5	0.01 – 0.18
Cholesterol and calcium carbonate	7	15.2	0.06 – 0.29

* 95% confidence interval was calculated by using exact method.

Our results showed that females were more affected with cholelithiasis than males, with a female to male ratio of 1.6:1. According to the Central Department of Statistics, Saudi Arabia, female to male ratio of the total Saudi population was 100:102 in 2005 (28). The female predominance of cholelithiasis, as seen in the present study, is in agreement with findings from other provinces of Saudi Arabia, but is significantly lower ($P < 0.001$) than in Asir Province and Riyadh city (8,15). Reports from other countries, such as in India, Pakistan, Albania, and Jordan, also indicate that females are more affected by the disease than males (21,29–31). This might be due to the basic hormonal differences between males and females, together with the differences that might exist due to co-expression of sex hormone receptors in the gallbladder of both sexes. The medical records of the patients of the present study showed that most of the female patients had parity. This is also in agreement with other studies, which concluded that fertility and multiple pregnancies appeared to be a risk factor for gallstones among Saudi women (15). Increased levels of sex hormones as a result of pregnancy may increase cholesterol in the bile and decrease gallbladder movement, resulting in cholelithiasis.

The present investigation showed cholelithiasis in Al-Jouf Province was more frequent among people in their third decade of life. This is in agreement with Murshid's investigation from Saudi Arabia (15). Investigations concluded lower sensitivity of the gallbladder to cholecystokinin in older human volunteers (aged 60–84 years) in comparison with younger volunteers (aged 22–42 years) after ingestion of Lipomul (1.5 mL/kg) by both groups (7,32).

Cholesterol was the most common constituent (82.6%) of the gallstones, followed by calcium, bilirubin, and carbonate in the present investigation. This finding is in agreement with a study in the western region of Saudi Arabia, where 90.4% of the gallstones contained cholesterol (12). Reports from western countries, such as Germany and some Scandinavian countries, also showed cholesterol as the primary component of the gallstones, but different gallstone composition were reported in studies from Sub-Saharan Africa and China (21,33–35). The differences may be attributed to both metabolic abnormalities of cholesterol metabolism and different dietary conditions of the people in these countries. Formation of cholesterol calculi have been related to high carbohydrate diet, which leads to cholesterol supersaturation in the bile (36). Atherosclerosis, hyperlipidaemia, and hyperinsulinism have also been encountered as risk factors for cholesterol gallstone disease (25,26). The association between cholesterol intake and gallstone disease has been indicated by different studies (23,26). The results of the present investigation also indicated that cholesterol-containing stones were less frequent in males than in females ($P < 0.001$). This is in line with reports from other countries, such as Korea (37).

The findings of the present work showed that bilirubin was conjugated with calcium or cholesterol and that the stones occurred more frequently in the mixed forms rather than as pure bilirubin stones. This is contrary to the finding of the chemical analysis of gallstones from India (30). In addition, it has been reported that bacterial infection of the gall bladder helps in hydrolysis of conjugated bilirubin, forming free bilirubin in the form of calcium bilirubinate salt (38). The present work also indicated that gallstone calcium content was highest in bilirubin stones and lowest in cholesterol stones. It has been reported that calcium bilirubinate precipitates in the bile and play a critical role in cholelithiasis (30,39).

The hospitals records of Al-Jouf Province indicated that 82.6% of the patients included in the present study had a history of cholecystitis. Injury of the epithelial lining of the gall bladder might be a risk factor for calcium bilirubinate precipitation due to the release of β-glucoronidase (40). The records also showed that 54.3% of the patients had a family history of cholelithiasis. This is in agreement with some reports that correlated gallstone disease aetiology with genetic and environmental factors (27).

Conclusion

It is apparent from the findings of the present investigation that the most common gallstone in Al-Jouf Province of Saudi Arabia was cholesterol stone, and that the age group at risk of having gallstones was the third decade of life, with a higher risk for females than males. Additional studies are needed to understand the pathogenesis of cholelithiasis in Al-Jouf Province and other parts of Saudi Arabia and to clarify its relation with the lifestyle, especially the dietary habits.

Acknowledgement

Special thanks are given to Dr Wael Elayat for his help in the chemical analyses of the gallstones utilised in the present work, and to Yazun Jarrar for his help in the statistical analyses.

Authors' Contributions

Conception and design, collection, assembly, analysis, and interpretation of the data, drafting, critical revision, and final approval of the article. BMJ, MAA

Correspondence

Dr Bashir M Jarrar
PhD Histochemistry (Khartoum University)
Department of Clinical Laboratory Sciences
College of Applied Medical Sciences
Al-Jouf University
PO Box 2014
Skaka – Al-Jouf
Saudi Arabia
Tel: +00966-543647100
Fax: +00966-46257328
Email: bashirjarrar@yahoo.com

References

1. Berci G. Historical overview of surgical treatment of biliary stone disease. In: MacFadyen BV, Arregui M, Eubanks S, Olsen DO, Peters JH, Soper NJ, et al., editors. *Laparoscopic surgery of the abdomen*. New York (NY): Springer; 2004. p. 139–142.
2. Al-Mofleh IA. Gallstones. *Saudi J Gastr*. 1995;**1(3)**:173–179.
3. Alsaif MA. Variations in dietary intake between newly diagnosed gallstone patients and controls. *Pakistan J Nut*. 2005;**4(1)**:1–7.
4. Attasaranya S, Fogel EL, Lehman GA. Choledocholithiasis, ascending cholangitis, and gallstone pancreatitis. *Med Clin Am*. 2008;**92(4)**:925–960.
5. Kratzer W, Kachele V, Mason RA, Hill V, Hay B, Haug C, et al. Gallstone prevalence in Germany. The Ulm Gallbladder Stone Study. *Digest Dis Sci*. 1998;**43(6)**:1285–1291.
6. Lu SN, Chang WY, Wang LY, Hsieh MY, Chuang WL, Chen SC, et al. Risk factors for gallstones among Chinese in Taiwan. A community sonographic survey. *J Clin Gastroenterol*. 1990;**12(5)**:542–546.
7. Ahmed A, Cheung RC, Keeffe EB. Management of gallstones and their complications. *Am Fam Physcian*. 2000;**61(6)**:1673–1680, 1687–1688.
8. Abu-Eshy SA, Mahfouz AA, Badr A, El Gamal MN, Al-Shehri MY, Salati MI, et al. Prevalence and risk factors of gallstone disease in a high altitude Saudi population. *East Mediterr Health J*. 2007;**13(4)**:794–802.
9. Jensen KH, Jorgensen T. Incidence of gallstones in Danish population. *Gastroenterology*. 1991;**100(3)**:790–794.
10. Al-Sulaimani SH, Alam MK, Sengupta H, Girgis A. Incidence of cholelithiasis in patients attending King Abdulaziz University Hospital. *Saudi Med J* 1986;7:261–265.
11. Mofti AB, Al-Tameem MM, Al-Khudairy NN, Singh DN, Ahmad IA. Experience with elective cholecystectomy in King Khalid University Hospital. *Ann Saudi Med*. 1987;7:107–110.
12. Mokhtar AMA. Cholelithiasis in the western region of Saudi Arabia. *Est African Medical J*. 1990;**67(4)**:286–290.
13. Tamimi TM, Wosornu L, Abdul-Ghani A, Al-Khozaim A. Increased cholecystectomy rates in Saudi Arabia. *Lancet*. 1990;**336(8725)**:1235–1237.
14. Ahmed AF, El-Hassan OM, Mahmoud ME. Risk factors for gallstone formation in young Saudi women: A case control study. *Ann Saudi Med*. 1992;**12(4)**:395–399.
15. Murshid KR. Syptomatic gallstones: A disease of young Saudi women. *Saudi J Gastroenter*. 1998;**4(3)**:159–162.
16. Gowenlock AH, McMurray JR, McLauchlan DM. *Varley's practical clinical biochemistry*. 6th ed. London (UK); Heinemann Medical Books: 1988.
17. Allain CC, Poon LS, Chan CS, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem*. 1974;**20(4)**:470–475.
18. Jarrar BM, Taib NT. *Laboratory techniques for calculi analysis*. Riyadh (SA): King Saud University Press; 2003.
19. Dunlow N, Phillips C, Broder HL. Concurrent validity of the COHIP. *Community Dent Oral Epidemiol*. 2007;**35 Suppl 1**:41–49.
20. Lev MH, Farkas J, Gemmete JJ, Hossain ST, Hunter GJ, Koroshetz WJ, et al. Acute stroke: Improved nonenhanced CT detection-benefits of soft-copy interpretation by using variable window width and center level settings. *Radiology*. 1999;**213(1)**:150–155.
21. Bulo A, Refatllari E, Koci K, Zaganjori R, Isaraj A. Infrared spectroscopy in kidney and biliary stone disease. *Jugoslov Med Biochem*. 2004;**23(3)**:285–288.
22. Al-Sibaai AA, Kensara AM, Baghlaf AO. Element analysis as a strong tool for the determination of gallstones composition. *JKAU: Sci*. 2006;**18**:33–45.
23. Mjaland O, Adamsen S, Hjelmquist B, Ovaska J, Buanes T. Cholecystectomy rates, gallstone prevalence, and handling of bile duct injuries in Scandinavia. *Surg Endosc*. 1998;**12(12)**:1386–1389.
24. Marscall HU, Einarsson C. Gallstone disease. *J Intern Med*. 2007;**261**:259–542.
25. Amigo L, Zanlungo S, Mendoza H, Miquel JF, Nervi F. Risk factors and pathogenesis of cholesterol gallstones: State of the Art. *Eur Rev Med Pharmacol Sci*. 1999;**3(6)**:241–246.

26. Dowling RH. Review: Pathogenesis of gallstone. *Aliment Pharmacol Ther*. 2000;**14 Suppl 2**:39–47.

27. Cuevas A, Miquel JF, Reyes MS, Zanlungo S, Nervi F. Diet as a risk factor for cholesterol gallstone disease. *J Amer Coll Nutr*. 2004;**23(3)**:187–196.

28. Central Department of Statistics. *Population growth rate among the population in 2004 to 2010 censuses*. Riyadh (SA): Ministry of Economy and Planning, Saudi Arabia; 2010.

29. Jaddou HY, Ammari FF, Shreideh M, Ababneh K. Prevalence and risk factors of gallstone disease among female teachers in Northern Jordan. *Saudi Med J*. 1996;**17(2)**:137–144.

30. Chandran P, Kuchhal NK, Garg P, Pundir CS. An extended chemical analysis of gallstone. *Indian J Clin Biochem*. 2007;**22(2)**:145–150.

31. Channa NA, Khand FD, Khand TU, Leghari MH, Memon AN. Analysis of human gallstones by flourier transform infrared (FTIR). *Pak J Med Sci*. 2007;**23(4)**:546–550.

32. Khalil T, Walker JP, Wiener I, Fagan CJ, Townsend CM, Greeley GH, et al. Effect of aging on gallbladder contraction and release of cholecystokinin-33 in humans. *Surgery*. 1985;**98(3)**:423–429.

33. Angwafo III FF, Takongmo S, Griffith D. Determination of chemical composition of gall bladder stones: Basis for treatment strategies in patients from Yaounde, Cameron. *World J Gastroenterol*. 2004;**10(2)**:303–305.

34. Tsai WL, Lai KH, Lin CK, Chan HH, Lo CC, HSU PI, et al. Composition of common bile duct stones in Chinese patients during and after endoscopic sphincterotomy. *World J Gasteroenterol*. 2005;**11**:4246–4249.

35. Schafmayer C, Hartleb J, Tepel J, Albers S, Freitag S, Volzke H, et al. Predictors of gallstone composition in 1025 symptomatic gallstones from Northern Germany. *BMC Gastroenterology*. 2006;**6**:36.

36. Singh A, Bagga SPS, Jindal VP, Singh K, Rao SS. Gall bladder disease: An analytic report of 250 cases. *J Ind Med Assoc*. 1989;**87**:253–656.

37. Kim E, Lee Y. A descriptive study of gall stone patient's dietary habits and nutritional status. *Korean J Comm Nutr*. *2007*;**12(6)**:826–877.

38. LaMont JT, Ventola AS, Trotman BW, Soloway RD. Mucin glycoprotein content of human pigment stones. *Hepatology*. 1983;**3(3)**:377–382.

39. Moore EW. The role of calcium in the pathogenesis of gallstones. *Hepatology*. 1984;**4(5 Suppl)**:228S–243S.

40. Verma JR, Pandey AK, Bose SM, Prasad R. Study of serum calcium and trace elements in chronic cholelithiasis. *ANZ J Surg*. 2002;**72(8)**:596–599.

Original Article

Robotic Neurosurgery: A Preliminary Study Using an Active Vision-Guided Robotic Arm for Bone Drilling and Endoscopic Manoeuvres

Mohamed Saufi Awang[1], Mohd Zaid Abdullah[2]

Submitted: 3 Feb 2010
Accepted: 20 Mar 2010

[1] *Department of Neurosciences, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia*

[2] *School of Electrical Engineering, Universiti Sains Malaysia Engineering Campus, 14300 Nibong Tebal, Penang, Malaysia*

Abstract

Background: **Surgical robots have been appearing in operating rooms over the past decade, and neurosurgery has been one of the pioneers in this area. In neurosurgery, the clinical use of robots has been limited to stereotactic procedures and endoscopic manoeuvres, although the brain is a unique organ and well-suited for robotic application. The aim of this study was to assess the ability of our vision-guided robotic system to perform basic neurosurgical procedures.**

Methods: **The study was divided into two parts: bone drilling and endoscopic manoeuvres. The robotic system was instructed to recognise targets on artificial skull models placed in different positions (supine, lateral, sitting, and prone) and to make burr holes. A total of 10 selected burr holes were used to assess the capability of the robot to insert an endoscope.**

Results**: The accuracy ranged 0.1–1.0 mm with repeatability ranged 0.03–0.92 mm.**

Conclusion**: Generally, the present robotic system is able to perform the surgical tasks. However, further study is needed to refine the robotic system, including the safety mechanisms.**

Keywords: *computer-assisted surgery, endoscopes, neurosurgery, robotics, skull*

Introduction

Robots have been used in operation theatres as of the last few decades (1). Neurosurgery is one of the major fields in which the application of robots during surgery is feasible. Robotic technology has been incorporated into stereotactic and endoscopic procedures (2,3). Other key neurosurgical applications for robots include robotised microscope (4), telepresence (5), and tumour resection (6).

Technically, surgical robots can be divided into passive or active systems. A passive system is one in which the surgeon provides the physical energy to drive the surgical tool (7). An active robotic system is one in which the robot actively interacts with a patient, allowing more complicated motions to be realised. This latter system provides greater autonomy. In addition, the surgeon has the ability to supervise and intervene when necessary (8).

The surgical robots can also be classified by how the surgeon interacts with them. They are divided into supervisory-controlled system, telesurgical system, and shared-control system. In a supervisory-controlled system, the robot automatically performs the task based on the downloaded surgical plan and is supervised by the surgeon. The surgical plan is programmed using either computed tomography (CT) scan or magnetic resonance brain images of a patient. The robotic telesurgical system is a system in which the surgeon controls the robot in real time via the haptic interface. The robot replicates the surgeon's motions from the interface. In a shared-control system, the surgeon has full control of the procedure and the robot offers steady hand manipulation of the instrument (9).

In this study, we examined the ability of our industrial robotic arm to perform basic neurosurgical procedures, namely bone drilling and endoscopic manoeuvres, on artificial skull models. The robotic system was fully guided by a visual system, thus making this system different from the aforementioned robotic systems. A program was created to transform visual coordinates to the robotic coordinates, thus enabling the robot to execute the tasks. The robot's abilities were measured via the capability of the robot to recognise the target and perform the tasks. The accuracy of the robot was also assessed.

Materials and Methods

The robot used in this study was an Adept Cobra 600 robot (Adept Technology Inc., San Jose, CA). The Adept Cobra 600 robot (Figure 1) is a selective compliant assembly robot arm (SCARA) robot with 4 joints. Joints 1, 2, and 4 provide rotational movements, and joint 3 moves in translation. Joint 1 is also referred to as the shoulder and has motion limited to approximately 105°. Joint 2, which also referred to as the elbow, has motion limited to approximately 105°. Joint 3 allows vertical translation of the quill with a maximum stroke of 210 mm. Joint 4, also referred to as the wrist, allows approximately 360° of rotational movement.

A 25-mm lens charge-coupled device (CCD) camera functioned as the visual system. The camera was mounted to the robotic arm. The camera had input and output channels, and the lens could be focused manually. The images produced were in the greyscale form.

Preparation of artificial skull models

The artificial skull models were made using the stereolithography apparatus (SLA) system. The brain CT scan images were transferred to the workstation, and using special software, the images were translated. The skull models were constructed using acrylic resin. Subsequently, the skull model was cut into two parts using a saw. Plasticine was moulded and wrapped with thin plastic and placed into the skull (Figure 2). The purpose of this step was to create soft material in the skull that would act like a brain. This detail is important because the Midax Rex perforator uses a mechanical sensor and will only stop once it senses the soft component. Two basic surgical procedures were tested in this study: bone drilling and endoscopic manoeuvres.

Bone drilling

The skull model was placed into different surgical positions, simulating a real operation: supine with head in neutral position, supine with head in left or right lateral position, sitting position, and prone position. To avoid movement during the procedure, the skull models were clamped on a Mayfield three-pin clamp. The Midax Rex perforator was attached to the gripper and held tightly with screws. The tubing was fixed to the gas tank and foot pedal.

A total of 4 targets were placed in supine position with the head in neutral position. There were also 10 targets at different sites in the sitting position, 5 targets at each side in lateral positions,

Figure 1: Adept Cobra 600

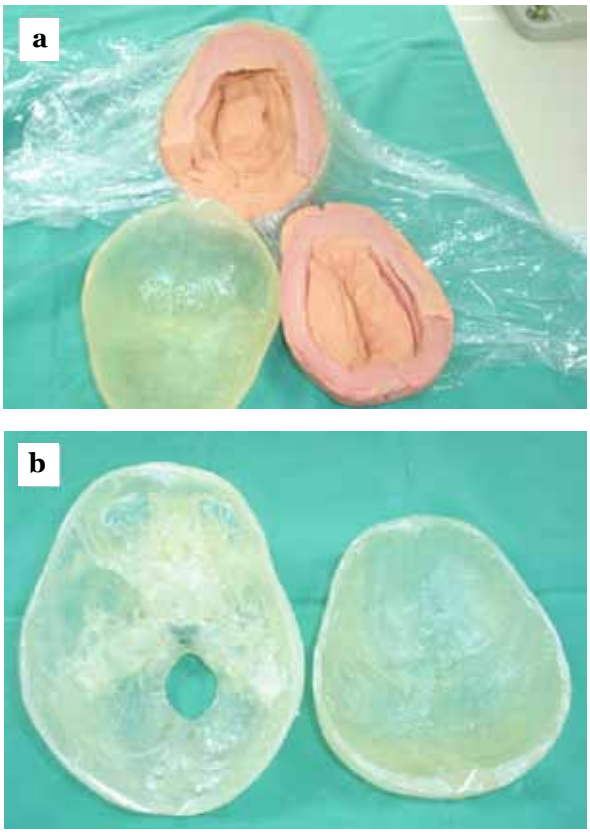

Figure 2: Artificial skull model (a) cut halfway and (b) molded with plasticine.

and 6 targets placed on the skull surface in the prone position. These targets were black, rounded cardboard, each measuring 1 cm in diameter. The targets were glued to the skull surface. Only 1 target was exposed at a time for image capturing; the remaining targets were covered with surgical towel. The camera was placed at 54.5 cm from the skull surface, similar to the position where the camera was calibrated. The image of the first

target was captured. Using the V+ program, a specific set of commands were created to analyse the image. Image processing involved many steps. First, in the image-capturing stage, the image was stored in pixels. Pixel is the basic unit of a vision system. The number of pixels that a system can process determines its resolution and influences the computer processing time needed to analyse the image. Subsequently, using a Gaussian filter, the image was filtered to reduce the noise and prepare the image for further processing. Later, the edge of the image was detected using a Sobel operator (edge detection). Finally, the image centroid was determined via the method of moments. Using a mathematical calculation that was set in the program, the image coordinates were transformed into robot coordinates.

Next, the task was executed. The robotic arm together with the perforator moved to the target. The perforator was instructed to descend until it touched the skull surface. Using the mechanical sensor located at joint 4, the program was constructed in such a way that the perforator would stop automatically once the sensor detected a force of more than 2 pounds.

At this stage, the accuracy of the robot was assessed by measuring the distance, using the computer, between the centre of the target and the point at which the perforator hit the target. The robotic arm was then instructed to return to home position. The procedure was repeated twice. The repetitive value (repeatability) was recorded. After the second attempt, the robotic arm was given a force speed at 0.5% of maximum velocity and as soon as the perforator hit the target, the pedal was pressed and the perforator was allowed to spin and drill the skull (Figure 3). The perforator continued to drill and stopped automatically when it sensed the soft part (plasticine). The robotic arm was then instructed to return to home position. These steps were repeated for all targets located at different sites and different positions.

Endoscopic Manoeuvre

In this section, only the burr holes that were perpendicular to the endoscope were chosen. There were 10 burr holes in total, and the centroid of the targets were determined via image processing. These coordinates were transformed into robotic coordinates and the task was executed. Upon execution, the robotic arm together with the endoscope moved to the targeted burr hole. On command, the endoscope descended and entered the burr hole to touch the target marker. The accuracy was measured. Following that, the robotic arm was instructed to ascend and move to home position. These steps were repeated twice. The repetitive values were measured. Once the accuracy and repetitive values were measured, the endoscope was instructed to return to the burr hole and descend. The endoscope was given some minimal force to penetrate the plasticine and descend on command (Figure 4). The ability of the robotic arm to recognise and insert the endoscope into the specific burr hole on command was assessed. These procedures were repeated for the rest of the selected burr holes.

Results

In the supine position, the accuracy was 1.0 mm for all targets. The repetitive values ranged 0.04–0.17. In the sitting position, a total of 8 burr holes were successfully performed. The accuracy ranged 0.1 –1.0 with the repetitive values ranging 0.10 –0.92. In the prone position, the accuracy ranged 0.5 –1.0 with the repetitive values ranging 0.08 –0.31. In the left lateral position, only 2 burr holes were successfully performed. The accuracy was 1.0 mm. The repetitive values for these 2 left

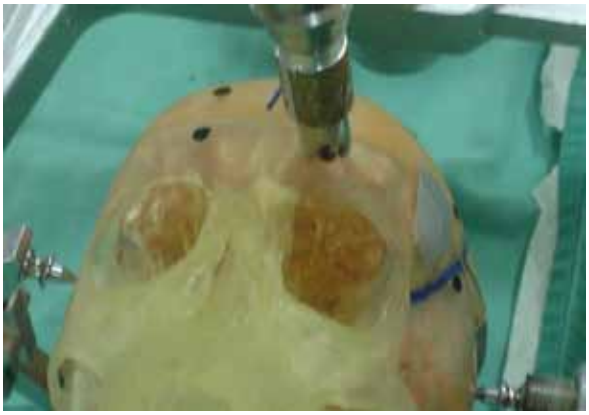

Figure 3: The bone drilling stage.

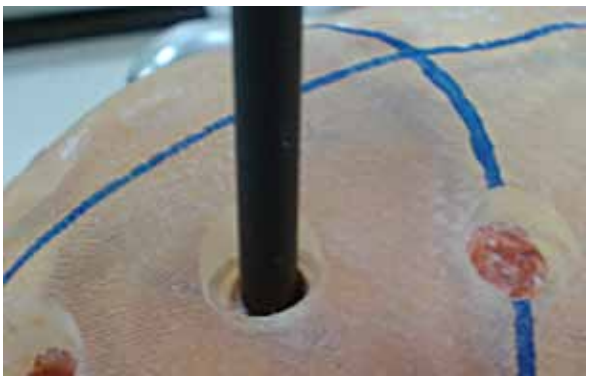

Figure 4: Insertion of an endoscope into a selected burr hole.

lateral burr holes were 0.03 and 0.11, respectively. Similarly, in the right lateral position only 2 burr holes were able to be performed. The calculated accuracy was 1.0 and the repetitive value was 0.10. The results are summarised in Table 1. For the endoscopic manoeuvre, the accuracy ranged 0.3–1.0, and the repetitive values ranged 0.31–0.77.

Discussion

In our robotic system, the ability to perform the tasks was limited by the degree of freedom (DOF). DOF referred to the number of possible movements that could be made at a joint. The movements could either be translational or rotational. For complete freedom of movement, 6 DOFs are required. If we apply this principle to the human upper limb, the elbow has 1 rotational DOF, the elbow and wrist have 3 rotational DOFs, and the palm is considered to have 7 DOFs as a result of the sum of the shoulder, elbow, and wrist. With 7 DOFs, therefore, better precision can be obtained. Four DOFs would limit the surgeon's ability (10). One study was done comparing 4-DOF and 6-DOF robots performing some endoscopic procedures. The study revealed that the time taken and error rate to perform the procedures by 6-DOF robot were significantly less as compared with the 4-DOF robot (11). Our robot has 4 DOFs. Because of this fact, the robot could only perform some limited movements. The robotic could only make rotational motions (joints 1, 2, and 4) and vertical translational movements (joint 3). To make a burr hole using a perforator, the perforator has to be perpendicular to the surface. Therefore, with our present system, the robotic arm can only perform bone drilling if the arm is perpendicular to the skull surface (supine, prone, and some sitting positions). The wide angulation of the skull in the lateral position did not allow for the proper drilling of the bone. Similarly, with the endoscopic manoeuvre, the endoscope could only be inserted if the burr hole was perpendicular to the robotic arm.

The accuracy of our system was determined by many factors. First, the visual system was represented by a CCD 25-mm lens with an 8.1 pixel camera. The image taken by the camera was kept in greyscale form. Subsequently, the image was converted to binary form. Here, the centre of the image (target) was determined via image processing based on how much of the image represented by pixels was detected. If a higher pixel and higher resolution camera had been used, the image taken would have been better and the centroid coordinates more accurate. The problem with visual system applied to both bone drilling and endoscopic manoeuvres.

The other crucial factor that may affect the accuracy and repeatability was the inconsistency in the height of the camera from the skull surface. During the camera calibration, the height of the camera from the surface was fixed at 54.5 cm. Given that the skull surface was uneven and contoured, the height was different every time an image was captured.

Another factor that may influence the accuracy of our robotic system, particularly at different skull positions, was the amount of illumination. As the robot was located in a large laboratory, the amount of light that fell on the target was very difficult to control. Optimum illumination is crucial because it can influence the amount of pixel that can be detected by the camera. This problem can be overcome by providing additional illumination.

Safety was another issue that needed to be addressed. The traditional safety methods designed for industrial robots are not sufficient for medical robots. For instance, industrial robots are required to be kept in a locked room so that nobody can enter the room and interact with the robot. In contrast, the surgical robot required direct contact with the patient and surgeon. In addition, medical robots are used in patient care

Table 1: Number of targets and completed burr holes plus the accuracy and repeatability at different positions

Position	No of targets	No of burr holes	Accuracy (mm)	Repetition (mm)
Supine	4	4	1.0	0.04–0.17
Sitting	10	8	0.1–1.0	0.10–0.92
Prone	6	6	0.5–1.0	0.08–0.31
Left lateral	5	2	1.0	0.03–0.11
Right lateral	5	2	1.0	0.10

settings and have impacts on human life, whereas industrial robots deal with products produced in factories. Therefore, the safety requirements for medical robots are more stringent and critical (12–14).

Due to some limitations, the safety mechanism in our robot was still lacking. In this study, we had to stop the robot manually once the perforator stopped drilling. Similarly, with the endoscopic manoeuvre there was no specific safety system attached to the robot or the endoscope, although the robot was able to follow the command based on the program.

Conclusion

Our robotic system was able to behave like a surgical robot. The accuracy of the vision guided robotic arm ranged 0.1–1.0 mm. Much refinement in the use of robotic systems for neurosurgical procedures is needed. For future work, we would like to improve the number of DOFs, thus allowing for more joint movements. A mechanism is also needed to ensure that the height of the camera from the skull surface can be maintained even when the skull is placed into different positions. More importantly, safety mechanisms need to be developed and established before work can be extended in animal models.

Authors' Contributions

Obtaining funding, collection and assembly of the data, drafting of the article: MSA
Critical revision and final approval of the article: MZA

Correspondence

Dr Mohamed Saufi Awang
MBBS (Adelaide), MSurg Neurosurgery (USM)
Department of Neurosciences
School of Medical Sciences
Universiti Sains Malaysia Health Campus
16150 Kubang Kerian
Kelantan, Malaysia
Tel: +609-7676300
Fax: +609-764 8613
Email: saufiawang@yahoo.com

References

1. Howe RD, Matsuoka Y. Robotics for surgery. *Annu Rev Biomed Eng*. 1999;**1**:211–240.
2. Louw DF, Fielding T, McBeth PB, Gregoris D, Newhook P, Sutherland GR. Surgical robotics: A review and neurosurgical prototype development. *Neurosurgery*. 2004;**54(3)**:525–537.
3. Mc Beth PB, Louw DF, Rizun PR, Sutherland GR. Robotics in neurosurgery. *Am J Surg*. 2004;**188(4)**:68–75.
4. Giorgi C, Eisenberg H, Costi G, Gallo E, Garibotto G, Casolina DS. Robot-assisted microscope for neurosurgery. *J Image Guid Surg*. 1995;**1(3)**:158–163.
5. Hongo K, Goto T, Kakizawa Y, Koyama J, Kawai T, Kan K, et al. Micromanipulator system (NeuRobot): Clinical application in neurosurgery. *Int Congr Ser*. 2003;**1256**:509–513.
6. Benabid AL, Lavallee S, Hoffmann D, Cinquin P, Demongeot J, Danel F. Potential use of robots in endoscopic neurosurgery. *Acta Neurochir Suppl (Wien)*. 1992;**54**:93–97.
7. Mckay-Davies I, Bann S, Darzi A. Robotics in surgery. *Student BMJ*. 2002;**10**:215–258.
8. Kwoh YS, Hou J, Jonckheere EA, Hayati S. A robot with improved absolute positioning accuracy for stereotactic brain surgery. *IEEE Trans Biomed Eng*. 1988;**35(2)**:153–160.
9. Nathoo N, Cavusoglu MC, Vogelbaum MA, Barnett GH. In touch with robotics: Neurosurgery for the future. *Neurosurgery*. 2005;**56(3)**:421–433.
10. Cadeddu JA, Stoianovia D, Kavoussi LR. Robotics in urologic surgery. *Urology*. 1997;**49(4)**:501–507.
11. Shah J, Mackay S, Rockall T, Vale J, Darzi A. 'Urobotics': Robots in urology. *BJU Int*. 2001;**88(4)**:313–320.
12. Fei B, Ng WS, Chauhon S, Kwoh CK. The safety issues of medical robotic. *Reliab Eng Syst Safe*. 2001;**73(2)**:183–192.
13. Wikman TS, Branicky MS, Newman WS. Reflexia collision avoidance: A generalized approach. In: *Proceedings of the IEEE International Conference on Robotics and Automation;* 1993 May 2–6; Atlanta (GA). p. 31–36.
14. Davies B, Starkie S, Harris SJ, Agterhuis E, Paul V, Aur CM. Neurobot: A special-purpose robot for neurosurgery. In: *Proceedings of the IEEE International Conference on Robotics and Automation;* 2000 Apr 24–28; San Francisco (CA). p. 4103–4108.

Original Article

A Preliminary Study on the Prevalence of Cardiovascular Disease Risk Factors in Selected Rural Communities in Samarahan and Kuching Division, Sarawak, Malaysia

Cheah Whye Lian[1], Lee Ping Yein[2], Khatijah Yaman[1], Rasidah Abdul Wahab[1]

Submitted: 25 Apr 2010
Accepted: 28 Sep 2010

[1] *Department of Community Medicine and Public Health, Faculty of Medicine and Health Sciences, Universiti Malaysia Sarawak, Lot 77, Section 22 KTLD, Jalan Tun Ahmad Zaidi Adruce, 93150 Kuching, Sarawak, Malaysia*

[2] *Department of Family Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia,43400 Serdang, Selangor Darul Ehsan*

Abstract

Background: **It is important to understand the prevalence of risk factors for cardiovascular disease, especially in a rural setting.**

Methods: **A cross-sectional study was carried out in 238 rural households located in the Kuching and Samarahan divisions of Sarawak among individuals aged 16 years and above. Anthropometric measurements, blood levels of glucose and cholesterol, and blood pressure were collected.**

Results: **Prevalence of blood pressure in the hypertensive range was 43.1%. The highest rates of blood pressure in the hypertensive range were found in individuals aged above 60 years (38.6%) and 50–59 years old (31.8%). Age was one factor found to be significantly associated with blood pressure in the hypertensive range ($P < 0.001$). Prevalence of obesity was 49.0%. The highest prevalence of obesity was found among those aged 40–49 years (41.9%) and 50–59 years (29.9%). Gender was significantly associated with obesity ($P = 0.004$). The prevalence of blood cholesterol at risk was 21.6%, and the highest rate was found in the 40–49 years age group (34.0%). Fifty percent of respondents were found to have hyperglycaemia, with the highest prevalence in the 50–59 years age group (37.5%). A significant association was found between obesity, blood pressure in the hypertensive range and blood glucose level. When compared with non-obese individuals, those who were obese were more likely to have blood pressure in the hypertensive range and hyperglycaemia.**

Conclusion: **The risk of developing lifestyle-related diseases is no longer based on geographical or socio-economic factors.**

Keywords: *blood pressure, cardiovascular diseases, hypercholesterolaemia, hyperglycaemia, medical screening and epidemiology, risk factors, rural communities*

Introduction

Mortality rates from coronary vascular disease, stroke, cancer, and diabetes are currently increasing in most industrialised countries, and they account for almost 5.5 million deaths annually in developed regions (1). In Malaysia, as in many other developing and developed countries, the major causes of morbidity and mortality have shifted from communicable to non-communicable diseases. Two of the leading causes of death in Malaysia in 2005 were heart disease and cerebrovascular disease (2). The Malaysian Ministry of Health's annual report (3) indicates that mortality from heart and pulmonary diseases accounted for 10.31% of all deaths. These 2 diseases were also classified among the top 10 causes of hospitalisation in government hospitals. It is well known that these non-communicable diseases can often be prevented through lifestyle changes, particularly modification of risk factors such as obesity, hypertension, hypercholesterolaemia, and hyperglycaemia.

Low-income communities are always associated with poverty-related diseases (4). Fundamental changes in food supply patterns in recent decades have led not only to the increase in the amount of food available, but also to the changes in diet composition.

The implementation of public interventions that encourage a healthy lifestyle may need to be reviewed to determine whether the delivery should be targeted to the entire population or catered specifically to affected groups. This is particularly relevant where data on the cardiovascular disease (CVD) risk factors in the rural community are inadequately published. The objective of this study was to determine the prevalence of cardiovascular disease risk factors in selected rural communities in Sarawak, Malaysia.

Subjects and Methods

Sarawak, situated on the island of Borneo, is the largest state in Malaysia, with an area of 124 000 km^2 (37.5% of the country's total land mass). With a population of approximately 2.4 million, Sarawak is the least densely populated of Malaysia's 13 states. Based on geographical classification, there are 11 divisions with 31 districts in Sarawak. Under the criteria of peripheral or adjacent areas of a city or town, 2 divisions were chosen: Kuching and Kota Samarahan. A district was randomly selected for both divisions. A list of rural villages was collected from the state district office, and 5 villages were randomly selected from each district. With the help of the respective Sarawak Administration Officers, informed consent forms were sent out to the head of each village. Of all the villages to which informed consent forms were sent, only 3 agreed to participate in the study (Table 1). Baseline data on population size was then obtained through surveys administered in each of the villages.

The minimum sample size for this cross-sectional study was determined using the formula for single proportion (EpiInfo 3.3.2, Center for Disease Control and Prevention, US). Based on a 25% national prevalence of CVD and a sampling frame of 4128, the minimum sample size to achieve at least a 95% confidence rate was estimated to be approximately 269, which allowed for 10% non-response. The precision of the prevalence of CVD chosen was 5%. Sample size for each village was determined based on its proportion of the sampling frame.

The survey was administered in 2007. Ethical approval was obtained from the Ethics Committee of Universiti Malaysia Sarawak. All residents aged 16 years and above in the selected households were recruited. As the financing was limited, a 1-day event was organized in each of the villages, and all the identified households were invited and gathered at the community hall. The village heads informed all respondents in advance to fast overnight. A participant would be classified as a non-responder if he or she did not attend the event. An informed consent was obtained from each survey respondent. The data collection was carried out in the morning to enable respondents to have their breakfast after the blood test. Data were collected by 2 of the authors using a pre-tested and validated questionnaire. The information collected included the following items:

- Family socio-economic and demographic background
- Body mass index
- Blood pressure
- Blood cholesterol level
- Blood glucose level

Blood pressure measurements were taken using a mercury column sphygmomanometer (Accoson, UK) based on the Malaysian Clinical Practice Guidelines on Management of Hypertension (5). Although blood pressure was taken twice to determine an average reading, this study could only determine the prevalence for blood pressure in the hypertensive range. To make a diagnosis of hypertension, blood pressure must be taken on 2 or more separate occasions or clinical visits. Classification of blood pressure was based on the schema used by the Ministry of Health (5); a systolic reading of 140 mmHg and above and/or a diastolic reading of 90 mmHg and above was classified as hypertensive. For the measurement of body mass index (BMI; weight in kg divided by height in m^2), height was measured using a body meter (Seca, UK) suspended upright against a straight wall, and body weight was measured using a digital weighing scale (Seca, UK). Classification of BMI was based on

Table 1: List of villages enrolled in the study

Village identified	No. of Population	*n* (%)
Kampung Buntal, Kuching	2482	161 (59.9)
Kampung Baru, Samarahan	1035	67 (24.9)
Kampung Pangkalan Kuap, Kota Samarahan	611	41 (15.2)

the World Health Organization/International Association for the Study of Obesity/International Obesity Task Force (WHO/IASO/IOTF) guidelines (6), where a BMI of 23 kg/m² and above is classified as overweight and a BMI of more than 25 kg/m² is classified as obese. Due to limitations of delivery and laboratory arrangement, blood cholesterol and glucose levels were determined using a handheld Accutrend cholesterol meter and Accu-Chek Advantage meter (Roche Diagnostics, Germany), respectively. Blood was obtained using the finger stick skin puncture method with disposable lancets based on Lynn (7). Classification of fasting total cholesterol and glucose levels was based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (8) and the Malaysian Diabetes Mellitus Guidelines (2009) (9). Based on these guidelines, fasting total cholesterol of more than 5.2 mmol/L is classified as borderline high and 6.2 mmol/L and above is high risk for hypercholesterolaemia. For blood glucose level, any reading of more than 5.6 mmol/L is classified as high risk for hyperglycaemia.

Data was analysed using SPSS version 14 (SPSS Inc., Chicago, IL), which included common descriptive analyses. Significant associations between variables were determined using inferential statistics, based on a *P* value of less than 0.5. Data were cleaned and checked for normality. Odds ratios were presented based on a 95% confidence interval (CI).

Results

A total of 238 respondents agreed to participate in the study, giving a response rate of 88.4% (238 out of 269). The age range for this study was 16–89 years, with a mean of 49.9 years. Distribution of gender was relatively even (46.5% were males and 53.5%, females). The majority of the respondents were Malays, with only 1% were Iban and 1%, Kadazan. Table 2 presents the clinical characteristics of the studied population. Looking at the number of cardiovascular risk factors displayed by participants, 31.5% had 1 risk factor, and 44.4% had more than 1 risk factor.

Table 3 shows the prevalence of blood pressure in the hypertensive range, obesity, blood cholesterol level, and blood glucose level in the at-risk range and their relationships with socio-demographic factors. The prevalence of blood pressure in the hypertensive range was 43.1%. Within the affected group, the highest percentage was found among the older age group (above 60 years), and the prevalence of high blood pressure increased as age increased. This difference was found to be significant (*P* = 0.001). Females were found to have higher blood pressure readings than males, but this difference was not significant (*P* = 0.413). The systolic blood pressure (SBP) of the respondents ranged 90–180 mmHg, with a mean of 125.3 mmHg (SD 13.8). The diastolic blood pressure (DBP) ranged 50–100 mmHg, with a mean of 80.9 mmHg (SD 12.2). The mean SBP for males (125 mmHg, SD 12.6) was not significantly different from that of females (125 mmHg, SD 14.8). Similarly, the mean DBP for males (81 mmHg, SD 13.9) was not significantly different from that of females (81 mmHg,SD 10.5).

The prevalence of obesity was 49.0%. The highest rate of obesity was found among those who were 40–49 years old (41.9%), followed by those who were 50–59 years old (29.9%). The mean BMI was 25.26 kg/m² (SD 5.04). The BMI of respondents ranged 11.58–56.29 kg/m². Obesity prevalence was higher among females than males.

The blood cholesterol level of the respondents ranged 2.59–7.71 mmol/L, with a mean of 4.6 mmol/L (SD 0.8). The cholesterol level increased as age increased, with the highest levels found in the 50–59 year-old age group. Females were found to have higher blood cholesterol levels than males.

The blood glucose levels ranged 0.3–28.0 mmol/L, with a mean of 7.4 mmol/L (SD 3.4). Similar to blood cholesterol level, blood glucose level showed the same pattern of increasing with age. The age group with the highest prevalence of at-risk blood glucose levels was the 50–59 year-old group. This difference was found to be significant (*P* = 0.008). In terms of gender, males had higher blood glucose levels than females.

In determining an association between BMI and hypertension, the study found that those who were obese were 2.6 times more likely to have blood pressure readings in the hypertensive range than those who were not obese (Table 4). Similar patterns were found for blood glucose level; obese participants had 2.9 times the risk of having at-risk blood glucose levels than those with a normal BMI. All these associations were found to be significant.

Discussion

The overall prevalence of blood pressure in the hypertensive range was higher in our study (43.1%), compared with the 36.9% in rural areas reported in the 3rd Malaysian National Health and Morbidity Survey (NHMS 3) (10). This could be due to the mean age of 49.87 years old in our

Table 2: Clinical characteristics of the studied population

Characteristics	All (n = 238)	Males (n = 111)	Females (n = 127)
Age (year)	49.87 (11.83)	52.97 (12.08)	47.17 (10.95)
Weight (kg)	62.37 (14.16)	63.52 (14.73)	61.38 (13.63)
Height (m)	1.57 (0.08)	1.62 (0.07)	1.53 (0.06)
BMI (kg/m^2)	25.26 (5.04)	24.19 (4.91)	26.18 (4.99)
Systolic BP (mmHg)	125.28 (13.78)	125.36 (12.6)	125.22 (14.77)
Diastolic BP (mmHg)	80.92 (12.24)	81.18 (13.99)	80.7 (10.53)
Total cholesterol (mmol/L)	4.56 (0.82)	4.47 (0.74)	4.63 (0.87)
Fasting blood sugar (mmol/L)	7.40 (3.39)	7.62 (3.49)	7.21 (3.29)

Data are expressed in mean (SD).
Abbreviations: BMI = body mass index, BP = blood pressure

Table 3: Prevalence of blood pressure at hypertensive range, obesity, blood cholesterol level, and blood glucose level at risk of cardiovascular diseases in relation to age group and gender

Factors	Blood pressure at the hypertensive range[c] (n = 44)		Obesity (n = 117)		Blood cholesterol at risk[d] (n = 50)		Blood glucose at risk[e] (n = 120)	
Age group (years)[a]								
<39	4.5	(2.4,12.1)	12.8	(22.1,53.0)	12.0	(3.0,26.6)	10.0	(15.2,44.3)
40–49	25.0	(6.7,21.4)	41.9	(49.0,71.4)	34.0	(12.2,29.5)	30.0	(32.0,54.4)
50–59	31.8	(11.2,30.8)	29.9	(39.3,64.0)	32.0	(13.6,33.7)	37.5	(54.3,77.1)
>60	38.6	(21.1,49.0)	15.4	(23.0,52.1)	22.0	(11.0,35.3)	22.5	(42.9,71.2)
P value	0.001		0.083		0.724		0.008	
Gender[b]								
Male	40.9	(9.6,23.5)	39.9	(32.0,50.0)	40.0	(11.0,25.5)	51.7	(46.0,65.3)
Female	59.1	(13.2,27.0)	60.1	(48.8,65.1)	60.0	(16.3,31.0)	48.3	(36.1,54.0)
P value	0.413		0.004		0.192		0.136	

Data are expressed in prevalence in percentage (95% confidence interval). Statistical analysis was done using [a]Fisher exact test and [b]chi-square test. [c]Blood pressure at hypertensive range (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) , [d]Blood cholesterol level >5.2 mmol/L, and [e]Blood glucose level <5.6mmol/L were considered as at risk of cardiovascular diseases.

study population, which is much older than the mean age nationally. In comparison with other Asian countries, the prevalence of blood pressure in the hypertensive range reported herein was higher than that reported for the adult urban and rural populations of China (11) and other countries (11,12).

The prevalence of hypertension varies between 15% and 35% in urban adult populations of Asia. In rural populations, the prevalence is 2 to 3 times lower than that in urban populations (12). However, in the NHMS 3 (10), rural areas were found to have a higher prevalence of hypertension than urban areas. One possibility is that the rural population in Malaysia is older than the urban population, and the risk of hypertension increases with age. Looking at gender specifically, our study found that females had a higher prevalence of blood pressure in the hypertensive range than males (59.1% versus 40.9%, respectively);

Table 4: Association of blood pressure at hypertensive range, obesity, blood cholesterol and glucose at risk to obesity

Factors	Category of BMI						*P* value	Odd ratio (95% CI)
	Non-obese		Obese		Total			
Blood Pressure								
Normal	107	(55.2)	87	(44.8)	194	(100)	0.007	2.635
At risk[a]	14	(31.8)	30	(68.2)	44	(100)		(1.32, 5.28)
Blood cholesterol level								
Normal	101	(53.4)	88	(46.6)	189	(100)	0.149	1.664
At risk[b]	20	(40.8)	29	(36.1)	49	(100)		(0.88, 3.15)
Blood glucose level								
Normal	76	(63.9)	43	(36.1)	119	(100)	<0.001	2.906
At risk[c]	45	(37.8)	72	(60.5)	119	(100)		(1.72, 4.92)

Data are expressed in number of participants (percentage). Statistical analysis was done using chi-square test. [a]Blood pressure at hypertensive range (systolic ≥140 mmHg and/or diastolic ≥90 mmHg) , [b]blood cholesterol level >5.2 mmol/L, and [c]blood glucose level <5.6mmol/L were considered as at risk of cardiovascular diseases.
Abbreviations: BMI = body mass index.

however, these differences were not significant. This finding is consistent with the Malay sample in Singapore (13), but it contradicts a national study in Malaysia (14). This is likely due to the fact that more than one-third of the studied population was more than 60 years old and may have undergone menopause, thus their endogenous oestrogen levels were lower and the protective effect of oestrogen on blood pressure was diminished. However, as this is a preliminary study, a more comprehensive study should be done to confirm this finding.

Participants who were above 60 years old had the highest prevalence of blood pressure in the hypertensive range (38.6%) compared with other age groups. This finding is consistent with 2 local studies (15,16) and the study on the adult population in China (11); hypertension, namely systolic hypertension, has been shown to increase with age.

The overall mean BMI was 25.26 kg/m^2, with the highest obesity rate (41.9%) found among those in the 40–49 year-old age group. The overall prevalence of obesity was 49.0%, a figure that is alarming when compared with studies in other Asian countries, including China (11,17,18) and India (19). This figure is comparable to the findings of a study that involved 4 communities of Latin American countries where a BMI of more than 25 kg/m^2 was seen in more than 50% of their populations (20).

The prevalence rate of obesity reported by the NHMS 3 (10) was 29.1%. However, this figure reflects the BMI classification previously used by the Ministry of Health (21), wherein obesity was set at BMI of more than 30 kg/m^2. The latest BMI classification for obesity established by WHO/IASO/IOTF (6) was set at 25 kg/m^2. Females had a higher prevalence of BMI in the obese range than males: 60.1% and 39.9%, respectively. This finding is consistent with other local studies (10,15) in which females were found to have a higher prevalence of obesity than males. This issue has become an emerging paradox in most developing countries. A possible explanation is that females tend to gain the greatest amount of weight during their childbearing years (between 25 and 44 years old) (22). Some women engage in binge eating, even though food is consistently available (23). As the studied population comes from rural areas, another possible cause of obesity among females is the consumption of cheaper and less nutritious (more calorie-dense) food. The lack of choices with respect to availability and type of food can influence the intake of food.

The mean cholesterol levels of males and females were 4.47 mmol/L (SD 0.74) and 4.64 mmol/L (SD 0.87), respectively. These findings were comparable to those reported in a study in a rural population in India (19), but they were lower than those reported in a study of a rural population in Papua New Guinea (24). There was no significant difference by gender; both males and females had mean blood cholesterol level of less than 5.2 mmol/L, as recommended by the NCEP ATPIII (8). Based on this cut-off point,

21.6% of participants were found to be at high risk of hypercholesterolaemia, with the 40–49 age group having the highest prevalence of at-risk cholesterol levels (34.0%), followed closely by the 50-59 age group (32.0%). The overall prevalence rate was similar to that reported in a study in Singapore where the overall prevalence for both males and females was 23.5% (13). However, this prevalence is lower than that reported in urban and rural populations in China (11), even though the Chinese population has a lower prevalence of hypertension. This is rather interesting as cholesterol level is usually associated with hypertension. This difference could be due to ethnic variation, as the majority of the respondents in this study consisted of Malay and the Chinese study consisted only of Chinese. The cultural practices that influence behaviour in terms of eating and socializing could have contributed to this difference in health status. This study found that females had a higher prevalence of blood cholesterol in the at-risk range than males, which contradicts the study conducted in Singapore (13). However, the differences found in this study were not significant.

The blood glucose profile followed a slightly different pattern than blood cholesterol profile, where the highest prevalence for blood glucose in the at-risk range was among the 50–59 year-old age group (37.5%), followed closely by the 40–49 year-old age group (30.0%). This finding differs from the studies by Norimah and Haja (16) and Rampal et al. (25) in which both blood profiles increased with age. One possible explanation is that the older group's blood glucose level may have been under control due to medication. This study did not explore the question of whether respondents were previously diagnosed and were already under medical treatment or follow-up; therefore, this possibility cannot be explored further.

The overall mean blood glucose levels found herein were higher than those found in the rural population in China (11), with a difference of 2.5 mmol/L. It must be noted that the consumption of high sugar foods is very common in rural communities, particularly among the Malays; their drinks and cuisine tend to be high in sugar. Studies in Singapore (13) also report higher consumption of total energy among Malays than among Chinese.

As individuals approach the age of 50 and above, the chances of having more than 1 risk factor for CVD increases. We found that 44.4% of the participants had more than 1 risk factor, and 49.0% of the respondents were obese and thus more likely to have hypertension, hypercholesterolaemia, and hyperglycaemia than their non-obese counterparts. Female respondents showed a relatively higher prevalence of obesity, hypertensive blood pressure readings, and hypercholesterolaemia than males. Further studies need to be done to assess the main contributing factors associated with obesity, hypertensive blood pressure, and hypercholesterolaemia in this group of females.

Although it was speculated that the CVD risk factors for this rural population would occur in similar patterns to other rural communities (17,24), the findings indicated otherwise. In this survey, the prevalences of all CVD risk factors (BMI, SBP, DBP, total cholesterol, fasting blood glucose) were high, which was similar to the patterns found in an urban population in China (18). One possible reason could be that the villages were located adjacent to the city and thus were exposed to the influence of urbanization. Such influences include those that affect lifestyle and eating behaviours.

This is a preliminary study assessing the prevalence of several modifiable CVD risk factors. Because this study was carried out among selected villages in the rural areas of Kuching and Samarahan division, generalisation can only be extended to other sites with similar socio-demographic characteristics. The determination of cholesterol and glucose by finger-prick method was a preliminary screening and only provided initial information regarding the state of the respondents. Further comprehensive diagnostic measures would be needed to confirm the condition of respondents. Additional information about CVD-related disease status, family history of CVD-related disease, behavioural risk factors, eating habits, and smoking would help us to understand more about the relationship between CVD and its risk factors. We hope that with these preliminary findings, a more comprehensive study can be carried out in the future.

Conclusion

The overall results indicate that the risk of developing lifestyle-related diseases is no longer based on geographic or socio-economic factors, including the differences between urban and rural populations. Assessment of the effectiveness of current health interventions needs to be carried out more frequently to ensure that all segments of society acquire the necessary knowledge. Various health promotion modalities, such as mobile health screening clinics and radio shows,

should be carried out at the community level to reach villagers, and these health promotion activities should be continuously monitor and motivate community to change their lifestyle and eating habits. In addition, public health capacity and infrastructure must be strengthened in rural areas to provide adequate surveillance and the assurance that best practices are implemented. Moreover, future approaches in the design and delivery of health education need to consider the factors discussed here.

Acknowledgement

The authors thank Dr Mohamad Taha Arif for his assistance with the editing of the draft.

Authors' Contributions

Conception and design, obtaining of funding, analysis and interpretation of the data, drafting of the article: CWL
Provision of study materials or patients, collection and assembly of data, administrative, technical, or logistic support: CWL, KY, RAW
Statistical expertise, critical revision and final approval of the article: CWL, LPY

Correspondence

Dr Cheah Whye Lian
MSc Public Health (UNIMAS), PhD Community Nutrition (USM)
Department of Community Medicine & Public Health
Faculty of Medicine and Health Sciences
Universiti Malaysia Sarawak
Lot 77, Section 22 KTLD
Jalan Tun Ahmad Zaidi Adruce
93150 Kuching
Sarawak, Malaysia
Tel: +608-241 6550
Fax: +608-242 2564
Email: wlcheah@fmhs.unimas.my

References

1. Murray JL, Lopez AD. *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020*. Cambridge: Harvard University Press; 1996.

2. Ministry of Health (MY). *Annual report 2005*. Kuala Lumpur: Ministry of Health; 2005.

3. Ministry of Health (MY). *Annual report 2003*. Kuala Lumpur: Ministry of Health; 2003.

4. Wilkinson RG. National mortality rates: The impact of inequality? *Am J Public Health*. 1992;**82(8)**: 1082–1084.

5. Ministry of Health (MY). *Clinical practice guidelines on management of hypertension*. 3rd edition. Kuala Lumpur: Ministry of Health; 2008.

6. World Health Organisation, International Association for the Study of Obesity, International Obesity TaskForce. *The Asia-Pacific perspective: Redefining obesity and its treatment*. Sydney: Health Communications; 2000.

7. Lynn BH. *The clinical laboratory manual series: Phlebotomy*. New York: Delmar Publishers; 1995.

8. National Cholesterol Education Programme Adult Treatment Panel III. *Report of the expert panel on the detection, evaluation and treatment of high cholesterol in adults*. Kuala Lumpur: National Institute of Health; 2001.

9. Ministry of Health Malaysia. *Clinical Practice Guidelines on management of type 2 diabetes mellitus*. 4th edition. Kuala Lumpur: Ministry of Health; 2009.

10. Ministry of Health (MY). *Report of the Third National Health and Morbidity Survey (NHMS 3)*. Kuala Lumpur: Institute for Public Health, Ministry of Health Malaysia; 2006.

11. Gu D, Gupta A, Muntner P, Hu S, Duan X, Chen J, et al. Prevalence of cardiovascular disease risk factor clustering among the adult population of China: Results from the International Collaborative Study of Cardiovascular Disease in Asia (InterAsia). *Circulation*. 2005;**112(5)**:658–665.

12. Singh RB, Suh IL, Singh VP, Chaithiraphan S, Laothavorn P, Sy RG, et al. Hypertension and stroke in Asia: Prevalence, control and strategies in developing countries for prevention. *J Hum Hypertens*. 2000;**14(10–11)**:749–763.

13. Cutter J, Tan BY, Chew SK. Levels of cardiovascular disease risk factors in Singapore following a national intervention programme. *Bull World Health Organ*. 2001;**79(10)**:908–915.

14. Rampal L, Rampal S, Azhar MZ, Rahman AR. Prevalence, awareness, treatment and control of hypertension in Malaysia: A national study of 16,440 subjects. *Public Health* 2008;**122(1)**:11–18.

15. Mohd Yunus A, Sherina MS, Nor Afiah MZ, Rampal L, Tiew KH. Prevalence of cardiovascular risk factors in a rural community in Mukim Dengkil, Selangor. *Mal J Nutr*. 2004;**10(1)**:5–11.

16. Norimah AK, Haja MMK. Nutritional status and food habits of middle-aged adults in selected areas of Selangor. *Mal J Nutr*. 2003;**9(2)**:125–136.

17. Le C, Chongsuvivatwong V, Geater A. Contextual socioeconomic determinants of cardiovascular risk factors in rural south-west China: A multilevel analysis. *BMC Public Health*. 2007;**7**:72.

18. Yu Z, Nissinen A, Vartiainen E, Song G, Guo Z, Tian H. Changes in cardiovascular risk factors in different socioeconomic groups: Seven year trends in a Chinese urban population. *J Epidemiol Community Health*. 2000;**54(9)**:692–696.

19. Chow C, Cardona M, Raju PK, Iyengar S, Sukumar A, Raju R, et al. Cardiovascular disease and risk factors among 345 adults in rural India—The Andhra Pradesh Rural Health Initiative. *Int J Cardiol*. 2007;**116(2)**:180-185.

20. Risk factors for cardiovascular disease in the developing world. A multicentre collaborative study in the International Clinical Epidemiology Network (INCLEN). INCLEN Multicentre Collaborative Group. *J Clin Epidemiol*. 1992;**45(8)**:841–847.

21. Ministry of Health (MY). *Malaysia consensus guidelines on hyperlipidaemia*. Kuala Lumpur: Ministry of Health; 1999.

22. Siega-Riz AM, Evenson KR, Dole N. Pregnancy-related weight gain—A link to obesity? *Nutr Rev*. 2004; **62(7 Pt 2)**:S105–S111.

23. Khor GL, Zalilah MS. Dual forms of malnutrition in the same households in Malaysia—A case study among Malay rural households. *Asia P J Clin Nutr*. 2003;**12(4)**:427–438.

24. Lindeberg S, Berntorp E, Nilsson-Ehle P, Terent A, Vessby B. Age relations of cardiovascular risk factors in a traditional Melanesian society: The Kitava Study. *Am J Clin Nutr*. 1997;**66(4)**:845–852.

25. Rampal S, Rampal L, Rahmat R, Zain AM, Yap YG, Mohamed M, et al. Variation in prevalence, awareness, and control of diabetes in a multiethnic population: A nationwide population study in Malaysia. *Asia Pac J Public Health*. 2010;**22(2)**:194–202.

Brief Communication

BCG Adenitis—Need for Increased Awareness

Krishna Kumar Govindarajan, Feng Yih Chai

Paediatric Surgical Unit, Department of Surgery, Hospital Tengku Ampuan Afzan, 25300 Kuantan, Pahang, Malaysia

Submitted: 30 Nov 2010
Accepted: 29 Dec 2010

Abstract

Bacille Calmette–Guerin (BCG) vaccination for protection against tuberculosis has been in use for long. Although the vaccine is safe, its administration can result in complications such as BCG adenitis. We report here a series of children with BCG adenitis with a view to recognise and manage this condition. It is hoped that this case series would encourage the increased identification of this condition.

Keywords: *adverse effects, axilla, BCG, children, lymphadenitis, vaccines*

Introduction

The incidence of smear-positive tuberculosis (TB) was 63.6 per 100 000 population in 1997 and 45 per 100 000 in 2007 (1). Bacille Calmette–Guerin (BCG) vaccination was introduced in the Malaysian Immunization Scheme since 1961 (2). Malaysian healthcare system practices BCG vaccination by giving a single intradermal injection of 0.05 mL Tokyo 172 BCG strain for children less than 1 year old at left deltoid soon after birth. A repeat dose of 0.1ml is given for children at 6 years of age if no scar was formed after the first injection (1). The incidence of suppurative lymphadenitis due to BCG vaccination is 100–1000 per million doses administered (3).

Subjects and methods

We reviewed the case notes of children with BCG adenitis attending the paediatric surgical clinic from January 2009 to January 2010. The children were followed-up to document the course of adenitis within the study period. The parents of these children were human immunodeficiency virus (HIV)-negative.

BCG adenitis was labeled based on the following criteria: isolated axillary or supraclavicular lymph node enlargement, BCG vaccination on the ipsilateral arm, and the absence of local or systemic signs of inflammation (4).

Results

Over the 1-year study period, 6 children presented with BCG adenitis to the paediatric surgical clinic. The age range was 2–5 months at presentation. Clinical presentation included left axillary nodes and BCG scar in all cases, with supraclavicular neck nodes and chest wall mass in case each. Three patients were referred from the emergency department, and the remaining 3 were referred by general practitioner, paediatric clinic, and district clinic.

Out of the 6 children, 3 children were subjected to needle aspiration in view of the node size and suppuration, and the outcomes were good. Acid-fast staining of the aspirated pus failed to show presence of acid-fast bacilli. Cultures of the aspirates were negative. Further tests, such as the polymerase chain reaction assay, were not available and hence not done. On follow-up, 4 children showed complete resolution of the nodes over a period of 4–6 months, and 2 children with partial resolution are currently under review as the follow-up is less than 2 months. None of the children required excision or anti-TB therapy. The results are summarized in the Table 1.

Discussion

BCG vaccine was introduced to the world in 1921. It was incorporated in the World Health Organization (WHO)'s Expanded Program on Immunization in 1974 to strengthen the fight against TB meningitis and disseminated TB in young children and infant of developing country. To date, BCG is the only TB vaccine available. Although it does not prevent the establishment of

Table 1: Summary of case series

Case 1	**Site**	**Presenting symptom**	**Size**
Age: 2 months	Left axilla	Painless firm mass	2 × 2 cm
	Referral	**Management**	**Follow-Up**
	General practitioner	Conservative	Complete resolution (4 months)
Case 2	**Site**	**Presenting symptom**	**Size**
Age: 3 months	Left axilla, left supra-clavicular	Suppurative mass	3 × 2 cm, 1 × 1 cm
	Referral	**Management**	**Follow-Up**
	Emergency department	Needle aspiration	Complete resolution (5 months)
Case 3	**Site**	**Presenting symptom**	**Size**
Age: 3 months	Left axilla	Fluctuant mass	2 x 2 cm, 1 x 1 cm
	Referral	**Management**	**Follow-Up**
	District clinic	Needle aspiration	Partial resolution, on follow-up (2 months)
Case 4	**Site**	**Presenting symptom**	**Size**
Age: 3 months	Left axilla	Painless firm mass (Figure 1)	2 × 2 cm
	Referral	**Management**	**Follow-Up**
	Emergency department	Conservative	Complete resolution (4 months)
Case 5	**Site**	**Presenting symptom**	**Size**
Age: 4 months	Left axilla	Painless firm mass	2 × 1 cm
	Referral	**Management**	**Follow-Up**
	Paediatric clinic	Conservative	Partial resolution (4 months)
Case 6	**Site**	**Presenting symptom**	**Size**
Age: 5 months	Left chest, left axilla	Painless fluctuant chest mass, painless firm axillary mass	2 × 1 cm, 1 × 1 cm
	Referral	**Management**	**Follow-Up**
	Emergency department	Chest wall suppuration aspirated	Complete resolution (6 months)

primary TB infection or the reactivation of latent TB, BCG vaccine is considered an important part of TB control measure in endemic areas. In 2004, WHO has recommended general BCG vaccination in countries with high burden of TB. At present, it is estimated that 100 million children receive BCG vaccination each year (5).

The original BCG vaccine is a live-attenuated form of *Mycobacterium bovis*. Four main BCG vaccine strains, namely Pasteur strain 1173, Danish strain 1331, Glaxo strain 1077, and Tokyo strain 172, account for almost 90% vaccination worldwide. According to the different strains and their production, the concentration ranges from 50 thousand to 3 million live particles per dosage (3). Among those BCG strains available, Tokyo 172 strain was registered as an International Reference Strain in 1965 by WHO (6). According to Smith et al. (7), animal immunogenicity study showed that Glaxo 1077 and Tokyo 172 are "weak" strains, whereas Pasteur 1173 and Danish 1331 are "strong" strains; the BCG vaccination complication rate differs between "strong" and "weak" strains. Hooi et al. (8) reported a series of

Figure 1: The hollow arrow points to the BCG adenitis. The solid arrow indicates the BCG scar.

638 BCG-related lymphadenitis in infants due to the change in the vaccine strain from Tokyo-172 to Pasteur-1173. The incidence of lymphadenitis declined after the Tokyo strain was reintroduced. The BCG strain, immunization technique, dose, age, and physique of the vaccinees influence the incidence of complications (4,6).

Complications due to BCG vaccination can be classified into mild and severe. Mild complications are usually localized, and the most commonly seen complication is regional lymphadenitis. Cutaneous complications, such as lupoid reaction and eczema vaccinatum, form part of the mild spectrum of complications. The incidence of mild complication due to BCG is less than 1 per 1000 cases (5). Severe complications caused by BCG are suppurative lymphadenitis, osteitis/osteomyelitis, and disseminated BCG infection. Their incidence rates are 100–1000 cases, 1–700 cases, and 2 cases per 1 million vaccinations, respectively (3). In our series, true incidence could not be determined as all post-BCG children were not seen routinely in the surgical clinic.

Mild complications due to BCG usually heal spontaneously and require no treatment (1). In the natural course of BCG lymphadenitis, it could develop into simple, non-suppurative form and suppurative form. Diagnosis of BCG lymphadenitis is clinical, and its criteria are as listed in the Subjects and Methods section. Simple BCG lymphadenitis will regress spontaneously over a period of a few weeks without the need for anti-TB therapy. Treatment with oral erythromycin and anti-TB drugs do not hasten the regression or prevent progression into suppuration (4,9). Reassurance and follow-up until resolution is recommended. In our series, all of the children responded well to the management of drainage or needle aspiration without the need for excision.

The suppurative form of BCG lymphadenitis is considered as a severe complication. Its incidence is declining due to better inoculations technique by well-trained staff, using a standardized freeze-dried vaccine (3). It is distinguished by the fluctuant consistency of the swelling, with erythema and oedema of the overlying skin. The suppuration could develop into spontaneous rupture, sinus formation, and later, healing by cicatrization. The sinus may persist for a few months. To prevent these complications and to hasten healing process, needle aspiration is recommended. It is safe, and usually, one aspiration is adequate, but some patients might need repeated aspiration. Surgical excision is recommended in cases with draining sinus or failed needle aspiration due to multiloculated abscess or matted lymph node (4).

We ascertained that the children in the series were vaccinated by trained staff, though we could not confirm the technique or dosage.

The incidence of chest wall abscess associated with BCG vaccination is unknown due to its rarity. Although the effort on isolating BCG from the drained pus is futile, diagnosis could be confirmed either by demonstration of characteristic features in histopathology of the lesion or through genetic analysis with polymerase chain reaction assay (10). Confirmed cases can be treated surgically and followed by a course of anti-TB therapy for 6 to 12 months based on the culture and sensitivity result (11). A recent review states that node size of more than 3 cm warrants surgical therapy and does not respond to medical treatment (12). None of the children in our series required additional treatment, such as node excision or anti-TB therapy.

BCG osteitis/osteomyelitis and disseminated BCG infection are rare but potentially lethal conditions (10). They are associated with immunodeficient vaccinees with primary immunodeficiency disorder such as severe combined immunodeficiency, chronic granulomatous disease, DiGeorge syndrome, type 1 cytokine axis defects, and HIV infection (3,5,13,14). Treatment with anti-TB drugs, including isoniazid and rifampicin, has been shown to be effective (13). As a preventive measure, BCG vaccine is contraindicated in patients with known impaired immunity or undergoing immunosuppressive therapy (3,5).

A preliminary survey among paramedical personnel at our institution revealed that only 60% acknowledged the entity of BCG adenitis.

Conclusion

Simple BCG lymphadenitis is best managed conservatively, but suppuration should be aspirated to enhance recovery and prevent sinus formation. Surgical excision, but not incision, is recommended if needle aspiration fails. Other complications, such as chest wall abscess, might necessitate surgical intervention followed by a course of anti-TB therapy. Screening of immunodeficiency disorder needs to be considered in children who develop severe complication due to BCG vaccination. Parental education and awareness among paramedical personnel, including general practitioners, is essential so that prompt recognition and management of BCG adenitis can be ensured.

Authors' Contributions

Conception and design, drafting of the article: FYC
Critical revision and final approval of the article: KKG

Correspondence

Dr Krishna Kumar Govindarajan
MRCS Ed (UK), MCh (India)
Paediatric Surgical Unit
Department of Surgery
Hospital Tengku Ampuan Afzan
25300 Kuantan
Pahang, Malaysia
Fax: +609-557 2803
Email: sasisang@rediffmail.com

References

1. BCG vaccine. In: *Clinical practice guidelines: Childhood immunisation*. Kuala Lumpur: Ministry of Health Malaysia, Academy of Medicine; 2004. p. 3–4.

2. Childhood immunisation. In: *Clinical practice guidelines: Childhood immunisation*. Kuala Lumpur: Ministry of Health Malaysia, Academy of Medicine; 2004. p. 1–2.

3. Department of Vaccines and Biologicals, World Health Organization. *Supplementary information on vaccine safety: Part 2: Background and rates of adverse events following immunization*. Clements CJ, editor. Geneva: World Health Organization; 2000.

4. Goraya JS, Virdi VS. Baccile Calmette-Guerin lymphadenitis. *Postgrad Med J*. 2002;**78(920)**: 327–329.

5. World Health Organization. BCG vaccine. WHO position paper. *Wkly Epidemiol Rec*. 2004;**79(4)**: 27–38.

6. Yamamoto S, Yamamoto T. Historical review of BCG vaccine in Japan. *Jpn J Infect Dis*. 2007;**60(6)**: 331–336.

7. Smith D, Harding C, Chan J, Edwards M, Hank J, Muller D, et al. Potency of 10 BCG vaccines as evaluated by their influence on the bacillemic phase of experimental airborne tuberculosis in guinea-pigs. *J Biol Stand*. 1979;**7(3)**:179–197.

8. Hooi LN, Athiyah SO. An outbreak of BCG related lymphadenitis in Malaysian infants. *Med J Malaysia*. 1994;**49(4)**:327–335.

9. Goraya JS, Virdi VS. Treatment of Calmette-Guerin bacillus adenitis: A metaanalysis. *Pediatr Infect Dis J*. 2001;**20(6)**:632–634.

10. Su WJ, Huang CY, Huang CY, Perng RP. Utility of PCR assays for rapid diagnosis of BCG infection in children. *Int J Tuberc Lung Dis*. 2001;**5(4)**:380–384.

11. Aribas OK, Kanat F, Gormus N, Turk E. Cold abscess of the chest wall as an unusual complication of BCG vaccination. *Eur J Cardiothorac Surg*. 2002;**21(2)**:352–354.

12. Nazir Z, Qazi SH. Bacillus Calmette-Guerin (BCG) lymphadenitis-changing trends and management. *J Ayub Med Coll Abbottabad*. 2005;**17(4)**:16–18.

13. Rezai MS, Khotaei G, Mamishi S, Kheirkhah M, Parvaneh N. Disseminated Bacillus Calmette-Guerin infection after BCG vaccination. *J Trop Pediatr*. 2008;**54(6)**:413–416.

14. Ottenhoff TH, Verreck FA, Hoeve MA, van de Vosse E. Control of human host immunity to mycobacteria. *Tuberculosis*. 2005;**85(1–2)**:53–64.

Case Report

The Value of Pre-Operative Embolisation in Primary Inferior Vena Cava Paraganglioma

Faizah Mohd Zaki[1], Syazarina Sharis Osman[1], Zaleha Abdul Manaf[2], Jeyaledchumy Mahadevan[2], Mazri Yahya[3]

Submitted: 11 Aug 2010
Accepted: 5 Nov 2010

[1] *Department of Radiology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latiff, Cheras, 56000 Kuala Lumpur, Malaysia*

[2] *Department of Diagnostic Imaging, Kuala Lumpur General Hospital, Jalan Pahang, 51000 Kuala Lumpur, Malaysia*

[3] *Department of Surgery, Kuala Lumpur General Hospital, Jalan Pahang, 51000 Kuala Lumpur, Malaysia*

Abstract

We report a case of a 13-year-old boy who complained of progressive abdominal distension and symptoms of anaemia. Radiological investigations revealed that the child had a hypervascular tumour of the inferior vena cava (IVC). Unfortunately, the child presented with acute lower gastrointestinal bleed soon after the investigation. He underwent an urgent pre-operative embolisation, aimed to reduce the tumour vascularity. A total resection of the tumour, right nephrectomy, and partial duodenal resection were done within 24 hours post-embolisation. The child was stable post-operatively. The histopathological examination revealed chromogranin-positive paraganglioma originating from the IVC. We highlight the radiological findings of rare primary IVC paraganglioma and the role of embolisation prior to surgical removal of the tumour.

Keywords: *children, inferior vena cava, paraganglioma, radiology, therapeutic embolisation*

Introduction

Primary tumours originating from blood vessels are rare. They almost exclusively arise from veins and most commonly originate in the inferior vena cava (IVC). Their histology is almost exclusively leiomyosarcoma (1). Therefore, paraganglioma is even rarer to originate from IVC, as it is a tumour of neuroectodermal origin and classified as extra-adrenal paraganglioma. A study done in a large paediatric cancer centre over a 22-year period showed that extra-adrenal paraganglioma constitutes only 0.034% of the patients evaluated for non-haematological malignancy (2). Unfortunately, both IVC tumours and paragangliomas are largely vascular tumours, which makes pre-operative tissue diagnosis and complete surgical clearance challenging and, possibly, mutilating (3). This case report discusses the imaging features of a rare cause of IVC tumour and the value of pre-operative embolisation of the tumour supply prior to operation.

Case Report

A previously healthy 13-year-old boy presented with a 3-month history of lethargy and shortness of breath, with associated progressive abdominal distension. He was found to be anaemic in his initial blood investigation; he was then transfused with packed cells. There was no associated symptom of high catecholamine, such as hypertension or tachycardia. Initial computed tomography (CT) scan showed an IVC tumour.

A presumptive diagnosis of IVC tumour was made, and he was referred to our institution's vascular team for further management. The issue of pre-operative biopsy was discussed at length. A detailed ultrasound of the abdomen with Doppler study was done to assess the vascularity of the tumour. It showed a circumferential mass within the IVC wall. It was highly vascular and demonstrated a floating intraluminal thrombus (Figure 1). Based on the vascularity of the tumour, an ultrasound-guided biopsy with interventional and surgical backup was planned. He was allowed home leave before the planned high-risk procedure.

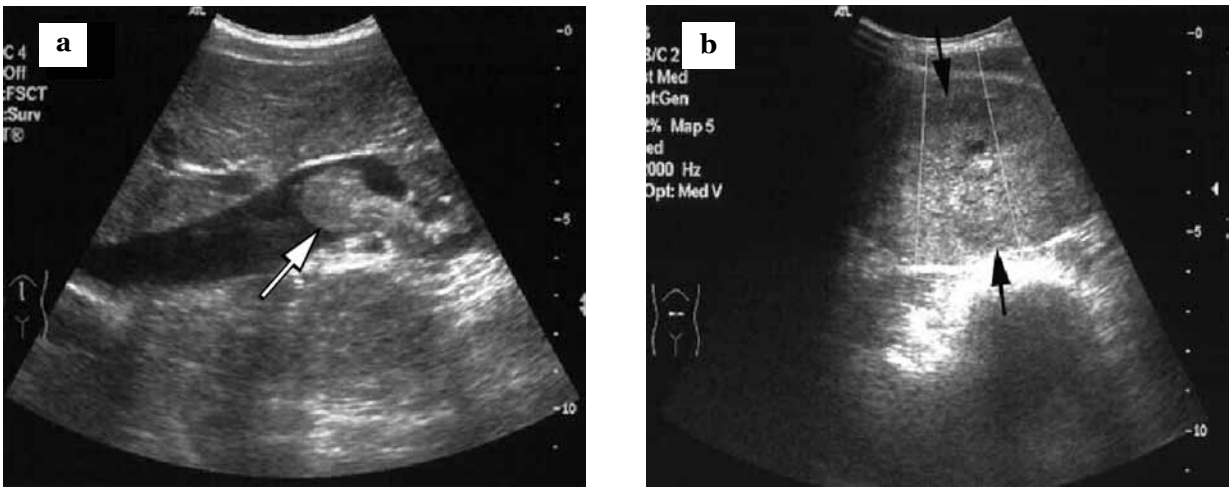

Figure 1: Abdominal ultrasound of the patient in (a) longitudinal and (b) transverse view at the level of supraumbilicus. (a) There is a mass arising from the inferior vena cava (IVC) wall, which protrudes into the lumen (arrow). (b) The mass circumferentially involved the IVC wall, causing narrowing of the lumen (arrows).

Unfortunately, the child developed malaena and haemetemesis at home, with associated symptoms of anaemia. An urgent CT scan of the abdomen was done to rule out intra-abdominal gastrointestinal bleed due to tumour invasion. It showed a huge IVC tumour with intraluminal thrombus (Figure 2). In view of the active gastrointestinal bleed, pre-operative angiography was performed with an anticipation of embolising the major feeding vessels. Pre-embolisation anatomy revealed major feeding vessels from the 3 right lumbar arteries and ileocolic branch of the superior mesenteric artery (SMA); 2 of the lumbar arteries and the SMA branch were successfully embolised with gold particulates (EmboGold) using a 4Fr microcatheter. Post-embolisation films showed marked reduction in the vascularity of the lesion (Figure 3). Pre-operative diagnosis at that time was IVC tumour, most likely leiomyosarcoma.

The child underwent laparatomy 1 day after the embolisation. Intra-operative findings showed an intraluminal IVC tumour that was densely adhered to the right kidney as well as the second and third part of duodenum. The right ureter was wrapped by the tumour and displaced laterally. Therefore, the whole tumour was dissected away from the aorta and resected. Right nephrectomy and resection of the second and third part of duodenum were done. Sutures closed both ends of the IVC stump. There was minimal intra-operative blood loss (less than 1 litre).

Figure 2: Abdominal computed tomography scan that was done at the time the child presented with gastrointestinal bleed shows a large heterogeneous inferior vena cava (IVC) mass, which is highly vascular with thrombus within the IVC lumen (white arrow). There is no clear fat plane between the mass and aorta (black arrow).

The post-operative period was uneventful, and the child was discharged after Day 15, when oral feeding was well tolerated. Histopathological examination was reported as IVC paraganglioma with positive chromogranin. There was no evidence of invasion of the right kidney or the adherent duodenum. There was also no evidence of metastatic lymph nodes in the specimen. The child was well upon follow-up at 1 month after discharge.

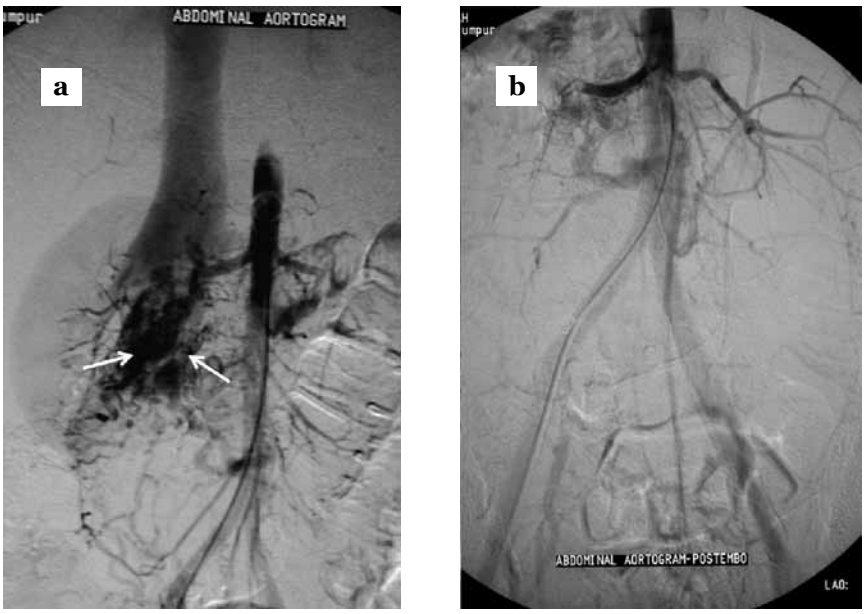

Figure 3: (a) Abdominal aortogram shows tumour blush (white arrows) at the inferior vena cava. (b) Post-embolisation abdominal aortogram shows complete absence of the tumour blush.

Discussion

Paragangliomas are rare neural crest neoplasms arbitrarily classified by their relationship to the adrenal gland. Adrenal-medullary tumour (phaeochromocytomas) occurs 9–10 times more often than the extra-adrenal paragangliomas (2–4).

The most common sites of extra-adrenal paragangliomas are the para-aortic region at the level of renal hila (46%), at the organ of Zuckerkandl (29%), thoracic para spinal region (10%), bladder (10%), and head and neck (2%–4%). Paragangliomas may be multicentric, manifesting as unilateral or bilateral lesions, and occurring synchronously or metachronously (3). Extra-adrenal paragangliomas are more likely to be malignant (40%) than adrenal phaeochromocytomas (2%–11%). It can be associated with several familial syndromes, including multiple endocrine neoplasia type 2A and type 2B, neurofibromatosis type 1, and Carneys triad (2,4,5).

These tumours secrete epinephrine and norepinephrine, which clinically result in hypertension, headaches, sweating, and palpitations (2,6). The biochemical diagnosis is aimed in determining catecholamine levels (epinephrine, norepinephrine, and dopamine) as well as their 24-hour urine metabolites, which was found to be around 90% sensitive (7). The patient did not have any catecholamine symptoms,which made the diagnosis of paraganglioma was not suspected prior to surgery. The urine catecholamine test was not performed in this patient, as he did not show symptoms of high catecholamines pre- and post-surgery. Tekautz et al. (2) reviewed 8 paediatric patients (mean age of 11.4 years) with extra-adrenal paraganglioma and reported that urine catecholamine test was not done routinely in these cases. In his review, urine catecholamines were measured in only 1 patient after operation when he was hypertensive post-operatively, whereby the results were within the normal limits.

Extra-adrenal paragangliomas, by virtue of their rarity, are less described with regard to the imaging features. Extra-adrenal paragangliomas have nearly identical imaging features, including a homogenous or heterogeneous hyperenhancing soft-tissue mass at CT, multiple areas of signal void interspersed with hyperintense foci (salt–pepper appearance) within tumour mass at magnetic resonance imaging (MRI), and an intense tumour blush with enlarged feeding arteries at angiography (5).

Sahdev et al. (4) described that 13 of the 15 cases of extra-adrenal paraganglioma in their series showed heterogeneous masses on CT and MRI, with avid enhancement. There was central necrosis, but with avid peripheral enhancement in the larger tumour section, as in this case. The

study concluded that the large retroperitoneal paragangliomas demonstrated no unique features on CT and MRI. Their appearances overlapped with the reported appearances of other retroperitoneal tumours, particularly neurofibromas, neuromas, and sarcomas.

Angiography of the tumour prior to operation helps to provide information concerning vascular supply of the tumour, patency of the arterial supply of the surrounding organs (i.e., bowels and kidneys), and allows subsequent pre-operative embolisation, which is valuable for pre-operative planning. Most tumours are hypervascular and have blood supply from more than one artery. The primary vessels supplying these tumours are the lumbar arteries. In addition, other vascular supplies of the tumour are the celiac, mesenteric, or renal arteries (8). Bourke et al. (3) reported a case of a retroperitoneal paraganglioma that received vascular supplies from 3 lumbar arteries and a right lower pole renal vessel. Our patient had arterial supply from the lumbar arteries as well as superior mesenteric artery.

Pre-operative embolisation is a useful procedure to optimize operative conditions as it allows avoidance of excessive intra-operative blood loss and possible injury to nearby structures from poor operative field visualization (3). Experienced interventional radiologist is needed to plan the degree and timing of intervention; this is to avoid complications in the child, such as pain and infection. Bourke et al. (3) suggested that embolisation is best undertaken within 24 hours of expected definitive operation. In fact, our patient underwent the surgical debulking of the IVC tumour within 24 hours post-embolisation, with an excellent result of complete resection and minimal blood loss.

In conclusion, the long-term outcome of paragangliomas can be difficult to predict, but complete surgical resection gives the best chance of long-term cure (3). Despite of absence of high-catecholamine symptoms, such as hypertension, the diagnosis of paraganglioma need to be considered in a retroperitoneal tumour, which then warrants further biochemical investigation. Even though there is no specific imaging feature for retroperitoneal IVC paraganglioma, CT scan and MRI would help in planning the plane of the tumour with surrounding structures. In addition, angiography helps in terms of identifying the feeding vessels with definitive pre-operative embolisation of the feeding arteries, which will reduce the risk of intra- and post-operative morbidity.

Authors' Contributions

Conception and design: FMZ, ZAM, JM
Analysis and interpretation of the data: FMZ, ZAM, JM, MY
Drafting and final approval of the article: FMZ
Critical revision of the article: SSO

Correspondence

Dr Faizah Mohd Zaki
MD (UKM), MMed Radiology (UKM)
Department of Radiology
Universiti Kebangsaan Malaysia Medical Centre
Jalan Yaacob Latiff
56000 Cheras
Kuala Lumpur, Malaysia
Tel: +6019-273 7282
Fax: +603-9173 7824
Email: faizahbangi@yahoo.co.uk

References

1. Lipton M, Sprayregen S, Kutcher, Frost A. Venous invasion in renal vein leiomyosarcoma: Case report and review of literature review. *Abdom Imaging*. 1995;**20(1)**:64–67.

2. Tekautz TM, Pratt CB, Jenkins JJ, Spunt SL. Pediatric extraadrenal paraganglioma. *J Pediatric Surg*. 2003;**38(9)**:1317–1321.

3. Bourke CJ, Lynch S, Irving H, Borzi PA. Retroperitoneal paraganglioma in a child: Resection and vena cava reconstruction. *Pediatr Surg Int*. 2002;**18(5–6)**:505-508.

4. Sahdev A, Sohaib A, Monson JP, Grossman AB, Chew SL, Reznek RH. CT and MR imaging of unusual locations of extra-adrenal paragangliomas (pheochromocytomas). *Eur Radiol*. 2005;**15(1)**: 85–92.

5. Lee KY, Oh YW, Noh HJ, Lee YJ, Yong HS, Kang EY, et al. Extraadrenal paragangliomas of the body: Imaging features. *AJR Am J Roentgenol*. 2006;**187(2)**: 492–504.

6. Rosing JH, Jeffrey RB, Longacre TA, Greco RS. Massive extra-adrenal retroperitoneal paraganglioma: Pre-operative embolization and resection. *Dig Dis Sci*. 2009;**54(8)**:1621–1624.

7. Arrabal-Polo MA, Arrabal-Martin M, Lopez-Leon VM, Abad-Menor F, Valle-Diaz de la Guardia F, Mijan-Ortiz JL, et al. Spontaneous retroperitoneal abscess as the first clinical manifestation of a non-functioning retroperitoneal paraganglioma. *Ann R Coll Surg Engl*. 2010;**92(3)**:92.

8. Hartman DS, Hayes WS, Choyke PL, Tibbetts GP. Leiomyosarcoma of the retroperitoneum and inferior vena cava: Radiologic-pathologic correlation. *Radiographics*. 1992;**12(6)**:1203–1220.

Case Report

Clavicle Fracture and Subclavian Vessels Disruption with Massive Haemothorax Mimic Intrathoracic Injury

Wan Ismail Faisham[1], Paiman Mohammad[1], Haron Juhara[2], Nik Mahdi Munirah[2], Hassan Shamsulkamaruljan[3], Ghazali Mohamad Ziyadi[4]

Submitted: 18 Apr 2010
Accepted: 14 Dec 2010

[1] *Department of Orthopaedic, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia*

[2] *Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia*

[3] *Department of Anaesthesiology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia*

[4] *Cardiothoracic Unit, Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kubang Kerian, Kelantan, Malaysia*

Abstract

We report a case of open fracture of the clavicle with subclavian artery and vein laceration and perforation of the parietal pleural below the first rib that caused massive haemothorax. Emergency thoracotomy and exploration followed by repair of both vessels were able to salvage the patient and the extremity.

Keywords: *bone fractures, clavicle, haemothorax, subclavian artery, trauma*

Introduction

Fracture of the clavicle is common, accounting 5% of all fracture cases. Damage to the neurovascular structure associated with fracture of the clavicle, however, is rare and more frequently related to penetrating injuries (1). To the best of the authors' knowledge, the incidence of open fracture of the clavicle and subclavian vascular injury with penetrating injury to the pleura has not been documented in the literature.

Case Report

A previously healthy 19-year-old helmeted man on a motorbike had a head-on collision with a lorry at the speed of approximately 100 km/h. He was brought by passers-by to our institution within an hour after the accident. The patient was alert and oriented, with continuous bleeding from a 4.0-cm wound in the upper left chest, which was packed with sterile gauze and compressive dressing. The left upper limb was dusky, with absence of radial and ulnar pulses. Emergency chest radiography revealed extensive left pneumo-haemothorax, with mediastinal shift to the right side and left medial third clavicle fracture with significant displacement (Figure 1). He also had left femur and segmental mandible fracture.

A left tube thoracostomy initially returned 1000 mL of blood, with continuous drainage of 800 mL over 2-hour period. Aortic arch and selective left subclavian artery angiography revealed tapering of subclavian artery, with filling defect at the distal end due to spasm-associated complete thrombosis (Figure 2). Upper limb venography showed non-opacification of the distal cephalic vein and multiple collaterals seen from the cephalic and subclavian veins that resulted from compressive dressing (Figure 3). There was no evidence of extravasation of intravenous contrast from the vessels into the chest or around the injured area.

While the patient was induced and under mechanical ventilation prior to the surgery, there was gushing of blood from the wound; local exploration at the time was highly suspicious of intra-thoracic bleeding. Thoracotomy through left posterolateral approach revealed a collection of 1500 mL of blood and clots, with a 2.0-cm

laceration at the left middle lobe and apical lung contusion. There was 2.0 × 2.0 cm perforation of apical pleural below the first rib with avulsion fracture of the latter. Exploration of the subclavian vessels revealed 1.0-cm laceration of vein with active bleeding, segmental spasm of subclavian artery, and contused brachial plexus (Figure 4). Both artery and vein was resected and bypassed with reverse saphenous graft (Figure 5). Pleural perforation was repaired and medial clavicle was stabilised with inter-osseous wiring. The fractured femur and mandible were stabilised with plate and screwed 48 hours later.

The patient was ventilated for 48 hours and tube thoracostomy was removed at day 3 post-operatively. There was presence of lower plexus neuropraxia, evidenced by weak handgrips, power of grade 3. Subsequent chest radiograph showed full lung expansion with minimal local pulmonary contusion. The patient returned home after 12 days of hospitalization with full strength and sensation of the left upper limb. At 3-month follow-up, his radial pulse was equal with no neurological deficits and the fractured clavicle had united with the help of the in situ wire (Figure 6).

Figure 1: Chest radiograph showed massive left pneumo-haemothorax and shift of the mediastinum to the right. Note also the fracture of the medial third of the clavicle, indenting the pleural surface inwardly.

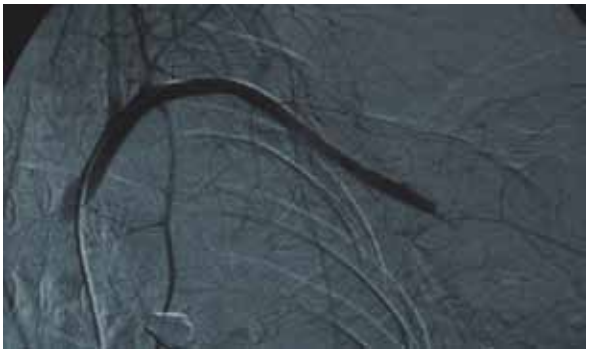

Figure 2: Angiography revealed complete cut-off of the left subclavian artery flow. However, there was no leak of intravenous contrast to suggest extravasation.

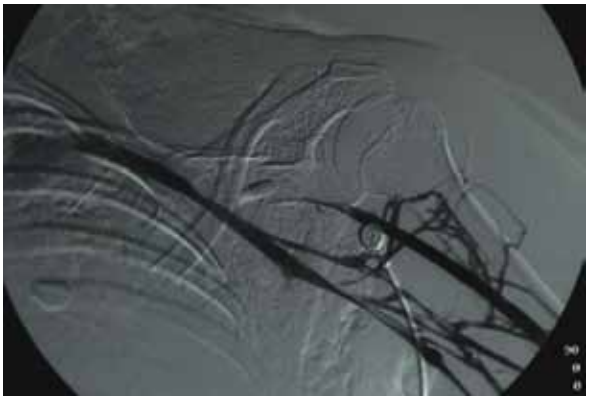

Figure 3: Venography of the left upper limb showed multiple collaterals and non-opacification of distal cephalic vein before draining into the subclavian vein.

Figure 4: Pleural perforation below first rib. Vascular clamp used to control bleeding from injured subclavian vein. Subclavian artery was spasmed and thrombosed.

Figure 5: Both subclavian vessels were resected and bypassed with reverse saphenous vein graft.

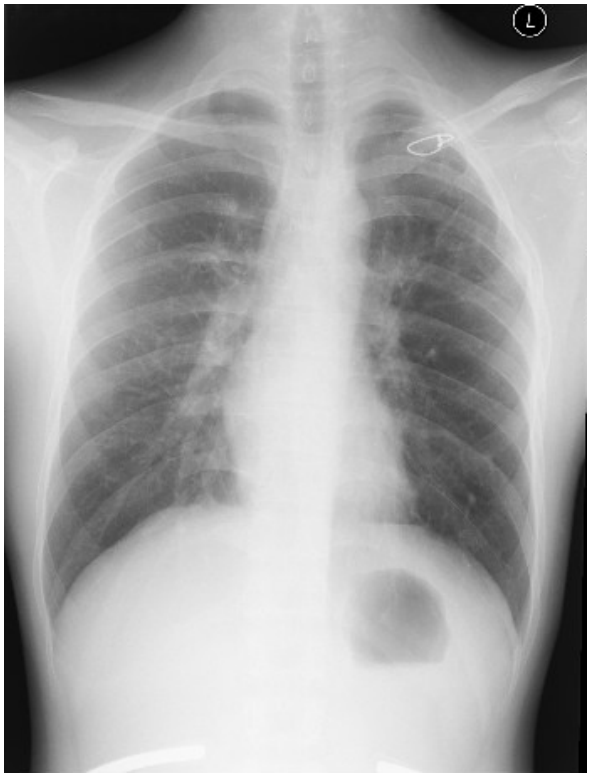

Figure 6: Chest radiograph showed normal lung field with united clavicle fracture and inter-osseous wire in situ.

Discussion

The initial approaches in subclavian vessels injury include aggressive resuscitation of hypovolaemic shock, assessment of other injuries, and diagnostic angiography, if time permits (2,3). External bleeding from the subclavian artery must be controlled rapidly, and associated pneumo-haemothorax must be managed by urgent chest thoracostomy. Direct pressure and compressive dressing are effective in controlling bleeding in urgent situation, particularly in the emergency department. Proper compression to the subclavian vessels injury produces tamponade, and this method is effective in most of the cases. Pleural perforation within the injured area can drain blood from the injured vessels to the pleural cavity, producing massive haemothorax; this condition may mislead the judgment that ongoing bleeding was controlled. This case highlighted that the mediastinum was a potential space with negative pressure that was able to collect huge amount of ongoing bleeding, which led to persistent hypovolaemic shock (3–6).

The mediastinum and pleural space are potential areas to develop hematoma due to negative pressure. This will lead to false clinical judgment as external bleeding was well controlled despite of deteriorating haemodynamic status. Lung ventilation produces positive pressure and the haemothorax will be pushed through pleural perforation mimicking intrathoracic massive bleeding.

Conclusion

Clavicle fracture is known as a benign condition, but it can potentially lead to intrathoracic vascular injury and massive haemothorax.

Authors' Contributions

Concept and design: WIF
Critical revision of article: HS
Final approval of the article: NMM
Drafting of the article: HJ, PM
Provision of study materials and patients: WIF, PM, MGZ

Correspondence

Associate Professor Dr Faisham Wan Ismail
MD (UKM), MMed Ortho (USM)
Department of Orthopaedic
School of Medical Sciences
Universiti Sains Malaysia Health Campus
16150 Kubang Kerian
Kelantan, Malaysia
Tel: +609-767 6381
Fax: +609-767 4510
Email: faisham@kb.usm.my

References

1. Raviraja A, Chandrashekar CM, Roshan SD, Srinivas JV. Subclavian artery and vein injury following clavicle fracture. *Injury Extra*. 2009;**40(2)**:36–38.

2. Leblang SD, Dolich MO. Imaging of penetrating thorasic trauma. *J Thorasic Imaging*. 2000;**15(2)**:128–135.

3. Hyre CE, Cikrit DF, Lalka SG, Sawchuk AP, Dalsing MC. Aggressive management of vascular injuries of the thorasic outlet. *J Vasc Surg*. 1998;**27(5)**:880–885.

4. Kendall KM, Burton JH, Cushing B. Fatal subclavian artery transaction from isolated clavicle fracture. *J Trauma*. 2000;**48(2)**:316–318.

5. Baikoussis NG, Siminelakis SN, Matsagas M, Michalis LK. Massive haemothorax due to subclavian artery rupture: Emergency thoracotomy or primary stent grafting? *Heart Lung Circ*. 2010;**19(7)**:431.

6. Kidd JN, Drummond-Webb JJ, Vandevanter SH, Wagner CW. Subclavian artery disruption caused by blunt trauma in an adolescent: Case report and review of the literature. *J Trauma*. 2005; **58(4)**:845–847.

Case Report

A Rare Case of a Subcutaneous Phaeomycotic Cyst with a Brief Review of Literature

Madhavan Manoharan[1], Natarajan Shanmugam[2], Saveetha Veeriyan[3]

Submitted: 31 Aug 2010
Accepted: 24 Sep 2010

[1] *Department of Pathology, Saveetha Medical College, Thandalam, Kanchipuram District, India, 605102*

[2] *Department of Orthopaedics, Saveetha Medical College, Thandalam, Kanchipuram District, India, 605102*

[3] *Department of Radiology, Saveetha Medical College, Thandalam, Kanchipuram District, India, 605102*

Abstract

Phaeohyphomycosis consists of a heterogeneous group of fungal infections caused by more than 80 genera and species. Subcutaneous infection usually follows traumatic implantation of a fungus by a wooden splinter that the fungus inh abits as a saprophyte. The growth of the fungus forms verrucous plaques or a painless subcutaneous abscess. We report a subcutaneous cyst (phaeomycotic cyst) in the leg of a 60-year-old woman that developed after a thorn prick at that site. With the provisional diagnosis of an epidermoid cyst, she was treated with a simple excision of the cyst. However, histopathological examination of the cyst revealed the typical features of fungus, and a definitive diagnosis of a phaeomycotic cyst was made. As the infective aetiology was not considered clinically, the specimen was not sent for microbiological culture, and hence the exact species was not identified. As the lesion was localised, simple excision was sufficient treatment, and no recurrence was observed during 12 months of follow-up.

Keywords: *clinical microbiology, cyst, dermatomycosis, diagnosis, female, leg dermatoses*

Introduction

Phaeohyphomycosis is a heterogeneous group of fungal infections caused by a variety of naturally pigmented fungi. The aetiological agents of this mycosis, which include more than 80 genera and species, are common saprophytes found in soil, wood, and decaying vegetable matter (1,2). Phaeohyphomycosis is rare, although it is more common in immunocompromised individuals (3). Phaeohyphomycosis affects either superficial tissues, such as the skin, cornea, and subcutaneous tissue, or deep tissues, such as the brain, and cases of phaeohyphomycosis are classified accordingly (2). Subcutaneous infection is usually caused by *Exophiala* and *Phialophora* species (4). The infection typically follows traumatic implantation of the fungi by a wooden splinter or a thorn prick and manifests as a cystic lesion. Herein, we report a typical case of a subcutaneous phaeomycotic cyst occurring in an elderly woman.

Case Report

A 60-year-old woman presented with painless swelling over the anterior aspect of the right leg for the past one and half years. It started as a small swelling and gradually reached the present size. The patient, a labourer, was pricked by a thorn while clearing wild bushes two years ago. Swelling was noticed a few months after the incident. On examination, her general condition was good. She was afebrile. Other systemic examination results were within normal limits. Local examination revealed a firm, fluctuant, mobile swelling measuring about 3×3 cm situated over the anterior aspect of the right leg. It was not painful or tender. It was not attached to the underlying bone. An X-ray of the right leg showed a well-circumscribed soft tissue nodule in the subcutaneous plane in the anterior aspect of the shin (Figure 1). The underlying bone appeared normal, with no abnormal lytic or sclerotic lesions or cortical breaks. The chest roentgenogram was normal. Her haemoglobin level was 9.0 gm/dL, sugar 82 mg/dL, urea 34 mg/dL, and creatinine 1.0 mg/dL. The urinalysis results were normal.

Operative findings

The soft tissue mass was easily separated from the surrounding tissue and was removed in toto. When the excised cyst was cut open in the surgical theatre, it expelled purulent material (Figure 2). The cyst was immersed in 10% formalin and sent for histopathological examination.

Histopathological examination

Microscopy revealed a fibrocollagenous cyst wall lined by granulomas, composed of foreign-body giant cells, epithelioid cells, xanthoma cells, and lymphoplasma cells. Some of the giant cells contained fungal hyphae. The hyphae were pigmented (Figure 3) and septate. Constrictions were present at a few septations, forming a structure similar to a bamboo stem (Figure 4). With these histological characteristics, the diagnosis of a phaeomycotic cyst was made. As the specimen was preserved in formalin, fungal culture to identify the species could not be performed.

Follow-up

The suture was removed after 2 weeks, and the wound healed well. There was no recurrence observed during the 12 months of follow-up.

Figure 1: X-ray showing a well-delineated soft tissue mass anterior to the tibia.

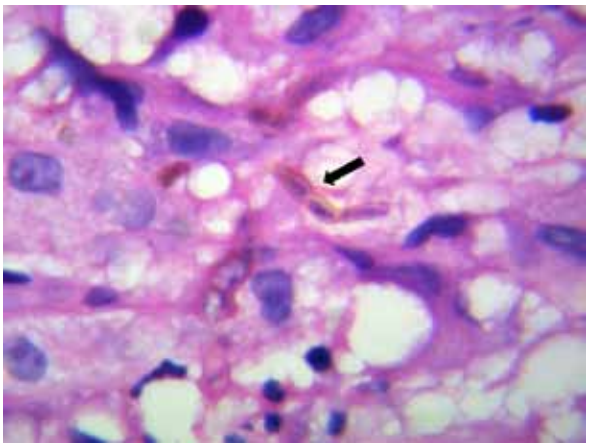

Figure 3: Haematoxylin and eosin staining of the cyst wall (100× magnification). Hyphae are brown in colour (arrow).

Figure 2: The cyst contained purulent material.

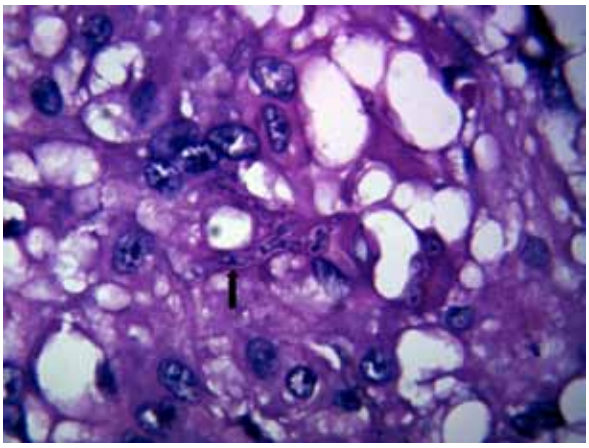

Figure 4: Haematoxylin and eosin staining of the cyst wall (100× magnification). Hyphae showed constriction at the septation, similar to bamboo stem (arrow).

Discussion

Phaeohyphomycosis infections occur worldwide in both animals and humans. These infections are more common in immunodeficient or debilitated hosts and rarely affect healthy individuals (3). Phaeohyphomycosis has been clinically divided into superficial (cutaneous and corneal), subcutaneous, and systemic phaeohyphomycosis by McGinnis (2).

Subcutaneous phaeohyphomycosis is usually caused by *Exophiala* and *Phialophora* species (4). Occasional cases caused by *Fonsecaea* species have also been reported (5). Subcutaneous phaeohyphomycosis usually results in a painless subcutaneous abscess or in verrucous plaques on the hand, arm, face, or neck. Although phaeohyphomycosis has distinct clinical features, it is occasionally confused with chromoblastomycosis (Table 1).

Typically, phaeohyphomycosis follows traumatic implantation of the fungus by a wooden splinter, as in our case. Lymphangitis and regional lymphadenopathy are unusual. Hence, infective aetiologies are usually not considered. Our case was clinically suspected to be an epidermoid cyst.

The host reaction to phaeohyphomycosis is similar regardless of the aetiological agent and the anatomic site of involvement. The lesion is usually situated in the dermis and the subcutaneous plane and is characterised by cyst formation with dense collagenous connective tissue and central suppurative necrosis. The overlying epidermis is usually normal. The wall contains compact aggregates of epithelioid histiocytes and numerous giant cells. Pigmented moniliform fungal elements are usually present inside the giant cells or extracellularly in the necrotic debris. Fungi may vary in their degree of pigmentation and may also appear as infrequently branching hyphae measuring 2–6 μm wide. The fungi are closely septate and constricted at their prominent septations (3). Our case exhibited the typical features of phaeohyphomycosis.

In many cases, identification of the exact species is not attempted, as phaeohyphomycosis is not suspected clinically. Similarly, in our case, an infective aetiology was not suspected, and after excision in the operation theatre, the cyst was fixed in formalin. When culture and identification of species is not pursued, the cyst can be histologically differentiated from black grain eumycotic mycetoma (Table 2) and chromoblastomycosis (Table 3).

Regarding the management of subcutaneous phaeohyphomycosis, excision of the localised lesion is usually curative (6). In our case, after the local excision, there was no recurrence found during the 12 months of follow-up.

Conclusion

Subcutaneous phaeohyphomycosis is a rare fungal infection caused by a wide variety of dematiaceous fungi. A high index of suspicion for infective aetiologies is needed to make a proper clinical diagnosis. For a localised lesion, simple excision is usually curative. When phaeohyphomycosis is not suspected and the identification of species by culture is not pursued, routine histopathological examination is sufficient to arrive at a diagnosis of phaeohyphomycosis.

Table 1: Clinical differences between chromoblastomycosis and phaeohyphomycosis

Chromoblastomycosis	Phaeohyphomycosis
• Starts as a papule that usually develops into a nodule and progresses to multiple nodules involving a large portion of the body	• Usually forms a single subcutaneous cyst and rarely multiple cysts
• Skin surface is scaly, cracked, or verrucous	• Skin surface is usually smooth and uninvolved
• Body reactions against the fungus are ineffective, and the infection spreads	• Body reactions produce an effective fibrocollagenous tissue capsule around the infection and arrest its spread
• Systemic involvement is rare	• Cerebral involvement develops from respiratory infection
• Excision of the early lesion alone is curative; advanced lesions require prolonged antifungal treatment	• Local excision is curative; only systemic infection requires antifungal treatment

Table 2: Histological differences between black grain eumycotic mycetoma and phaeohyphomycosis

Black grain eumycotic mycetoma	Phaeohyphomycosis
• Forms distinct granules	• Never forms tissue granules
• Composed of interwoven mycelial aggregates	• Composed of scattered individual polymorphous fungal elements
• Organised	• Unorganised
• Nearly always extracellular	• Often intracellular

Table 3: Histological differences between chromoblastomycosis and phaeohyphomycosis

Chromoblastomycosis	Phaeohyphomycosis
• Brown, spherical to polyhedral thick-walled muriform cells	• Moniliform cells
• 5–12 µm	• 2–6 µm
• Muriform cells reproduce by septation in 1 or 2 planes	• Moniliform cells
• Do not produce chains of cells	• Do produce chains of cells
• Epidermis is hyperplastic	• Epidermis is normal

Acknowledgement

We sincerely thank the Medical Director, Saveetha Medical College Hospital, and the Vice Chancellor, Saveetha University, for allowing us to submit this case for publication.

Authors' Contributions

Conception and design, drafting of the article: MM
Provision of patients: NS, SV
Final approval of the article: MM, NS, SV

Correspondence

Associate Professor Dr Manoharan Madhavan
MBBS (University of Madras), MD Path (Pondicherry University)
Saveetha Medical College
Thandalam, Kanchipuram District
India, 605102
Tel: +91-90-9403 3599
Fax: +91-44-2681 1171
Email: madhavan6@gmail.com

References

1. Fader RC, McGinnis MR. Infections caused by dematiaceous fungi: Chromoblastomycosis and phaeohyphomycosis. *Infect Dis Clin North Am.* 1998;**2(4)**:925–938.
2. McGinnis MR. Chromoblastomycosis and phaeohyphomycosis: New concepts, diagnosis, and mycology. *J Am Acad Dermatol.* 1983;**8(1)**:1–16.
3. Tendolkar UM, Kerkar P, Jerajani H, Gogate A, Padhye AA. Phaeohyphomycotic ulcer caused by Phialophora verrucosa: Successful treatment with itraconazole. *J Infect*. 1998;**36(1)**:122–125.
4. Saha R, Rudra S. Phaeomycotic cyst—A case report. *J Indian Med Assoc.* 2005;**103(10)**:555–556.
5. Padhye AA, Ajello L, Chandler FW, Banos JE, Hernandez-Perez E, Llerena J, Llerena J, et al. Phaeohyphomycosis in El Salvador caused by *Exophiala spinifera*. *Am J Trop Med Hyg.* 1983;**32(4)**:799–803.
6. Chandler FW, Watts JC. Phaeohyphomycosis. In: Connor DH, Chandler FW, Schwartz DA, Manz HJ, Lack EE, editors. *Pathology of infectious diseases.* Hong Kong: Appleton & Lange; 1997. p. 1059–1066.

Case Report

Isolated Ipsilateral Nipple Recurrence: Important Lessons to Learn

Shahrun Niza Abdullah Suhami[1], Rohaizak Muhammad[1], Ibrahim Naqiyah[1], Srijit Das[2], Noraidah Masir[3]

Submitted: 20 Aug 2010
Accepted: 20 Dec 2010

[1] *Department of Surgery, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaakub Latiff, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia*

[2] *Department of Anatomy, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaakub Latiff, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia*

[3] *Department of Pathology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaakub Latiff, Bandar Tun Razak, 56000 Kuala Lumpur, Malaysia*

Abstract

Most breast cancer recurrences occur in the surgical scars or within other quadrants of the same breast. Isolated tumour recurrence occurring in the nipple after breast-conserving surgery and radiotherapy is extremely unusual. The reason for this is unknown, but is speculated to be due to involved surgical margins or an occult involvement of the nipple–areolar complex in a breast cancer of the same breast. We present a case of a 44-year-old Indian woman who had recurrent tumour over her right nipple after an ipsilateral breast-conserving surgery that was followed by adjuvant chemotherapy and radiotherapy. There was no typical malignancy features from the mammogram. However, histopathological study confirmed a malignant growth that infiltrated into the dermis and the underneath breast tissue. Completion mastectomy was then performed and the patient was later treated with Taxane-based chemotherapy. Nipple recurrence after breast-conserving surgery and adjuvant radiotherapy may be confused with other nipple conditions such as Paget's disease of the breast. Comprehensive assessments, which include mammogram and biopsy, have proved that such recurrence do occur, as presented in this case. This warrants a specific management strategy.

Keywords: *breast-conserving surgery, diagnosis, nipple, recurrence, surgical oncology*

Introduction

Breast-conserving surgery is used to treat early breast cancer (1–6). Among the risks involved using this strategy is ipsilateral breast tumour recurrence, which requires further radical treatment including completion mastectomy. The incidence of local recurrence from breast-conserving surgery in early breast cancer is reported to be as high as 14.3% (3). The tumour may recur at the surgical scar or the surrounding quadrants of the affected breast. The reason for such phenomenon is unknown, but unclear resection margins or unidentified occult tumor tissue may be the cause. We report our experience of managing isolated ipsilateral nipple recurrence occurring after breast-conserving surgery. The case involved a complete re-assessment of the local recurrence using radiological and histopathological examinations.

Case Report

A 44-year-old woman had breast-conserving surgery for a T2N1M0 right breast infiltrating ductal carcinoma on October 2007. She had no significant high risk factor for breast cancer or any past medical history. The tumour was located at the right upper quadrant of the breast. Mammogram and fine-needle aspiration biopsy showed malignancy. The histopathological examination showed a grade 3 tumour measuring 4.5 × 3.0 × 3.5 cm. The entire surgical margins were free. An axillary dissection showed 1 of the 17 lymph nodes had metastasis. The tumour was negative for estrogen receptor (ER) and progesterone receptor (PR) but was strongly positive (3+) for c-erb-2 oncoprotein. The patient completed 6 cycles of FEC (5-fluorouracil, epirubicin, cyclophosphamide) adjuvant chemotherapy, followed by 40 Gy of radiotherapy given in 15 fractions and a booster dose of 10 Gy in 5 fractions afterwards. At 5-month follow-up,

she developed an ipsilateral nipple pain with bloody discharge. A 1.0-cm, rounded, ulcerative growth appeared over the nipple. A subsequent mammogram did not show any malignant features, but histopathological examination from a wedge biopsy confirmed a recurrent infiltrating ductal carcinoma with similar histological features to her previous primary breast carcinoma. There was no evidence of distance metastasis. A completion right mastectomy was performed. The final histology was of grade 3, ER negative, PR negative, and c-erb-2 oncoprotein, again, strongly positive. Six axillary lymph nodes were further recovered this time and 3 of them were involved. The patient received another 4 cycles of Taxane-based chemotherapy, and currently under regular follow-up without evidence of further recurrence.

Discussion

Isolated local recurrence over the nipple at ipsilateral breast after breast-conserving surgery or nipple sparing mastectomy is rare (12). There was only 1 case reported in the literature (13), even though some authors have reported local recurrence of breast cancer in the form of Paget's disease of the nipple (7,8), which suggested an underlying tumour recurrence in the ipsilateral breast, occurring 5–16 months after radiotherapy. However, our case was different; the patient presented with a nodulo-ulcerative lesion that developed 5 months after breast-conserving surgery. It was not a Paget's disease of the nipple, and her mammogram was normal. The similarity of the histopathological studies between the first and second tumour had brought about the diagnosis of a local tumour recurrence. Furthermore, the tumour recurred only 5 months after the first surgery. This tumour was of the aggressive type based on its high grade, ER and PR negativity, and c-erb-2 oncoprotein positivity. This explains the loco-regional recurrence despite adjuvant chemotherapy and radiotherapy.

The real reason for an isolated ipsilateral nipple recurrence after a breast-conserving surgery remains a mystery. It is believed that unclear surgical margins, implantation phenomenon, or occult tumour at the nipple–areolar complex (9) may give rise to this phenomenon. The incidence of occult nipple involvement may be as low as 5.6% to 50.0% (9). Studies have discrepancies on parameters that might predict nipple involvement. Several studies showed that the tumour grade, size, and stage, tumour–nipple distance, and c-erb-2 positivity were significant predictors for occult nipple involvement in breast cancer (11,14,15), but other studies reported contrasting findings (9,10). However, all of them agreed that the location of the tumour has an influence on nipple involvement (9–11,14,15). The incidence of nipple recurrence is higher for tumours located at the central or retroareolar area (10,11,14,15) compared with other 4 quadrants of the breast. Therefore, the decision to perform breast-conserving surgical procedures should not be based on the tumour location alone, but also on the size and stage of the cancer as well as the immunohistochemistry results and c-erb-2 status. This case increases our awareness of nipple recurrence and the importance of carefully selecting the appropriate breast conservation patients for nipple preservation.

Conclusion

A true infiltrating lesion as presented above is very rare. Comprehensive assessments such as mammogram and biopsy have proven that such recurrences do occur; this warrants a different management strategy. Tumour stage, grade, and location may play a vital role in predicting occult nipple involvement in breast cancer. Breast cancer patients must be carefully selected for breast-conserving surgery; failure to do so may later results in nipple recurrence.

Authors' Contributions

Conception and design, analysis and interpretation of the data, final approval of the article: SNAS, RM
Provision of patient: NI, NM
Collection and assembly of the data, drafting of the article: SNAS
Critical revision of the article: RM
Administrative, technical, or logistic support: SD

Correspondence

Professor Dr Rohaizak Muhammad
BSc (St Andrews Univ), MBChB (Glasg), MS (UKM), FRCS (Glasg)
Department of Surgery
Universiti Kebangsaan Malaysia Medical Centre
Jalan Yaakub Latiff, Bandar Tun Razak
56000 Kuala Lumpur
Malaysia
Tel: +603-9170 2315
Fax: +603-9173 7831
Email: rohaizak@hotmail.com

References

1. Fisher B, Redmond C. Lumpectomy for breast cancer: An update for NSABP experience. National Surgical Adjuvant Breast and Bowel Project. *J Natl Cancer Inst Monogr*. 1992;**(11)**:7–13.
2. Van Dongen JA, Bartelink H, Fentiman IS, Lerut T, Mignolet F, Olthuis G, et al. Randomised clinical trial to assess the value of breast-conserving therapy in Stage I and Stage II breast cancer, EORTC 1080 Trial. *J Natl Cancer Inst*. 1992;**(11)**:15–18.
3. Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med*. 1995;**333(22)**:1456–1461.
4. Veronessi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, et al. Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med*. 1981;**305(1)**:6–11.
5. Fisher ER, Constantino J, Fisher B, Palekar AS, Paik SM, Suarez CM, et al. Pathologic findings from the National Surgical Adjuvant Breast Project (NSABP) protocol B-17. Five-year observations concerning lobular carcinoma in situ. *Cancer*. 1996;**78(7)**:1403–1416.
6. Christian MC, McCabe MS, Korn EL, Abrams JS, Kaplan RS, Friedman MA. The National Cancer Institute audit of the National Surgical Adjuvant Breast and Bowel Project Protocol B-06. *N Eng J Med*. 1995;**333(22)**:1469–1474.
7. Plastaras JP, Harris EE, Solin LJ. Paget's disease of the nipple as local recurrence after breast-conserving treatment for early-stage breast cancer. *Clin Breast Cancer*. 2005;**6(4)**:349–353.
8. Menzies D, Barr L, Ellis H. Paget's disease of the nipple occurring after wide local excision and radiotherapy for carcinoma of the breast. *Eur J Surg Oncol*. 1989;**15(3)**:271–273.
9. Laronga C, Kemp B, Johnston D, Robb GL, Singletary SE. The incidence of occult nipple areolar complex involvement in breast cancer patients receiving a skin-sparing mastectomy. *Ann Surg Oncol*. 1999;**6(6)**:609–613.
10. Simmons RM, Brennan M, Christos P, King V, Osborne M. Analysis of nipple/areolar involvement with mastectomy: Can the areola be preserved? *Ann Surg Oncol*. 2002;**9(2)**:165–168.
11. Lambert PA, Kolm P, Perry RR. Parameters that predict nipple involvement in breast cancer. *J Am Coll Surg*. 2000;**191(4)**:354–359.
12. Edge SB. Nipple-sparing mastectomy: How often is the nipple involved? *J Clin Oncol*. 2009;**27(30)**:4930–4932.
13. Srivastava A, Webster DJ. Isolated nipple recurrence seventeen years after subcutaneous mastectomy for breast cancer—A case report. *Eur J Surg Oncol*. 1987;**13(5)**:459–461 .
14. Vlajcic Z, Zic R, Stanec S, Lambasa S, Petrovecki M, Stanec Z. Nipple-areolar complex preservation: predictive factors of neoplastic nipple-areola complex invasion. *Ann Plast Surg*. 2005;**55(3)**:240–244.
15. Brachtel EF, Rusby JE, Michaelson JS, Chen LL, Muzikansky A, Smith BL, et al. Occult nipple involvement in breast cancer: Clinicopathologic findings in 316 consecutive mastectomy specimens. *J Clin Oncol*. 2009;**27(30)**:4949–4955.

Guideline For Authors

The MJMS welcomes manuscripts on all aspects of medicine/health science from any part of the world. We are members of World Association of Medical Editors (WAME) and Council of Science Editors (CSE).

Manuscripts must be submitted in English. Manuscripts are considered for publication in MJMS with the understanding that they have not been published or submitted for publication elsewhere. The manuscript should be submitted to the Editor, Professor Jafri Malin Abdullah via Manuscript Central http://mc.manuscriptcentral.com/maljms. Please note that at the moment, we do not accept Miscrosoft Word 2007 documents (*.docx). Please use Ms Word's "Save As" option to save your document as an older (.doc) file type
The guidelines listed below are in accordance with the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (October 2008 revision) of the International Committee of Medical Journal Editors.

Forms

When submitting manuscripts, authors are required to sign the Authorship Agreement Form, Patient Consent Form (if the manuscript includes identifiable patients) and the Publication Agreement Form.

Types of Manuscripts

MJMS publishes the following types of manuscripts.

Editorials (E): Brief, substantiated commentary on subjects of topical interest.
Abstracts: Not required
Text: Not more than 1200 words (excluding references and figure/table legends)
Tables and figures: Not more than 1
References: Not more than 20

Original Article (OA): Reports of original clinical or investigative laboratory research.
Abstract: Not more than 275 words
Text: Not more than 3500 words (excluding references and figure/table legends)

Review Article (RA): A review article aims to give an overview of a particular subject suitable for a wide audience. Review articles should be recent rather than a historical review of the article on the topic.
Abstract: Unstructured Abstract not more than 275 words
Text: Not more than 4500 words (excluding references and figure/table legends)
References: Not more than 80

Case Report (CR): Brief case reports of unusual interest.
Abstract: Unstructured abstract, not more than 175 words
Text: Not more than 2000 words
References: Not more than 10
Figures and tables: Less than 3 figures and tables

Brief Communications (BC): A Brief Communication is suitable for recording the results of complete small investigations or giving details of new models or hypotheses, innovative methods, techniques or apparatus.
Abstract: Not more than 175 words
Text: Not more than 1500 words
References: Less than 20
Figures and tables: Not more than 3

Special communications (SC): These manuscripts describe an important issue in clinical medicine, public health, health policy, or medical research in a scholarly, thorough, well-referenced, systematic or evidence-based manner.
Abstract: A narrative (unstructured) abstract of 200 words or fewer is required
Text: Not more than 3000 words (excluding tables, figures, or reference
References: Less than 80

Letter to the Editor (LE): Comments on articles published within 6 months in MJMS or articles of interest to the biomedical community
Text: Should not exceed 500 words
References: Not more than 6 references

Letters in reply (LR): Replies by authors
Text: should not exceed 500 words
References: Not more than 6

Extended abstracts (EA): Only published as supplementary issues during conferences. Extended abstracts are also peer reviewed. Authors who intend to submit extended abstracts should contact directly via email at mjms.usm@gmail.com.

Ethical requirements

In experiments on human subjects, authors should mention whether the methods followed were in agreement with the ethical standards of the responsible committee (institutional and national) and the Declaration of Helsinki (October 2008 revision). Similarly, the use of animals in research must conform to the institutional and national guidelines.

Patient consent

The author must provide the Malaysian Journal of Medical Sciences with a written consent signed by the patient, or the patient's parents/legal guardian, when submitting a patient video or photograph in which a patient is identifiable (See Patient Consent Form). This form can be downloaded from our website.

Style manuscript and Format

Text: Use subheadings for long articles and double-space all portions of the manuscript

Title page: The title page should have the following information:

i. Article title without abbreviation
ii. Authors' names and institutional affiliations: Full names are required, indicate last name with SMALL CAPS. For example, Mohammed Ali JAMALUDDIN.
iii. Contact information for corresponding authors. The name, address, email of one author who is responsible for all communication concerning the manuscript are required.

Abstract: The length of abstract depends on the type of manuscript submitted. The abstract should state the purpose of the study, a brief description of the procedures employed, main findings and principal conclusions. Abbreviations, foot notes, references and subheadings should be avoided. For original articles, the abstract format is structured as background, methods, results, and conclusion. For other articles, the abstract format is unstructured.

Keywords: Authors must provide between three and six keywords that characterize the main topics of the article. Use recognized vocabularies related to the discipline discussed, such as the MeSH thesaurus http://www.nlm.nih.gov/mesh/MBrowser.html. We encourage the use of synonyms for terms provided in the article title, this is to aid database searches.

Tables: Tables must be numbered sequentially and in the order in which they are mentioned in the text. Tables must have brief descriptive title. Preferably, tables must be prepared according to the guides in Chicago Manual of Style.

Figures: Figures must be numbered sequentially and in the order in which they are mentioned in the text. Figure legends are needed for all figures. Grayscale and color artwork should have a minimum resolution of 300 dpi.

Videos: We also welcome submission of short videos as supplementary file. Videos may be useful for demonstrating complex laboratory, surgical or medical procedures. The demonstration of the experiment must be shown in orderly fashion, including a demonstration of quipment and reagent. Researchers should be properly attired when handling animals, reagents and chemicals. Each video file must be under 5 minutes. We accept .mov, .avi, .swf formats. The video should make a specific point; particularly, it should demonstrate the features described in the text of the manuscript. Special effects or text are not permitted to be inserted in the video. Unfortunately, we do not do video editing and production.

Reference: References should be numbered consecutively in the order in which they are first mentioned in the text (citation-sequence)—the Vancouver style. Identify references in text, tables and legends by Arabic numerals in parentheses. For formatting end references, we recommend following the guidelines of the Council of Science Editors (CSE) which can be accessed through http://library.duke.edu/research/citing/workscited/

Journal article: The titles of journal should be abbreviated according to the style used in http://www.ncbi.nlm.nih.gov/sites/entrez?Db=journals&Cmd=DetailsSearch&Term=currently indexed[All] or http://www.efm.leeds.ac.uk/~mark/ISIabbr/A_abrvjt.html

> Theriault A, Caao JT, Gapor A. Tocotrienol is the most effective vitamin E for reducing endothelial expression of adhesion molecule and adhesion to monocytes. *Atherosclerosis.* 2002; **160(1)**:21-30.

If there are more than six authors, list the first six authors and use "et al." for the subsequent authors.

Books: Authors' surname Initials. *Title of book*. # ed. [if not 1st]. Place of publication. Publisher's name; Year of publication.

> Carlson BM. *Human embryology and developmental biology*. 3rd ed. St Louis: Mosby; 2004.

Online article: Journal articles in electronic format: Authors' surname Initials. Title of article. Abbreviated title of journal [Internet]. Year of publication [cited YYYY MMM DD]. Available from: URL.

> Rabbani SI, Devi K, Khanam S. Role of pioglitazone with metformin or glimepiride on oxidative stress-

induced nuclear damage and reproductive toxicity in diabetic rats. *Malaysian J Med Sci* [Internet]. 2010 [cited 2010 Mar 21];**17(1)**:3–11. Available from: http://ernd.usm.my/journal/journal/02-171OA1pioglitazone.pdf

For other forms of reference, please refer to the National Library of Medicine http://www.nlm.nih.gov/pubs/formats/recommendedformats.html

Editing

A manuscript may be corrected for length, grammatical correctness, sentence structure and journal style. Accepted manuscripts are edited in accordance with the *CSE Manual of Style, 7th edition* and *Chicago Manual of Style 15th edition*. The final proof of the manuscript will be sent to the corresponding author for final checking. The author should not make any changes to the contents of the manuscript at this stage.

Editorial policies for authors

Authors are required to sign the Authorship Agreement Form when submitting a manuscript to MJMS. In addition, authors are required to identify their contributions to the work described in the manuscript. If requested to see the original data, authors must provide the data and must cooperate in obtaining and providing the data on which the manuscript is based.

Conflicts of Interest and Financial Disclosures

A conflict of interest may arise when an author (or the author's institution or employer) has financial or personal relationships that could influence the author's decisions, work, or manuscript. All authors are required to disclose all potential conflicts of interest, including specific financial interests and relationships and affiliations (other than those affiliations listed in the title page of the manuscript) relevant to the subject of their manuscript. Please refer to the Authorship Agreement Form.

Authors are expected to provide detailed information about all relevant financial interests and relationships or financial conflicts within the past 5 years and for the foreseeable future, particularly those present at the time the research was conducted and through publication, as well as other financial interests (such as patent applications in preparation), that represent potential future financial gain. Authors may do so in the covering letter submitted via Manuscript Central.

Funding/Support and Role of Sponsor

All financial and material support for the research and the work should be clearly and completely identified in an Acknowledgment section of the manuscript. The specific role of the funding organization or sponsor in each of the following should be specified: "design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

References

1. Council of Science Editors, Scientific Style and Format. The CSE Manual for Authors, Editors and Publishers. 7th ed. Reston (VA): The Council; 2006.
   Council; 2006.
2. The Chicago manual of style. 15th ed. Chicago: The University of Chicago Press; 2003.
3. Uniform Requirements for Manuscripts Submitted to biomedical journals: Writing and Editing for biomedical publication [Internet]. International Committee of Medical Journal Editors: 2009. Available from: http://www.icmje.org/

Authorship Agreement Form

Date: .....

Manuscript title: .....

The completed forms must be mailed to the Editor, Malaysian Journal of Medical Sciences, USM Press, c/o School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, 16150 Kota Bharu, Malaysia, or faxed to +609 767 2359

Ethical Requirement

The authors attest that full and informed consent was obtained from human subjects and that the work was performed in accordance with the humane and ethical principles of research outlined in the Helsinki guidelines. In countries where institutional review is established, this statement also attests to the approval of that institution of the protocol for all aspects of the investigation presented in a manuscript involving humans or animals.

Conflict Of Interest And Financial Support

The undersigned authors agree that any financial interests that exist for individual contributors in connection with this manuscript have been disclosed in the covering letter submitted through Manuscript Central. Sources of financial support of the project are named in the covering letter as well as in the Acknowledgements.

Duplicate Publications

The undersigned Author(s) certify that neither this manuscript nor one with substantially similar content under their authorship has been published or being considered for publication elsewhere in any language. They also certify that any previous presentations of this paper in meetings are mentioned in the covering letter.

Authorship

Author(s) attest that all persons designated as authors qualify for authorship and all those who qualify are listed. All others who contributed to the work but are not authors (if any) are named in the Acknowledgements of the manuscript.

In the space marked "Contribution Codes", authors should mark those code letters from the box that designate their own substantive contribution(s) to the paper.

Contribution codes

A: Conception and design
B: Analysis and interpretation of the data
C: Drafting of the article
D: Critical revision of the article for important intellectual content
E: Final approval of the article
F: Provision of study materials or patients
G: Statistical expertise
H: Obtaining of funding
I: Administrative, technical, or logistic support
J: Collection and assembly of data

Names of all authors

Contribution codes*	Author's Name	Signature

Patient Consent Form

I give my permission for the following material to appear in the print and online versions of the Malaysian Journal of Medical Sciences. The completed forms must be mailed to the Editor, Malaysian Journal of Medical Sciences, USM Press, c/o School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kubang Kerian, 16150 Kota Bharu, Malaysia, faxed to +609 767 2359, or emailed to mjms.usm@gmail.com

Title or subject of article, photograph or video:

I understand that my name will not be published but that complete anonymity cannot be guaranteed.

Please check the appropriate box below after reading each statement.

☐ I have read the manuscript or a general description of what the manuscript contains and reviewed all photographs, illustrations, or video files (if included) in which I am included that will be published.

☐ I have been offered the opportunity to read the manuscript and to see all photographs, illustrations, or video files (if included) in which I am included, but I waive my right to do so.

Signature of patient or guardian : .....
Name : .....
Date : .....

Copyright Transfer Form

The Universiti Sains Malaysia Press ("USM Press") is pleased to undertake the publication of your work tentatively titled _____ _____(the "Contribution") in its publication _____ (the "Publication").

You, the undersigned individual(s), will retain copyright to the Contribution as author(s); and you grant us, as publisher, the limited rights detailed below, which are expressly conditioned on the terms of this agreement.

We both acknowledge that a static agreement may not be able to contemplate all possible licensing arrangements, technologies or future developments, and therefore we both agree to cooperate in good faith to achieve our mutual goals of maximizing dissemination of your Contribution while ensuring the sustainability of scholarly publishing.

Accordingly, we submit the following terms of publication for your consideration.

1. ***License grant***
   You grant to USM Press a worldwide, royalty-free, non-exclusive license to:
   (i) reproduce, publicly display, publicly perform and distribute the Contribution in the Publication;
   (ii) authorise third party users of the Publication in electronic or digital (or other intangible) form to download and print out copies of the Contribution for their personal or internal institutional use;
   (iii) authorize others to reproduce, publicly display, publicly perform and distribute the Contribution as part of the Publication through any distribution channels and in any media or format through which USM Press may distribute or make available substantially all the contents of the Publication; and
   (iv) deposit with or otherwise make the Contribution available to digital repositories as required by your funding sources upon your request.

   The above rights may be exercised in all media and formats, whether now known or hereafter devised, [and in all languages] in which the Publication as a whole (or substantially all its contents) may be distributed, whether or not the Contribution may be individually or partially accessed or retrieved. The above rights include the right to edit [and translate] the Contribution and to make such modifications as are technically necessary or desirable to exercise these rights in differing media and formats.

2. ***Exclusive rights***
   You grant to USM Press the worldwide, royalty-free, exclusive right to first publish the Contribution.

3. ***Author Rights***
   You retain the rights to
   (i) reproduce and distribute a reasonable number of copies of any version of the Contribution, including but not limited to the published version, or portions or derivative works thereof, in the course of your teaching, research, conference presentations and similar professional, scientific, or academic activities (but not permit commercial publication or widespread distribution of the Contribution or any significant portion or derivative work thereof);
   (ii) post or otherwise make any version of the Contribution, or portions or derivative works thereof, available on your personal web site; and
   (iii) [if and as required by your employing institution(s) or your funding source(s),] make any version of the Contribution available on digital repositories; provided in each case [acronym/abbreviation] (and Publication) is cited as the first/forthcoming publisher of the Contribution and you accurately distinguish any modified version of the Contribution from that published or to be published by us.

4. ***Editing***
   USM Press will make no material modification to the content of the Contribution without your consent. The Contribution will also be subjected to editing for language clarity and conciseness, should we deemed it necessary. However, if you fail to return the edited manuscript or proofs of the Contribution by the reasonable deadline set by us, you will be deemed to have consented to that modified version.

5. ***Credit***
   USM Press agrees to make commercially reasonable efforts to include (and require its sublicensees to include) appropriate credit to the author(s) in customary placement with every copy or use of the Contribution as described in Sections 1 and 2.

6. ***Warranties***
   You warrant that
   (i) you are the creator of the Contribution or otherwise have the rights necessary to grant the licenses granted to USM Press herein; and
   (ii) the Contribution contains no material that infringes or violates any intellectual property or contractual rights of others or that constitutes defamation or invasion of privacy. The foregoing warranties apply only to the Contribution in the form submitted by you to USM Press, and not to any modifications or additions made by USM Press, reviewers or other third parties.

7. ***Termination***
   If we do not publish the Contribution in the Publication within [twelve (12)] months following submission of the Contribution, extended to the extent of any delays caused by you, you may terminate this agreement and the licenses granted to us hereunder by providing us with written notice of termination, unless we publish the Contribution within [three (3)] months following receipt of such notice. Such termination of this agreement will be your exclusive remedy for any failure by us to publish the Contribution.

8. ***Miscellaneous***
   This agreement contains the entire understanding of the parties and will be governed by the laws of the State of [state], without reference to its conflicts of laws principles. This agreement can only be modified by an agreement in writing signed by the parties. This agreement may be executed in one or more counterparts (including, without limitation, by facsimile or .pdf signature) each of which will be deemed an original and all of which will be taken together and deemed to be one instrument. USM Press may assign this agreement in connection with a sale of the Publication or a sale, merger or reorganization of our organization.

If the foregoing terms are acceptable, please sign and date this agreement. All joint authors must sign. Please return the original to USM Press immediately and retain a copy for your records.

Corresponding author name (print or type):	
Address:	**Author signature:** **Date:**

Joint author name (print or type):	
Address:	**Author signature:** **Date:**

Joint author name (print or type):	
Address:	**Author signature:** **Date:**

Joint author name (print or type):	
Address:	**Author signature:** **Date:**

Joint author name (print or type):	
Address:	**Author signature:** **Date:**

Joint author name (print or type):	
Address:	**Author signature:** **Date:**

The completed form should be scanned/emailed to mjms.usm@gmail.com or alternatively, faxed to +609-767 2359.

Subscription Form

Name : .....
Address : .....
.....
.....
Tel : .....
Fax : .....
Email : .....
Date : .....

I would like to subscribe copy/copies of the following:

Volume 18, No. 2, 2011	MYR 30 (within Malaysia)	Quantity: .....
	USD 30 (International)	

* Previous issues are available on request and are subjected to availability.

Payment should be made in Malaysian Ringgit or US Dollar.
Methods of payment are as follows:

Crossed Cheque:

Made payable to
BENDAHARI UNIVERSITI SAINS MALAYSIA
Address
The Malaysian Journal of Medical Sciences
Penerbit Universiti Sains Malaysia
Universiti Sains Malaysia
11800 USM Pulau Pinang
MALAYSIA

Bank:

Payment may be made through banks to
Bank name: Bank Muamalat Malaysia Berhad
Branch: USM
Account number: 0702-0001054-71-6
Swift Code: BMMBMYK1

For more information, please contact Journal Division, Penerbit Universiti Sains Malaysia, by telephone at +604-6534423, by fax at +604-6575714, or by email at journal@usm.my.