THE MALAYSIAN JOURNAL OF
MEDICAL SCIENCES
Volume 16, No. 1 ISSN 13-94-195X e-ISSN 2180-4303 2009

Penerbit Universiti Sains Malaysia

Abstracts are indexed in Scopus, the Elsevier Bibliographic Databases, The Netherlands, Bioline, EBSCO Publishing, Index Copernicus The British Library Inside database and 21 other international and Malaysian database.

THE MALAYSIAN JOURNAL OF MEDICAL SCIENCES

Publisher

PENERBIT USM
Bangunan D34, Universiti Sains Malaysia
11800 USM, Pulau Pinang

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Malaysian Journal of Medical Sciences, Vol. 16, No. 1, January - March 2009

EDITORIAL

USM Apex University Status: Transforming Higher Education For A Sustainable Tomorrow

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Vice Chancellor, Universiti Sains Malaysia

This special editorial for the month of January 2009 is "THE" interview with Professor Tan Sri Dato' Dzulkifli Abdul Razak, Vice Chancellor of the Universiti Sains Malaysia (USM). He talked to us about the Apex University status that was conferred on 3rd September 2008. While most newspapers and the rest of the media were in frenzy interviewing him that month, MJMS decided to catch up with him on Monday 15th December 2008 just before the celebration at the Dewan Utama, Universiti Sains Malaysia Health Sciences Campus to commemorate the 25th anniversary of the establishment of the Hospital University Sains Malaysia by Yang Berhormat, Minister of Higher Education Datuk Seri Mohamed Khaled Nordin. References to USM as an APEX University are included at the end of this editorial especially for non-USM readers.

The questions that MJMS Editor Prof. Jafri Malin Abdullah asked were focused mainly on the new APEX status. We were interested to learn how this would impact human resources, research and infrastructure concerning the medical, dental, pharmacy, health and biomedical sciences communities over the next few years. On the local front, much discussion has taken place (in both print and electronic media) on the measures taken by the various agencies on the front line of this outbreak. While there are some who feel that too much is being done, so much so that everyday activities are being hampered, there is probably an equally sizeable group in our population who feel that the measures taken have been insufficient. During an outbreak, especially one of global magnitude, many forces influence our reactions to the perceived threat. The operative word here is perceived, and perception is a heterogeneous entity that is governed by myriad factors. Hence, it is imperative that our reactions be as evidence-based as possible. Our responses should therefore always be based on sound science. At the same time, they must be guided by common sense and a clear understanding of local realities, both of our strengths and our limitations.

MJMS : *What are your views on how USM as an Apex University can enhance the biomedical research currently being performed by the Schools of Medical Sciences, Pharmacy, Dentistry, Health Sciences, and by the Advanced Medical and Dental Institute, the Institute for Molecular Medicine and other new institutes as well as Hospital Universiti Sains Malaysia? How do you plan to retask the "classical service oriented" clinical or paraclinical staff to fit the APEXUniversity template?*

Professor Tan Sri Dato' Dzulkifli Abd Razak : APEX is an acronym that stands for Accelerated Program for Excellence, which means that it has wide boundaries in terms of its definition. The extent of these boundaries is open to interpretation. In the context of this university, we have decided that APEX should encompass a global dimension.

One factor that is particularly relevant to APEX university status, taking excellence into account, must be related to the "Bottom Billions" group. This refers to the four billion people, roughly two-thirds of the world population, who are neglected in terms of education, health, socialeconomic parameters, and quality of life, since they survive on about three US dollars per day.

These are the groups that we feel must be given attention as part of our global agenda, and this is especially true if we wish to promote longterm peace and a harmonious world. Someone needs to focus on these groups and make sure that the gaps that exist today are not widening and, instead, are being bridged as swiftly as possible.

We project that the world's population will reach 7 or 9 billion people in a few years' time. We run the risk that these already-neglected groups will come to comprise even more people, and that the problems will worsen further.

Already we see that that globalisation has increased the wealth of a few people, while the gap between the rich and the poor continues to widen -

a fact that is seldom acknowledged by proponents of a global economy.

As we see more people becoming marginalised, it becomes ever more important for APEX USM to work directly with these groups of people. We often talk about how we want to reach out to the majority of the world's population of the world – especially those who deserve a quality education.

We do not confine ourselves only to Malaysia, especially given that Malaysia's problems relative to that of the developing world are somewhat manageable. In general, the poor in Malaysia are substantially better off than the poorest individuals in other countries in other parts of the world.

Accordingly - if we want USM to be a global player, we must have a global agenda and remain committed to it. We cannot be a global player without any commitment to a global agenda. Our global agenda is basically to reach out to the four billion people at the bottom of the socio-economic pyramid, in tandem with the United Nations Millennium Development Goals (MDG).

In terms of unifying the facilities and institutions at USM toward this goal, we essentially have to focus on reorientating some of these services to the needs of the MDG target groups. In general, I would say we want to focus on the major problems at this level of the pyramid.

The example that I normally give would be to look into the needs of the majority as compared to needs of the wealthy few. Let us talk about the eradication of disease within the MDG framework. Our focus would be on the basic infectious and communicable diseases, rather than the diseases of affluence that often are the preoccupation of the developed countries. In other words, there must be some conscious effort to tackle the diseases of the poor, namely, the neglected tropical diseases or the NTD for short, including typhoid, malaria, and cholera – the root of suffering for millions of people worldwide, Zimbabwe being the most significant example of late.

We still do not understand why such a large percentage of the world's population have not received their fair share of drug discoveries directed at treating these diseases. It is certainly not a question of technology, because the technology is available. The technology exists, but what is lacking is the political will!

It is also not a question of finances, because the solutions to these problems are low tech – or at least they can be low tech for the time being. It is all a question of how we strategise and actually improve the so-called scientific and technological approaches to these diseases.

I believe that the classical example that the USM has offered in this area is our innovative work on typhoid diagnostics. At one time, it took a couple of days to diagnose typhoid, and the need for a cold chain to perform the diagnosis. This meant that if you wanted to treat typhoid in the deepest jungle of the world, say in Africa or even Malaysia, it is not something that can be easily done because of a lack of refrigeration. Most of the poorest and most remote places are without electricity, and are associated with a myriad of other problems that pose severe logistical challenges.

Fortunately, our scientists have managed to innovatively change the technology to a short 15-minute diagnosis that does not refrigeration and is low-cost. Our technology is feasible for deployment in jungles and many other environments. In other words, these are the kind of priority-based mind shifts that we want to encourage by using modern technology to reach out to the greater part of humankind.

In fact, these are the challenges that we must face in all fields - including medical sciences, pharmacy, dentistry, health sciences, and emerging areas such as brain/cognitive sciences. Specifically, how can we can leverage the present body of knowledge to level up the quality of life for the majority of people, by enhancing technology to make it more accessible, available and affordable. We must address the issues of quality and equity simultaneously. This calls for experts to work together across disciplines - a transdisciplinary mode of discovery. One example in the context of brain sciences, is the deployment of robots with innovative power supply to replace human personel to treat ill people in remote areas of the Third World where doctors are scarce.

Our very innovative approach would allow medical procedures to be carried out in places that are currently out of medical reach due to the lack of talent and facilities, for instance. We need to think differently in these contexts. We have to systematise our mission of trying to reach out to the bottom billions. Most importantly, our work must be guided by our own ingenuity, our own resourcefulness, our own innovation, taking into account our values and cultural norms.

At this juncture, it is appropriate to define or describe APEX, and how it is from the classical service orientation.

In general, when we talk about APEX, we think about new ways of doing things, with significant future-orientated intent. That alone is sufficient to differentiate APEX. In other words, we need to dispense with the "old" ways. Whenever we encounter something "old," we need to assess how we can do better - the future will be different.

To move forward we really need to create our own future. However, at the same time we must pay attention to situations where "old" refers to some very basic fundamental principle. We cannot change our roots, because those are the essence of our being.

As an APEX status university, we will reexamine the assumptions that we often take for granted, and we will break down barriers that impede our progress toward the future.

To start with, we ask the question - what do we want to do now? We want to break down the artificial silos that are really an artifact of scholarship after it was forced into a "reductionist" model. While human beings will always remain "whole" people, science has torn the human apart into bits and pieces, metaphorically speaking. So too in the context of medicine, where everything is examined "separately" and not "holistically." To piece the patient together again becomes problematic. Most of us would already face difficulty putting parts of a machine back together again after it had been dismantled. Imagine the much greater difficulty in the case of a living organism. In other words, the "reductionist" approach is not entirely satisfactory, moving forward.

While it is important to recognise that there are various disciplines in the sciences, it is also equally important to recognise that all these disciplines are meaningless on their own (do not overspecialise!) if we do not understand how they all relate to one another, and to other non-science disciplines as well. This is the age of convergence. After all, it is not too long ago that Science was better known as Natural Philosophy!

Again, from the "old" experience we begin to see how one can span as many disciplines as possible. The fusion of health sciences with technical science, for example, (as in biomedical engineering) can bring enriching ideas. It is only natural to expect much more from various other cross-fertilisation approaches, as in the case of neuro-economics or neuro-marketing. Symbolically, APEX can be seen as a unification of data, information, knowledge and wisdom, in order to reach the truth. In similar ways, as we adopt APEX status, we too want to see the larger base (made up of numerous disciplines) adopting transdisciplinary approaches to power our search for truth.

In other words, we cannot remain static and silo-like. To pursue only one discipline is almost like digging a hole in the ground that becomes deeper and deeper and deeper, until it gets so deep that we lose sight of where we are. Below the Earth's surface, it is hard to measure one's depth. We consider it important to also dig sideways, namely by joining the silos and creating a new workspace where things are interconnected. There is both depth and breath in the notion of a number of disciplines that converge all at once. This is what we refer to as "transdisciplinarity."

Transdisciplinarity means that we work not only with our own group of people who are experts in their areas, but also that we work with experts from other disciplines, including the users, who are experts in their own right. The more important thing is that we also remain in constant touch with one another, so that we can be alerted almost immediately to what is relevant. This is a new mindset, beyond the usual inter- or multidisciplinarity where most academicians remain very much within their own domain, and rarely interact with their counterparts. This the mainstream way of doing things today, as well as the dominan orientation in terms of both teaching and learning. For this reason alone, I believe that the structure of the university must change.

The concept of schools may need to be more liberal than how we understand it today. Perhaps we need to think of clusters that combine elements from virtually every school. Moreover, the clusters cannot be confined to within the universities. They could operate beyond the universities, creatin clusters with any institution within Malaysia, or even outside Malaysia. I think a good start perhaps is the Universiti Sains Malaysia - University of Sydney (USMUS) programme. We plan to pursue a similar collaboration with the University of Gent in Belgium. We would like to explore industrial partnership possibilities as well. Creating similar clusters across disciplines is something important in trying to move APEX forward, thus ushering in an era of "new" sciences.

Our thinking reflects the reality of the 21-st century, where people as well as knowledge are converging once again into "one" whole, be it as "one" human race or one holistic body of knowledge. We need to meet the demands of the borderless world and address the problems it has created. Consider environmental issues, for example. There is no single discipline that can handle this problem. There must be multiplicity and transdisciplinary approaches in any real solution. Increasingly, ethical question are becoming just as important - previously one could do science without placing much emphasis on ethics (which explains several current environmental problems), especially in developing countries. This is no longer true today, and the same applies to the question of morality. We need to pay particular attention to other non-scientific disciplines, which requires the expertise of several different groups of people, i.e., the

social scientists and those in the humanities who can offer guidance as to what is possible and not possible and what transcends human dignity and rights.

In summary, the so-called classical or traditional approaches based on the "old" way of thinking must adapt to the "new" way of thinking and move into the APEX mode of collaboration in the context of transdisciplinary clusters.

MJMS : *Where do you see our institution in 2013? Which centres or facilities will slow down the rest of USM (for example, only 15% of the lecturers in the School of Medical Sciences have PhD degrees compared to other Schools or Centres)?*

Professor Tan Sri Dato' Dzulkifli Abdul Razak : We have five years to work on these issues. I think this is a very short time frame, given the amount of work that needs to be done. Nevertheless, certain elements must be in position such that, come 2013, we should already have defined the direction in terms of where universities in Malaysia (not only USM) ought to be if they want to compete on the world stage.

By 2013 we need to have signalled to the international community that Malaysia, and USM in particular, has expertise to offer to the world. At that particular time, we should already be able to push out or create a dent in the "old" ways of doing things. At the onset, we were questioning and debating the metaphor of existing universities, at least in Malaysia, which was akin to factories producing tangible items. This "factory" metaphor talks about producing students that we called products, some labelled doctors, others pharmacists or dentists, as though they are "lifeless" items. Indeed, we basically used to organise our university like a factory.

For example, the new students were considered the raw materials or ingredients to be processed by the university ('the factory'). The students are streamed into assembly lines (it is no coincidence that assemblies are held in schools) so that the processing can begin. It is like going through a conveyer belt every year, depending on the courses. It could be three to four conveyer belts for the sciences and arts, and an additional one for medicine. However, at the end of each conveyer belt there is a quality control step (our final year examinations) to determine what happens next. If they pass then they move on to the next conveyer belt. Otherwise they go for remedial work, to be rectified, and if this does not succeed, they are written-off - in other words, they fail and exit the system, since they were unable to meet the quality standards.

For those who manage to pass through several successive conveyer belts, they are ultimately ready to be sold at the marketplace. We call this employment. If they are not employed, we say they are useless, and if employed and not doing a good job, then it does not meet the standards set by the marketplace. Indeed, the best fit is the product that is tailor-made for the market!

The factory-cum-market metaphor came into being during the era of the industrial revolution. It sought to re-train people so that they could transition from agriculture to factory shop floors. They needed to create a system that could change behaviour and habits to suit the needs of the industrial economy. What better place to do that, if not in schools and universities? This has not changed in any significant way since. In fact, as the marketplace becomes increasingly dominant, universities gradually continue to lose what the little educational identity remains.

Going forward, the question we must ask ourselves is as follows: if we are in the 21-st century and in the post-industrial age, why are we still using the "old" and "dysfunctional" industrial metaphor to run a university? The immediate challenge for us is to understand the more accurate metaphor for the 21-st century, as people now move from the factory shop floors into a more sublime digital space, which is quickly transforming the economy and society based on knowledge. Individuals are no longer regular blue or white-collar workers, they are knowledge-workers - some call them the "gold"- collar workers.

For USM, our tagline 'The University in a Garden' has been a "new" metaphor designed to reflect the notion that our university is no longer a factory. Why a garden? This is to reflect the diversity (transdisciplinarity) which is an important component of today's learning paradigms. A good garden will have a diversity of flowering plants, various types of big and small trees, and shrubs. A bad garden is more like a plantation, and stands for the university of today – uniformity, sameness, and standardisation. It will be a formidable challenge to work across disciplines and create even more diversity. Indeed, the whole concept of diversity has become a vital element of the new university. In the old factory model, diversity was unimportant.

More specifically, let us look at the metaphor of a tree. While we appreciate trees as something naturally beautiful - the lushness of the leaves, the colourful flowers and so on - we often forget that the tree is anchored to the ground, without which there would be no trees. In other words,

the anchoring is what makes a tree viable; if it is not well anchored by its roots then it will be less of a tree, because any strong winds, like the winds of globalisation, can force the tree to fall or get uprooted. Some of our questions include: what should be the role of the roots that anchor the tree? How well developed are these roots? How extensive is the network that penetrates into the soil? Yet, these are often not the measures we would use to evaluate a tree, or even a garden for that matter. In metaphorical terms, we wonder what should be the role of our own indigenous wisdom, intellectual values, and cultural norms that are underlined by our centuries-old culture and civilisation? By this I mean our own values; Islamic, Malay, and Malaysian values and way of life. More specific to the Malay values for example, the ideology of *padi* - "lagi tunduk apabila berisi" [you are more humble as you become more successful] can be a significant factor in determining the way forward in the 21-st century. Therefore, even if we adopt the garden metaphor, we cannot forget the value system – the questions of ethics and moral values which are an integral part of the education system.

We sometimes see medical doctors who at the beginning of the course said they want to save the lives of other human beings but, at the end of the day, they care only about materialistic issues. They want to create as much wealth for themselves at the expense of everything else; when asked to serve rural areas, they are reluctant because they do not wish to consider a pay reduction. When you ask them to do something slightly challenging they will stubbornly refuse: pay becomes an issue, long hours become an issue, being overworked becomes an issue. The irony is that they know about all of these challenges before becoming a doctor, yet they still choose this profession. The value in making sacrifices seems somehow misplaced in a profession that demands exactly that. Therefore, it is our responsibility to instil those values, not just for our medical students, but as a culture for all of our campuses. We need to nurture and cultivate passion in people and in humanity, engendering a passion to create a more just and equal society. We need to go back to the very principle of what medicine is all about, and how it became into being.

That is why I am very critical when I realise that appropriate values have not been holistically imparted to our students by "us". I think that the whole notion of being compassionate, and having passion in what they doing, making sacrifices for people ought to be the mainstay of the university, just like a gardener tending to his garden. In this particular context, by the year 2013 we should be able to reinstitute what we have lost in the course of moving from the factory to a garden metaphor. Our progress should not be hampered by the number of staff who lack PhD qualifications and similar metrics. I am more worried about staff with bad attitudes and poor aptitudes. Such staff must be terminated as soon as possible.

To me, qualification is never an issue because we can always train people to acquire various competencies. It will not be a major barrier. The important factor is to change people's attitudes, mindsets, and willingness to undertake work on the basis of trust, honesty and sincerity, and not on the basis of material wealth. The types of factors will slow us down, and in fact may even lead to failure. It is very difficult to change people's attitude. We cannot send people for training to change their attitude, as readily as we send them to get extra qualifications with probable success. Worst, of course, are when both are absent!

The question of attitude and aptitude is crucial. Under APEX, we will start attitude/ aptitude testing with the 2009/2010 intake of new students that apply directly to USM. When they apply to join us, we will institute various criteria to evaluate their attitude and aptitude. We are keen to understand their academic performance, but we will have to go beyond just that. For example, traditionally if a student gets a 4-point GPA, they will automatically get to do medicine. Under the new system, we would not allow such a student to read medicine if they were to fail our aptitude and attitude evaluation. We will assess values in terms of a willingness to alleviate suffering and raise people's quality of life.

The time has come for us to characterise the kind of students we want to eventually become doctors, where this also applies to the rest of our subjects. All students must demonstrate the desired level of compassion, passion and interest in what they want to do and in what they wish to pursue as a profession. In this way, the university will emphasize education and talent development. Moving forward, all new staff will undergo similar evaluations.

MJMS : *What are your plans to improve the related centres' and institutions' infrastructure? Five years seems such a short time to implement important steps to bring USM to the next level.*

Professor Tan Sri Dato' Dzulkifli Abd Razak : Under APEX status, we will have flagship programmes: advanced study initiatives that are meant to reflect the kind of cutting-edge knowledge that we want to fast track. These programmes will give high visibility to USM, and will also offer

relevance for the future. As soon as we decide what these initiatives are, the allocation of resources will be expedited and researchers will be able to control their own budgets. The level of bureaucracy involved will hopefully be minimal, if not totally eliminated. The choice of talent that is required will also be independent of the university's central administration, as long as it follows generally accepted guidelines. We were already experimenting with this concept when we created the Centre for Chemical Biology. This programme is the first of its kind in USM, and it will be fast tracked under our APEX status. Brain sciences will potentially be another such area. In other words, we will choose the fields that are not crowded but that are crucial to the future of our country. Another area is sustainability studies - something that is essential to our understanding of global warming, climatic change, etc. which is currently in its infancy. It is understood that these fast-tracked initiatives should raise the profile of APEX and motivate other universities to follow suit. All of these programmes will be transdisciplinary in nature, capturing all the arguments made before.

Other on-going scientific or art projects will continue to be supported depending on the type of activity. If the activity corresponds to the research-orientated KPI, support should be forthcoming. APEX will allow us to increase the number of academic staff to 5,000, up from 1,500. Significant investment will go into training, recruiting new talent and encouraging professionals to assume university lecturer positions. All new hires will need to demonstrate an appropriate attitude. By then, the USM population will already have been transformed to at least 50 per cent graduate students and 50 percent undergraduates. As the emphasis will be on research, all schools and departments must start to promote, create and generate more post-graduate activities in their own domain. This change needs to happen in the next 5 years, building up postgraduate courses in a manner that is pertinent to shaping the future of USM and bolstering the Malaysian higher education landscape for the 21-st century. Ultimately, post-graduate students will make up two-thirds of the campus population.

In the nutshell, APEX is about creating our future, and not about doing the same thing repeatedly even though we may doing it better each time. We are talking about what lies ahead in the education sector, and making it happen in the shortest possible time. We need to do a lot of thinking, a lot of forecasting and a lot of future-building (something USM has engaged in since May 2005) so that we can be precise as to our direction as the 21st century unfolds. That is our main challenge. For this reason alone, we need to be brave in creating our Blue Ocean Strategy by writing our own rules and excelling and executing them without compromising our values. We must realise that "failure is not an option."

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Note

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REVIEW ARTICLE

Pre-Eclampsia: Is It All In The Placenta?

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Submitted: 6 March 2007
Accepted: 1st December 2007

Abstract

Hypertensive disorders of pregnancy complicate almost 7 – 10 % of all pregnancies. The dyad of hypertension and proteinuria after 20 weeks of gestation is referred to as pre-eclampsia. It is a major cause of maternal morbidity and mortality and is also associated with increased perinatal problems. Despite intensive research over the years the exact cause of pre-eclampsia remains unknown. Nevertheless, information gleaned from published studies point to the placenta as the probable pathogenetic focus of pre-eclampsia, as the disease usually resolves within 24 – 48 hours after delivery of the placenta. Although the precise involvement of the placenta in pre-eclampsia remains unclear there are indications that the trophoblastic invasion of the uterine spiral arteries is abnormal in women who develop pre-eclampsia. This impaired invasion leads to decreased placental perfusion and ultimately to placental hypoxia. The distressed or ischaemic placenta then secretes a factor(s) into the maternal circulation, which cause/s widespread endothelial cell dysfunction characterized by vasospasm, activation of coagulation system and organ ischaemia. The cause of the defective cytotrophoblastic invasion of the spiral arteries and the link between placental ischaemia and generalized maternal endothelial dysfunction remain unknown. Although the placenta appears to have a major role in the pathogenesis of pre-eclampsia, evidence also suggests that factors like maternal genetic predisposition, dietary, environmental and behaviour, which surface during the stress of pregnancy might also be involved in the development of pre-eclampsia. It is known that not all women with poor cytotrophoblast invasion develop pre-eclampsia and not all women with preeclampsia show poor cytotrophoblast invasion. Over the years, a number of potential risk factors associated with the development of pre-eclampsia are being recognized and it might be appropriate now to develop some preventative strategies based upon the available information.

Keywords: *pre-eclampsia, placenta, medical sciences*

Introduction

Hypertensive disorders of pregnancy complicate almost 7 – 10 % of all pregnancies. The dyad of hypertension and proteinuria after 20 weeks of gestation is referred to as pre-eclampsia. It is a major cause of maternal morbidity and mortality and is also associated with increased perinatal problems. In spite of the intensive research over the years, the exact cause of pre-eclampsia remains unknown. Numerous causes have been proposed leading some to aptly refer to it as a "disease of theories". Nevertheless, considerable progress has been made towards the elucidation of a number of placental and maternal abnormalities that are associated with this disorder.

Historically, the first report of this disorder dates back to nearly 2000 years when Celsus reported an account of seizures in pregnant women that abated after delivery (1). This abnormality was given the name "eclampsia", which in Greek means "lighting", to describe its rapid and unexpected appearance. Sometime during the middle of the 1800s, examination of urine for protein in women with eclampsia revealed severe proteinuria that antedated the seizures. In the latter part of the 1800s, when it became possible to measure blood pressure with a sphygmomanometer, it further

became apparent that eclamptic women also had high blood pressure, and like proteinuria this also antedated the seizures. As proteinuria and hypertension antedated eclampsia, the term "pre-eclampsia" was applied to the development of hypertension and proteinuria during gestation. Today the term pre-eclampsia is used when there is raised blood pressure and proteinuria after 20 weeks of gestation. The mechanisms responsible for these are still unclear.

Placenta and pre-eclampsia

Pre-eclampsia-eclampsia is not a consequence of raised blood pressure or proteinuria *per se*, rather these are markers of multi-organ dysfunction in the mother. Women with pre-eclampsia seem to show disturbances in vasomotor activity, plasma volume and the coagulation system, which have been attributed to endothelial cell dysfunction or activation. The role of endothelial cells in the pathogenesis of pre-eclampsia is indicated by (i) the presence of high circulating levels of von Willebrand factor (2,3), (ii) morphologic evidence of endothelial cell injury e.g. glomerular endotheliosis (4), which is often seen in eclampsia but found in no other forms of hypertension, (iii) high circulating levels of cellular fibronectin (5, 6), (iv) high circulating levels of endothelins (7,8), (v) disturbances in the total plasminogen activator (tPA) and plasminogen activator/ inhibitor-1 balance (9), (vi) altered prostacyclin (PG12)/thromboxane (TXA2) balance (10) These morphologic and functional changes of the endothelial cells can be held directly responsible for triggering arterial vasospasm, increased thrombocyte aggregation, and increased capillary permeability that lead to hypertension, proteinuria, oedema and sometimes thrombocytopenia and hypoperfusion of organs (HELLP syndrome).

What causes the endothelial dysfunction remains a speculation. It has been proposed that some factor/s originating from the distressed placenta might be responsible for this disturbance or enhanced endothelial function. That the abnormality may indeed be in the placenta, to begin with, is supported by numerous clinical, biochemical and morphological observations, and possibly from some animal studies too. It is well known that the pathophysiological and pathological changes abate after delivery of the feto-placental unit. It is also known that the frequency of pre-eclampsia is increased in hydatidiform mole indicating that the presence of the fetus is not necessary (11,12). There has also been a report of pre-eclampsia in a woman with abdominal pregnancy, implying the irrelevance of the decidua or a distended uterus (13). The precise nature of the abnormality in the placenta or what is responsible for it however remains unclear. Nevertheless, there is evidence to suggest placental hypoperfusion and consequent ischaemia (14) probably secondary to poor cytotrophoblast invasion of the uterine wall. It is known that cytotrophoblastic invasion, though generally continuous, occurs in two stages i.e. during the first two weeks of gestation and then between 12 and 20 weeks of gestation in normal pregnancy. During this time there is invasion of the maternal spiral uterine arteries by the extravillous cytotrophoblasts. The invasion extends from the intervillous space up to the inner third of the myometrium (15,16). There is evidence that in women with pre-eclampsia the invasion by the trophoblast is defective where it remains limited to the decidual portion of the spiral arteries, with the myometrial segments maintaining their smooth muscle layer (17,18,19). These vessels have diameters that are only 40 percent of those vessels of normal pregnancies (20). Some spiral arteries are also atherosed (21). What causes the defective placentation is not apparent but there, reportedly, is a failure of the invading cytotrophoblasts to express the necessary invasive and adhesive properties or characteristics and signal molecules that are required for proper placentation, cytotrophoblast differentiation, invasion, angiogenesis and vasculogenesis. In normal pregnancy, placental cytotrophoblasts that invade the uterus downregulate the expression of adhesion molecules like Ecadherin and integrin a6b4 and aVb6 that inhibit invasion and up regulate receptors like a1b1, aVb3 and VE cadherin that promote invasion (22,23). In pre-eclampsia however, cytotrophoblasts fail to differentiate completely and continue to express Ecadherin, integrin a6b4 and aVb6. They also fail to up-regulate the expression of a1b1, aVb3 and VE cadherin, vascular adhesion molecule (VCAM-1) and platelet endothelial adhesion molecule-1 (PECAM-1) (24,25). The reason for the failure of the cytotrophoblast to differentiate and for placentation to occur satisfactorily is unknown.

In addition to these molecules that aid invasion, there are probably also a number of other molecules that are required for vasculogenesis and angiogenesis. One potential group consists of the *Eph* receptors and their ligands known as *Ephrins*. Their potential involvement in vascular patterning was first suspected when deletion of either EphB4 receptor or its primary ligand, ephrin B2, resulted in a general failure in angiogenic remodeling of the primary vascular plexus and subsequent embryonic lethality at mid-gestation in mice (26). Our

preliminary investigations into the expression of these molecules in normal and pre-eclamptic placentae revealed no expression of the ligand Ephrin B2 in pre-eclamptic placentae ranging in gestation from 26 to 40 weeks (27). It is believed that the poor angiogenesis and vasculogenesis that ensue are responsible for the distress in the placenta. In fact administration of sFlt-1 (an inhibitor of angiogenesis) to pregnant rats has been found to produce hypertension, proteinuria and glomerular endotheliosis (28). The reason for the altered or disturbed expression of these signaling molecules that are necessary for proper implantation of the placenta remains unclear. Recent report suggests of a lack of downregulation of transforming growth factor beta 3 (TGF-beta3) in pre-eclamptic placentae (29). TGF-beta3 is produced by the placenta very early on during gestation and it inhibits trophoblast differentiation. Its level begins to fall after about ten weeks of gestation. Why there is a failure to down regulate TGF-beta3 and what its role is in the impaired placentation in pre-eclampsia is unclear.

In addition to the failure to down-regulate TGFbeta3, placental hypoxia might also contribute to this defect. Evidence from experiments in vitro suggests that cytotrophoblast differentiation is significantly influenced by hypoxia. When cytotrophoblasts were cultured in hypoxic conditions (2% oxygen) they continued to proliferate without proper differentiation. However, when these cytotrophoblasts were cultured in 20% oxygen they stopped proliferating and differentiated normally (29,30). It appears that ischaemia or hypoxia during the second wave of invasion might restrict the development invasive properties by the cytotrophoblasts, consequently affecting the invasion of the myometrium by some segments of the placenta. In addition to poor angiogenesis and vasculogenesis, there is also a possibility that the hypothesized poor placental perfusion might be due to an imbalance of vaso-active factors in the placenta. The placenta lacks neural innervation and blood flow is principally regulated by humoral factors. An imbalance of these in favour of vasoconstrictors might compromise blood flow to and also in the placenta. Numerous vaso-active factors have been identified, some of which include the products of the renin-angiotensin system, kallikrienkinin-kininogen system, endothelins, nitric oxide, catecholamines, and vasodilatory and vasoconstrictive eicosanoids. Our observations of these have highlighted the existence of numerous abnormalities in some of these factors in the preeclamptic placentae. For example, placentae from women with pre-eclampsia were found to have significantly higher levels of prorenin and renin (31), leptin (32) and endothelin-1 (33), and significantly lower levels of kininogen (34), indicating a probable imbalance between vasodilator and vasoconstrictor factors.

Apart from an imbalance between vaso-active factors, there also exists a possibility of the role of immune maladaptation in cytotrophoblast invasion. This possibility is supported by the presence of immunopathology in women with pre-eclampsia where immune complex deposition in the spiral arteries, placenta, kidney and liver have been observed. There is also evidence of increased circulating immune complexes and the presence of acute atherosis in women with pre-eclampsia (35). Whether the immune maladaptation is due to poor maternal desensitization or due to some other factor is unclear. It has however been observed that in normal pregnancy the cytotrophoblasts, which invade the decidua suppress the expression of MHC Class II antigen HLA-A and instead express a nonclassical class I antigen HLA-G. Some of the cytotrophoblasts from women with pre-eclampsia have been reported to be devoid of HLA-G (36,37).

In addition to this, there is also circumstantial evidence that supports the role of immune maladaptation in pre-eclampsia. It is known that a previous pregnancy or abortion by the same father is associated with a lowered incidence of preeclampsia (38). Furthermore, the protective effect of multiparity is lost with a change of male partner (39,40,41) although an earlier study had failed to show this (42). This also suggests that pre-eclampsia may be a problem of primipaternity rather than primigravidity. Moreover, the length of exposure to sperm and cohabitation before pregnancy correlate negatively with pre-eclampsia (43,44). Interestingly, in a couple of isolated studies the incidence of intraoral ejaculation before pregnancy has been observed to be somewhat higher in normalpregnant women when compared to women with pre-eclampsia (45,46). Women using barrier contraceptives have twice the likelihood of developing pre-eclampsia (47,48). Artificial donor 10 insemination has been shown to be associated with a higher risk of pre-eclampsia (49). These observations collectively suggest that a longer exposure to the partner's sperm before pregnancy decreases the maternal immune sensitivity to the fetal allograft, and that in preeclampsia this normal tolerance process of the fetal allograft has not developed completely. Evidently fewer than 4 months of cohabitation among users of barrier methods for contraception is associated with increased risk for pre-eclampsia (50).

Information to date suggests that there exists some abnormality in the placenta, which might be due either to an imbalance in the levels of vaso-active factors or to immune maladaptation, and this abnormality is responsible for the maternal syndrome. To explain this disorder, a two compartment model has been proposed. It hypothesises that to begin with there exists an abnormality in the placenta possibly due to an imbalance in vasoactive factors or immune maladaptation that results in poor cytotrophoblast invasion and consequently placental insufficiency. The distressed placenta then releases some factor/s, which crosses the maternal placental barrier and causes endothelial dysfunction in the mother. The exact nature of this factor/s has not been identified but a number of them have been implicated. The proposed agents include syncytiotrophoblast microvillus membranes shed into the maternal circulation (51), interleukin-1 and 6 (52), tissue necrosis factor-a (53), and VCAM-1 (54), elastase produced by activated neutrophils in the deciduas and released into the maternal circulation (55), neurokinin B (56), AT1 autoantibodies (57) and placental renin (58). In addition to these, there is also a possibility of the involvement of free radicals and lipid peroxides released from the distressed placentae in pre-eclampsia. Owing to hypoxia, ischaemia and infarction of the placenta, there is a possibility that uric acid production may be higher in placentae from pre-eclamptic women. Xanthine oxidase activity generates reactive oxygen species like super oxide and hydrogen peroxide (59,60). Circulating levels of lipid peroxides have been observed to be higher in women with pre-eclampsia (61). Mitochondria from pre-eclamptic placentae are larger and evidently generate more lipid peroxides than those from normal placentae (62). In addition to the production of more oxidants in the form of superoxides there is also evidence for decreased antioxidant activity in the sera of pre-eclamptic women (63, 64). It is unclear if the decreased antioxidant activity is due to decreased production of antioxidants or an increased production of oxidants. Tissue vitamin E levels, activities of Cu-Zn Superoxide dismutase and gluthathione peroxidase are lower in pre-eclamptic placentae (65). It is possible the excess free radicals and lipid peroxides might be responsible for the maternal endothelial activation or dysfunction.

Although existing evidence consistently points to the placenta having a major role in the pathogenesis of the maternal syndrome, there nevertheless are indications that seem to suggest a role of some yet to be identified genetic, maternal, and even environmental factors, that might surface during the stress of pregnancy in some instances of pre-eclampsia. Maternal predisposition, for example, might also account for the maternal symptoms, and consequently affect the placenta and the developing fetus. In this regard it is known that not all cases of pre-eclampsia reveal an abnormal placentation or cytotrophoblast invasion or for that matter placental hypoperfusion. Moreover, not all women with poor cytotrophoblast invasion go on to develop preeclampsia e.g. in some cases of IUGR. In addition, the biochemical abnormalities reported by us, although were significantly different when examined by groups; they were however not present in every pre-eclamptic placenta, although a clear diagnosis of pre-eclampsia was evident in all the cases studied. There was a tendency for slight overlap between values. Furthermore, a higher incidence of preeclampsia in women born of eclamptic pregnancy, and in the first pregnancy in sisters, indicate the presence of some maternal predisposition (66,67, 68). The knowledge that the incidence of preeclampsia is higher in the first pregnancy than subsequent pregnancies and the evident discordance between identical twins (69), no doubt, weakens the role of genetic or familial disposition somewhat. Interestingly, women with blood group AB are somewhat more susceptible to pre-eclampsia (70). Pre-existing hypertension, diabetes mellitus, increased insulin resistance, and increased blood homocysteine increases the risk of pre-eclampsia. Once again interestingly, these are also risk factors for other endothelial diseases like atherosclerosis and the late complications of diabetes mellitus. Even a strong family history of aggregate cardiovascular risk has also been found to increase the likelihood for developing pre-eclampsia and transient hypertension during pregnancy (71).

That there may be other factors outside of the placenta, such as diet and environment that might Harbindar Jeet Singh also be involved is supported by the finding that the prevalence of pregnancy-induced hypertension is higher in populations in areas where calcium consumption is lower, and lower in populations given calcium supplementation during pregnancy (72,73,74). The role of calcium in the pathogenesis of PIH and pre-eclampsia is unclear but numerous small scale studies have indicated a reduced incidence of PIH and preeclampsia in populations given calcium supplementation during pregnancy (75, 76). One large-scale study however found no significant effects of calcium supplementation on preeclampsia, pregnancy-induced hypertension, or any adverse outcomes for that matter, when given to healthy nulliparous women (77). The authors

however do concede that in populations with a low dietary calcium intake, calcium supplements might have a role in preventing pre-eclampsia. A recent report in the Cochrane database systemic review concludes from studies to date that calcium supplementation during pregnancy appears to almost halve the risk of pre-eclampsia (78). Significant disturbances in calcium homeostasis and possibly also magnesium in women with pre-eclampsia and pregnancy-induced hypertension have been reported (79, 80, 81, 82). Although calcium status is rarely assessed during pregnancy, it is known that serum total calcium falls during normal pregnancy, accompanied by a fall in urinary calcium excretion (83). This usually occurs during the latter part of the second trimester and during the third trimester of pregnancy when there is increased fetal accretion of calcium. The fall in serum calcium is however somewhat greater in women with PIH and preeclampsia. A recent study also found significantly lower levels of 25(OH) D in women with preeclampsia (84). They report of a monotonic doseresponse relation between serum 25(OH) D concentrations at <22 weeks and risk of preeclampsia. A 50-nmol/l decline in 25(OH) D concentration evidently doubled the risk of pre-eclampsia.

In addition to genetic and dietary factors, there may also be environmental and behavioural factors that might affect the risk of pre-eclampsia. For example, a recent report from 12 hospitals in America found that the incidence of pre-eclampsia decreases during the summer months in white women but not in black women (85). In addition, IgG seropositivity forChlamydia pneumoniae is more common among women with pre-eclampsia (86,87). The incidence of pre-eclampsia is reportedly lower in women who smoke (88).

Clearly, the aetiology and pathogenesis of preeclampsia still remains an enigma and there is a continued need for further study and the realisation that pre-eclampsia might not have a single aetiology, and that it might be a heterogeneous entity.

While all the research endeavours continue to unravel the precise aetiology of this disorder, it might be appropriate now to formulate and implement some actions, based on what we know so far, that could help reduce or prevent the incidence of pre-eclampsia. Until such time that we fully understand the causes of pre-eclampsia, we should continue to explore ways to also help prevent or minimize the influence of some of the suspected risk factors in this disorder. One approach that might be useful is the 'risk factor approach' that has been successfully implemented in the reduction of cardiovascular disease. Of consideration here would be the use of calcium supplements, possible also antioxidants, planning of pregnancy and even physical activity. Of these, calcium supplementation appears by far the most promising and with less adverse effects. The use of vitamin E supplementation in some instances although has been found to reduce the risk of pre-eclampsia and small-for-gestational age babies, there however seems to be an increased risk of pre-term birth (89). Vitamin C supplementation has produced no significant effec on the incidence of pre-eclampsia (90).

Planning of pregnancy with sufficient prior exposure to the partner's semen might also be worth the consideration. Although the precise duration ofexposure before conception has not been determined, but from the little available evidence there is a period of at least 4-6 months might be the minimum required (50).

Although the role of exercise in the reduction in the risk of hypertension and other cardiovascular complications is well documented for the normal population, its role in the prevention of preeclampsia has not been examined. It is known that women who are most physically active have the lowest prevalence of gestational diabetes. Given that preeclampsia, atherosclerosis, and diabetes share a common dyslipidaemia i.e. increased triglycerides, decreased HDL, and increased LDL concentrations, it is proposed that the incidence of pre-eclampsia might also be similarly lower in women who are regularly physically active. It is therefore not unreasonable to propose that all women, particularly those with a family history of cardiovascular diseases, diabetes mellitus and pre-eclampsia should exercise regularly to ensure an adequate level of prenatal fitness, which might help reduce the risk of them developing pre-eclampsia. exercise regularly to ensure an adequate level of prenatal fitness, which might help reduce the risk of them developing pre-eclampsia.

Conclusions

In conclusion, although the pathogenesis of pre-eclampsia still remains an enigma, and evidence points to the major role for the placenta in this disorder, there nevertheless is a lot of convincing evidence that seems to suggest a role for factors like maternal genetic predisposition, dietary, environmental and behaviour that might independently contribute to the development of preeclampsia. It appears that pre-eclampsia is a heterogenous disorder with multi-factorial aetiology, and we have to keep that in focus when studying this disease. There is a continued need

to explore the role of these factors and a lot has still to be done to be able to have some semblance of understanding of this enigmatic disorder. Nevertheless, while this is being pursued, we need to also seriously consider initiating actions, based on the available information, to prevent or minimize the influence of some of the risk factors that have been associated with preeclampsia. It is possible, attention to diet, family history, planning of pregnancy, and perhaps physical activity might help to reduce the incidence of this disease.

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Malaysian Journal of Medical Sciences, Vol. 16, No. 1, January - March 2009

HISTORICAL PERSPECTIVE

Hospital Universiti Sains Malaysia (HUSM): 25 Years Of Excellent Service

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Submitted: 1 October 2008
Accepted: 30 December 2008

Abstract

Our Hospital University Sains Malaysia (HUSM) was given the Cabinet approval to exist under the Ministry of Education on 23 November 1982. The Deputy Prime Minister during that period, Yang Berhormat Tun Musa Hitam announced this after the cabinet meeting was held together with the presence of the Yang Berhormat Ministers of Health; and Education, Director of the Public Works Department and the Implementation and Coordinating Unit, Prime Minister's Department. The first patients moved in on 14 March 1983 and the inauguration of HUSM was done on 26 August 1984 by the Duli Yang Maha Mulia Tuanku Ismail Petra Ibni Al-Marhum Sultan Yahya Petra, the Sultan of Kelantan Darul Naim. HUSM celebrated it's 25th anniversary at the Dewan Utama, USM Health Campus on the 15th December 2008 which was inaugurated by Yang Berhormat, Minister of Higher Education Dato' Seri Mohamed Khaled Nordin. USM's Vice Chancellor Professor Tan Sri Dato' Dzulkifli Abdul Razak, Chairman of the USM Board of Directors Tan Sri Dato' Haji Dr. Ani bin Arope, Health Campus Director Professor Dato' Dr. Mafauzy Mohamed, former Campus Director, Dato' Prof Mohd Roslani Abdul Majid, the current and previous Hospital Directors and Deputy Directors since 1983 were present. The achievements of HUSM since its establishment and its vision to fulfil the University's Accelerated Programme for Excellence (APEX) are elaborated.

Kelantan Darul Naim is one of the 14 states of Malaysia. It is located on the East Coast of Peninsular Malaysia, facing the South China Sea, with an area of 14,922 square kilometres, representing 4.4% of the total area of the entire Peninsular Malaysia (Figure 1).

Historically, the state of Kelantan devoted itself to cultivating Islamic knowledge. Huge numbers of 'Pondok' institutions which were nearly similar to the madrasah established in certain areas of the state.

This phenomenon led to the foundation of famous religious teachers or ulama that actively promoted Islamic education. Because of the importance of Islamic learning there, Kelantan was nicknamed Malaysia's "Serambi Mekah"(Figure 2).

During that period, one Haji Mohd. Yusoff Ahmad, better known as "Tok Kenali" by many, was born in Kampong Kenali, Kubang Kerian Kota Bharu in 1870 (1287H). Kubang Kerian, then a small village located six kilometres from Kota Bharu, started to grow in 1983 when a federal government project established a health campus there.

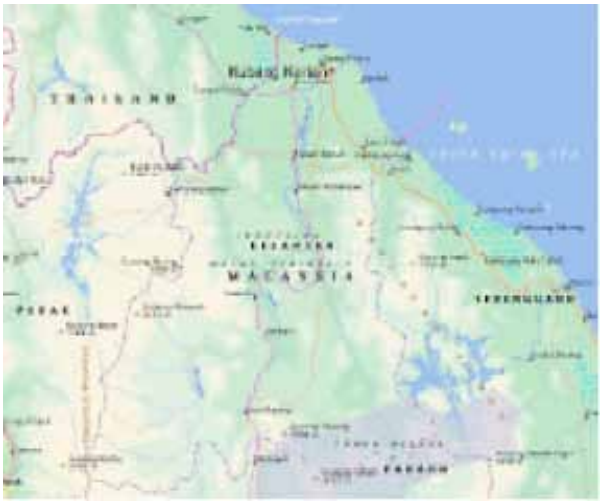

Figure 1: Kelantan Darul Naim on the map of Peninsular Malaysia.

Figure 2: The centre of Kota Bharu, Kelantan, or better know as the Istana Balai Besar square

Figure 4: First director of HUSM (1983-1992) Prof. Dr. Kamaruzaman Wan Su

Kubang Kerian became known when the Health Campus of Universiti Sains Malaysia (USM) was developed in 1983 on 72.84 hectares of paddy land that had been previously owned by poor farmers. This led to the beginning of a new era of health sciences in Kelantan. It gradually came to be a reality over a period of twenty-five years.

The Health Campus of Universiti Sains Malaysia (USM), an establishment of higher learning in medical science, became known as the Hospital Universiti Sains Malaysia (HUSM) in 1983 (Figure 3). HUSM has been headed by several directors, named as follows (Figure 4 to 6) :

i. Dr. Kamaruzaman Wan Su (1983 to 1992)
ii. Dr. Haji Ramli Saad (1992 to 2005)
iii. Dr. Zaidun Kamari (2005 to present)

Figure 5: Second director of HUSM (1992-2005) Dr. Haji Ramli Saad

The director is assisted by three deputy directors and the heads of the various departments and units. At present, 2,672 staff members work at HUSM in management and clinical disciplines. A record of excellent community service has made the name of HUSM better recognised in the local community. Based on this fact, HUSM is regarded as one of the best teaching hospitals in Kelantan and the East Coast. Furthermore, with new approaches to improve services, new specialist clinics have been developed to provide better treatment to the East Coast community.

Figure 3: The centre of Kota Bharu, Kelantan, or better know as the Istana Balai Besar square

The mission of Hospital University Science Malaysia, "to provide new patient services and thus become a full-fledged medical centre that provides only excellent services using the latest medical technology breakthroughs", will become a reality soon.

To achieve this goal, HUSM (Figure 7) has taken proactive steps in order to be known as:

1) A referral hospital that provides a higher level of medical science, dentistry and general health services to the public.
2) A teaching hospital that provides learning and research facilities in the fields of medical science, dentistry and general health.

Figure 6: Director of HUSM (2005-present) Dr. Zaidun Kamari

HUSM provides treatment services to its patients based on dedicated administration and management approaches using high quality services, a commitment to teaching and research, optimal financial strategies, core human resources values, and sensitivity to the social needs of the East Coast community.

In order to compete at the international level, HUSM has initiated a few centre of excellence projects, such as Cardiology and Cardiothoracic Surgery, Burn and Reconstructive Surgery, Neurosciences, and Tissue Banking.

The Cardiothoracic services were established to help the patients who needed heart and lung surgery, as well as to function as a cardiothoracic surgical resource centre on the East Coast of West Malaysia. It also provides an invaluable learning exposure to heart and lung surgery to the medical fraternity (undergraduates and post graduates students in biomedical sciences) and the nursing students in line with HUSM's functions as a teaching hospital.

The services that are available in this unit are open-heart surgery (such as closure of septal defects), valve replacement and coronary artery bypass grafting, closed-heart surgery with ligation of patent ductus arteriosus, pericardectomy, lung surgery, and mediastinum growth removal. HUSM provides invasive and non-invasive cardiology services such as echo cardiogram and cardiac+angiogram in the Invasive Cardiology Laboratory where cardiologists are able to perform invasive procedures like coronary angiogram and coronary angioplasty (Figure 8). HUSM has also established special units to cater patients with heart problems: the Cardiac Intensive Care unit (CICU), providing intensive care post surgery, and the Cardiac High Dependency Unit. The CICU

Figure 7: Officiation of the Hospital Universiti Sains Malaysia on 26th of August 1984 by the Duli Yang Maha Mulia Tuanku Ismail Petra Ibni Al-Marhum Sultan Yahya Petra.

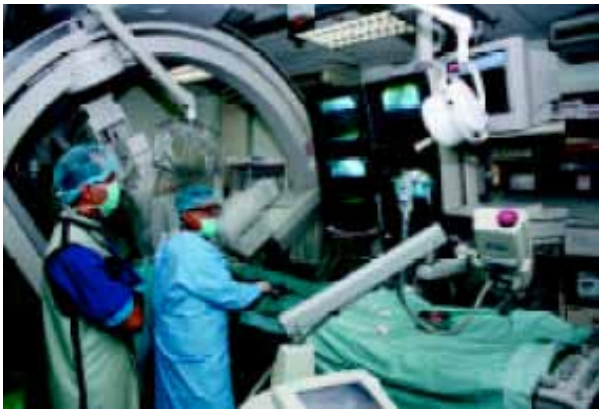

Figure 8: Officiation of the Hospital Universiti Sains Malaysia on 26th of August 1984 by the Duli Yang Maha Mulia Tuanku Ismail Petra Ibni Al-Marhum Sultan Yahya Petra.

is headed by both cardiac medical and surgical specialists and is supported by paramedical staff. At this moment there are 2 perfusionists, 5 surgical nurses and 21 CICU nurses (10 cardiac-trained nurses and 11 nurses undergoing in-house training). In addition, HUSM had a Memorandum of Understanding (MoU) with the National Cardiology Institute (IJN) regarding technical equipment as well as progressive paramedical training and expertise training.

The first three patients who underwent successful cardiothoracic operations were:

1) Aten Gemok, 19 years old, and Puan Hamidah Mat, 37 years old, for closure of arterial septal defects
2) Encik Azahari Zakaria, 47 years old, for coronary artery bypass surgery.

The operations were headed by a cardiac surgeon from IJN and HUSM'S cardiothoracic surgeon, Prof Madya Dr Mohamad Ziyadi Haji Ghazali. These success stories started a new era of surgery for local patients from the East Coast. The current types of surgery performed are:

i. Coronary artery bypass grafting
ii. Valve replacement
iii. Closure of septal defect
iv. Closed-heart surgery
v. Open-heart surgery
vi. Thoracic and mediastinal surgery
vii. Trauma (Heart/Lung)
viii. Ligation of patent ductus arteriosus

HUSM hopes that these services will make their mark and that HUSM will thus become a referral centre for those who need expert help in heart and lung surgery, as well as being one of the training centres for cardiothoracic surgeons in Malaysia.

Neurosciences

This project was initiated in early 1984 and became a second project with the following objectives for HUSM:

1) To be the centre of academic excellence in the field of Neurosciences.
2) To be a resource centre offering high-level, neuroscience-based medical and surgical services.
3) To be a leader in neuroscience research and innovations at the national and international levels.
4) To be a training centre in various biohealth science fields such as basic, applied and clinical neurosciences including pain and spinal surgery (neurology, neurosurgery, neuropsychology and neurosciences) (Figure 9 to 10).

With the establishment of the Neuroscience Unit in 2001, which became a department in 2004, HUSM has made history by becoming the first local university to offer a Masters in Surgery (Neurosurgery) program in 2001 and an Advanced Masters of Internal Medicine (Neurology) in 2007 with the cooperation of the Ministry of Health of Malaysia and other local universities. It has also

Figure 9: Neurosciences patients being managed by multimodality monitoring

Figure 10: Neurosciences Intensive Care Unit

offered MSc and PhD programs in Neurosciences since 2004. This department has been recognised as the most active unit in research, especially in the field of Traumatic Brain Injury, Haemorrhagic Stroke and Neuroncology in Southeast Asia.

As an active department in international research, it has contributed to studies such as CRASH, STICH, VITATOPS, ENOS, HAMLET, PERFORM, PROFESS and Rescue ICP study.

Majlis Kanser Negara (MAKNA) has chosen the Department of Neuroscience as a place to conduct research for a new brain cancer vaccine with the collaboration of University Putra Malaysia. In addition, the Department of Neuroscience was assigned as consultants for the Dewan Bahasa dan Pustaka, a body responsible and advancement of the Malay language in Malaysia, regarding neurosciences terminology.

Another project that proves HUSM to be an excellent hospital is the development of the Burn Injury Treatment Unit, under the Reconstructive Science Unit (Figure 11). This

Figure 11: Reconstructive procedure done in HUSM

Figure 12: Burn Ward

service was established with the objective to create a comprehensive healing program for burn victims and to return these victims to their communities in the highest possible physically, psychologically and socially functional state.

These services were incorporated into the Burn Unit.

1) Treatment for burn victims from the early stages of injury.
2) Continuous treatment by developing a network of long-term support, including rehabilitation.
3) A training centre for burn victim treatment procedures.
4) Preparing training and education for paramedics and the community in various aspects such as prevention, first aid, treatment, and recovery procedures.
5) Research into medical technology related to the management of burn cases.
6) Supporting activities for burn victims and their close relatives such as "Burn Camp" and "Burn Support Group".
7) Establishment of outreach services program and education for the community through fire prevention programs, fire treatment programs and fire awareness programs in schools.

The actions of PETRONAS have made HUSM proud. They sponsored the travel of patient Zawardy Abdul Latiff, who had serious third degree burn injuries, from Texas in the United States for follow-up treatments.

In its effort to create a successful unit, the staff has been sent to various other institutions to improve their skills and knowledge regarding burn victims' treatment and management (Figure 12).

These initiatives include:

1) Requests for fire treatment protocols from Hospital Universiti Kebangsaan Malaysia
2) Attachment of HUSM staff at the Fire Burn Treatment Centre in HKL
3) A study-visit program to Beverwijk Burn Centre, Amsterdam
4) Learning from the experienced staff at the Centre of Fire Burn and Reconstructive Surgery in Singapore General Hospital.

Stereotactic Radiosurgery is another strength of HUSM, and it has a multimodality treatment group which make it one of the better cancer treatment centres in the country today.

In May 2002, HUSM made history again when it successfully performed radiosurgery on "Head and Neck Cancer" using a mini multileaf collimator for the first time in Malaysia.

This excellent work by the HUSM units allows us to look forward to new level of service on par with other international medical centres throughout the world.

HUSM also offers an Out-Patient Service which consists of:

1) A Community Medicine Clinic that is open on all working days from 8:30 a.m. until 4:30 p.m.
2) A Specialist Clinic open from Saturday to Wednesday where patients are seen by referrals and appointments
3) An Accident and Emergency Unit that is open around the clock to attend to all kinds of urgent cases

As a teaching hospital and a referral centre, HUSM has undertaken the challenge to provide the best in-patient services possible. Relevant specialists who are also lecturers in the School of Medical Sciences, Dental Sciences and Health Sciences are appointed as consultants on all cases being treated in HUSM (Figure 13).

Figure 13: Hospital Universiti Sains Malaysia in 2009

HUSM has numerous important support services such as the Department of Radiology, the Department of Nuclear Medicine, and the different Diagnostic Laboratories and Clinical Departments. The Blood Bank supplies blood and blood components as well as other haematological tests and screening. The Physiotherapy Unit and the Haemodialysis Unit provide necessary therapies for certain patients. The Dietetics Unit prepares food for all in-patients and offers diet counselling services. The Laundry Unit ensures a constant supply of linen to the wards while the Housekeeping Unit is responsible for the cleanliness of all general areas in the hospital.

The Department of Pharmacy at HUSM is one-of-a-kind in Malaysia (Figure 14). Its services go beyond dispensing and therapeutic drug monitoring services. The department is also involved in the clinical pharmacy training of the pharmacy students in their final year at the university.

The Medical Records Unit handles the registration of all patients that seek treatment. (Figure 15). It also provides research facilities where access to patients' medical records for the doctors and medical undergraduates is provided. This unit is authorised by the National Registration Department to issue birth certificates for babies born in HUSM as well as death certificates. Moreover, medical reports for legal proceedings

Figure 14: Out-patient Pharmacy

Figure 15: Medical Records Unit

are also dealt with by this unit.

In addition, there are several facilities for patients and their families, (Figure 16 and 17) such as:

1) Desa Rakyat -Accommodation for patients' relatives/families at reasonable rates
2) A sports complex especially for the campus community, but available to the public on request
3) A bank and post office that provide both counter and automated services.
4) A golf course where membership is open to all health campus staff.

Figure 16: Desa Rakyat

Figure 16: Sports Complex

5) Town bus and taxi service – town buses service the campus while a taxi station is situated outside the HUSM main gate.

Conclusion

Hospital USM began with a 36-bed in 1983 and now provides a 747-bed service. Over the past 25 years, it has achieved excellence despite being situated in the East Coast of Peninsular Malaysia. Over the course of the past few Malaysian Plans, HUSM has managed to be both a service and clinical research centre of excellence with the establishment of new buildings, services and units in the 9th Malaysian Plan. USM was selected as an APEX University on September 3, 2008, thus giving HUSM more responsibility for the health campus and USM as a whole to increase its impact and presence in the national and international fields of research and publication.

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SPECIAL COMMUNICATION

Radioiodine I-131 For The Therapy Of Graves' Disease

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Submitted: 20 February 2007
Accepted: 3 December 2008

Abstract

Graves' disease is a common cause of hyperthyroidism. Treatment options for Graves' disease include antithyroid medication, surgery or radioactive iodine (I-31) or RAI. This review will focus on the approach to RAI therapy; discussing dose selection, patient preparation, and consideration before and after administering RAI, examining aspects of pre-treatment with antithyroid medication as well as discussing possible adverse events including hypothyroidism and possible worsening of thyroid-associated opthalmopathy. Follow-up is lifelong with the aim of ensuring the patient remains euthyroid or on replacement therapy if there is evidence of hypothyroidism. While there are controversies in treatment of thyrotoxicosis with RAI, with appropriate patient selection and regular follow-up, radioiodine is a safe and effective modality in achieving high cure rates.

***Keywords*:** *radioactive iodine, Graves' disease, thyroid, treatment, medical sciences*

Introduction

Radioactive iodine (I-131) or RAI as it shall now be referred to, has been commonly used for the treatment of both benign and malignant thyroid conditions since the 1940s. The aim of therapy is to treat hyperthyroidism by destroying sufficient thyroid tissue to render the patient either euthyroid or hypothyroid. Iodine-131 is a beta-emitting radionuclide with a maximum energy of 0.61 MeV, an average energy of 0.192 MeV, and a range in tissue of 0.8 mm. It remains the radionuclide of choice for therapy because of its long half-life of just over 8 days.

The mechanism of action of RAI is physiological. Iodine is the precursor of thyroxine. The radioactive form of iodine is taken up by iodide transporter of the thyroid the same way as natural iodine and is similarly processed. The b particle destroys the follicular cell, gradually leading to volume reduction and control of the thyrotoxicosis. The indications and contraindications for RAI therapy are shown in Table 1.

Graves' disease (GD) is an autoimmune condition characterised by elevated levels of thyroid stimulating (TSH) receptor antibodies with increased production of thyroid hormone. Among patients with hyperthyroidism, 60–80% have GD. It is 5–10 times more common in women than in men or children and is associated with a firm diffuse goitre, as well as clinically evident opthalmopathy in 50% (1). Various important issues in therapeutic use of RAI are discussed in this review. Treatment options for GD include antithyroid medication,

Table 1 : Indications and contraindications for RAI therapy

The main indications for RAI therapy include the following conditions
1. Hyperthyroidism due to: a. Grave's disease b. Toxic multinodular giotre or c. Hyperfunctioning thyroid nodules 2. Non-toxic multinodular goitre 3. Thyroid cancer.
Contra-indications for RAI therapy
1. Pregnancy 2. Breast feeding 3. Severe uncontrolled thyrotoxicosis

surgery and RAI therapy. The choice of treatment may differ from country to country but generally very few patients with uncomplicated GD are treated surgically (2).

Approach to RAI therapy

1. Selecting the appropriate dose of RAI

RAI is the most widely used treatment for patients with GD in the United States (2). Although therapy is well established for definitive treatment of GD, the approach to dosing remains controversial. This is due to differing goals of treatment (control of hyperthyroidism vs. avoidance of hypothyroidism).

Various techniques have been used to deliver adequate doses of radiation to the thyroid gland. These include calculations based on ultrasound determination of the volume of the gland and iodine uptake (3–5). Some authors advocate high doses of I-131 to render the gland hypothyroid in view of the complications that may occur with longstanding disease (6,7). This kind of approach is complex and increases hospital visits prior to therapy (8). The other is a fixed dose approach (2).

There is little evidence that using a calculated dose has any advantage over a fixed dose regimen in terms of preventing hypothyroidism (9,10). It is clear that no matter what the method used to determine the dose of therapy, most patients will ultimately become hypothyroid after RAI (11-13). A fixed dose regime is more convenient to use.

What is the optimal dose of RAI?

In a study comparing treatment with two single fixed first doses of RAI (14) of 185 MBq and 370 MBq, cure after RAI (defined by either euthyroid of all medications or biochemical hypothyroidism on a thyroxine replacement), was achieved in 85% of patients who received 370 MBq and 70% in the lower dose group. In addition, the second dose was administered to 30% of the lower dose group compared to only 15% of the higher dose group. The incidence of hypothyroidism at 1 year was 71.4% in the high dose group and 66.4% in the low dose group who required a second dose of RAI. The advantages of lower hypothyroid rates were lost if a second dose was administered. The authors concluded that a single fixed dose of 370 MBq is highly effective. Similar findings were noted from a study of 605 patients who were given various doses of RAI (15). Eighty-seven percent of those who were given 370 MBq were either hypo- or euthyroid.

Other authors argue that a larger fixed dose will minimise the need for re-treatment, and the morbidity and costs of the ineffective primary treatment. This approach uses high doses of RAI to deliver a dose of approximately 8 MCi (296 MBq) to the thyroid at 24 hours. This requires a dose of 15 MCi (555 MBq) to be given (16). Cure rates were 86% at 1 year. Similarly, Kendal-Taylor et al. (17) used 555 MBq as a fixed dose and demonstrated that 64% of their patients were hypothyroid and 30% were euthyroid 1 year after therapy.

2. Considerations before RAI therapy

Patient preparation ensures efficacy of RAI and reduces the potential complications. Important issues like the consent procedure, pregnancy issues and timing of stopping medication, restarting therapy and possible complications of therapy should be discussed with the patient (18) and are summarised in Table 2. Certain medications and other substances such as radiographic contrast materials can interfere with RAI uptake and should be stopped before treatment. These are highlighted in Table 3. Some of these issues include:

Iodine restriction

All patients must discontinue use of all iodine containing medications and must be placed on an iodine-restricted diet to ensure adequate RAI uptake. While the timing of dietary restrictions is unclear for benign thyroid disease, recommendations for thyroid cancer patients may be as long as 10–14 days.

Antithyroid medication

Carbimazole (CMZ), Methimazole (MTZ) and propylthiouracil (PTU) are used for the primary treatment of thyrotoxicosis due to GD or as a means of preparing the patient for definitive therapy with surgery or RAI (19). Pre-treatment of selected patients is indicated in older patients, in those with severe hyperthyroidism and cardiovascular complications. In such patients it is common practice to achieve euthyroidism to reduce the risk of worsening of thyrotoxicosis due to radiation induced leakage of stored thyroid hormone, which can occur soon after RAI therapy (20).

Worsening of the thyroid function has been described in approximately 10% of patients given RAI and 0.3% may experience a thyroid storm whether they are pre-treated or not. While there may be a transient rise in hormone levels in all patients, in pre-treated patients, this increase does not lead to an exacerbation due to lower baseline thyroid function (21). Adjunctive antithyroid drugs reduce the biochemical exacerbation of hyperthyroidism directly after radioiodine treatment. Patients who are at lower risk may be treated with only beta-blockers, with significant improvement of symptoms particularly if the RAI can be given without too much delay.

Table 2: Important practical issues prior to administration of RAI Adapted from The Society of Nuclear Medicine Guidelines (18)

	Informed consent must be obtained after adequate discussion of the issues outlined below
Adequate explanation: Written information should be provided to the patient	1. Pre-treatment issues 2. Fasting prior to therapy 3. How the iodine will be administered (liquid vs. capsules) 4. Possible complications and side effects 5. Alternative treatment options: antithyroid medication and surgery 6. Expected outcome to the patient: aims of therapy 7. The risk of hypothyriodism and lifelong L-thyroxine replacement 8. In women: Issues about delaying pregnancy for 4-6 months after the last dose of iodine In men: avoid fathering a child for a similar period of time 9. The necessity of lifelong follow up must be made clear
Written notification	1. Date of stopping antithyroid medication 2. Date of resuming antithyroid medication 3. Date and time of therapy 4. Date of follow up visit
Radiation protection issues	1. Patients must adhere to instructions 2. Precautions to avoid unnecessary exposure to family and co-workers, children and pregnant women 3. Mandatory urine pregnancy test performed <72 hours prior to RAI therapy

Table 3: Medications and other substances such as radiographic contrast materials that can interfere with RAI uptake and should be stopped before treatment

Type of medication or Substance	Duration of stopping treatment before RAI
Antithyroid medication (e.g., propylthiouracil, methimazole, carbimazole) and multivitamins	1-2 weeks for antithyroid drugs. Note: Beta Blockers can be continued 7 d for multivitamins
Expectorants, agar, Lugol's iodine, potassium iodide ("SSKI")	2-3 weeks, depending on iodide content
Radiographic contrast agents Intravenous (water soluble)	3-4 weeks (assuming normal renal function)
Amiodarone	3-6 monts or longer

Adapted from:
The Society of nuclear Medicine Guidelines (18), Martin A Walter, Matthias Briel, et al. BMJ 2007(26);334;514

Carbimazole and Propylthiouracil

PTU appears to be radioprotective. This effect persists for at least 7 days and for up to 55 days (22). The evidence suggests a reduced efficacy of RAI when patients are pre-treated with PTU (22,23). Unless the drug can be withdrawn for up to 2 weeks prior to therapy, it may be necessary to use a larger dose of RAI to overcome this problem. A dose of up to 555 MBq may be required (24). CMZ however does not appear to have this effect on efficacy of RAI therapy (22,25) as long as the treatment is stopped from 3–5 days prior to therapy (18). A recent meta-analysis suggests that all antithyroid medication should be withheld for at least a week prior to therapy (26). MTZ should be stopped a few days before therapy to improve the outcome (27). Based on the evidence it is compelling to stop PTU for up to 2 weeks prior to therapy and CMZ or MMZ for a few days but preferably 1 week prior to RAI.

Resuming antithyroid medication after RAI therapy

Resuming antithyroid therapy is not associated with an increased risk of recurrence of the hyperthyroid state or progression to hypothyroidism (28) unless given within a week before or after radioiodine where there is an increased failure rate of therapy and reduced the hypothyroidism rates respectively (26). MTZ restarted on the seventh day after RAI had no impact on thyroid function. There was however a difference in the final thyroid gland volume reduction at 12 months, 36% vs. 47%.

Lithium carbonate

Lithium is highly concentrated in the thyroid gland against a concentration gradient, probably by active transport. It induces a marked decrease in the release of preformed thyroid hormone from the thyroid. In higher doses it can also inhibit organic binding reactions (29). The use of lithium carbonate as an adjunctive therapy has been shown to be effective by some authors (30). The effect of lithium is to delay the release of the RAI from the thyroid, thus potentiating its therapeutic effects. Other authors have shown prospectively that lithium use for 3 weeks from the time of RAI compared to a control group without lithium therapy had little effect on cure rate (31).

3. Adverse events of therapy

While it is generally safe to give RAI, patients may experience some side effects of therapy. The risk of eventual hypothyroidism is high, especially after treatment of GD. There can be transient exacerbation of hyperthyroid symptoms due to radiation thyroiditis. Perhaps the most worrying and potentially troublesome is potential worsening of thyroid associated opthalmopathy (TAO) (18).

Thyroid Associated Opthalmopathy

The definition of TAO may vary. Bartley et al. (32) provide the most acceptable definition. Patients with TAO may require specialist assessment (33) to determine the degree of severity, particularly when the prevalence of TAO in a local population was found to be 34.7%, with smokers 2.8 times more likely to have TAO than non-smokers (34,35). The natural history of TAO in GD is somewhat unclear. It may develop before, with or even after the onset of hyperthyroidism (36). It is generally accepted that treatment of thyrotoxicosis with antithyroid drugs does not affect the course of TAO (37) and neither does near-total thyroidectomy (38).

Progression of Thyroid Associated Opthalmopathy (TAO)

One of the more controversial aspects of RAI therapy is whether RAI has any significant impact on TAO. The evidence is conflicting, perhaps related to the early study designs and retrospective nature of these studies. Various non-randomised studies that show exacerbation of TAO following RAI have been quoted; worsening is seen in as few as 3% of patients and as many as 53%. Bonnema et al. (24) discuss various non-randomised studies. The results on randomised studies on this issue are more consistent. These show a worsening of TAO in a proportion of patients. Tallstedt et al. (39) reported similar incidences of progression of TAO after antithyroid therapy (10%) and surgery (16%) but significantly higher rate after RAI (33%).

Bartelena and co-workers were able to prospectively demonstrate that while a number of patients have transient TAO after RAI, 5% have permanent TAO, which required treatment. This is not seen with MTZ therapy or in the group patients who received I-131 and predinisone (40). The patients in this study had mild opthalmopathy (proptosis < 22 mm, intermittent diplopia or none, mild conjunctival or periorbital inflammation). The steroid treatment regime used oral prednisone at 0.4-0.5 mg/kg given daily, starting 2-3 days after RAI therapy and continued for 1 month. The dose of prednisone was then gradually reduced over the subsequent 2 months and stopped.

In another study (41), patients with minimally active TAO were treated with 405±12.9 MBq of RAI. Antithyroid medications were withdrawn prior to therapy. Thyroxine replacement was commenced 2 weeks after I-131. The authors concluded that progression of TAO was not seen following RAI due to early treatment to prevent hypothyroidism.

Hypothyroidism

The issue of risk of developing hypothyroidism has also been discussed earlier under the heading of the optimal dose of therapy. Hypothyroidism rates within the first year are very much dependent on the dose of RAI. The incidence of hypothyroidism after the first year is 2 to 3 percent per year. Hypothyroidism within the first year may be transient. In a study of 260 patients who received radioiodine therapy for GD, 67 developed hypothyroidism within 12 months. The hypothyroidism was transient in 58%. However, 70% of those with transient hypothyroidism became permanently hypothyroid in the subsequent 2 to 11 years (42).

4. Other Issues

RAI and pregnancy

The foetal thyroid at 10–12 weeks of gestation is capable of forming colloid, concentrating iodine, and synthesising thyroid hormones (43). RAI treatment is absolutely contraindicated in pregnancy, because it is readily transferred across the placenta. The damage to the foetal thyroid gland results in hypothyroidism and irreversible mental retardation (44,45). Despite the recommendations for routine pregnancy testing prior to RAI therapy (18,46), pregnant patients are inadvertently given RAI. There are reports of administration of RAI in early pregnancy (45). Radiation exposure in utero is determined by the gestational age, foetal thyroid activity and maternal thyroid uptake (47). Administration of a maximum dose of 15 mCi (550MBq) given up to 10 weeks of gestation does not severely affect foetal thyroid function and the low fetal exposure does not justify termination (48). There is no increase in birth defects or childhood malignancy in children born to mothers who had received radioactive iodine before the 10th week of gestation (49).

Limited evidence suggests that RAI given after 10–12 weeks results in neonatal hypothyroidism or cretinism. Termination of pregnancy may be advocated but dosimetry studies should be performed. If pregnancy is to follow to term, early screening for hypothyroidism is recommended (50).

Cardiovascular outcomes following RAI

A recent study (51) showed that chronic hyperthyroidism and not the treatment modality, is a cause of excess cardiovascular (CV) mortality. This can be attributed to cerebrovascular disease and atrial fibrillation (AF). AF occurs in 5–15% of patients with hyperthyroidism (52). In a large study extending over 40 years (53) most of the excess deaths, which occurred in the first year after treatment, were related to the hyperthyroidism. Other factors contributing to the excess deaths were CV disease and femoral fractures. Radioiodine could not be accountable for the excess morbidity and mortality.

Radioiodine and risk of malignancy

The link between external head and neck irradiation and increased rate of thyroid carcinomas dramatically shown by the Chernobyl disaster of 1986 (54,55), has naturally raised concerns of possible carcinogenic effects of RAI as a source of ionising radiation. Although there are case reports suggesting a link, large epidemiologic studies revealed no association between RAI for GD and subsequent development of thyroid carcinoma (56–58).

The Cooperative Thyrotoxicosis Follow-up Study did demonstrate an excess risk of death from thyroid carcinoma in patients with RAI treated toxic Multi-nodular goitre (MNG). This association raises the consideration of genetic predisposition of those with MNG to thyroid cancer as in those with familial PTC have increased familial incidence of thyroid nodules and MNG (59).

There is no evidence for increased mortality from any other forms of cancer (58,59), including leukaemia (60). A recent cohort study (51) showed increased mortality from cancer (RR1.29) after RAI for hyperthyroidism, with an increased risk of death in patients older than 60 years at treatment. Mortality rose with the amount of RAI given and in those with nodular thyroid disease. There was also a suggestion of increased upper GI cancer in elderly males, but this observation has not been confirmed by other studies.

5. Follow Up of Patients who have received RAI

The efficacy of treatment of hyperthyroidism is best assessed with a Free Thyroxine level (FT4). Serum TSH may remain suppressed for long periods of time, weeks to months even when the patient is clinically euthyroid (61,62). It is important to monitor the patient for evidence of treatment failure or progressive hypothyroidism. Serum TSH should be measured at 6 to 12 month intervals. The patient should be aware that follow up is lifelong. As longstanding hyperthyroidism is associated with AF and osteoporosis (53), clinicians should be vigilant during follow up visits.

Conclusion

Based on current evidence, a fixed dose of RAI is effective to achieve treatment goals. Patients should be on a reduced iodine diet and antithyroid medication should be stopped prior to therapy and resumed one week after RAI if necessary. Patients with mild TAO may benefit from a course of prednisone to prevent worsening or progression of disease. Hypothyroidism need to be detected early and treated to prevent progression of TAO. There is little evidence to support increased risk of malignancy and worsening of CV disease following RAI therapy. Lifelong follow-up is important to ensure that recurrence of disease or hypothyroidism can be treated. In conclusion, RAI is a safe and effective modality for the treatment of GD.

Review criteria

Searching PubMed using the following search terms "Radioiodine for Graves' disease" and " I-131 therapy for thyrotoxicosis" performed a review of the literature". Abstracts and full-text papers published between 1990 and 2008 were the primary source of data. Some older abstracts from the 1960s and 1970s provided additional information.

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Malaysian Journal of Medical Sciences, Vol. 16, No. 1, January - March 2009

ORIGINAL ARTICLE

Labour Induction With Randomized Comparison Of Oral And Intravaginal Misoprostol In Post Date Multigravida Women

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Submitted: 20 February 2007
Accepted: 3 December 2008

Abstract

The efficacy and safety of oral versus vaginal misoprostol for elective induction of labor in post date multigravida with an unfavourable cervix was compared over a period of one year in the Bahawal Victoria Hospital, Bahawalpur, Pakistan. Eightyeight multigravida post date women were divided into two groups and given 50 mg misoprostol orally and 50 mg intravaginally, respectively. The induction to onset of significant uterine contractions and delivery intervals were lower in the first group (7.8 h vs. 8.9 h) when compared to (10.4 h vs. 12 h). The first group had a higher rate of Caesarean section (7% vs. 4%; p>0.05), uterine hyperstimulation (9% vs. 5%; p>0.05), uterine tachysystole (23% vs. 14%; p>0.05) and neonatal admissions to intensive care unit (12% vs. 4%; p>0.05) when compared to second group. Fifty mg oral misoprostol has the potential to induce labor as safely and effectively as the intravaginal route.

***Keywords*:** *Misoprostol, induction, labor, medical sciences*

Introduction

Lingering pregnancy is one of the most common indications of labour induction even though it has been carried out also for other indications of maternal and fetal origin and it has been done for approximately one in six pregnancies exceeding 24 weeks' gestation in the United States (1). Recent studies have suggested that by continuing pregnancy beyond 41 weeks, there is a statistically significant higher perinatal morbidity and mortality as well as an increased risk to the mother (2,3). Attempted induction with an unripe cervix is exigent and seldom results in success (4). Although many methods of preinduction cervical ripening have been anticipated but prostaglandins are the up to date agents of choice (5,6). Many evidences have highlighted the importance of prostaglandins for initiation and normal progress of labour (7) as well as to induce cervical ripening and stimulate uterine contractions at a variety of doses and routes of administration i.e. orally or vaginally (8,9). Misoprostol have been compared satisfactorily with the presently agreed agent dinoprostone in cost and storage requirements. The most advantageous dosing regimen, timing, and route of administration lingered the focus of enduring research (10–12). Misoprostol is a reasonably priced synthetic prostaglandin E1 analogue (13), and its oral administration has obvious appeal because it offers ease and higher patient satisfactoriness and promises outpatient administration if proved safe and effective for cervical ripening and labour induction but it has been studied less comprehensively.

This study was a comparative analysis of the effectiveness and safety of oral misoprostol and intravaginal misoprostol for the use in the process of cervical ripening and inducing labour in multigravida post date pregnancies with a live fetus.

Materials and Methods

This study was conducted from December 1, 2004 until November 30, 2005. Eighty women were selected for the study where 44 were randomized in the oral group (group A) and the remaining in the intravaginal group B. All of the women were recruited at Bahawal Victoria Hospital, Bahawalpur, Pakistan, a 1300 bedded tertiary referral center with an average annual delivery rate of 2500. The Hospital Research Committee approved the study and all participants gave their written informed consent after they had been made aware of the purpose of the study.

Inclusion criteria were those whose age were between 26-40 years, multigravida, accurate dating of gestation, singleton viable pregnancy, gestational age 40-42 weeks, cephalic presentation, unfavourable cervical status defined as a Bishop score (BS) of <6, intact membranes, patient's height more than 150 cm. Exclusion criteria were patients with known contraindications to receiving prostaglandins, placenta previa, previous uterine surgery and any antenatal complications (medical/ obstetrical). The detailed history with general physical examination included vital signs and abdominal examination. A fetal cardiotocographic (CTG) trace to confirm fetal well-being was performed. Digital examination was done to confirm the BS. Baseline investigations included complete blood and urine examination, blood grouping and Rh factor were sent.

Gestational age was estimated by ultrasound biometry via Crown rump length (CRL) measurements in the first trimester of pregnancy in cases where there was more than 3 days difference from that obtained from the last menstrual period (LMP) (14). Uterine tachysystole was defined as >5 contractions of moderate to severe intensity per 10 minutes, uterine hypertonus as when one contraction lasted more than 2 minutes and hyperstimulation syndrome as the presence of non-reassuring FHR tracing combined with either tachysystole or hypertonus (15).

The patients were divided into group A and group B by randomization for induction with oral and vaginal misoprostol, respectively. The randomization was done by opening sequentially numbered opaque envelops containing cards stating the drug for induction. Bishop's score was performed prior to administration of either preparation, if it was less than six; the patient was planned for induction of labour.

Misoprostol of 50 mcg tablet was given orally for induction in group A, and in group B induction was done by placing same dose high in posterior fornix digitally, tablets were repeated after every four hours to a maximum of six doses if there was no uterine activity or if the uterine contractions were less than two mild contractions in ten minutes with the patient being comfortable. Fetal CTG was done to confirm fetal well-being before each close.

When uterine activity suggested the onset of labour, vaginal assessment was performed and the women would be sent to the labour ward. During all the proceeding, maternal vitals were monitored at 4 hours interval. The time of dose introduction, beginning of significant uterine contractions (significant uterine contractions mean 3-5 contractions of moderate to severe intensity in 10 minutes) and delivery was noted. Adequate analgesia (pethidine) was given. Continuous fetal and maternal monitoring and progress of labor was recorded on partogram.

Failed induction of labour was defined as vaginal delivery not achieved within 24 hours of initiating induction of labour (16). The indications for Caesarean section (CS) were failed induction, maternal request after 24 hours of induction, uncontrolled hyper stimulation and fetal distress. The complications faced during induction procedure were recorded carefully and managed accordingly. Paediatrician was called to examine and resuscitate the baby at the time of delivery. Further management of neonates was done accordingly.

The primary outcome measures were time from induction to onset of significant uterine contractions and induction to delivery. The secondary outcomes were the CS rate, the incidence of uterine tachysystole, uterine hyperstimulation and fetal/neonatal complications.

Data were analyzed on SPSS and subjected to descriptive analysis. Z-Test: Two samples for mean were applied to numerical data (interval of induction to significant uterine contractions and delivery) while remaining categorical data was analyzed with Chi-squared test. P-value <0.05 was considered significant.

Results

Mean age in group A was 34.3 as compared to 35.9 years in group B, while mean + standard deviation (SD) of gravidity was 3.6+1.6 in group A and 3.2+1.4 in group B respectively. On the other hand, mean + SD of parity in group A was 2.9+1.1 while group B had 2.4+0.9. In group A 13 subjects (30%) had active labor after insertion of single dose of misoprostol as compared to 12 (27%) in group B. The mean + standard error (SE) of induction to onset of significant uterine contractions interval

was 7.8 +0.6 hours in group A, while 8.9 + 0.5 hours in Group B (p>0.05). Similarly the mean induction to delivery interval was 10.4 + 0.8 hours in group A while 12 + 0.7 hours in group B (p>0.05). Failed induction was little bit less frequent in group A than group B (16% vs. 23%; p>0.05) (Table 1).

There were more subjects with uterine hyperstimulation and tachysystole in group A than group B i.e. (14% vs. 5%; p>0.05) and (23% vs. 14%; p>0.05) respectively but not statistically significant. Caesarean sections were performed in all subjects with uterine hyperstimulation syndrome in both groups. Meconium stained liquor was also found in four subjects in group A (Table 2). There were more neonatal admissions to intensive care unit in group A (12% vs. 5%; p>0.05). Perinatal death was noted in group B due to meconium aspiration syndrome (Table 3).

Discussion

Interest in oral misoprostol for cervical ripening and labor induction is growing day by day (17-21). The present study was the one that compared oral misoprostol with intravaginal in such well homogenized groups. All of the women were multigravida with intact membranes and at more than forty weeks' gestation with no antenatal complications. Our rationale was to identify effectiveness and safety of oral misoprostol regimen with intravaginal regimen. We found that giving 50 mg of misoprostol every 4 hours was as effective and safe as vaginal administration of 50 mg doses every 4 hours, with no significant differences in maternal or neonatal outcomes. Although not statistically significant, in group A we found shorter mean intervals from start of induction to delivery and a higher propensity for vaginal delivery within 24 hours.

Table 1 : Obstetrical outcome

Variables		Group A n=44	Group B n=44	P - Value
Prostaglandin Doses For Active Labor	Single	13(30%)	12(27%)	NS‡
	Two	18(41%)	17(39%)	NS
	Three	6(14%)	8(18%)	NS
	Four	4(9%)	3(7%)	NS
	Five	3(7%)	4(9%)	NS
Interval (Mean ± SE†) (Hours)	Induction to Onset of SUC*	7.8 ± 0.6	8.9 ± 0.5	NS
	Induction to Vaginal Delivery	10.4 ± 0.8	12 ± 0.7	NS
Induction to Vaginal Delivery Interval Detail	<12 hours	20(45%)	18(41%)	NS
	12≥ to ≤24 hours	17(39%)	16(36%)	NS
Mode of Delivery (within 24 hours of induction)	Vaginal Delivery	37(84%)	34(77%)	NS
	C-Section	3(7%)	2(4%)	NS

* Significant Uterine Contractions (3-5 moderate to severe contraction in 10 minutes)
† Standard Error
‡ Non Significant

Table 2 : Complications during cervical ripening

Variables	Group A n=44	Group B n=44	P - Value
Urine Hyper Stimulation	4(9%)	2(5%)	NS
Uterine Tachysystole	10(23%)	6(14%)	NS
Allergic Reaction	2(5%)	2(5%)	NS
Nausea and Vomitting	3(7%)	1(2%)	NS
Meconium Stained Liquor	4(9%)	2(5%)	NS

Table 3 : Neonatal Outcome

Variables		Group A n=44	Group B n=44	P - Value
Birth weight (g)*		2965 ± 430	3073 ± 390	NS
Perinatal death		0	1(2%)	NS
Ambo ventilation		5(11%)	2(5%)	NS
Intubations in labor room		3(7%)	1(2%)	NS
APGAR < 7	1 min	6(14%)	5(11%)	NS
	5 min	1(2%)	0	NS
ICU Admissions	Within 24 hours	2(5%)	1(2%)	NS
	After 24 hours	3(7%)	1(2%)	NS

*Values expressed as mean ± SD

In previous studies, 50 mg of oral misoprostol given every 4 hours was associated with longer intervals to delivery compared with vaginal misoprostol (13, 20). In one Egyptian research, 100 mg of oral misoprostol was administered to 20 subjects, then doubled the dose after 3 hours if there was inadequate clinical response. They compared that regimen with repeated doses of 100 mg of vaginal misoprostol and found greater efficacy but more fetal heart rate and uterine contraction abnormalities with vaginal administration (19).

In our investigation, uterine contractile abnormalities were more frequent in women treated with oral misoprostol, although the abnormalities did not differ significantly from those of women who received vaginal misoprostol. Less than 15% of women who received vaginal misoprostol had tachysystole, which is lower incidence in our experience as in other studies (22-24). The relatively long half-life of misoprostol and its metabolites in maternal serum after vaginal administration also might account for delayed tachysystole in women than those who received the medication orally (14).

On the other hand, if we took into account the neonatal outcome, the oral dose was associated with a higher chance of admittance to the neonatal intensive care unit but this was not statistically significant.

Our limited data supported the use of 50 mg doses of oral misoprostol for preinduction cervical ripening and labor initiation because it had almost same efficacy and safety as its vaginal analogue. Oral route approach offered convenience, higher patient acceptance, ease of administration, and reduction of nursing interventions.

In order to clarify the aforesaid side effects of misoprostol use, it appeared that the adverse effects were not only misoprostol-related but it may be dose as well as dose interval dependent and probably has a large inter-patient variability in terms of pharmacokinetics.

Conclusion

Our results indicated that, in a closely supervised hospital setting with adequate monitoring, 50mg oral misoprostol has the potential to induce labor as safely and effectively as its vaginal route. Additional research is needed to categorically determine the most effective dosing regimens and intervals. We also believe further studies on safety with larger numbers of women need to be conducted before we advocate routine oral misoprostol.

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Malaysian Journal of Medical Sciences, Vol. 16, No. 1, January - March 2009

ORIGINAL ARTICLE

Neuropsychological Assessment In Epilepsy Surgery – Preliminary Experience In A Rural Tertiary Care Hospital In North East Malaysia

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Submitted: 2 October 2008
Accepted: 30 December 2008

Abstract

We present our preliminary experience in neuropsychological testing in epilepsy surgery patients to demonstrate how these tests contributed to decide the laterality of epileptic focus, and to assess the effect of surgery on patient's cognitive function and quality of life. Preoperative neuropsychological tests consisting of Wechsler Adult Intelligence Scale-III (WAIS) for IQ, Wechsler Memory Scale-III (WMS) for memory and patients' quality of life (QOLIE 31) were administered to refractory epilepsy patients under evaluation for surgical treatment. These tests were repeated one year after surgery and we studied any changes in trends. A total of seven patients were recruited in this study between July 2004 and July 2006. The aetiologies of refractory epilepsy were pure mesial temporal sclerosis (MTS) in five patients, dysembryogenic neuroepithelial tumour (DNET) in one and dual lesion of cavernous angioma with ipsilateral MTS in one. The preoperative neuropsychological tests were all in concordance to MRI finding, and showed good contralateral function; five lateralises to the right and two to the left. The post-operative Engel seizure count (median 8.00, IQR 7.00–8.75), general IQ (88 vs. 79), performance IQ (94 vs. 79), verbal memory (89 vs. 71), non-verbal memory (88 vs. 75) and QOLIE (53.14 vs. 44.71) were better compared to preoperative values. The verbal IQ (84 vs. 84) was unchanged. Neuropsychological tests are useful as ancillary investigations to determine the laterality of seizure focus and integrity of function in the contralateral temporal lobe. Following successful surgical treatment, there is a trend towards improvement in memory, IQ and quality of life scores in this small group of patients.

***Keywords*:** *Neuropsychological tests, epilepsy surgery, Wechsler Adult Intelligence Scale-III (WAIS), Wechsler Memory Scale-III (WMS), Quality of Life in Epilepsy-31 (QOLIE 31), neurosciences*

Introduction

The concept of epilepsy surgery is based on the principle that there is a localized abnormality in a part of the cerebral cortex that acts as epileptogenic foci. The success of the procedure would therefore depend heavily on accurate multimodal preoperative evaluation (1,2,3,4,5,6) and on confirmation by identification of a structural lesion of the cortex (7,8). Neuropsychological tests are standard pre and postoperative assessment for Epilepsy Surgery (9) to assess the temporal lobe function of both the affected and sides (10,11). It helped to predict the functional outcome postoperatively (12,13), and the preoperative test result were used for baseline value to compare to that of the post-operative.

The aim of this study is to evaluate the role of neuropsychological tests in the screening of refractory epilepsy patients, to determine the laterality of seizure onset and degree of functional loss of the contralateral temporal lobe, to look for changes of neuropsychological tests postoperatively and lastly, to observe the impact of surgery on patient's cognitive function and their quality of life.

Materials and Methods

This is a prospective, observational pilot study conducted from July 2004 to July 2007 in Hospital University Sains Malaysia (HUSM). All refractory epilepsy patients were evaluated for their suitability for surgical management by performing the following screening tests: scalp electroencephalogram (EEG), video EEG, brain MRI and neuropsychological evaluation using the WAIS-III, WMS-III, and Quality of Life in Epilepsy (QOLIE 31) scale. Surgery was offered to patients with precise electroclinico-radiological concordance, and with good contralateral lobe memory functions.

Patients with dual pathological lesions were only offered surgery if they were ipsilateral lesions. The surgery that was offered to patients includes lesionectomy, anterior temporal lobectomy (ATL) and amygdalahippocampectomy (AH) or combination of them. All patients were followedup at three monthly interval and seizure frequency and any complications were recorded. Neuropsychological tests were repeated at one year following surgery and any differences in the scores compared to preoperative values were investigated. No statistical tests for significance were done due to a very small sample size.

Results

There were seven patients that completed one year follow up, four males and three females. All except one were right-handed. The patients' age at surgery ranged between twelve years to forty-seven years (29.00 ± 12.2). Age of seizure onset ranged from four to twenty five years old (16.33 ± 12.5) and the duration of seizure between 3 and 43 years (12.67 ± 5.8).

The aetiologies of refractory were pure mesial temporal sclerosis (MTS) in five patients, dysembronic neuroepithelial tumour (DNET) in one and dual lesion of cavernous angioma with ipsilateral MTS in one. Total of three hippocampal volumetry studies were in agreement with the diagnosis of right MTS (right 1780.67 ± 344.18 vs. left 2516.33 ± 104.46) and showed same lateralization by scalp, video EEG and neuropsychological test results. At the same time, the MRI brain showed no atrophy on the contralateral side nor any additional lesion.

Preoperative neuropsychological assessments results are tabulated in Table 1. It compares the neuropsychological assessment results with reference to the site of lesion detected on the MRI. The verbal IQ (84.4 ± 7.23) was better than the performance IQ (81.2 ± 10.21) in patients with pathological lesion on the non-dominant (rightsided) hemisphere. Similarly, their verbal memory (82.2 ± 19.82) was better than non-verbal memory (43.2 ± 4.15). Their verbal memory (43.0

Table 1 : Comparison between preoperative verbal IQ and performed IQ based on side of lesion

Side of Lesion	IQ (Verbal)		IQ (Perform)		Memory (Verbal)		Memory (NonVerbal)	
	Right	Left	Right	Left	Right	Left	Right	Left
1		89		87		46		62
2	77		79		43		71	
3	78		73		45		62	
4		78		79		40		77
5	84		77		49		71	
6	94		78		38		102	
7	89		99		41		105	
Mean	84.40	83.50	81.20	83.00	43.20	43.00	82.20	69.50
Std. Deviation	7.232	7.778	10.208	5.657	4.147	4.243	19.817	10.607
Minimum	77	78	73	87	38	40	62	62
Maximum	94	81	99	87	49	46	105	

± 4.24) was worse than nonverbal memory (69.5 ± 10.60) in patients with pathological lesion on the dominant (left-sided) hemisphere. Poor verbal scores indicate lesion in left temporal lobe and poor nonverbal scores indicate lesion on the right side. In all the cases, there was good concordance with both MRI and neuropsychological lateralization.

The follow-up neuropsychological testing for our series was done at one year postoperatively as outlined in Table 2. The postoperative general IQ (median 88.00, IQR 78.00–97.00) is higher compared to preoperative general IQ (median 79.00, IQR 76.00 –88.00). The postoperative verbal IQ (median 84.00, IQR 82.00–97.00) is equal to preoperative verbal IQ (median 84.00, IQR 78.00–89.00). The postoperative non-verbal memory (median 88.00, IQR 81.00–91.00) is higher compared to preoperative non-verbal memory (median 75.00, IQR 57.00–80.00). Lastly, the patients' survey on quality of life postoperative QOLIE (median 53.0, ± IQR 46.0–62.0) values showed modest improvements when compared to the preoperative values (43.0 ± IQR 40.0–49.0).

In this study, the patients' seizure scores drastically improved postoperatively, five (71.42%) of the patients became seizure free (ILAE outcome seizure score of 1) while the other two had only occasional simple partial seizure (ILAE outcome seizure score of 3). Similarly the postoperative seizure count when translated into "Engel Seizure Count" showed marked improvement of the patients' seizure counts. The postoperative Engel counts (median 2.50, IQR 2.00–3.00) is lower compared to preoperative Engel counts (median 8.00, IQR 7.00–8.75).

Discussion

Neuropsychological testing plays a significant role in preoperative investigations for localizing and lateralizing the epileptogenic region. One important contribution is its predictability to determine the pathological side. Patients with left-sided lesions have been known to exhibit poorer verbal memory compared to the non-verbal component. This is the basis where neuropsychological testing can help further in lateralizing the lesion (12,13). The preliminary results in this investigation clearly indicate a trend demonstrating this. Patients with left-sided lesions had lower scores in verbal memory than non-verbal memory (43.0 vs. 82.2). Similarly, those with lesions situated on the right-side performed poorer in non-verbal tasks than in verbal tasks. Memory testing also contributes to the assessment of the functional integrity of the contralateral lobe. Should testing suggest severe memory and language deficiencies in the contralateral hemisphere, the risk of developing postoperative memory and language impairment are high.

Table 2 : The results for all the neuropsychological testing of pre- and postoperative result. The highlighted are result for patient whom undergone left sided surgery. Med= Median, IQR=Interval Quotient Ratio, Min=Minimum, Max=Maximum.

	IQ (Verbal)		**IQ (Perform)**		**Memory (Verbal)**		**Memory (NonVerbal)**		**QOLIE 31**			
	Pre Op	Post Op	Pre Op	Post Op	Pre Op	Post Op	Pre Op	Post Op	Pre Op	Post Op	Pre Op	Post Op
1	88	78	89	73	87	87	62	50	88	91	46	62
2	76	88	77	84	79	94	71	94	75	97	43	57
3	74	78	78	72	73	89	62	77	57	88	45	53
4	77	78	78	82	79	75	77	80	57	81	40	53
5	79	86	84	83	77	91	71	86	53	81	49	64
6	87	96	94	97	78	94	102	89	75	84	38	37
7	94	97	89	97	99	100	105	99	80	88	41	46
Med	79.0	88.0	84.0	84.0	79.0	94.0	71.0	89.0	75.0	88.0	43.0	53.0
IQR	76.0 - 88.0	78.0 - 97.0	78.0 - 89.0	82.0 - 97.0	77.0 - 87.0	89.0 - 100	62.0 - 102	80.0 - 97.0	57.0 - 80.0	81.0 - 91.0	40.0 - 49.0	46.0 - 62.0
Min	61	77	77	72	73	75	62	77	53	81	38	37
Max	102	97	94	97	99	102	105	99	88	91	57	64

The general IQ of these 7 patients assessed postoperatively (median 88.00, IQR 78.00–97.00) were better than the preoperative results (median 79.00, IQR 76.00–88.00). Three of the five patients rendered seizure-free following surgery had remarkable increase in IQ points on the side contralateral to the surgery. In a retrospective study by Engman et al. (14), 25 patients with epilepsy who underwent ATL resection demonstrated significant increments in IQ scores after medium-term followup. However, at long-term follow-up, these scores declined, returning toward baseline figures. Longterm follow-up on the patients in our study as well as increasing the sample size would allow the observation on whether these improvements in general IQ will revert to baseline values as shown by Engman et al. (14). Uncontrolled refractory epilepsy patients have been shown to have progressive intellectual decline. Though it is well known that following surgery, the neuropsychological test results of the resected side is slightly poorer compared to the preoperative value, the exact opposite occurs to the non-resected side so that the overall memory and IQ performance show improvement (1,9,15,16). Our results are in agreement with those from other studies (14).

It is well-documented that medicallyrefractory patients who underwent epilepsy surgery reported improved quality of life. In this study, slight improvements were observed (43.00 vs. 53.00) in overall quality of life with patients indicating improved confidence in both cognitive and social functioning and decreased anxiety.

In conclusion, our initial results suggest that neuropsychological tests are helpful in lateralizing the lesion with very high concordance to MRI finding. Following successful surgery, general IQ, performance IQ, verbal and non-verbal memory as well as the QOLIE are all showing a trend towards improvement.

Acknowledgements

We would like to thank Prof Jafri Malin Abdullah who initiated the Epilepsy Surgery Programme in the Department of Neurosciences, Hospital Universiti Sains Malaysia. He was also nvolved in the surgery of 2 patients in this reported group.

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ORIGINAL ARTICLE

A Pilot Study On Percent Free Prostate Specific Antigen As An Additional Tool In Prostate Cancer Screening

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Submitted: 20 February 2007
Accepted: 3 December 2008

Abstract

A cross sectional pilot study was carried out to look into the usefulness of percent free prostate specific antigen (fPSA) in the diagnosis of prostatic cancer in HUSM patients. All patients who attended surgical clinic and admitted to surgical wards with signs and symptoms of prostate problems during the study period were taken as the study subjects. Total prostate specific antigen (tPSA) was estimated by immunoassay technique and those values of 4 ng/mL or more were proceeded for estimation of fPSA. Using the cut-off value of less than 25% fPSA for diagnosing patients with prostate cancer, our study showed that majority of the prostate cancer patients have a ratio of fPSA:tPSA more than 25% and a significantly higher level of total prostate specific antigen (P<0.005) when compared with patients with benign prostatic hyperplasia (BPH). Unexpectedly, the fPSA values were high in patients diagnosed as prostate cancer compared to BPH. Ratio of percent fPSA to tPSA was found not to be sensitive and specific, in diagnosing prostate cancer at the cut-off value of 25%. In conclusion, total PSA is a more useful biochemical test for diagnosing prostate cancer in our patients.

***Keywords*:** *Percent free prostate specific antigen, total prostate specific antigen, prostatic cancer, medical sciences*

Introduction

Prostate Specific Antigen (PSA) is a protein manufactured solely in the prostate. The prostate glands manufacture this protein in large quantities. The PSA level in the blood can vary by about 20% from day to day (1). The Food and Drug Administration (FDA) in 1994 approved serum PSA to be used as an early detection of prostate cancer. Like so many serum tumour markers, it is produced by both normal and cancerous glands. In men with prostate cancer, the serum levels can be elevated in both localized and advanced or disseminated disease. PSA levels are generally proportional to the size of the tumour. However, there is a significant overlap between PSA levels found in cancer and benign prostatic hyperplasia cases (BPH) (2).

The introduction of free PSA (fPSA) testing has introduced a greater level of specificity in identifying early prostate cancer (3,4). In 1998, the FDA approved fPSA testing as a diagnostic aid for men with total PSA (tPSA) values between 4.0-10.0 ng/mL. In men without prostatic cancer, the ratio of fPSA / tPSA is more than 25%. A ratio of less than 25% is found in men with prostatic adenocarcinoma (5).

The usage of ratio of fPSA to tPSA as a tool for prostate cancer screening has not been introduced in this hospital. This could be due to lack of local evidence on the usefulness of fPSA as a screening tool for prostate cancer. This pilot study was thus, carried out to determine the benefits of introducing the test in HUSM.

Materials and Methods

A cross-sectional study was carried out beginning October 2006 until the end of December 2006 whereby all patients who attended surgical clinics and admitted to surgical wards with symptoms and signs of prostate problems were screened for PSA.

Patients' samples were initially analyzed for tPSA and results of tPSA of more than 4.0 ng/mL were further analyzed for fPSA. Total PSA and fPSA were measured using immunoassay method. The ratio of fPSA to tPSA (%fPSA) at a cut-off value of 25% was taken to suggest prostatic cancer (PCa). The clinical findings of these patients were noted and examined for correlation with the %fPSA. Statistical analyses using t-independent test were performed to investigate the potential utility of %fPSA or its combinations with tPSA in discriminating between BPH and PCa. PCa was confirmed by prostate biopsy.

Results

A total of 100 serum samples were analyzed for tPSA. The mean age of these patients were 68.2 and ranges from 45 to 90 years of age. Out of the 100 samples, 50 were noted to have serum tPSA results of more than 4.0 ng/mL. These samples which were further analyzed for fPSA had the percentage ratio ranging from 6% to 90% with a mean of 24.4% (Table 1).

Based on the 50 serum samples analyzed for fPSA, 8 samples were from patients diagnosed as PCa and 39 samples were from patients diagnosed as BPH. The other 3 serum samples were from patients diagnosed as other cancers. Table 2 shows the number of cases of PCa and BPH when 25% cut-off value of %fPSA was implemented.

Table 3 shows the means of tPSA, fPSA and %fPSA were significantly higher in patients with PCa as compared to patients with BPH ($p < 0.05$ for all the three assays), especially for the fPSA. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at 25% cut-off value of %fPSA were 50%, 41%, 14.8% and 80.0% respectively.

Discussion

Total PSA (tPSA) is comprised of free PSA (fPSA) and complex PSA. Although it has been used as an aid in early detection of prostate cancer (PCa), it is not an ideal tumour marker (6) as it lacks specificity to diagnose PCa. Because of this lack in specificity, many researchers have tried using free and complex PSA to improve the clinical value of PSA.

Different methods to differentiate PCa from BPH have been developed such as using human glandular kallikrein which displays a structural homology to PSA (7), PSA complexed to a1-antichymotrypsin (8) and the use of percentage fPSA (9,10).

Free PSA constitutes approximately 20% of the total PSA, and is found to be in abundance in patients with BPH (6). In PCa, fPSA:tPSA ratio has been recommended as an effective tool for screening (9). The ratio, expressed in the form of percentage, enhances the specificity of PSA testing

Table 1 : Range, median and mean of Prostate Specific Antigen measured in study samples

Group	Parameter	Mean ± SD	Median	Range
Total Serum Samples (N=100)	tPSA (ng/mL)	13.54 ± 21.95	4.00	1.0 — 101.0
Samples with serum tPSA > 4ng/mL (N=50)	tPSA(ng/mL)	24.84 ± 26.68	13.00	4.0 — 101.0
	fPSA (ng/mL)	6.24 ± 10.29	3.00	1.0 — 51.0
	%fPSA	24.46 ± 15.61	21.50	6.0 — 90.0

Note: tPSA = total prostate specific antigen
fPSA = free prostate specific antigen
%fPSA = the ratio of free to total PSA in percentage

Table 2 : Final diagnosis of the patients based on cut-off value of 25% fPSA [Benign prostatic hyperplasia (BPH), prostate cancer (Pca) and others cancers (Others)]

%PCa	No of Patients (%)			
	PCa	BPH	Others	Total
<25%	4 (8)	23 (46)	2 (4)	29 (58)
>25%	4 (8)	16 (32)	1 (2)	21 (42)
Total	8 (16)	39 (78)	3 (6)	50 (100)

Table 3 : The means of tPSA, fPSA and %PSA in prostate cancer (PCa) and benign prostatic hyperplasia (BPH) patients.

Parameters		Mean ± SD	Median	Range
tPSA(ng/mL)	**PCa**	49.50 ± 34.66	3.249	0.002
	BPH	19.26 ± 21.44		
fPSA (ng/mL)	**PCa**	19.75 ± 20.57	4.747	0.000
	BPH	3.67 ± 3.49		
%fPSA	**PCa**	37.38 ± 30.69	2.576	0.013
	BPH	22.36 ± 9.67		

for prostate cancer detection. A lower percent fPSA is associated with a higher probability of PCa (11). In our laboratory, percent fPSA is not used to aid the diagnosis of prostate cancer, perhaps due to lack of local evidence that support this notion.

This pilot study looked into the common biochemical tests used such as tPSA and fPSA and their usefulness in diagnosing and differentiating between PCa and BPH in our surgical patients.

In our study, tPSA which is used widely seems to be the most useful indicator in differentiating between PCa and BPH whereby the mean tPSA was significantly higher ($t = 3.249$, $df = 45$, $P<0.005$) in PCa compared to BPH.

Free PSA values in patients with PCa were also noted to be significantly higher ($t = 4.747$, $df= 45$, $P<0.001$) than in patients with BPH resulting in higher fPSA:tPSA ratio in PCa patients.

When the cut-off value of 25% fPSA was implemented to differentiate between PCa and BPH, %fPSA was found to be neither sensitive nor specific for diagnosing PCa. Free PSA and %fPSA failed to discriminate efficiently between PCa and BPH. An attempt to look at different cut-off value also failed to produce significant results. Other researchers, however, published contradictory results (6,12) whereby a cut-off value of fPSA below 25% was found to be associated with PCa.

In conclusion, the results of our study indicate that only tPSA is useful as an indicator of PCa. However, since many research found that a combination of tPSA, fPSA and %fPSA results could aid in diagnosis and provides an opportunity to reduce the demand for biopsy in doubtful cases of PCa, this study may need to be extended to include larger sample size involving other centers (9,11,13). It is recognized that the small sample size, especially the PCa patients involved in this study could be the main reason why the results were not significant. Although this study did not look at complex PSA, this option should be considered in future studies as an alternative tool in diagnosing PCa.

Acknowledgements

We would like to acknowledge the cooperation given by all the Chemical Pathology laboratory staff in helping us out with the samples received. We would like to thank Roche for supplying fPSA kit for this study. Finally we would like to acknowledge PPSP for the funding that we got through the incentive grant to permit us with this work.

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Malaysian Journal of Medical Sciences, Vol. 16, No. 1, January - March 2009

CASE REPORT

A Gluteal Mass Of Langerhans Cell Histiocytosis Mimicking Malignancy In A Two-Year-Old Boy: A Case Report

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Submitted: 20 February 2007
Accepted: 3 December 2008

Abstract

Langerhans cell histiocytosis is a disease primarily affects the bone. More than 50 percent of the disease occurs between the age of 1 and 15. We reported a case of a 2 year old boy who presented with a gluteal mass. Radiographic imaging showed an osteolytic lesion suspicious of malignancy. However, the histological diagnosis was Langerhans cell histiocytosis.

***Keywords*:** *Langerhans cell histiocytosis, gluteal mass, medical sciences*

Introduction

Langerhans cell histiocytosis (LCH) affected 5.4 million children per year. The disease peaks at age 1 to 4 (1). Bone involvement with or without other associated sites is the most common manifestation of LCH, It has been observed in 80–100% of cases (1). Langerhans cells are a member of the dendritic cells family. The cells are believed to arise from multipotent bone marrow stem cells, which are efficient antigen-presenting cells for Tcell mediated immunity (1). Bone involvement of LCH is characterized by expanding erosive accumulation of Langerhans cells usually within the medullary cavity of bone. The aetiology and pathogenesis of LCH remain largely obscured. Fortunately, most cases demonstrate a favourable natural history without treatment (1). Radiologically, the destructive radiographic appearance of lesions may mimic the radiographic appearance of primary bone infection or sarcoma, such as Ewing sarcoma and osteosarcoma (1). For this reason, LCH is sometimes referred to as the "great imitator." Therefore, it must be definitively differentiated from malignancy. The aim of this paper is to highlight the importance of LCH in the ifferential diagnosis of an osteolytic lesion in children.

Case Report

A two year-old boy presented with two weeks history of a left gluteal swelling associated with pain, a visible limp and mild fever. He had a fall while playing, two months prior to the swelling. On examination, he had a mild fever of 37.4°C but otherwise well and active. There was a diffuse and mildly tender gluteal swelling measuring 7 cm by 4cm. The range of movement of the left hip was reduced. Examinations of other systems were unremarkable.

Radiological investigations showed an osteolytic main bone lesion at the left ilium and a small lesion in the skull with features suspicious of malignancy. Biopsy led to the diagnosis of Langerhans cell histiocytosis. Immunohistochemical study showed positivity towards S100 and CD1a which confirmed the diagnosis. The patient was later commenced on chemotherapy with prednisolone and vinblastine. He responded well to the treatment. About 1 year after the diagnosis, he is ambulating with no residual limp.

Discussion

Skeletal involvement is one of the most common features presented in LCH which can occur in any bone. In this case, the patient presented with multifocal unisystem LCH. The age group and clinical presentation were consistent with the diagnosis.

Plain radiographs and MRI are the most useful mode of radiological investigation in predicting the nature of osseous disease. Aggressive pathological features with ill-defined margins, bone cortex destruction and soft tissue mass were present (Fig. 1). Hence, malignant diagnosis was seriously considered. However, radiological diagnoses can only suggest whether a lesion is of an aggressive nature or otherwise. Aggressive lesions do not necessarily indicate malignancy as benign bone diseases like LCH and osteomyelitis can also present with similar appearance (2).

On histology, features of LCH were distinctive (Fig. 2). Identification of only a few cells with the above histological appearance in any of these sites not necessarily means that the patient has LCH (3). Significant sizable number of cells needs to be present before the diagnosis can be entertained as exemplified in this case. LCH can also be diagnosed by fine needle aspiration cytology (4).

The diagnosis of LCH is based on the clinical features, histopathology, and special immunohistochemical techniques. For a definitive diagnosis, identification of Birbeck granules and CD1a antigens are required. Electron microscopy for Birbeck granules could not be performed in this case due to practical constraint.

Laboratory studies are rarely helpful in LCH. We did not encounter eosinophilia. Immunoglobulin levels and tests of cellular immunity are usually within normal limits.

Treatment is directed by the clinical situation. The more aggressive approaches are used in patients with more extensive multisystem involvement (1). Surgical curettage, radiotherapy and chemotherapy can be used alone or in combination. Curretage is commonly performed for unifocal involvement. For a multifocal unisystem involvement, many patients experience spontaneous regression and other can be successfully treated by chemotherapy (5). Recurrence rate depend on the treatment method and location of the lesion. It was reported to range from 1.6% to 25% and patients should be closely followed up for a long period of time (6).

Clinical prognosis of patients with LCH will become worse with the growing number of organs involvement, number of organ dysfunctions, rapid disease progression and limited treatment response. Probably the most significant prognostic factor is the number of involved organs (6).

In conclusion, LCH presentation may closely resembles features of malignancy. Therefore, it should always be considered in a case of paediatric osteolytic lesion.

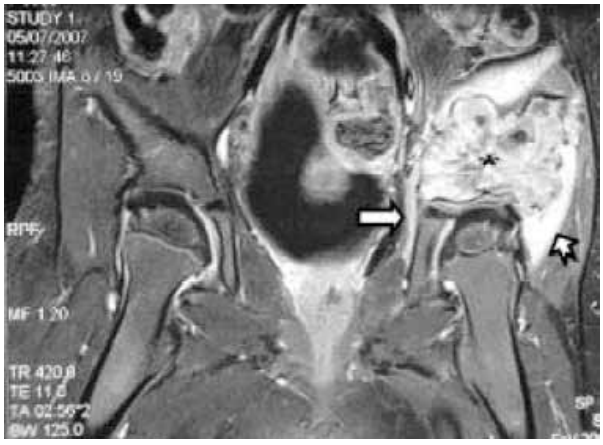

Figure 1: Gadolinium enhanced T1WI MRI in coronal plane showed avidly enhancing left iliac tumor mass (*) with involvement of the left gluteus medius muscle laterally (solid arrowhead) and the left obturator internus muscle medially (arrow). These features are highly suggestive of malignancy.

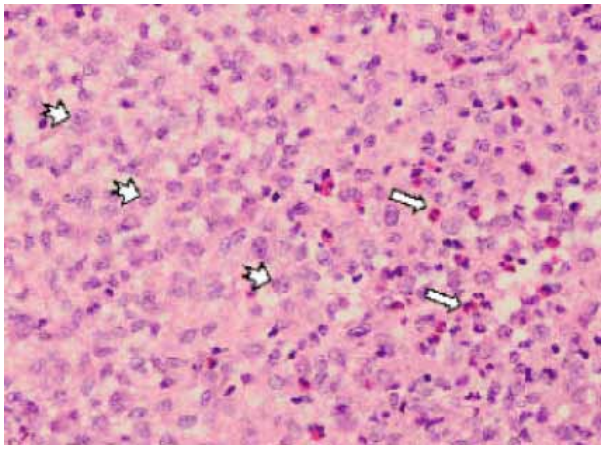

Figure 2: Biopsy revealed Langerhans cells histiocytosis with irregular nuclear margin, nuclear grooving and nuclear indentation (arrow heads) with abundant cytoplasm. There was eosinophils infiltration (arrow).

Acknowledgements

The authors wish to thank the Director of Sarawak General Hospital, Dr Mohd Zulkarnaen A.Narihan, Dr.Dayangku Norlida A.Ojep, Dr Manjubala Talekar, Dr Jamil Dolkadir and Dr. Jacqueline Wong Oy Leng for their contribution in the writing-up of this case report.

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> 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**:21-30.

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

Books

Author 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:
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> Reid R, Bulusu R, Buckels J, Carroll N, Eatock M, Geh I et al. Guidelines for the management of gastrointestinal stromal tumors (GISTs). Sept 2005. [Internet]. Available from:http://www.augis.org/news/articles/gist%20mngmnt%20gdlns%20071205%20final.pdf

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1. Council of Science Editors, Scientific Style and Format. The CSE Manual for Authors, Editors and Publishers. 7th ed. Reston (VA): The Council; 2006.
2. The Chicago Manual of Style. 15th ed. 2003.
3. ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication [Internet] Available from: http://www.icmje.org/

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