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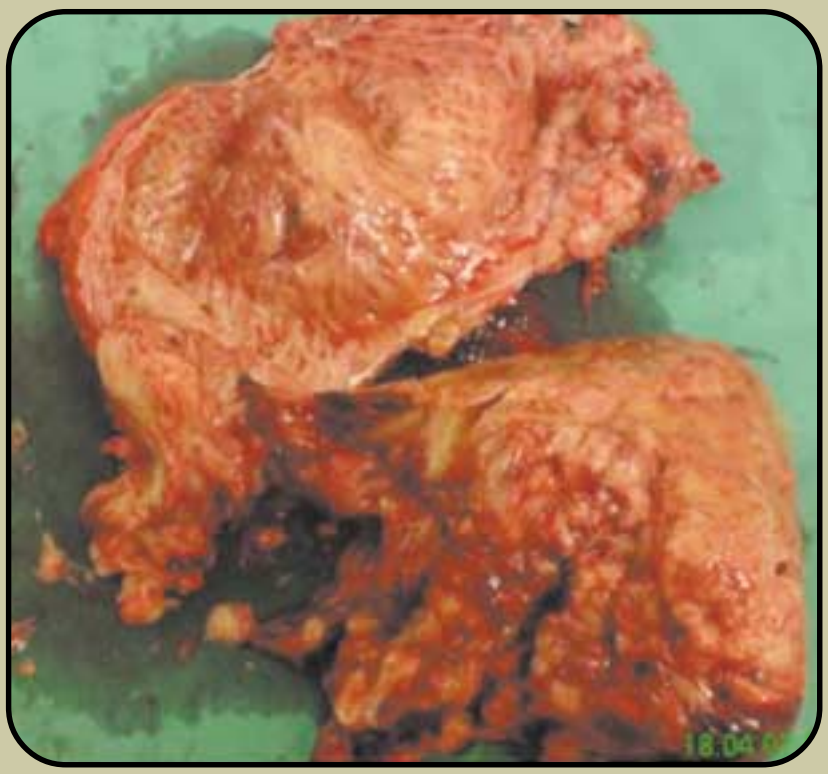

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Cover

Lesion in the bladder cavity and solitary site of tumour invasion
(courtesy of Dr Shanggar Kuppusamy, Division of Urology, Department of Surgery, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia)

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LEADERSHIP IN HEALTH ORGANISATIONS

Leadership and management in health organisations are essential and frequent topics of discussion among professionals and other staff, who are directly or indirectly involved with the operation of the said organisations. In a hospital setting for example, managers are appointed at different functional or unit levels. Though more often than not, we refer to them as the heads or managers or by any other names, the leadership component might be assumed to be just part but not the most important aspect of their roles. A vivid picture of the typical hospital managers' regular tasks would be like the planning and budgeting meetings they have to chair, listening to the frustrated statements expressed about the lack of staff for the existing services; what more with the plans to expand additional services, thinking about the contractors who had abandoned the projects for additional facilities, wondering how to pacify the chairman of the board of management as a result of the complaints in the local papers... the list goes on.

Leadership is more than management. Leaders set the vision of the organisations they are in charge of, then plan the correct strategies, get the change process going, and produce the results as envisioned. Since leadership is a dynamic process, leaders need to create a balance between the needs of staff members, the divisions within and the organisations' goals.

Are leaders born or made? Need leaders be intelligent, charismatic, trustworthy and adopt specific or a combination of leadership styles to be successful? Leadership style is one of the relevant topics in this issue of JUMMEC. The question asked is whether leadership style and organisational success are inter-related. In a study conducted by Khatijah (1) on the leadership style of three employees with leadership responsibilities in a hospital setting. They are interviewed on leadership behaviours followed by a self administered leadership questionnaire. Each of the participants' colleagues is asked to voluntarily express their perception on his/her leadership style. The individuals want to be transformational but the responses are more characteristic of transactional style. Barriers such as organisational culture, inter-professional dynamics and lack of leadership development are cited as the obstacles. The author concludes on the joint responsibilities for both the employees and the organisation to develop the leadership styles and its facilitation respectively.

Public health initiatives on coping with menopause are recommended and necessary as shown by a study that examines the level of knowledge and perception of menopause among young to middle-aged 15 to 49 years Malaysian women by Wong and Liyana (2). A cross-sectional survey, questionnaire-based is conducted in three randomly chosen districts. The result shows that subjects are aware of the meaning of the term menopause and its symptoms but lacked comprehensive understanding about the health risks associated with menopause. Part of the study looks at the major source of information on menopause where magazines and family members play major roles compared to official sources from health care personnel. The respondents display positive thinking towards menopause though combined with feelings of sadness and nervousness upon its approach.

A cancer predominantly affecting paediatric patients, Rhabdomyosarcoma is reported in an adult by Shanggar, Muhilan, Dublin, *et al* (3). It occupies the bladder producing specific complications. The report covers the unusual CT and macroscopic appearance, followed by the literature review and a discussion on management strategies.

In a case study by Lim and Tan (4), the salvage therapy used for severe Systemic lupus erythematosus (SLE) is Intravenous Immunoglobulin (IVIG). The authors highlight the efficacy and safety of high dose IVIG in SLE patients with multi-organ involvement particularly, lupus nephritis and reviewed literature on the usage of IVIG for lupus nephritis. It is recommending for more studies to determine the optimal therapeutic dosage plus the regime for IVIG. Patient groups for therapy need to be identified too.

The trend towards community-based care in psychiatry is reported in this study by Tan, Nor Zuraida, Mohamad Omer *et al* (5). The treatment of schizophrenia through deinstitutionalisation as compared to hospitalised patients reflects a growing trend. This cross-sectional study compares the two groups and measures the levels of depression and function, as depression is prevalent among Schizophrenia patients. The assessment tools used were the Calgary Depression Scale for Schizophrenia (CDSS) and Global Assessment of Functioning scale (GAF). The important finding is that the community-based services is seen to

be more effective than long stay in-patient services in preventing depression and promoting better functional levels.

From clinical medicine on to rehabilitation medicine, the latter comprehensively optimises patients' function and health. International Classification of Functioning, Disability and Health (ICF) by World Health Organization (WHO) is a conceptual framework for assessment of these patients. Lydia and Nazirah (6) describe the applications of ICF at the University of Malaya Medical Centre, Kuala Lumpur. ICF categories though exhaustive are not applicable and practical in entirety and have to be adopted to be usable, especially in research, clinical practice and as tools in education. However, it is agreed to be an essential tool in addressing disability among professionals and for communication between stakeholders.

It has been proven that rectal delivery of drugs is effective in terms of drug absorption and distribution, comparable to other routes. Noordin and Chung (7) developed two new suppository bases using combinations of locally sourced hydrogenated palm kernel oil, hydrogenated palm kernel stearin and hydrogenated palm kernel olein with mixtures of stearic acid and glyceryl monostearate. These bases produce suppositories with acceptable characteristics when combined with aspirin. A study was conducted using the aspirin suppositories on twelve healthy subjects. The authors quantified aspirin from the urine samples (the excretion of salicylic acid) of the subjects to determine the relative availability of the different suppository preparations relative to an oral dose. The results showed that these palm kernel oil blends are suitable suppository bases.

This current issue of *JUMMEC* contains a wide and balanced range of subjects from the study on leadership to clinical and rehabilitation medicine which would be very useful for all readers.

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THE TRANSITION FROM SAMPLE TO POPULATION EPIDEMIOLOGY

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ABSTRACT: This review is based on analysis of original research reports in one 2006 volume from each of three major epidemiology journals: The American Journal of Epidemiology, The International Journal of Epidemiology, and the European Journal of Epidemiology. A total of 149 research reports were included in the review. The pattern that emerged from the analysis was the tendency towards large epidemiological studies that utilise all available population-based data without resort to sampling. The tendency was to use data in existing data bases instead of field data collection. Developments in information technology enabled linkage between various data bases to extend the range of hypotheses that could be tested. The transition from sample epidemiology to population epidemiology had advantages and disadvantages. The main advantage was external validity (results of the study were applicable to the population). The main disadvantage was loss of internal validity that could be achieved in small studies with higher data quality and personal familiarity of the epidemiologist with the data. It is envisioned that in the future web-based data collection will be feasible. It will also be possible to use a wider range of data routinely collected online on citizens including credit card, shopping, and other financial transactions. (JUMMEC 2007; 10(2):3-15)

KEYWORDS: Birth cohort, defined population, data linkage, large data set

Introduction

Epidemiological research is moving in several directions. One of the most exciting being the transition from research based on population samples, using subjects counted in the tens or low hundreds, to the start of large population-based studies, using subjects counted in thousands and millions.

The preference for large studies was either motivated by editorial policy or was motivated by the fact that authors increasingly submitted large studies. The connection between the two motivations is undeniable. There were, however, small studies with subjects in the low 10s that got published because of their quality (1) but these were an endangered species.

A theoretical discussion can be made about what the main driver of the new epidemiology is. Is it a desire for large studies (possible only with use of large data bases) or is it availability of large data bases (no need for sampling since the population data can be analysed easily)? My inclination is to the latter option because large studies are way above the minimum study size required for statistical validity.

Three epochs in the development of epidemiological research in relation to data collection can be identified. The pre-1950 epoch can be called sample epidemiology because studies were based on data collection from samples with the attempt being made to make the samples as small as was compatible with statistical validity. The number of subjects was in the tens or low hundreds which minimised the cost of epidemiological research. The second phase, 1950-1980, witnessed larger studies using cohorts and defined population groups that became increasingly easy to assemble because of developments in information technology. The third epoch starting about the year1980 witnessed the emergence of a brave new world of epidemiological research using large population and health data bases with the number of subjects counted in the hundreds of thousands. By the early 1980s, information technology had developed to the level that

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epidemiologists could study the whole population without the need to sample or use specific cohorts. That was the birth of what I want to call population epidemiology. The transition from sample to population epidemiology, with serious practical and theoretical implications, has produced an arm chair epidemiologist who designs and analyses large data studies using information from data bases many of them already online.

I am proud of having witnessed the birth of population epidemiology. I was in the generation of epidemiologists who in the early 1980s made the transition from using hand calculators to desk top personal computers for data analysis. The newly developed information technology led to far-reaching changes in the practice of epidemiology. Epidemiologists realised that basic socio demographic and health-related data about the whole population was collected routinely and was stored unused in government and non-government electronic data bases. They also realised that the new information and communication technology could enable them identify and follow up research subjects as well as collect data from and/or about them without even meeting them physically. The ability to link various data-bases enabled assembling data on a single individual from several data bases and to carry out arm chair *adhoc* research. A new era for epidemiology had dawned.

Before the information age, we distinguished between the field epidemiologists (who collected and analysed data) from the arm chair epidemiologists (who dabbled in theoretical epidemiology) and did not want to 'dirty' their hands with field data collection. Today, arm chair epidemiologists collect and analyse data while sitting in their offices.

Methodology of the review

Original research reports that involved data collection and analysis were identified in volume 163 of the *American Journal of Epidemiology*, volume 35 of the International Journal of Epidemiology, and volume 21 of the *European Journal of Epidemiology*. The following basic characteristics of each report were abstracted: type of study design (cross-sectional, case control, and follow up), type of study population (defined group, general population, and ongoing study), type of data collection (new data collection, routinely collected data, previously collected data), and total study size. The mean number of subjects was computed for each grouping of research reports. The computations were carried out separately for studies below 100,000 and those above 100,000 subjects. Excluded from the computation of means were research reports based on large national populations like that of the US.

Statistical Results of the Review

The mean number of subjects in birth cohorts at enrolment was 13,614. Table 1 shows the mean number of research subjects according to study design and data collection methods for the rest of research reports. The data shows a tendency towards large studies above 1000 research subjects.

Table 1. Statistical results of the review: mean number of subjects

		Mean (for no. of subjects <100,000)		**Mean (for no. of subjects >100,000)**	
		Defined groups	**Population**	**Defined groups**	**Population**
Cross-sectional	Newly collected	2,627	10,275	6,240,130*	-
	Routinely collected	810	13,963	-	925,704
	Previously collected	1,245*	1,067	-	-
Case Control	Newly collected	1,840	1466		-
	Routinely collected	1,330	1628	1,194,357	-
	Previously collected	-	-	-	-
Non-birth Cohort	Newly collected	4,038	-	246,146*	-
	Routinely collected	28,293	31,164	1,299,177*	-
	Previously collected	56,214*	-	-	-
Randomised	Newly collected	3186*	-	-	-

* Based on a single research report

Sample Epidemiology

To understand the brave new world of population epidemiology, we need to remind ourselves of the erstwhile sample epidemiology. In this review, the word population is used in its true meaning of referring to a large number of humans and not in its statistical meaning that refers to a set of objects (humans, non-humans, or events) with a common observable characteristic or attribute.

Before the information age, epidemiologists made other researchers envious because they could get information easily from small samples and could make inferences about the general population at minimal expense. Sampling for survey research underwent a lot of change since it was first introduced in the closing years of the 19th century. Sophisticated sampling methods and theories were developed to ensure that sample-based inferences reflected population reality. Statistical analytic techniques suitable for small samples (the student *t* test and Fisher's exact tests) were developed for analysis of very small samples because large sample statistics did not give valid answers. The vision was to be able to reach valid inferences using hand calculators and from the smallest sample possible.

In the early period, there was no alternative to small samples. Sophisticated data management and data analysis software capable of handling large data sets were not yet available. Epidemiologists preferred sample to population studies because data collection from a sample was logistically easier and financially more cost effective (the biggest impact from the least expenditure in terms of manpower, time, and money). Data from samples was considered more accurate and of higher quality because the epidemiologists had a smaller number of research subjects to work on and could have 'personal' knowledge of the research subjects and their data. This knowledge could enable epidemiologists spot inconsistencies and errors in the data. It could also enable them identify potential confounders more easily and realistically.

A sample was supposed to be a representative subset of the population but this might not be true in practice and disastrous conclusions could result as happened in the US presidential election of 1936 (2). Sampling started by defining a sampling frame which was enumeration of the population by sampling units (a technical term for individuals to be sampled). The arduous task was assembling the sampling frame; the actual sampling being thereafter relatively easier.

At the beginning simple random sampling was used when the population was approximately homogenous. It was realised that simple random sampling did not perform well in representing various sub-groups of a heterogeneous population. Stratified random sampling was developed to make sure that that the eventual sample correctly represented the population heterogeneity. In this type of sampling the population was divided into approximately homogenous groups and simple random sampling was carried out in each group separately with the samples derived being combined to make the study sample. Other techniques used to improve the practical logistics of random sampling were: sampling with unequal probabilities (if it was desired to over-represent one segment of the population), systematic sampling, cluster sampling, and multi-stage sampling. Development of computer technology and existence of databases on local and area wide networks make simple random sampling much easier because construction of sampling frames became easier and databases over long distances could be sampled and analysed while sitting at one's office desktop computer.

Probability theory enabled inferring sample data to target population. Probability theory also enabled assessment of precision and avoidance of bias in sample selection. If the sample was selected at random and if the assumptions of the central limit theorem held, sample data represented accurately the underlying population probabilistic events and sample distribution corresponded to the population probability mass function or the probability density function. Relationships found in samples were inferred to be the same as those in the population and sample data was used to predict population parameters. The validity of inferences based on samples was not questioned for a long time however a few doubts did surface for example extrapolation from sample to the general population was found to be unreliable empirically (3).

Concern about precision and bias was always a nagging problem in sample epidemiology for fear that public health decisions based on sample data might not reflect the reality in the population. Despite all measures taken to ensure that samples accurately represented population experience, epidemiologists were aware that sampling errors and sampling biases were inevitable. Statistical theory and practice therefore, developed to characterise and measure the magnitude of sampling errors and sampling biases and thus be able to assess their impact on the conclusions from data analysis. The accuracy of estimators could be expressed as a function of sample size, population size, and probability characteristics. It was therefore, obvious that the larger the sample the more precise were the estimates. The problem of precision was addressed by giving effect measures with 95% confidence intervals quoted around them to indicate the degree of precision. The larger

the sample size, the narrower the confidence interval, and hence the higher the precision. There reached a point at which further gains in precision were not worth the expense of increasing sample size. Techniques for dealing with bias (confounding, misclassification, and selection biases) were developed to prevent bias at the design stage or cure it at the analysis stage.

Epidemiological studies based on birth cohorts

Birth cohorts were used over the past half-century to provide longitudinal and cross-sectional information (at 'sweeps' carried out every few years). The primary motivation was mostly from governments that wanted to obtain data for formulating health policies (4, 5). The study of birth cohorts enabled understanding the natural history of morbidity as well as the longitudinal relationship between risk, disease, and health-related behaviours (4). Theay could have the advantages of being national in representation if recruited from the general population (5, 6). They had the advantage of longitudinal data collection (5) which enabled linkage of childhood experience with adult disease outcomes (4). Data quality was high because of trained and experienced researchers (5) who worked on the same study for years. Comparisons among cohorts enabled studying secular changes in risk factors and disease outcomes as well as the relationship between the two. Usually cohorts generated more data than the investigators desired or could analyse. There were therefore, a lot of data archives that could be mined by later researchers. Data from birth cohorts was increasingly available to other researchers (7) sometimes on online for free or at a fee (4).

Table 2 shows details of birth cohorts covered in this review. The cohorts were recruited as babies born in a certain week of a year in the whole country (4), a city (6), or a part of the country. The cohorts were followed up until adulthood. Data was collected either from the whole cohort or from a sample (5). Collection from the whole cohort was preferable to sampling (8). Birth cohorts could also be animals for example a birth cohort of cattle was studied to investigate BSE (9).

Table 3 shows the range of information collected from birth cohorts. Data collection was more frequent in infancy and childhood but less frequent in adulthood (5). Data was collected by postal questionnaires (5), interviews by trained researchers (5) or by telephone. In many cases, information was obtained directly from data bases of routinely collected administrative, vital, and health data. This was possible because of data linkage using unique identifying numbers enabled assembling data from population registers, disease registers, pharmacy records, hospital records, conscript data, and death registers (7, 10). Some cohorts were based solely on data linkage for example the Stockholm Birth Cohort Study of 1953. Linkage to parents' data was also done (10). Record linkage also enabled tracing from anonymized records by matching certain variables (10, 11).

The main cause of loss to follow up was change of address by participants who failed to notify the study administration of their new address (4). A second cause was refusal to participate at subsequent sweeps. Death was a minor but expected cause of loss to follow up. A few were lost due to emigration.

Recorded losses to follow up were small. In 2004, 16,078 members were traced; this represented 91% of the 17,634 recruited in 1958 in the British Birth Cohort (4). At age 53, 82.6% of the original 1946 British Birth Cohort was contacted and they provided

Table 2. Studies of birth cohorts

Authors and Ref	Years	Place	Title	No of Subjects
1. Wadsworth *et al.* (5)	1946	UK	1946 National Birth Cohort	16,695
2. Leon. (11)	1950-	UK	The Aberdeen Children of the 1950s Study	12,150
3. Osler *et al.* (7)	1953-	Denmark	The Metropolit 1953 Danish Male Birth Cohort	12,270
4. Stenberg *et al.* (10)	1953-	Sweden	The Stockholm birth cohort of 1953	15,117
5. Power *et al.* (4)	1958-	UK	1958 British Birth Cohort	17,000
6. Elliott *et al.* (12)	1970-	UK	1970 British Birth Cohort	17,287
7. Victoria *et al.* (8)	1982	Brazil	The 1982 Pelotas (Brazil) Birth Cohort Study	5,914
8. Inskip *et al.* (6)	1998-	UK	The Southampton Women's Study	12,579
			Mean	13,614

Table 3. Data collected from birth cohorts at various phases of the life cycle

Ante-natal:	Socio economic data, socio demographic data, maternal smoking, maternal hypertension, labour and delivery, ante-natal care.
Infancy:	Birth weight, perinatal morbidity, neonatal morbidity
Early childhood:	Nutrition, immunisation, anthropometry, morbidity, development (physical and cognitive), education
Later childhood:	Morbidity, Behaviour, Anthropometry, Vision, Psychological assessment, Development: cognitive, education
Adolescence:	Morbidity, behaviour, anthropometry, vision, development, puberty, education
Young adulthood:	Morbidity, vision, psychology, anthropometry, smoking, alcohol, physical exercise, education, work fertility, contraception, sexual practice, health KAP
Middle age:	Reproductive history, emotional problems, morbidity, nutrition, cardiovascular assessment, respiratory assessment, anthropometric assessment, cognitive assessment, mental health assessment: depression, midlife/menopausal issues, neurological assessment, hearing, life style: alcohol, smoking, drugs, religious practice; health seeking behavior: exercise; vision; hearing; work; partnerships
Others:	Environment, health services utilisation

information (5). The Stockholm Birth Cohort of 1953 had an attrition rate of only 4% (10); this being explained by the ability to trace persons using large databases. The Aberdeen Study was able to trace 99% of the original cohort using government records (11). Losses to follow up due to refusal were also low. In the 1958, British birth cohort refusal rates were 7.1% at age 23, 11.1% at age 33, and 13.2% at age 42 (4). Follow up of children in the Southampton study was 95, 93, 86, and 81% at 6 months, 1 year, 2 years and 3 years respectively (6). Losses due to death in the 1946 British Birth Cohort were 8.7% at age 53 (5). Losses due to emigration were 8.6% (5) and to living abroad were 2.2% (5). Problems of attrition progressively lessened over the past twenty years because of availability of government or health insurance records about citizens that enabled tracing those who had changes addresses. Some information about those lost to follow up could still be obtained from data bases such as those of health insurance (5), cancer registries (5), and population registers.

In the pre-1980 era, fewer variables were collected because the work was manual and too much data could not be handled efficiently. Limited funding sources could also have contributed to limiting the amount of information collected. With availability of information technology and more funding as the value of cohort data was appreciated by funding sources, more data was collected. However, not all of the data was collected directly from the cohort participants. Researchers had access to population and health data bases and using various forms of data linkage could obtain information on cohort participants.

Data collection over a long period spanning decades had its own problems. It was difficult to maintain consistency of the data for accurate longitudinal analysis because the type and may be the quality of data collected could change with time. The relevance of some forms of data could also vary with socio-demographic changes and development of biomedical knowledge. Over long periods of follow up of up to 50 years, administrative and scientific responsibility for the cohort changed from one institution to another accompanied by changes in procedures (4). The coverage and objectives of the study could also change in response to new scientific knowledge or social and lifestyle changes in the community. In some cases, cohorts were abandoned and some were revitalised later when funding became available and new interests developed (11).

The frequency and intensity of follow up varied according to availability of funding (8). Funding sources changed as interest in the cohort waned or grew (4). Funding agencies could develop fatigue in funding a study running over decades (8).

The impact of cohort studies on policy was profound (4). This is not surprising because this was their raison d'etre. They also influenced health knowledge and practice by their voluminous publications. As of 2006, a total of 900 publications issued out of the 1958 British

Birth Cohort (4). As of 2006, a total of eight books had been published from the 1946 British Birth Cohort (5). The 1953 Stockholm Birth Cohort Study generated more than 100 publications (10). The 1970 British Birth Cohort generated over 300 publications (12).

Epidemiological Studies Based On Defined Groups

Defined groups were used by epidemiologists to study disease consequences of specific exposures. Defined groups were opportunities of getting data from a captive population that was easy to reach. They were identified based on geographical / political units or a defining characteristic of relevance to health. Epidemiologic opportunism was used when participants in a previous study were identified as a defined group for new research (13, 14).

Many studies were based on groups defined on the basis of geography or institution. The Framingham Heart Study based on a middle class cohort in the town of Framingham in Massachusetts USA, was one of the most famous geographical cohorts. The Mexico City Prospective Study involved following up 150,000 adult men and women aged 35 years to study risk factors of mortality (15). The Guangzhou Cohort Study followed adults and collected biological samples (16). Several ways of assembling and studying cohorts were used. Some cohorts were assembled by linkage of databases (17). Some cohorts were recruited at a significant event such as entry into school (18). Geographically defined groups were often rural or urban communities (19, 25). Disease outbreaks on isolated islands provided opportunities to study a whole community (26). The information obtained was useful for outbreak control and also for further analysis of other epidemiological hypotheses.

Military groups were studied because of good military record keeping. Studies were made of military recruits, conscripts, volunteers (27, 29) and war veterans (30, 31). Educational institutions were used because of ease of subject identification, access, and follow up. Research was carried out in schools (32, 35) and universities (36). Civil servants were a very stable and a cooperative group (37) liked by researchers. Occupational groups with unique exposures were explored at low cost such as textile factories (38, 39) and pesticide workers (40). Research was based on groups that experienced an event of health importance such as birth (41) or travel overseas to disease endemic areas (42). Studies were carried out on population groups with unique characteristics such as homosexuals (43), and members of HIV clinics (44).

Health facilities such as physician clinics provided a good opportunity for recruiting study subjects (45, 46). Networks of general practitioners collaborated by providing research data on their patients (47, 48). Some of this data was available in databases (49, 50). Data was also obtained from prenatal clinics (51, 52) and obstetric practices (53). Expectant mothers provided a stable pool of subjects who could be observed over a period of time and whose children could be recruited into cohort studies. Research was also based on patients on the ward (54, 55).

Health insurance organisations (56) and health maintenance organisations (57, 58) recruited a large number of participants counted in the thousands and had records on them spanning a long period of time. They had a lot of routinely collected data that could be analyzed to test hypotheses about healthcare delivery systems. Health related data was obtained from hospital admission records (59, 61), hospital discharge records (62), and other hospital data (63, 64). Hospital medical record departments were a rich source of data that was not exploited because of missing and incomplete information. Use of medical records may need to be supplemented by interviews (65) to obtain the missing information. Biological specimens like blood were collected from visitors to health centres (66), hospitals (67), blood donation centers (68).

Completed or on-going cohort studies have been used as a convenient source of study subjects for new studies. This practice is becoming a regular feature of research (69, 70). Recruitment of research subjects from other studies is facilitated by availability of data on socio-demographic and biomedical variables. Even more important is availability of contact information and familiarity of the subjects with being participants in research.

Epidemiological Studies based on the General Population

Large data studies attempted to collect information from the general population. This process was very daunting in the past when the decennial census was the only population-wide data collection undertaken. With availability of extensive data bases on social, health, and demographic variables about whole cities, districts, or even nations, collection of data from the general population has become an armchair exercise. Population-based research could be analysis of data from national health surveys (71). Such data was collected at great expense and was stored with minimal analysis. It was better for a researcher with a new hypothesis to analyse existing data than to go out to collect new data. Data covering several countries was obtained from international organisations such as the United Nations and the World Health Organization (72). Such data enabled study across many countries

of death rates (73), cancer incidence rates (74), and morbidity rates (75). Case control studies had been touted as having the advantage of getting information using a few subjects counted in the tens but the new era witnessed population-based case control studies with thousands of subjects (76, 86).

Studies were based on registries of diseases such as stroke registers (87), cancer registers (88, 89, 90, 91, 92), myocardial infarction registers (93), and congenital anomalies registers (94). Prescription data bases (95) could be linked with other data bases to explore many interesting hypotheses. Subjects identified from the electoral roll (96) could be recruited into research projects.

It was a bureaucratic paradox that a lot of socio-demographic and health-related data (census, vital statistics, and routine healthcare data) was collected at great expense with limited benefit. The data was a mine of information that researchers should have used to learn about health and disease in populations. Only a few statistics were usually published for administrative purposes. There were, however, some attempts to make use of that data. Using vital statistics data, analyses were made of death records (97, 104). Health data collected in the general population census contributed to public health (105). Disease notification and surveillance data was analysed (106, 111). With the ease of data access from databases, it was not surprising that one study might obtain data from more than one source for example data from vital statistics could be combined with data from a survey (112). Existing records of previously collected data were exploited with new analyses or repeat analyses using either new techniques or testing novel hypotheses. Analysis of historical data (113, 114) provided information on disease and risk factor trends.

Data linkage became an increasingly dominant mode of research. It enabled studying causal relations while controlling for a wide range of potential confounding variables. Vaccination data was linked to hospitalisation data (115, 116). The population register was linked with the psychiatry register (117), the multiple sclerosis register (118), social insurance data base (119), and mammography screening data (120). Birth data was linked to mortality data (121, 122) and health records (123). Census data was linked to mortality data (124, 125). Military data was linked to occupational, hospital, and death data (126, 127) as well as to population data (128). Autopsy records were linked to police records (129). Reproductive outcome data was linked to occupational data (130).

Even the random sample had a renaissance with many publications mentioning population-based random samples that were often very large (131). This was because the logistics of data collection were easier with large population-based data bases that supplied the sampling frame (132). Random samples were taken from towns (133), and population registers (134, 139), and schools (140). In the age of sophistication, reports of convenience samples were published (141) showing that old habits die hard.

The environment became a subject of intense political interest and spawned many studies. Existence of continuous environmental monitoring systems contributed to large data epidemiology. Studies were based on linking routinely collected environmental data with routine health data (142, 149).

Future frontiers

We can extrapolate into the future of population epidemiology. Web-based data collection will become common. Other data sources like credit card data will be used. Video recording of signs will be possible by video cameras attached to personal or laptop computers. Small hand held laboratories may be mailed to people in their homes and they may put biological samples like urine or saliva for analysis with the results being transmitted online to the data center. Some of these ideas look like science fiction today but could well become the daily reality within a few years.

Using online data collection may open up new frontiers but few epidemiologists so far have experience of virtual world research. A feasibility study of web-based questionnaires was carried out in Sweden (150). It investigated differences in response between a group invited to answer a web-based questionnaire and another group invited to answer a paper questionnaire. The web-based questionnaire had a higher response. There were no significant differences in socio-demographic and health-related variables between the two groups of responders. The investigators concluded that web-based questionnaires were a feasible tool for data collection in large population based epidemiological studies.

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THE APPLICATIONS OF INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY AND HEALTH (ICF) BY WORLD HEALTH ORGANIZATION (WHO) IN REHABILITATION MEDICINE PRACTICE

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ABSTRACT:
Context: Rehabilitation Medicine is dedicated to optimise patients function and health in the most comprehensive manner. ICF, the latest International Classification by World Health Organization (WHO) is a conceptual framework for the assessment of functioning, disability and health. The purpose of this paper is to describe the applications of ICF in Rehabilitation Medicine practice in the Medical Rehabilitation Unit, University of Malaya Medical Centre (UMMC), Kuala Lumpur. ***Issues:*** ICF consists of body function, structure, activity, participation and environmental factor. ICF categories are exhaustive, but are not practical to be used entirely and not applicable in clinical practice on their own. How is ICF used from the clinical perspective? It has to be adapted to make it usable. In Rehabilitation Medicine settings, the following are ways ICF is applied in clinical practice: research in terms of validating the use of available ICF Core Sets and development of new ICF Core Set; clinical practice based on the ICF-based sheet; and educational tools. ***Conclusion:*** The practice of Rehabilitation Medicine is in line and compatible with the concept of ICF and can serve as a new important language that can improve the practice of Rehabilitation Medicine. It can be a universal language in functioning, disability and health and can improve understanding in addressing issues on disability within the medical community, improve multi professionals' communication among patients, healthcare providers and stakeholders. *(JUMMEC 2007; 10 (2):16-21)*

KEYWORDS: ICF, Clinical application, rehabilitation medicine

Introduction

The work on International Classification of Functioning, Disability and Health (ICF) has generated worldwide interest including here in Malaysia. It has provided a platform for international collaboration in research for academic excellence and clinical practice. ICF is a multipurpose classification designed to serve the various aspects of health. ICF belongs to the 'family' of International Classification developed by World Health Organization (WHO) (1). The collaboration work on ICF in Malaysia started in 2004 spearheaded by the Department of Rehabilitation Medicine, Faculty of Medicine, University of Malaya (UM), the official study centre for ICF in Malaysia.

Rehabilitation Medicine is dedicated to optimise patients' function and health in the most comprehensive manner. Rehabilitation Medicine is the medical specialty concerned with the diagnosis, evaluation and treatment of persons with limited function as a consequence of disease or injury. It has been recognised as an integral component of modern health care and is one of the recent medical specialties emerging in Malaysia. It is fairly established in many parts of the world, especially in developed countries. Rehabilitation is a dynamic process that aims to: *limit impairment*, decrease activity limitation (*disability*) and prevent participation restriction (*handicap*). Rehabilitation management is dedicated to optimise not only patients but other factors that may influence patients' well-being or health. Attention is given to potentially disabling behaviours and

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environmental factors that can increase disablement. At the same time, attention is also given to potentially beneficial behaviours and environmental factors that help to minimise symptoms and disability. It involves identification of problems and needs, the relation of problems to impaired body functions and structures and factors of the person and environment. In rehabilitation practice, patients can present with arrays of problem, e.g., medical issues, diagnostic issues, psychological issues and functional issues. It is thus necessary to set priorities by selecting target problems, define goals and to get a realistic time frame to achieve them. Rehabilitation should start early. The rehabilitation cycle can be summarised as follows:

1 Phase 1: Evaluation
   (a) Identify problems and needs

2 Phase 2: Goal-setting
   (a) Define treatment targets
   (b) Relate problem to modifiable and limiting factors

3 Phase 3: Delivery of rehabilitation management
   (a) Select appropriate measures
   (b) Plan, implement and coordinate intervention

4 Phase 4: Assess effects and re-evaluate

The perspective of functioning and health is different when viewed from the medical and the rehabilitation perspectives. From the rehabilitation perspective, a patient's function and health are associated with but not merely a consequence of a condition or disease. Furthermore, functioning and health are not only seen in association with a condition but also in association with personal and environmental factors and the rehabilitation context. From the medical perspective, functioning and health are seen primarily as a consequence of a disease or condition. Measures are thus typically disease-specific. Health indicators have traditionally focused on the mortality and diagnosis of the disease (2). While these are important data, they do not adequately capture health outcomes of individuals or populations. Diagnosis alone does not explain patient's ability or disability. Other information such as level of care, cost of treatment, discharge destination and functional outcome can only be postulated inaccurately from the diagnosis. The previous conceptual frameworks in the field of disability by WHO was the International Classification of Impairment, Disabilty and Handicap (ICIDH). In ICIDH, the framework illustrate a unidirectional interaction between the disabling process which in the true sense, is multidirectional. The classification did not include personal and environmental factors as part of disabling process. Therefore, it was not comprehensive and the term used (e.g., handicap) are also negative. Hence, WHO has developed a new classification known as International Classification of Functioning, Disability and Health (ICF) to provide an improved version and common framework for health outcome assessment. This paper aims to describe the applications of ICF in Rehabilitation Medicine practice in the University of Malaya Medical Centre (UMMC), Kuala Lumpur.

International Classification of Functioning, Disability and Health (ICF)

ICF is a multipurpose classification designed to serve various aspects of health. ICF belongs to the 'family' of International Classification developed by World Health Organization (WHO). It was endorsed in May 2001 by the World Health assembly and replaced the International Classification of Impairment Disabilities and Handicap (ICIDH). The ICF was designed to record and organise a wide range of information about health and health related issues in standardised common language thereby facilitating communication about functioning, disability, health and health care across the world. Its specific aims can be summarised as follows:

1. to provide a scientific basis for understanding and studying health and health-related states, outcomes and determinants;
2. to establish a common language for describing health and health related states in order to improve communication between different users, such as patients, health workers, researchers, policy-makers and other stake holders;
3. to permit comparison of data across countries, health care disciplines, services and health conditions; and
4. to provide a systematic coding scheme for health information systems.

ICF is a comprehensive conceptual framework for assessment of function, disability and health. The ICF has two parts, each containing two separate components. Part 1 covers Functioning and Disability and includes the components: body function (b) and structures (s) and activities and participations (d). Part 2 covers Contextual Factors and includes the components: environmental factors (e) and personal factors. The abbreviations (b), (s), (d) and (e) are used in the ICF coding system. Body functions are the physiological and psychological functions of the body system. Body structure represents the anatomical parts of the body, such as organs, limbs and their components. Activities and participations are given in the ICF in a single list that covers the full range of life area, from basic learning or watching, to composite areas

such as interpersonal interaction or employment. Environmental factors consist of the physical, social and attitudinal environment in which people live and conduct their lives. Personal factors are of an individual's life and living and comprise features of the individual that are not part of the health states. These factors may include gender, race, age, marital status, habits and many others. The personal factors are not yet classified in the ICF. The total ICF categories listed is 1454.

ICF categories are exhaustive and not practical to be used on its own. It has to be adopted to make it practical and usable for clinical practice and research across all specialties and disciplines (3). The ultimate aim is to make ICF meaningful and can be utilised by various consumers for health policy, quality assurance and outcome evaluations. In view of this, the ICF Core Sets were developed by a multiprofessional team of The ICF Research Branch Munich of the WHO Collaboration Centre of the Family of International Classifications at the Ludwig-Maximilian University, Germany, together with the Classification, Assessment and Survey (CAS) Team at WHO, with partner's organisation around the world including Malaysia (4).

The Application of ICF in Rehabilitation Medicine at the UMMC, Kuala Lumpur

Research

1 Validation of available ICF Core Sets

ICF Core Sets are an abbreviated list of the ICF categories. They are developed with the intention of making the ICF feasible in clinical practice, research, education or any other prospective areas for it to be use. To implement the ICF in medicine and other fields, practical tools need to be developed.

ICF Core Sets are the shorter version of ICF designed specifically to be used to assess the functioning and disability levels of a specific condition. Currently, ICF Core Sets have been developed for 12 common health conditions as follows:

(a) Low back pain
(b) Chronic widespread pain
(c) Osteoarthritis
(d) Osteoporosis
(e) Rheumatoid Arthritis
(f) Chronic Ischemic Heart Disease
(g) Obstructive Pulmonary Disease
(h) Diabetes Mellitus
(i) Obesity
(j) Depression
(k) Stroke
(l) Breast cancer

The use of ICF Core Sets in clinical practice, is currently undergoing multicentre validation testing worldwide.

2 Development of New ICF Core Sets

ICF Core Sets are being developed for many other conditions commonly seen in Rehabilitation Medicine practice such as spinal cord injury (SCI), traumatic brain injury, amputation and few others. These involved three main stages:

(a) Worldwide Expert Survey
This involved expert from various health professions (therapists, social officers, nurses, etc) and physicians with different specialisations to identify relevant issues in the ICF for the selected condition. This process is known as the Delphi exercise. Following this, the ICF Core Sets are derived for the condition.

(b) Worldwide Empirical Study
The ICF Core Sets that have been developed is then tested on patients for validation purpose. All WHO regions are involved in data collection. For example, in the development of ICF Core Sets for spinal cord injury patients, 40 individuals with SCI in early post-acute rehabilitation and 40 individuals with SCI in the chronic/post-acute rehabilitation were involved. The ICF Core Sets that have been developed is then tested on the patients through direct interview. The study designed is a cross sectional multicentre international validation study.

(c) Worldwide Qualitative Study
The final stage involves a qualitative study in each WHO region of the specific condition. These involved conducting Focus Group or individual interviews with patients in different settings. The patients that were selected were of the 12 conditions mentioned earlier. The aim was is to examine patients problem in subsets including in different countries, social economic factor (age, gender and other variables) disease characteristics and patients' outlook to their disease.

Based on the biopsychosocial model of functioning and disability by WHO, the rehabilitation assessment is of the most comprehensive assessment that follows this model. The ICF-based Sheet (Figure 1) is designed by the research team in Munich using the components of ICF. The sheet summarises the components of ICF. In UMMC, the ICF-based Sheet is used during

Clinical Practice
ICF-based Sheet

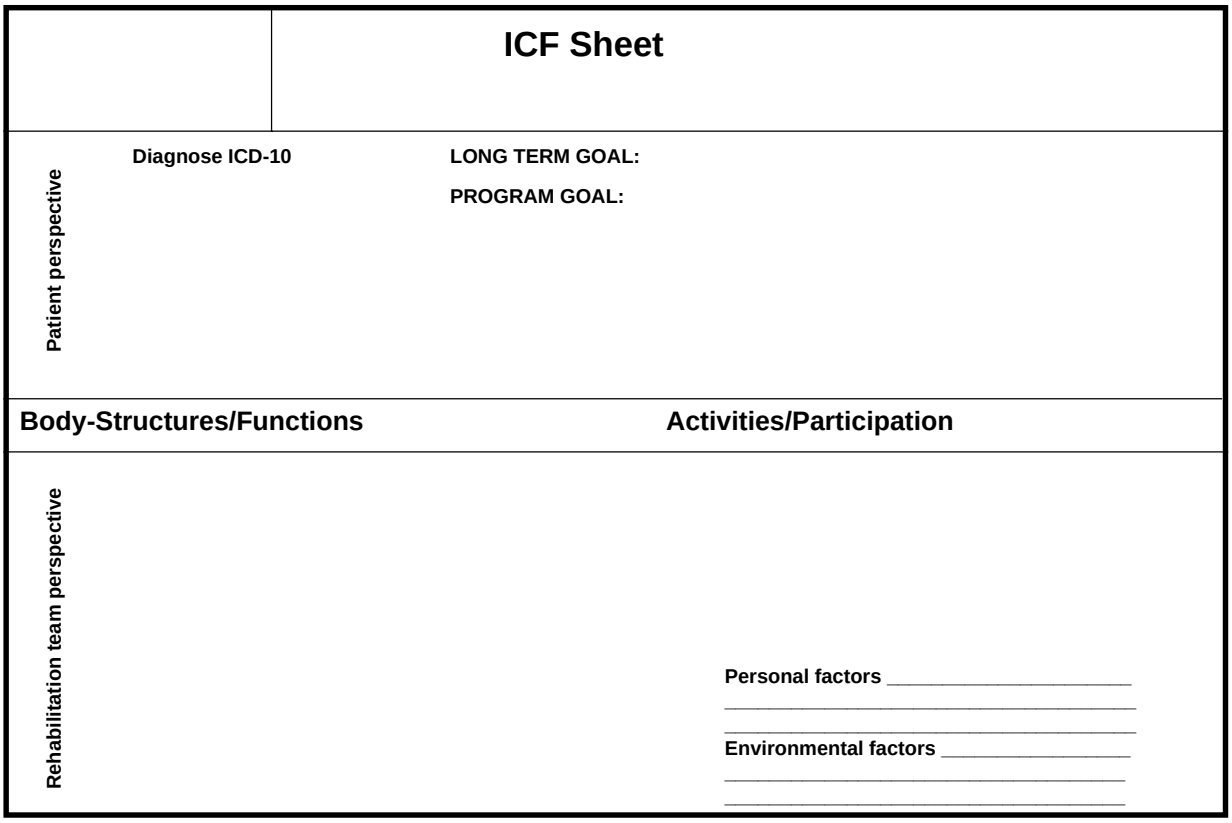

Figure 1. ICF-based Clinical Sheet. Obtained with permission from the ICF Research Branch, Munich

interdisciplinary team meeting of the Rehabilitation Medicine unit. The interdisciplinary team members include the Rehabilitation Physician, Medical Officers, Nurses, Physiotherapist, Occupational Therapist, Prosthetist and orthotist, Medical Social Workers and other relevant members. Using the ICF-based sheet it is easy to determine: what are the patients' problems from his and hers perspective, what are the patients' problems from the rehabilitation team's perspective and to determine the target problem. Figures 2 and 3 illustrate the use of the clinical-based sheet and the relationship of the ICF components in a patient with low back pain with radiculopathy due to discogenic pain. Using the form, it is easier to understand the relationship of patient's symptoms, body structures/function, activity limitation and participation restriction. Apart from these, it can also determine personal and environmental factors that are related to the target problem as shown. Following the assessment as illustrated in the clinical sheet, hence it is easier for the rehabilitation team to determine the treatment goals. Finally, with the completed sheet, the coding of the ICF can be applied.

The ICF-based Sheet is also used in case summary to describe level of functioning of the patient and also in case report of the Masters' students. This clinical sheet can be used across diseases and conditions. ICF-based sheet is currently being used in the Medical Rehabilitation Unit of the University of Malaya Medical Centre, Kuala Lumpur.

Education

The concept of ICF is used to teach and promote the issues of functioning and disability to student, health care professional and others. The concept is easily understood during the teaching of rehabilitation medicine especially to the medical student. Using the ICF, the definition of terms describing impairment and disability are clearer. It gives a clearer description on the level of functioning of the patients. The staff and students are encouraged to use the proper terms when describing patients' level of functioning. Furthermore, when the students write case reports, they are

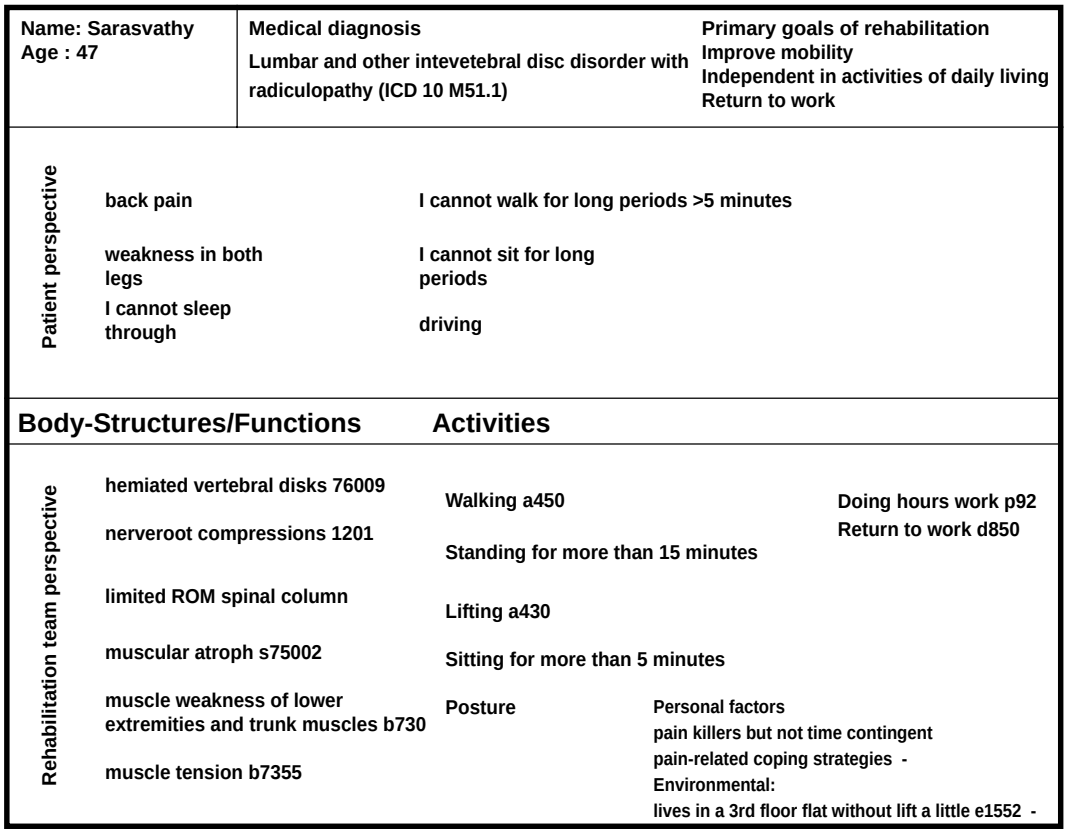

Figure 2. ICF-based clinical sheet for patient with low back pain with the ICF coding of the components

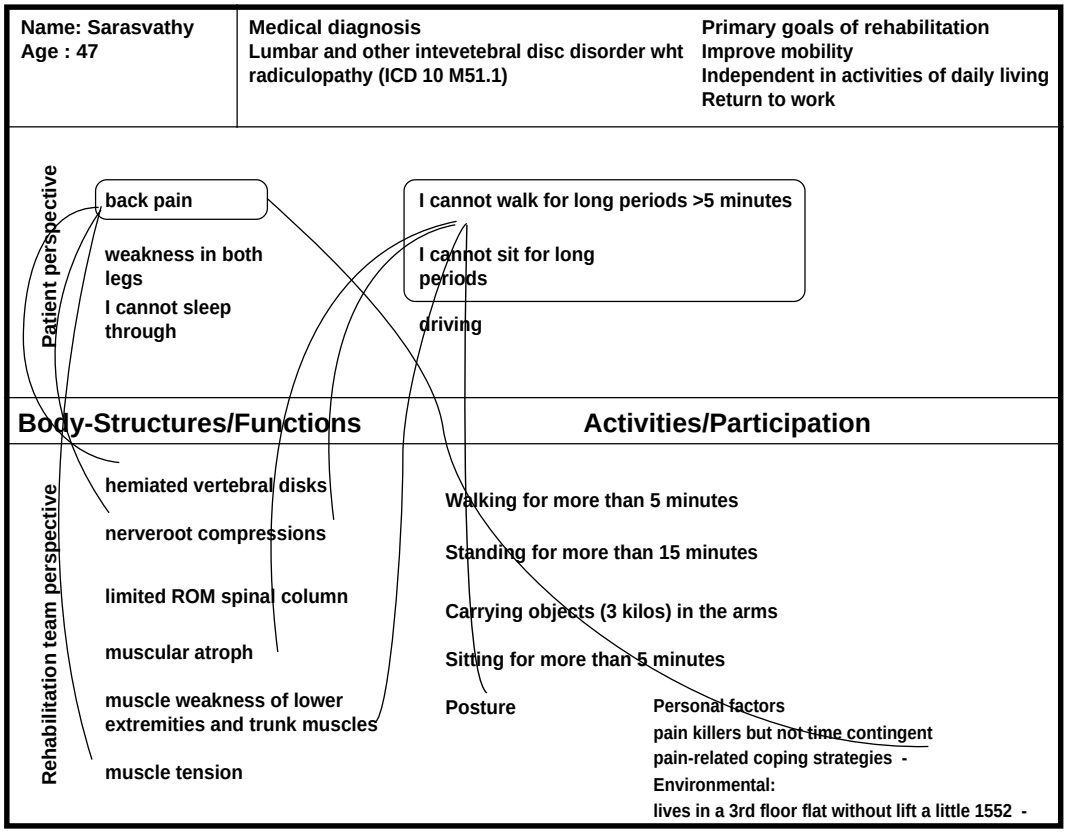

Figure 3. ICF-based clinical sheet for patient with low back pain showing how the ICF components can be used to structure patient's problems, findings and observation by rehbailitation team. Lines between patient's target problem, impaired body structure and function, personal and environmental factors.

encouraged to use the ICF to summarise the patients kevel of functioning, Hence, from the case reports that use ICF, apart from the disease and treatment process, the level of functioning of patients can be clearly derived. This will promote the concept of holistic management of the patient instead of only focussing on treating the disease only.

Conclusion

ICF has the potential to be a new important language that can improve the practice of rehabilitation medicine. The approaches in rehabilitation medicine are in line with the concept of ICF. International Classification of Functioning, Disability and Health (ICF): It can provide a new platform that may lead to a universal language in functioning disability and health. It can also lead to a better understanding of rehabilitation medicine practice within the medical community; improve multi-professional communication between patients, healthcare professionals, policy-makers and other stakeholders.The future use of ICF will be based on the outcomes of the study before definite conclusions can be made.

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A SURVEY OF KNOWLEDGE AND PERCEPTIONS OF MENOPAUSE AMONG YOUNG TO MIDDLE-AGED WOMEN IN FEDERAL TERRITORY, KUALA LUMPUR, MALAYSIA

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ABSTRACT: Prevalence and signs and symptoms of menopause have been extensively studied among Malaysian women but no one had investigated the level of knowledge and perception of menopause. This study aimed to examine the knowledge and perception of menopause among young to middle aged women (15 to 49 years old). A cross-sectional survey using 20-items questionnaire was conducted in three randomly chosen districts in Federal Territory, Kuala Lumpur. Women in this survey were aware of the meaning of the term menopause and its symptoms. However, the majority lacked comprehensive understanding about the health risks associated with menopause. Commonly cited sources of knowledge were magazines and family members. Lack of official sources for accurate information on menopause was reported. Communication with health care personnel regarding menopause was uncommon. An exploration into respondents' perceptions on menopause revealed that the majority displayed positive thinking towards menopause. Young respondents seemed to have better perception regarding menopause compared to middle aged women. Although the women had good knowledge about menopause, they expressed feelings of sadness and nervousness upon the approach of their own menopause. Our data provides insight on the knowledge and perception of menopause that will guide future public health initiatives for premenopausal women in order for them to cope better when approaching this stage of life cycle. *(JUMMEC 2007; 10(2):22-30)*

KEYWORDS: Premenopausal women, knowledge, perception, menopause, urban

Introduction

The exact age of menopause varies from population to population. In Malaysia, the average age of menopause among Malaysian women has been determined to be 50.7 years (1). The average life span of Malaysian women has been reported to have increased from 71.6 years in 1980 to 76.3 years in year 2006 (2).This implies that a significant proportion of Malaysian women live one third of their lives after menopause. Therefore, these women spend a great proportion of their lives in menopause, experiencing acute menopausal symptoms and associated adverse health as well as psychological effects.

Menopause can have a significant effect on a women's quality of life. Their health needs change significantly and it is important that women become aware of the new health risks they face and that there are options for preventing those risks. Studies revealed that women may avoid and reduce many adverse emotional and psychological symptoms of menopause by educating themselves about menopause to better equip themselves when approaching this stage of life cycle (3,4). Knowing more about menopause might empower women to cope better with menopausal changes (5,6). It has been suggested that lack of knowledge regarding menopause makes women more frightened when it is time to deal with menopause and this has negative effects on their emotional state (7). Changing women's perceptions on menopause by increasing their knowledge on menopause may cause less emotional disturbance (8).

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Study also revealed that stigma about menopause begins early in life, partly due to little accurate information or education about this life phase among young women, unless an open and proactive view is stressed by society or families (9). Also, culture and societal influence were discovered to play a role in determining how individuals think about menopause (10). Until quite recently, it was not the norm for a Malaysian woman to seek advice regarding symptoms during her transition into menopause. Sweating, aches and pains, insomnia were said to be part of growing old and are accepted by many Malaysian women (11).

Several local studies regarding menopause have put much emphasis and weight on the findings of prevalence, physiology, menopausal symptoms, and hormone replacement therapy (HRT) (12, 13). Little has been said and viewed on the knowledge and perception of Malaysian women on menopause and no studies have been conducted to address this issue among the premenopausal Malaysians. Therefore, this study aimed to investigate the young adults and middle-aged Malaysian women regarding their level of knowledge and perception of menopause.

Methods

A cross-sectional interview survey was conducted in the Federal Territory, Kuala Lumpur. The target population was young to middle-aged adult women, aged 15 to 49 years old. Based on the Population and Housing Census of Malaysia 2000 (14), total female population in Federal Territory, Kuala Lumpur was approximately 400,000. The calculated sample size was 385 based on margin error of 5% and 95% confidence intervals.

Two stage sampling methods were implemented. Random procedures by drawing lots were used to select three districts in Federal Territory and the selected districts were Ampang, Setapak and Petaling. In each district, total sample to be collected was calculated based on a proportional sampling of the total female population in the respective district. One town was selected at random by drawing lots in each of the districts. Subsequently, the households were selected from randomly selected list of addresses by random sampling scheme. Only one eligible member was randomly selected in each household. Where the respondents were not at home or not in a position to respond (e.g., due to busy work schedule or refused to be interviewed), the researcher would move on to the next household in the list of the selected addresses.

Data collection was conducted by face-to-face interviews using structured questionnaires as the interview guide. Interviews were carried out by one interviewer throughout the entire survey. The interviewer was trained to address the questions identically so that the questions have same meaning to all respondents. A questionnaire or interview guide consisting of twelve pages (averaging 15 minutes to complete) was developed for the use in this study. Health professionals were invited to examine and to validate the questionnaire, and after their approval, it was pilot tested. The questionnaire was pre-tested on a volunteer sample of twenty subjects before it was administered to the study participants. Complete questionnaire data were analysed for its reliability. Demographic questionnaire included questions on age, race, religion, highest educational level, occupation, marital status and menstrual status. The knowledge section assessed the respondents' understanding on the definition of menopause, signs and symptoms, associated health risks, treatment, source of information about menopause. Respondents were asked on perception of menopause in general and also how they perceive the approach of their own menopause.

The study was conducted after approval had been obtained from the Medical Ethics Committee, University of Malaya Medical Centre, Kuala Lumpur. All participants were informed of the objective of the study and written consents for interview were received from the respondents.

Data Analysis

Data entry and analysis was performed in SPSS version 13.0 (SPSS Inc, Chicago, Ill, USA). Missing data were corrected and data were presented as mean ±SD for continuous variables with normal distribution, median for continuous variables without normal distribution and proportions for categorical variables. The analysis was considered to be statistically significant at $p < 0.05$.

Results

Particulars of Respondents

A test of internal consistency conducted with the overall study sample, achieved a Cronbach alpha coefficient of 0.77, represent an acceptable level of internal consistency. The total respondents interviewed in this study were 399. The response rate was 84.7%. Premenopausal (n=3) and postmenopausal (n=1) women were excluded from the analysis.

Table 1 shows the socio demographic profile of the respondents. The mean age of the respondents was 28.7 years (SD=9.7); 190 (38%) of whom were young adults (15-24 years old) and 245 (62%) respondents were middle-aged women (25-49 years). From the total 395 subjects, 45.6 % were Malays, 31.9% Chinese and 21.7% Indians. Majority of the respondents have at least

Table 1. Socio demographic profile of women who participated in the study (n=395)

Sociodemographic	**n**	**%**
Ethnicity		
Malay	180	45.6
Chinese	126	31.9
Indians	86	21.7
Others	3	0.75
Age (years)		
Young Adults 15-24	150	38.0
Middle-aged		
25-34	135	34.2
35-44	81	20.5
45 and above	29	7.3
Level of Education		
Secondary School	195	49.4
Diploma	72	18.2
Tertiary	128	32.4
Marital Status		
Single	169	42.8
Married	225	57.0
Widowed	1	0.3
Occupational group		
Professional	77	19.5
Clerical Staff	80	20.3
Technician & Semi Professional	90	22.8
Staff of Retail & Sales Outlets	6	1.5
Handicraft & Sales of Products	1	0.3
Support staff	5	1.3
Student	111	28.1
Housewife	14	3.5
Jobless	11	2.8

some secondary education (49.4%), none of the respondents were illiterate and 32.4% were university graduates.

Knowledge of Menopause

Respondents had good knowledge of the definition of menopause, and definitions given varied widely. The study showed that 89.0% (95% CI, 85.8 to 92.0%) agreed that menopause refers to permanent cessation of menstruation, 72.2% (95% CI, 67.7 to 76.6%) noted menopause happens when ovaries stop estrogen production, and 62.8% (95% CI, 58.1 to 67.6%) believed menopause begins after age 50 years. A total of 216 respondents (54.6%; 95% CI, 49.8 to 59.6%) associated hot flushes as the physiological manifestations of menopause and 228 respondents (57.9%; 95% CI, 52.9 to 62.6%) defined menopause as a condition in which the ovaries stop functioning. Only ninety-nine respondents (24.8%; 95% CI, 20.8 to 29.3%) described menopause as any women above 35 years without having any menstrual period for one year. On the average, middle-aged women were more knowledgeable on the definition of menopause compared to young adults although the difference was not significant.

Majority of the respondents (*n*=160, 40.5%; 95% CI, 35.7 to 45.4%) noted menopause happens at the age of 51 to 55 years old. A total of one hundred and three (26.1%; 95% CI, 21.8 to 30.4%) accurately determined the onset of menopause generally occurs at age 46 to 50 years old. A total of twenty-four respondents (6.0%; 95% CI, 3.7 to 8.4%) noted that menopause happens at age 66-70 years old. Knowledge on age of menopause was generally better among middle-aged respondents compared to young adult respondents even though the difference was not significant.

There were no significant differences among respondents from all ethnic groups in the knowledge of the definition of menopause. The results also did not indicate that tertiary educated respondents were more knowledgeable than secondary school educated women.

Knowledge on Signs and Symptoms

Generally, all respondents have reasonably good knowledge on signs and symptoms attributed to menopause. Majority (86.5%; 95% CI, 83.2 to 89.9%) identified depression as a sign and symptom of menopause. Approximately 85.6% (95% CI, 82.1 to 89.0%) reported irritability as sign and symptom of menopause, whereas 80.5% (95% CI, 76.6 to 84.4%) noted vaginal dryness, 77.5% (95% CI, 73.4 to 81.6%) forgetfulness, 74.9% (95% CI, 70.7 to 79.2%) lethargy, 67.6% (95% CI, 63.0 to 72.2%) hot flushes, 67.1% (95% CI, 62.5 to 71.7%) skin dryness, 63.5% (95% CI, 58.8 to 68.3%) no sexual desire and 60.0% (95% CI, 55.2 to 64.8%) excessive sweating. Other signs and symptoms identified were weight gain 50.9% (95% CI, 46.0 to 55.8%), urine leakage 53.4% (95% CI, 48.5 to 58.3%), hair loss 49.1% (95% CI, 44.2 to 54.0%) and painful intercourse 48.9% (95% CI, 43.9 to 53.8%). There were significant difference between the young adults and middle-aged respondents for signs and symptoms of forgetfulness, vaginal dryness and no sexual desire. Significantly more middle-aged respondents noted vaginal dryness ($p<0.05$) and no sexual desire ($p<0.001$) compared to young adult respondents (Table 2). No differences were noted among ethnic groups for any of these signs and symptoms of menopause.

Majority (84.3%; 95% CI, 80.7 to 87.9%) cited signs and symptoms of menopause should be treated while 15.7% (95% CI, 12.1 to 19.3%) viewed them as a natural part of a woman's life and thus did not necessarily require treatment. For knowledge about ways to overcome signs and symptoms of menopause, most respondents quoted exercise (82.3%; 95% CI, 78.5 to 86.1%), vitamin and food supplement intake (76.5%; 95% CI, 72.3 to 80.6%) and stop smoking (for those who smoke) (66.8%; 95% CI, 62.2 to 71.5%). More than half (54.4%; 95% CI, 49.5 to 59.3%) did not agree that hormone replacement therapy can effectively control symptoms of menopause.

Findings also revealed that most respondents suggested no definitive treatment for menopause. Only 45.6% (95% CI; 40.7 to 50.5%) of the respondents agreed on hormone replacement therapy as a treatment option. Nearly half (45.8%; 95% CI, 40.9 to 50.7%) believed in traditional remedies for treatment of menopause.

Knowledge on associated health risks of menopause, respondents were much more likely (76.2%; 95% CI, 72.0 to 80.4%) to know that osteoporosis risk increased with menopause than to know that heart disease risk increased (36.5%; 95% CI, 31.7 to 41.2%) despite the much higher prevalence and severity of heart disease as a health problem of menopausal women. Findings also indicated that not many respondents associated breast cancer (32.2%; 95% CI, 27.5 to 36.8%), diabetes (37.0%; 95% CI, 32.2 to 41.7%), colon cancer (28.6%; 95% CI, 24.2 to 33.0%), stroke (40.0%; 95% CI, 35.2 to 44.8%), elevated blood pressure (43.8%; 95% CI, 38.9 to 48.7%) and cervical cancer (48.4%; 95% CI, 43.4 to 53.3%) as health risks associated to menopause (Table 3). Young adult respondents were more knowledgeable than middle-aged respondents on health risks associated to menopause. Young adults were significantly more aware that heart disease, diabetes, colon cancer, high

Table 2. Knowledge of young adult and middle-aged women on signs and symptoms of menopause (n=395).

Signs and symptoms	Total *n*=395 *n* (%)	Young adult *n*=150 *n* (%)	Middle-aged *n*=245 *n* (%)	*p* value
Irritability	338 (85.6)	126 (84.6)	216 (86.7)	0.448
Depression	342 (86.5)	122 (81.3)	221 (88.8)	0.061
Forgetfulness**	306 (77.5)	131 (87.3)	179 (68.3)	0.001
Vaginal Dryness*	318 (80.5)	109 (72.7)	210 (84.3)	0.050
No Sexual Desire**	251 (63.5)	77 (51.3)	175 (70.3)	0.001
Lethargy	296 (74.9)	98 (65.3)	199 (79.9)	0.060
Hot Flushes	267 (67.6)	100 (66.7)	171 (68.7)	0.677
Hair Loss	194 (49.1)	68 (45.3)	127 (51.0)	0.272
Short-sighted	138 (34.9)	53 (35.3)	85 (34.1)	0.808
Weight Gain	201 (50.9)	72 (48.0)	129 (51.8)	0.461
Excessive Sweating	237 (60.0)	86 (57.3)	155 (62.2)	0.331
Skin Dryness	265 (67.1)	102 (68.0)	167 (67.1)	0.847
Urine Leakage	211 (53.4)	89 (59.35)	126 (50.6)	0.090
Painful Intercourse	193 (48.9)	76 (50.7)	117 (47.0)	0.476

Table 3. Proportion who know the health risks of menopause

Health risks	Total *n*=395 *n* (%)	Young adult *n*=150 *n* (%)	Middle-aged *n*=245 (*n*) %	*p* value
Osteoporosis**	301 (76.2)	97 (67.4)	204 (82.3)	0.001
Cervical Cancer	191 (48.4)	39 (26.0)	88 (35.9)	0.052
High Blood Pressure**	173 (43.8)	77 (51.3)	67 (27.3)	0.001
Stroke	158 (40.0)	67 (44.7)	79 (32.2)	0.059
Diabetes**	147 (36.6)	64 (42.7)	49 (20.0)	0.001
Heart Disease**	144 (36.5)	91 (60.7)	86 (35.1)	0.001
Breast Cancer**	127 (32.2)	95 (63.3)	63 (25.7)	0.001
Colon Cancer	113 (28.6)	81 (54.0)	110 (44.9)	0.057

**Refers to significant *p*-value.

Table 4. Perception on menopause by young adult and middle-aged respondents.

Statement	Total *n*=395 *n* (%)	Young adults *n*=150 *n* (%)	Middle-aged *n*=245 *n* (%)	*p* value
Menopause is a sign of ageing	303 (76.7)	120 (80.0)	183 (74.7)	0.194
Loss of fertility	273 (69.1)	115 (76.7)	158 (64.5)	0.012
Menopause is a normal transition in ageing process	309 (78.2)	119 (79.3)	190 (77.6)	0.604
Freedom from menstrual, pregnancy and childbirth	237 (60.0)	99 (66.0)	138 (56.3)	0.064
Loss of youth	207 (52.4)	104 (69.3)	103 (42.0)	0.000
Not a real woman	93 (23.5)	48 (32.0)	45 (18.4)	0.001
Partial death	90 (22.8)	27 (18.0)	63 (25.7)	0.076
Not wanted anymore	92 (23.3)	47 (31.3)	45 (18.4)	0.001
Menopause is a disease	94 (23.8)	69 (46.0)	25 (10.2)	0.001
Old and useless	113 (28.6)	56 (37.3)	57 (23.3)	0.003
Regret when menses ceases	168 (42.5)	87 (58.0)	81 (33.1)	0.001
Loss of drive to perform daily routine	89 (22.5)	68 (45.3)	21 (8.6)	0.001
Menopause do not change women	162 (41.0)	57 (38.0)	105 (42.9)	0.291

blood pressure, stroke, and cervical cancer are health risks associated with menopause than middle-aged respondents. For osteoporosis and breast cancer, more middle-aged respondents cited them as risks associated with menopause compared to young adult respondents. There were no ethnic differences for knowledge on health risks of menopause.

Sources of Information

The main sources of information about menopause in descending order were magazines (85.3%; 95% CI, 81.8 to 88.8%), families (77.2%; 95% CI, 73.1% to 81.4%), books (58.7%; 95% CI, 53.9 to 63.6%), newspapers (58.0%; 95% CI, 53.1 to 62.8%), radio and television (56.2%; 95% CI, 51.3 to 61.1%), and friends (53.4%; 95% CI, 48.5 to 58.3%). Less than half of the respondents (40.8%; 95% CI, 35.9 to 45.6%) identified medical and health personnel as a source of information. Only 36.5% (95% CI, 31.7 to 41.2%) received information from the Internet and 36.2% from pamphlet. Three main sources of menopause information for young adult respondents were families (76.7%; 95% CI, 69.9 to 83.4%), magazines (76.0%; 95% CI, 69.2 to 82.8%) and books (54.0%; 95% CI, 46.0 to 62.0%). In contrast, for middle-aged respondents, their three main sources of information were magazines (91.0%; 95% CI, 87.4 to 94.6%), families (77.6%; 95% CI, 72.3 to 82.8%) and newspapers (67.8%; 95% CI, 61.9 to 73.6%). Significantly more ($p<0.01$) middle-aged respondents (25 years old and above) acquired menopause information from magazines, news papers and pamphlets than young adults respondents (15 to 24 years old).

On further questioning types of additional information needed about menopause, the respondents expressed overwhelming positive response. Three most required additional information were menopause treatment (96.5%; 95% CI, 94.6 to 98.3%), treatment of signs and symptoms of menopause (94.2%; 95% CI, 91.9 to 96.5%), and health risks associated with menopause (88.7%; 95% CI, 85.7 to 92.0%). The respondents' good knowledge on signs and symptoms of menopause may be the reason that the least required additional source of information was information on signs and symptoms of menopause (77.5%).

Sources of Support and Help

Family members were identified by the highest percentage of respondents (79.5%; 95% CI, 75.5 to

83.5%) the main source of support and help on problems related to menopause, followed by medical health personnel (68.1%; 95% CI, 63.5 to 48.272.7%) and friend or colleagues (59.7%; 95% CI, 54.9 to 64.6%). Only 43.5% (95% CI, 38.7 to 48.4%) would turn to a counselor for support and help. Young adults respondents were more likely than the middle-aged to seek support and help from family members ($p<0.01$). For the remaining sources of support, the middle-aged respondents outnumber the young adults ($p<0.01$).

Perception on Menopause

A majority of the respondents disagreed that menopause means no longer being 'real' women (76.5%; 95% CI, 72.3 to 80.6%), feeling not wanted by others (76.7%; 95% CI, 72.5 to 80.9%), feeling old and useless (71.4%; 95% CI, 66.9 to 75.9%) and it's a sign of partial death (77.2%; 95% CI, 73.1 to 81.4%). Most of them also disagreed that menopause is a disease (76.2%; 95% CI, 72.0 to 80.4%). Many held a positive attitude towards menopause and regarded menopause as a normal transition in the ageing process (78.2%; 95% CI, 74.2 to 82.3%) and it is just a sign of ageing (76.7%; 95% CI, 72.5 to 80.9%). Majority (77.5%; 73.4 to 81.6%) also do not feel menopause would result in loss of drive to perform their daily chores. Relatively low percentages of respondents (42.5%; 95% CI, 37.6 to 47.4%) express regrets if their menstrual period ceases approaching menopause. Although more than half of the respondents (59.0%; 95% CI, 54.1 to 63.8%) believed that menopause would not change women in any important way, the majority agreed that menopause means a loss of their youth (52.4%; 95% CI, 47.5 to 57.3%) and fertility (69.1%; 95% CI, 64.6 to 73.7%).

Table 4 shows that on the whole, middle-aged respondents have better perception on the approaching of their menopause compared to young adult respondents. Significantly more young adults compared to middle aged respondents ($p<0.01$) agreed with the statement that menopause means loss of youth, not being wanted anymore, menopause is a disease, feeling old and useless, regrets when menses ceases and loss of drive to perform daily routine. The statement, "menopause indicates partial death", was the only response whereby middle age respondents outnumber young adult respondents. Nevertheless, the difference was not statistically significant (p =0.07).

Responses to questions about the respondents' feelings towards the approach of their own menopause revealed that most of the respondents feel nervous (66.6%; 95% CI, 61.9 to 71.2%) and fear (63.8%; 95% CI, 59.1 to 68.5%) about their oncoming menopause. Other responses were feeling of sadness (46.3%; 95% CI, 41.4 to 51.3), disgust (34.9%; 95% CI,30.2 to 39.6%), relief (29.6%; 95% CI,25.1 to 34.1%), joy (18.2%; 95% CI, 14.4 to 22.0%). One hundred and forty eight (37.5%; 95% CI, 32.7 to 42.2%) respondents stated as do not care.

On the whole, tertiary-educated respondents were more positive regarding the approaching of their own menopause than secondary educated respondents. Significant differences ($p<0.01$) were observed between the two groups in statements where menopause denotes loss of youth, not a real women anymore, not wanted anymore, menopause is a disease, feeling old and useless, regret when menses ceases, and loss of drive to perform daily routine.

Discussion

Respondents held accurate ideas of the time of life when menopause occurs. Most respondents defined menopause as menstrual period termination. Though many identified the general definition of menopause accurately, some lacked comprehensive understanding of the meaning of the term menopause such as menopause being defined as, "without having any period for a year after age 35.".

Respondent were more aware of physical signs and symptoms of menopause such as depression, irritability, vaginal dryness and lethargy and least likely to know the physiological symptoms such as hot flushes, excessive sweating and urine leakage. Respondents' foremost knowledge on ways to overcome signs and symptoms, rather surprisingly, was not hormone replacement therapy. In their opinion, exercise and vitamins supplements may overcome signs and symptoms of menopause. Surprisingly, nearly half of the respondents believed in traditional remedies rather than in HRT, or they were unaware of HRT.

The most striking finding from the present study was the clear underestimation of menopause related risk factors such as cardiovascular diseases and cancer. Respondents' knowledge on health risks associated to menopause in this survey were similar to the other study (15). They were much more likely to identify osteoporosis rather than hypertension and heart diseases despite the fact that the risk of developing cardiovascular diseases is higher than osteoporosis (15). Middle-aged adult respondents appeared to be less knowledgeable on health risk associated to menopause. This raises concern because many in this group are now entering menopause and a lot more will reach menopause over the next decade.

According to our results, the most commonly cited as sources of information about menopause were reading

materials (magazines, books) and families. Little information was obtained from medical sources. This may denote lack of communication between healthcare personnel and women regarding menopause. Physicians may not be likely to discuss about menopause with women who have not reached menopause or vice versa. Apparently many respondents tend to learn about menopause from the media and were not well informed via specific education on menopause. Young adult respondents, on the other hand, particularly tend to look to family members for menopause related information. Similar to the study by Pan, *et al.* (16), Taiwanese women reported family members specify women from their own generation (mother or sisters) as most frequently chosen source of menopause-related information. This indicates the need for menopause related education programs targeted at young adults in school. Thus, it is important to encourage medical care providers, schools and other educational institutions to increase their efforts to educate women about menopause.

With regard to source of information needed by respondents, it appeared that the least additional information needed was information on signs and symptoms of menopause. The most required information was treatment of menopause. We can estimate that the respondents in this survey have adequate knowledge on signs and symptoms and least knowledge on the aspect of treatment.

Respondents in this study also held positive perception toward menopause. Although many agreed that menopause indicate loss of youth and fertility, and a sign indicates aging, generally responses relating positive reactions included believe that menopause is part of getting old and freedom from menstruation, pregnancy and childbirth. Negative perception of menopause such as menopause is a disease, feeling no longer like a'real' women, feeling old and useless and loss of drive to perform daily chores, were generally not accepted as true by many respondents. Rather surprisingly, despite positive attitude towards menopause, most respondents expressed nervousness, fear and sadness about the approach of their own menopause. In general, middle-aged respondents possessed better perception on menopause compared to young respondents. Therefore, this finding suggests that education on menopause should put more emphasis on young women.

This study is not without its limitation. The present study surveyed women in the urban setting as a preliminary study in investigating the knowledge and perception of menopause among Malaysian women. As expected urban participants are generally more educated. All the participants in this study had at least secondary school education and none had only primary education. Therefore, the result of this survey may be biased towards higher knowledge responses about menopause.

Conclusions

In conclusion, data from this study provides preliminary data regarding the level of knowledge and perception of menopause among women in three districts of the Federal Territory Kuala Lumpur. Young women in this country should be educated to remove stigmas about menopause from the school level. For the older group, it is important to emphasise on educating them about health risk and that adopting healthy lifestyle behaviour now can influence their risk for developing diseases associated to menopause in the near future.

The results of this study provides enormous guidance for future education on behavioural changes and exercise in improving women's views of this transition in their lives, and ultimately enable women to face this phase of life in a more positive approach. This study identifies the need for further research to examine the views and also to explore urban and rural differences in the aspect of knowledge as well as perception and attitude of women regarding menopause.

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DEPRESSION AND FUNCTIONAL LEVEL IN SCHIZOPHRENIA: A COMPARISON BETWEEN CHRONIC HOSPITALISED IN-PATIENTS AND COMMUNITY CARE PATIENTS

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ABSTRACT: Recent innovations in the treatment of schizophrenia reflect a growing trend towards community-based care. Malaysia had in the past few years attempted to deinstitutionalise mental patients in the mental hospitals. Therefore it is important to conduct research to compare the two groups of schizophrenia patients (community-based patients against chronic hospitalised patients) to ascertain if deinstitutionalisation has been beneficial. The main objective of the study was to compare levels of depression and function in community-based patients against chronic hospitalised patients as depression is prevalent among schizophrenia patients. This study was cross sectional in nature where data was collected from 51 inpatients in Hospital Bahagia Ulu Kinta (HBUK) and 23 community-based patients. Calgary Depression Scale for Schizophrenia (CDSS) and Global Assessment of Functioning scale (GAF) were the assessment tools used. Community-based patients were found to have significantly lower scores in the CDSS scale (1.96) as compared to chronic hospitalised patients (4.04); $p < 0.01$). They also showed higher functional capability between community-based and hospitalised patients respectively (74.04 vs 57.92) respectively. ($p < 0.001$). Community services appeared to be more effective than long stay in-patient services in preventing depression and promoting better functional levels. *(JUMMEC 2007; 10(2):31-36)*

KEYWORDS: Schizophrenia, depression, functionality, community, institutionalisation

Introduction

Schizophrenia is a devastating illness. It runs a chronic course where there is lifetime morbidity and diminished quality of life. Several studies have shown that over a five to ten-year period after the first psychiatric hospitalisation, only about ten to twenty per cent of the patients can be described as having had a good outcome. More than fifty per cent of the patients can be described as had a poor outcome, with repeated hospitalisations, exacerbations of symptoms, episodes of major mood disorders (especially depression) and suicidal attempts. Reported remission rates range only from ten to sixty per cent. There is only an estimated twenty to thirty per cent of schizophrenia patients that are able to lead somewhat normal lives. About twenty to thirty per cent of patients continue to experience moderate symptoms and forty to sixty per cent of patients remain significantly impaired by their disorder for their entire lives(1). The outcome of an illness is variable and can be relatively mild, with the patient suffering one (16%) or several (32%) episodes, and little or with no lasting impairment(2). However, for those experiencing repeated episodes the outcome is worse, with 9% suffering lasting impairment and 43% enduring increasing severe symptoms with no periods of complete remission (3). It was suggested that approximately 50% of persons diagnosed with schizophrenia eventually become significantly and permanently disabled (4).

Ever since Second World War, several factors led to changes being made in psychiatric hospitals as social attitudes had become more sympathetic towards psychiatric patients. The introduction of chlorpromazine in 1952 made it easier to manage disturbed behaviour, and therefore, easier to open wards, to engage patients in social activities and to discharge some of them into

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the community. After the initial success of discharging many institutionalised patients, it was optimistically proposed that large asylums could be closed and replaced by small psychiatric units in general hospitals with support from community facilities. This pace of change differed from country to country. One of the earliest countries to implement a shift towards Community Care was Italy, where in 1978, they passed a law, which was aimed to abolish mental hospitals and replaced them with a comprehensive system (5). Locally, the first step towards community care was initiated on 13 November 2000 in Johore state.

In Malaysia, there are currently four institutions, two in Peninsular Malaysia, one in Sabah and one in Sarawak. Hospital Bahagia Ulu Kinta (HBUK), where this study was carried out, is one of Malaysia's largest psychiatric institution. Currently, there are about 2200 in-patients, of whom some had been there ever since World War Two. In line with the global trends towards community care, HBUK started its community service in April 2001.

Recent innovations in the treatment of schizophrenia reflect a growing trend towards community-based care (6). These programs reduce psychiatric hospitalisation rates, improve residential stability, and result in improved satisfaction with care. Community care is more successful at maintaining clinical contact, are more valued by patients and offer greater opportunity for staff to deliver continuing and effective face-to-face treatments; they have produced improved patient outcomes in several domains, although notably not in symptom reduction (7,8,9).

On the well-being of chronic mental patients, it was found that long-term patients in mental homes with psychotic disorders were reported to have a lower quality of life than the general population (10,11). Long-term patients experienced loneliness after discharge from institutions (12). However, in a similar study in Norway, it was found that patients outside of institutions were the most socially active and had the most satisfying contact with their families. Patients reported a satisfactory quality of life, and those who lived outside institutions tended to be most satisfied with their living situation and reported a relatively high quality of life (13).

In Malaysia, there is limited local data on community psychiatry and we had to rely mainly on data from other countries which may not be applicable here. Realising this, we decided to embark on this study looking at depression and functional level in chronic hospitalised schizophrenia patients in HBUK in comparison with community care schizophrenia patients.

Methods

This was a cross sectional study where samples were collected from two groups of patients; in-patients and community care patients. Both groups of patients were included in the study only if they had agreed to participate in the study and agreed to be interviewed. The in-patients were recruited from the "medium stay" ward, where patients who had been admitted for more than a month. The matrons' in-charge from both the male and female wards selected schizophrenia patients through quasi randomisation. It was a blind procedure to the investigators as the matrons were not involved in the management of the patients. The interviewer was then given the list of patients for the interview. He was not aware about the patients' conditions and management prior to the interview. As for the community care patients, the patients were collected via convenient sampling depending on the dates picked for the visit. There were various teams visiting the patients daily. Not every team visited their patients daily. The dates picked were according to the availability of the researcher and the teams visiting their patients. The researcher recorded all the patients that were visited on that day. Patients fulfilling DSM IV criteria for schizophrenia were included. The patients were assessed on depression symptomatology and their functions. The rating scales used in the study were the Calgary Depression Scale for Schizophrenia (CDSS) and global assessment and functioning scale (GAF).

Calgary Depression Scale for Schizophrenia (CDS) is a validated and reliable tool used internationally and it is used for assessment of depressive symptoms, separating them from positive, negative and extra pyramidal symptoms in people with schizophrenia (14, 15, 16, 17, 18). It is an observer scale, semi-structured and goal directed in nature. Internal and inter-rater reliability of the scale has been shown to be good (16). From the receiver-operator curve for CDS, a score of above 5 has high sensitivity and specificity for depression. However, the Malay and Mandarin versions are translated versions by authors from Malaysia and Taiwan and they are not validated.

Statistical tests were carried on to compare the scores of these scales among the two groups. Separate analysis was also carried out after excluding those on antidepressant to omit the possible beneficial effects of antidepressant.

The study was approved by Ethics Committee in HBUK prior to the start of the data collections.

Results

A total of eighty patients were picked of whom two refused to be interviewed and four were deemed to be too psychotic to be assessed; of the remaining 74, 51(68.9%) were from the wards and 23(31.1%) from home care.The sociodemographic distribution of patient is shown in Table 1.

The clinical profiles of the patients is illustrated in the Table 2. There seems to be a wide variation in the duration of illness of the subjects. A majority of them have been suffering from schizophrenia for duration of between 6-10 years and 16-20 years. Average years of illness did not differ much from each other.

From the sample collected, there was a total of fifteen patients on antidepressants, representing 20% of the total sample. Five (22%) of those patients were from home care (3 males, 2 ladies) and 10(20%) were from the ward (6 males, 4 females). Some of them were started on antidepressants even prior to being included in the home care services. However, there was no statistical significance between the two groups (χ^2=0.45, p=0.833).

Using CDSS for assessing depressive symptoms, we found the mean score for home care and institutionalised patients were 1.96± 2.01 and 4.04± 3.64 respectively and this difference was statistically significant (t =-3.154, p< 0.005).

Further analysis after inclusion of those patients on antidepressant, we found that the CDSS mean score for home care patients were 1.89± 1.81 and for ward patients were 4.38± 3.75 (p< 0.001). CDSS score of more than five would be indicative of depression as proposed, there were 17(42%) out of the 40 in ward patients who were not on antidepressants could be depressed. As for the home care patients, 1(6%) out of the 18 patients not on antidepressants could be depressed. This difference was statistically significant (χ^2= 7.916, p<0.005).

Table 1. The sociodemographic distribution of patients

Characteristics		Home care N=23	In-patients N=51	Statistical significance
Mean age (years)		39.7	33.6	NS
Sex	Male	14	23	NS
	Female	9	28	
Marital	Married	3	13	NS
	Not married	20	38	
Education	< SRP	5	12	NS
	> SRP	18	39	
Race	Malay	5	25	NS
	Chinese	15	20	
	Others	3	6	

NS: non-significant
SRP: Sijil Rendah Pelajaran (Lower Certificate of Education)

Table 2. The clinical profile of both groups of patients

Clinical profile	Home care	In-patients	Statistical significance
Duration of illness	12.7± 7.54	13.8± 8.01	NS
Use of antidepressants	5	10	NS

NS: non-significant

The mean GAF score of home care and institutionalised patients were 74.0± 11.48 and 57.9± 12.65 respectively and this was statistically significant (t =-5.413, p< 0.005).

Further analysis after inclusion of those patients on antidepressants, the mean GAF score of home care patients was 74.2± 11.42 whereas ward patients' mean GAF score was 57.4± 12.04. It was still statistically significant (t =-5.102, p<0.0001). A negative correlation (r = -0.2) was shown between GAF score and CDSS but it is not statistically significant (p= 0.10).

Discussion

Several main findings were highlighted in this study. Firstly, more patients in the institution were depressed when compared to the patients in the community (42% vs 6%). Secondly, the patients who were in the community had higher functioning when compared to institutionalised patients.

Depressive symptoms seemed to be part and parcel of schizophrenia, even in a cohort specifically defined so as not to be in a major depressive episode or to have schizoaffective disorder. The estimates of the frequency of depressive episodes in patients with schizophrenia range from 20% to 80 % (19,20). In this study, it was shown that 42% of the chronic institutionalised were depressed as compared to only 6% of home care patients, implying that home care could be effective in preventing depression.

Home care patients were found to have higher functional ability when compared to the institutionalised patients. Home care patients scored an average of 74 in GAF score; whereas the institutionalised patients only scored an average of only 58. The difference remains after excluding patients on anti-depressant. This implies that home care could be effective in rehabilitating the patients or preventing further deterioration in functioning.

There could be various explanations regarding the significance depending on the depressive symptoms and functionality in these groups. Maslow proposed a theory of motivation in terms of a hierarchy of needs (physiological, safety, belongingness and love, esteem and self-actualisation) (21). Different types of need have been identified, namely felt (experienced), expressed (experienced and communicated), normative (based on judgement of professionals) and comparative (based on comparison with the position of other individuals or reference groups) (22). This takes into account the different perceptions of need that can exist (23) whether focussing on strengths, with a need indicating an area of potential development, or focusing on deficits, in which needs are for treatment. Thus, the shift of patients from institutions to community may have helped the patients. When the patients are in the community, all of them are staying with their respective families. They could have felt belonged and loved. They felt safe in the midst of their family members.

Also, in the community, there are also more potential areas for development such as jobs or careers of their preference, thus having more opportunity to explore their strengths and weakness, further strengthening their potential and also overcoming their weakness. Hence, their self-esteem and self-actualisation will improve. This could have been reflected on the higher functional and lesser depressive levels among the community patients. However, there was no significant correlation between overall functioning status and depressive levels in both groups, thus from this study, higher functioning status among the community patients may not be due to lower depressive level in these patients.

In a similar research conducted by Zlotnick, *et al* (24). who did a naturalistic follow-up research on the type of treatment, dysfunctional attitudes, social support, life events, and depressive symptoms. He found that fewer stressful events and more positive social support were related to less severe depression in both men and women. Thus, the community patients may have received the social support they needed and this may have helped produce better outcome.

We have seen improvements in functional ability and also a much lower rate of depression among the community based patients. These findings are important as the community usually has a much lower tolerance toward mentally ill patients. It is hoped that with these findings, it will encourage the family members and the community to take a much more proactive role to care for the patients. It will also act to refute the claims by the society that mental patients should be 'caged' in mental institutions. It is also hoped that with these findings, it will become an incentive to the visiting health staffs that their labour is not in vain.

These findings have strong implications for policy makers. Policy makers have always been concerned about the safety of the public if the mental patients are cared for in the community. They have long held on to the beliefs that mental patients should be in mental institutions.

Furthermore, deinstitutionalisation will mean that more services should be provided, i.e., more financial allocations. This report, will show policy-makers that it may be more cost effective to treat the patients in the

community than in hospitals. It is hoped that, the policy-makers will actively participate in rehabilitating these unfortunate people.

Several limitations are recognised in this study. Firstly, due to the cross sectional nature of the study, baseline functioning and depressive levels of the patients could not be ascertained to determine if the community care truly had a beneficial effect on functioning and depression. Secondly, the number of sample size was small. Thirdly, one has to be cautious and realise that the home care patients may have higher functioning to start with, therefore more likely to be treated in the community. However in this study, we were unable to do pre- and post -assessment of CDSS/ GAF. Fourthly, the community patients were selected based on the dates picked and the teams who visited their clients. Thus, in the future research should focus on larger sample size and also explore other factors that may influence functions

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AN INQUIRY INTO NURSING LEADERSHIP STYLE IN A HOSPITAL

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ABSTRACT: Leadership style has been shown to be an important determinant of organisational success. The aim of this preliminary study was to develop an understanding of leadership style of three employees with leadership responsibility in a hospital. All the participants were interviewed using a structured questionnaire around a framework on leadership behaviours followed by self administered T-P leadership questionnaire and voluntary completion of a leadership perception survey by each of the participant's colleagues.

The results suggest that whilst individuals are aspiring to be transformational in style, key barriers such as organisational culture, inter-professional dynamics and lack of leadership development meant responses more characteristic of a transactional style were encountered. There is a need to have joint responsibility between developing the individual leadership style and the organisation that facilitates such development for their leaders. The author concludes that a more analytical approach to leadership and mentorship opportunities for developments is required. *(JUMMEC 2007; 10(2):37-42)*

KEYWORDS: Leadership style, transformation, transactional.

Introduction

With increasing evidence to suggest that leadership style is key to success of an organisation (1), there is a need to understand the leadership style of those with leadership responsibility. This paper reports findings of leadership style of three senior leaders within a hospital. To present the data in a meaningful way a descriptive account of the key findings with concurrent discussion of the relevant literatures will be presented. This allows for emergence of themes and identification of areas for development.

Aim

The aim of this study is to develop an understanding of leadership style of three employees with leadership responsibility in a hospital.

The objectives are to:

1. investigate the leadership style of three employees with leadership responsibility within a hospital;
2. integrate findings with emergent literature; and to
3. make recommendations for leadership development.

Context and Background Information

Many theories that consider leadership style from the perspectives of individual traits (2), behaviour (3) and contingency (4) were found in existing leadership literatures. It has also been suggested that this developed thinking is about management rather than leadership (5, 6). More recently, there is evidence to suggest that a transformational leadership style is positively correlated with increased organisational productivity and positive subjective evaluations (7). This means there is a need to move away from focusing on the management exchange relationship which is characteristics of transactional approaches, to a follower focus that empowers and facilitates leadership in others.

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The hospital where the study was conducted provides specialist services to a population of one million people. All the participants have been in their existing posts for more than twelve months and had significant leadership experiences.

Methodology

It has been suggested that leadership style reflects the values, beliefs and assumptions about the fundamental nature and behaviour of their followers (8). The methodology of this investigation identifies the characteristics displayed by individuals engaged in leadership activities and their underlying beliefs and attitudes that inform their decisions. Consequently, a mix of ethnographic and survey methods were used and described below. As the aim is to understand leadership within an organisation, the selection of the participants was criterion-based, and purposeful sampling was used. Purposeful sampling is used in order to target individuals who have primarily a leadership role and to consider style from different perspectives within the organisation (9). All nursing staff that hold leadership positions in the identified hospital was approached (N= 10). However, only three (3) gave their consent and participated in this inquiry.

A thumbnail sketch of each participant follows:

Leader 1: Male senior manager with leadership responsibility for the whole organisation. Professional management background, non-clinical background

Leader 2: Female, senior consultant with leadership responsibility for clinical specialism. No direct line management responsibility.

Leader 3: Female, senior professional lead with key responsibilities for professional leadership. Line manager for 25 staff.

Structure of Investigation

Phase 1: Individual semi structured interview

Individual interviews were chosen as it has the advantage of gathering a rich response, and the ability to clarify ambiguity. It also allows flexibility, scope and depth (10). The interview schedule was constructed following the stages which consider focus, form and sequencing (9). Questions were structured around a framework on leadership behaviours (11).

This interview was piloted with a senior manager from a different organisation, which provided helpful feedback and enabled minor modifications to be made for clarity to some of the questions.

Phase 2: Self-administered completion of T-P Leadership Questionnaire.

The 'T-P Leader Questionnaire :An assessment of style' (12) was used to determine the two dimensions of task orientation and people orientation as it has been found to be a valid and reliable measurement.

Phase 3: Voluntary completion of a leadership perception survey by one of each leader's colleagues.

The Leadership Perception survey was adapted from a similar survey that was found in the London Leadership Programme (13). It consists of four statements about the leaders behaviour in each of the categories identified, giving a total of 28 statements. An ordinal scale was used to rate the behaviour (9). This questionnaire was completed voluntarily by one colleague of each leader (n=3). This was to assess how their colleagues viewed the leadership style. It also allowed for comparison with the data obtained from the interview. This was also piloted with several independent participants who provided helpful feedback.

In designing this investigation other methods were considered, such as the Transformational Leadership Questionnaire (14) to assess style. However, as this remains at an early stage of development, it would be worth considering in a future study.

Data analysis

The three phased approach helps to achieve triangulation of the findings and to neutralise any weakness of different methods thus strengthening the results (9).

Once the interview and questionnaire data had been received from each leader, they were combined and subjected to a thematic analysis to identify characteristics suggestive of a particular leadership style.

Ethical considerations

It is important to ensure that the methodology used is based on sound ethical principles. The study underpinned the sensitivity that emphasises on caring and respect for all respondents. The participants were provided with full information of the study and asked to provide consent to participate in the study. Anonymity and confidentiality of data was assured to the participants.

Findings and Discussion

Leader 1

As the person in one of the most senior positions within the organisation, Leader 1 emphasised the immediate

political influence on his role and style. He was very clear that enacting the political vision for the whole organisation was key to its ongoing success in providing an effective service to its users. Terms such as 'articulating direction' and 'having a big picture', were used to describe such activity, with the notion of enacting a new reality for people to pursue. He went further to describe such activity as 'exciting' and 'having a buzz feeling'. He was also quick to delegate or 'task people' in order to secure, as early as possible, a 'buy in' or 'having ownership' to the process.

For him, what was also essential to his inspirational style was to convey such values as openness, honesty and integrity in order to build trust. Through this process, he wanted to 'bind people together' in a common pursuit, which would also empower others to lead.

Role modeling was used to convey the message that it was safe and acceptable to take calculated risks whilst optimism was identified as the single most important element that 'conveyed confidence' that change was both possible and desirable. This appears to reflect 'inspirational motivation' and the essence of charisma which are components of transformational leadership (1). Through such modeling he was using transformational elements to inspire followers to transcend their self-interests.

There were indications that Leader 1 would adapt his style to fit the situation and would resort to more autocratic measures when time scales were too short to achieve commitment of the common vision, particularly, if this meant the differences of success or failure for the organisation. For example '*there are occasions when things have to be done, it isn't a choice, and it is directed from on high*' This echoed the contingency theories (15) that suggest effective leaders vary their style to suit the situation.

There was also a determination to challenge perceived professional intransigence of doing things differently or working across boundaries. Leader 1 admitted that this had at times meant fighting battles and having '*lively debate*' to convey an impression of '*little concern*' for personal criticisms. What was expressed seemed to be a more ideological perspective of how the organisation should function. This echoed the description of leaders who demonstrate strong determination but whose style is perceived as more distant from their colleagues and peers (16).

Such determination was also conveyed in his statements about change 'I embrace it', and the reactions of others, 'I have seen the consequences for those that resist.' Whilst acknowledging the possibility of 'casualties', Leader 1 added that it was sometimes necessary in the pursuit of something better: I'm aware there's going to be a certain level of resistance, however, it has to be done' In some ways, this perspective is supported by the results of the 'T-P leadership questionnaire (12) data for Leader 1 (*see* Table 1) which showed a greater task orientation towards achieving the organisation's goals. This was also reflected in his view of decision-making demonstrating that he had considerable experiences and certainly gave the impression that he did not shrink from the responsibility of making unpopular decisions.

The results of the leadership perception survey summarised in Box 1 are in many ways affirming of the interview data which suggest a predominantly transformational style.

It could be argued that he would need to develop the individualised consideration component in order to move closer to the transformational ideal (1).

Table 1. Result of the T-P Leadership Questionnaire for Leader 1

Leader	Task	Person
1	11	8

Box 1. Summary of the Leadership perception survey for leader 1

- A strong and determined but slightly distant leader
- Perceived as being responsive to organisation's goals and had a good reputation outside of the organisation
- Communicated visionary ideas
- Not afraid to make unpopular decisions and take risks
- Need to demonstrate more concern for individuals and teams
- Should value others' ideas even when they do not match their own
- Need to be more consistent in approach

Leader 2

Being a senior consultant clinician, Leader 2 felt her key drivers were clinical as well as political. What she experienced was often more complex than sometimes painted by senior colleagues and so key to this process was the interpretation of other's vision to make it 'more palatable' for her clinical colleagues to follow. This impacted significantly on her style whilst wanting to be an 'inspirational and visionary leader'. Due to the relentlessness of change in the organisation, she felt her role had become, out of necessity, a more stabilising

influence. The purpose was to provide some predictability for both staff and service users and to maintain morale which was key to the retention of an 'ever dwindling' staff resource. 'There is no point being a leader if there is no one to lead'. This approach has echoes of the transactional leader (17) that seeks to promote order. Rather than being seen negatively, it has been pointed out that transactional approaches remain of crucially important to complex organisations (5).

Much of the motivation for Leader 2's behaviour appeared to stem from the need to have 'clinical credibility.' For her, this was the embodiment of 'knowing' which she felt led to acceptance as a clinician and a leader. Therefore a dominant characteristic of her style was the formation of strong relationships within the network of her clinical specialty. It was evident from the interview, when compared to components of emotional intelligence (18) that she demonstrated particular strengths in the areas of self-awareness, self-regulation, empathy and social skill. Much of this had been derived from the many years of clinical supervision, which she was committed to maintain. Understanding her own strengths and weaknesses enabled her to motivate and value people. She emphasised the need to foster a flexible style due to the different requirements of each situation. This she argued could only be achieved through reflection in order to learn from decisions made and peoples' reactions to them. One of her concern was that much of her supervision and mentorship was received from 'like-minded individuals' who may not be sufficiently challenging and may maintain a rather inward-looking approach to her role.

In some ways her style or approach reflects description of a close or nearby leader (16). Perhaps this begins to indicate the need for a different emphasis in style according to the location or source of power within the organisation. Thus Leader 1, who has ultimate responsibility for the performance of the organisation, sustained a distance in order to maintain an ideological perspective that requires further interpretation and enactment by others. For Leader 2, shaping the future requires a greater emphasis on her clinical role and the relationships with her team. This is supported by the T-P leadership Questionnaire data revealing greater person orientation (Table 2).

Shaping the future for her clinical specialty implies change, which was an acknowledged anxiety that she felt, inhibited her style. Such inhibition was sometimes perceived as 'frustrating' for those around but 'very necessary when taking clinical risks'. When it came to decision-making, she described her style as 'calculated' with an emphasis on inclusion. She had also learnt that it was 'impossible to make the perfect decision'. For her, the skill was to demonstrate, as far as possible, there had been a democratic process although she remained anxious about critical feedback. This again appears to reinforce the impression of someone who fosters individualised consideration (1), but remains largely inward looking and rather keen to maintain the status-quo.

Once again the results of leadership perception survey in Box 2 demonstrate remarkable congruence between self and colleagues' assessments. Whilst there are similarities to Leader 1 in that there are transformational elements these are mixed with transactional behaviours which appear to be in response to the need to make sense of the future and inhibitions about change.

Table 2. Result of the T-P Leadership Questionnaire for Leader 2

Leader	Task	Person
2	8	10

Box 2. Summary of the Leadership perception survey for leader 2

- Perceived as a close/nearby and inclusive leader
- Valuing others and a good motivator
- High level of emotional intelligence with close relationship with peers and professionals
- Good communicator, confident and self-aware
- Need to be more decisive
- Need to take more risks in order not to miss opportunities
- Need to be more confidence in her decisions.

Leader 3

The role of a leader for a single professional group had presented particular challenges for Leader 3, and throughout the interview there was an overriding sense of an individual working through some difficult issues. These had largely stemmed from frustration at being unable to enact her profession's vision due to the influence of more powerful professional groups. Consequently, she was more critical of the environment and of the realities of the leadership role than either of the others but attempted to present these in a constructive way. She viewed her style as democratic and inclusive but frustrated at the constraints placed upon her.

She also expressed cynicism toward transformational approaches when working in a 'tribal' professional health care environment where power is unevenly distributed and one group dominates the vision - 'sometimes you are the boss and at other times and at different situation, you are not'. This is an issue which suggests that the type of power that the leader can exercise will determine leadership influence (8). Therefore, if Leader 3 is to be empowered to lead, the organisation will need to address these 'tribal' problems and overcome these barriers to change (11).

Whilst there were clearly organisational barriers, it was apparent from the interview there were also personal barriers which would impact on her style. These were reflected in her values and beliefs about the superiority of her own profession which were likely to be perceived as inflammatory. Whilst this could be attributed to a lack of self-awareness, it was also clear that she had not received the developmental opportunities that she may need to undertake her leadership role and work more effectively across boundaries. It has been suggested that support mechanism need to be established to enable people to evolve (19). Where such structures are absent, as suggested here, resistance is likely and a process of dissociation may occur.

This was in many ways reflected in her sense of frustration that 'preoccupation with the superficial' meant that the organisation had 'lost touch' with employees 'further down the hierarchy.' Whilst this was seemed as possible for those 'at the top' to vision, the reality for others was to maintain a reasonable service where 'the risks of failure and harm were high.' Again, similar to Leader 2, this conveyed a rather inward looking manager's response with echoes of transactional leadership behaviours. This was reflected in her comments about a lost image of the past 'when leaders had strong values' that reflected rigid codes of moral behaviour and 'professional values to which practitioners should inspire.' These appear to be in conflict with current notions of leadership being assigned authority from followers (14).

In the context of low morale and difficulties recruiting and retaining staff, strategies for acknowledging and valuing the contribution of staff were seen by Leader 3, as important for motivation. 'Rewarding' staff through training, developmental opportunities and promotions were important issues. Where change was complex or outcome uncertain the there was a need to allow people the time to assimilate the transitions and be supported throughout the process. This suggested a higher person orientation, which was reflected in the T-P leadership questionnaire rating (Table 3). Most revealing were the results of the leadership perceptions survey, which did not appear to reflect the personal struggles that she faced (Box 3).

What is perhaps important from a self-evaluative perspective is the view that she may need to be more actively involved in communicating the vision and in promoting innovation.

Table 3. Result of the T-P Leadership Questionnaire for Leader 3

Leader	Task	Person
3	9	11

Box 3. Summary of the Leadership perception survey for leader 3

- Good at organising and seeing a project through
- Open and honest with people
- Gets to know the staff and acts as a good advocate
- Need to be more clearer about where they are going
- Need to be more receptive to new ideas and different ways of doing things.

Conclusion

The findings of this investigation are in many ways supportive of the initial hypothesis that primarily transactional leadership roles would be most evident. Whilst all three displayed transformational components and high levels of emotional intelligence, the differences in style identified were influenced by their power and position within the organisation, personality characteristics, and the level of support available, their professional values and the prevailing culture. Arguably it was only the most senior, and most powerful individual, who displayed behaviours closest to the transformational ideal, but even he was perceived as distant and not always valuing others' involvement.

Whilst all three invested considerable energy to be effective, the apparent lack of unifying vision meant that their energy was wasted on a vision, possibly perceived as inspiring to one tribe, but perceived very differently by another. The conflict apparently highlights the reality, that with few exceptions, the success of any leader relies almost entirely on the symbiotic relationship with their followers (20).

Whilst there is no doubt about the interpersonal skills of each of the participants, what appeared to be hindering and frustrating them was an appreciation of the whole context of their leadership role. This lack of awareness was clearly inhibiting and resulting in behaviours that maintain the status-quo. There is a need to have joint responsibility between the individual to network and develop their leadership style and the organisation facilitating such development for their leaders.

It is perhaps also important to remember that leadership is only the authority assigned by followers (14). As was evident from this inquiry, it places particular demands on individual leaders and requires a style that can transcend and look beyond not only their own values but possibly even those of their professional group or team.

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PALM KERNEL OIL BLENDS AS SUPPOSITORY BASES IN THE DELIVERY OF ASPIRIN

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ABSTRACT: Rectal delivery of drugs has been proven to be effective in terms of drug absorption and distribution comparable with other routes such as oral, buccal, sublingual or even nasal. In this study, two new suppository bases were developed using combinations of locally sourced hydrogenated palm kernel oil, hydrogenated palm kernel stearin and hydrogenated palm kernel olein with mixtures of stearic acid and glyceryl monostearate. When formulated with aspirin, these bases produced suppositories with acceptable characteristics. These aspirin suppositories were tested on twelve healthy subjects after an approval from the Medical Ethics Committee, University of Malaya had been procured. We quantified aspirin from the urine samples of the subjects to determine the relative availability of the different suppository preparations relative to an oral dose. The excretion of salicylic acid, one of the metabolite of aspirin in human urine taking aspirin was quantified. The F value was found to range from 1.16 to 1.38. Hence, the excretion results showed that these palm kernel oil blends are suitable suppository bases. *(JUMMEC 2007; 10(2):43-50)*

KEYWORDS: Rectal delivery, palm kernel oil, suppository, aspirin, urine.

Introduction

Suppositories use oil only in the form of hard butter. Suppository bases have evolved from the traditional cocoa butter (theobroma) to currently available commercial bases such as the Witepsol(r) and Wecobee(r) which are made from the lauric component of coconut oil. These bases are replacing theobroma as it exhibits problems in the preparation and storage stages of the finished suppository product (1). As Malaysia is blessed with an abundant production of palm oil or palm kernel oil, new suppository bases can be formulated which can have characteristics similar or superior to the currently available commercial suppository bases mentioned earlier. For instance, the suppository bases made from palm oil and palm kernel oil can be made to be more robust and can be exposed to extreme temperatures without affecting the integrity of the finished product in terms of quality and effectiveness. This study was designed to determine the suitability of palm kernel oil blends as a base in the production of suppositories. In terms of drug release from the proposed suppository bases in human subjects, we only sampled urine from subjects taking aspirin in the form of suppositories made from the two selected blends of palm kernel oils and an oral capsule preparation. The interpretation of urine data is very straight forward as shown by Richardson (2) in his study on urine. Approval from the Medical Ethics Committee, University of Malaya on this study had been procured (Reference number: MEC 308.4).

Material and Methods

Material used in preparation of suppository bases
Hydrogenated palm kernel oil (batch no: 0040933801) and hydrogenated palm kernel stearin (batch no: 0091420002) were procured from Cargill (M) Sdn. Bhd., stearic acid (batch no: Tristar149) was donated by Hesego Industry (M) Sdn. Bhd. and glyceryl monostearate (batch no: E01/096) was donated by Esterchem (M) Sdn. Bhd.

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Preparation of palm kernel oil blend (PKOB) suppository bases

The PKOB suppository base was prepared by blending hydrogenated palm kernel oil and hydrogenated palm kernel stearin in the ratio of 9:1 for suppository base A and in the ration of 8:2 for suppository base B, with the addition of 5% stearic acid and 5% glyceryl monostearate using an Erweka mixer (Model No. AR 402) set at a temperature of 45ºC and with a stirrer speed of 100 rpm for each preparation. After being thoroughly mixed, the blends were set to solidify at 25ºC for one week before being refrigerated at 4ºC. The amount of each component in the bases was determined earlier by trial and error where different blends were prepared and tested for good characteristics as suppository bases such as good moulding characteristics with easy release of the resulting suppositories from the mould and producing suppositories with a melting point close to body temperature and with good liquefaction time and hardness.

Preparation of Samples

The oral aspirin capsules were prepared by placing 600mg of acetyl salicylic acid (obtained from Sigma Chemical Company (USA)) into a medium-sized empty capsule. For the rectal dosage, suppositories of 600 mg aspirin were prepared using the two different types of suppository bases, A and B. The double casting method was employed for the two 600 mg aspirin suppository preparations.

Study Protocol

A number of twelve volunteers weighing between 50 kg to 75 kg were identified where their inclusion criteria were as follows:

1. Aged above 18.
2. Were not allergic to aspirin or any other salicylic preparations
3. No history of allergy to any drug or preparation.
4. Did not suffer from any gastritis condition
5. No history of any stomach or intestinal bleeding
6. No history of stomach or intestinal ulcer
7. No history of asthmatic disease
8. No history of renal diseases
9. No history of liver diseases
10. No history of bowel disease such as hemorrhoids, bleeding or carcinoma
11. Normal bowel movement

A three-way cross-over study was carried out starting with blank urine samples collection from every subject before taking any aspirin preparation. The comparator oral dosage of 600 mg aspirin capsule was taken with approximately 300 ml of water. All subjects continued to drink approximately 200 ml of fluid per hour. Urine was collected after 30 minutes and then after one hour, then continuously collected at hourly intervals for seven hours. These samples were then analysed using HPLC.

After an interval of seven days of the wash out period the same subject came back for the rectal aspirin preparation, suppository A and the same procedure as above was applied. Again after an interval of another 7 days of the wash out period the same subject came back for the rectal aspirin preparation, suppository B and the same procedure as above was again applied.

Determination of Urine Salicylic Acid Using HPLC

The HPLC used was the Waters(r) Alliance System 2690 with auto capability and Millenium 32 Chromatography Manager Software. The detector attached was the Waters(r) 996 Photodiode Array Detector. The elution was performed from a reverse phase, Supelco(r) (Bellafonte, USA), 3 micron ODS 2, 5cm $\times$ 4.6mm column, with a mobile phase of a mixture of methanol (60%) and water (40%). The flow rate used was 1ml/min and the detection was done at 254nm. The injection volume used was 20 µl.

Standards curves for salicylic acid were created by injecting the HPLC with a range of different concentrations of its standard solution and 100 mcg/ml of methyl paraben as the internal standard in fresh urine. The salicylic acid concentrations used were 15, 25, 50, 75, 100, 150 and 200 mcg/ml. The peak ratios of aspirin against methyl paraben (as internal standard) were used to plot the standard curve. Methyl paraben was used as the internal standard as the structure of both salicylic acid and methyl paraben were comparable (Figure 1). To determine reproducibility of the results, tests were carried out at three different times in a day (morning, afternoon and evening) for three different days. Fresh standards and samples were prepared for each time. Fresh urine was spiked with salicylic acid in three concentrations: 60, 90 and 180 µg/ml. This mixture was than processed and quantified in the same way as the samples of urine collected from the subjects for quantification of salicylic acid. This was to determine the accuracy of the method used in this study.

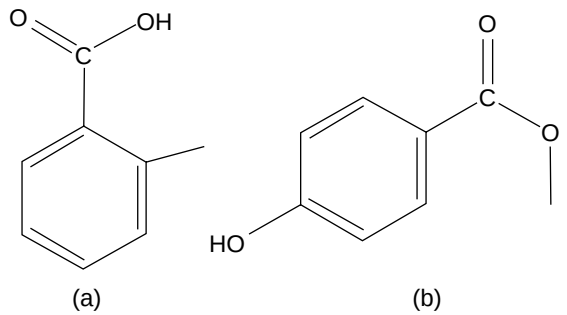

Figure 1. Structure of salicylic acid (a) and structure of methyl paraben (b)

Urine from subjects who had taken the aspirin preparation was analysed employing the following procedures:
A 2 ml aliquot of each of the urine samples was taken and mixed with concentrated ammonia solution and heated at 100°C for ten minutes. This was to break down the metabolic conjugates to release salicylic acid. The solutions were cooled and neutralized with 1M HCl solution, then transferred into 10 ml volumetric flasks where 1mg of methyl paraben was made up to 10 ml with distilled water. A 20 µl volume of the resulting solution was analyzed using the HPLC. The results were then compared with the standard curves obtained previously to establish the concentrations of the salicylic acid metabolites in the urine samples. Three injections were done for each sample, and the mean peak height ratio was taken for calculation of the sample concentrations.

Results and Discussion

Rectal delivery of drugs has been proven to be effective in terms of drug absorption and distribution in comparison with other routes such as oral, buccal, sublingual or even nasal (3). Aspirin was taken as the model drug in this study. It is a well-known drug in terms of its pharmacokinetics and its toxicity as it has been in the market for quite some time (4,5,6). Upon approval of the University of Malaya Ethics Committee, aspirin suppositories were prepared from the two blends and were tested on human subjects. Urine was sampled from the subjects and was assayed using HPLC.

The HPLC method exhibited good precision, where the RSD was found to be less than 2.8%. Figures 2 and 3 show representative chromatograms produced from this method. The HPLC method also showed a good degree of reproducibility where the statistical one-way anova analysis of the results from intra-day (morning, afternoon and evening) and for three different days showed equality of variances ($p>0.05$). Linearity was proven (Figure 4) when the standard concentration was plotted against the response (peak height ratio). The accuracy was determined by spiking three known amounts of salicylic acid to fresh urine (7), processing the urine, and quantifying the salicylic acid content again using the same method (Table 1). The paired t-test statistical analysis showed that there was no significant

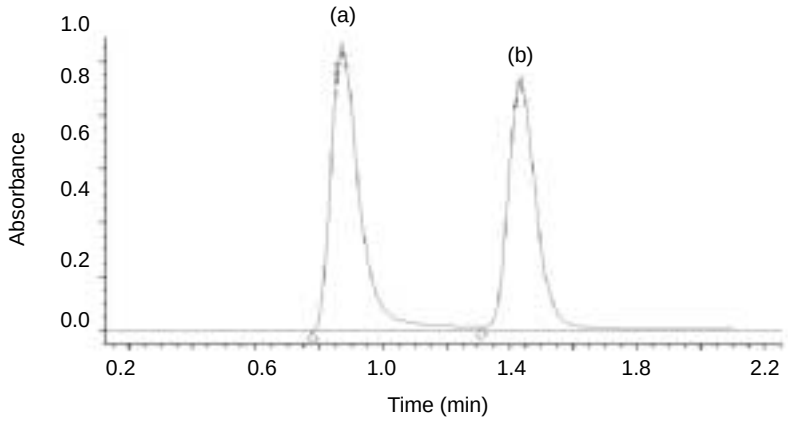

Figure 2. HPLC peaks for salicylic acid standard solution with concentration 50 µg/ml (a) and methyl paraben (internal standard) (b)

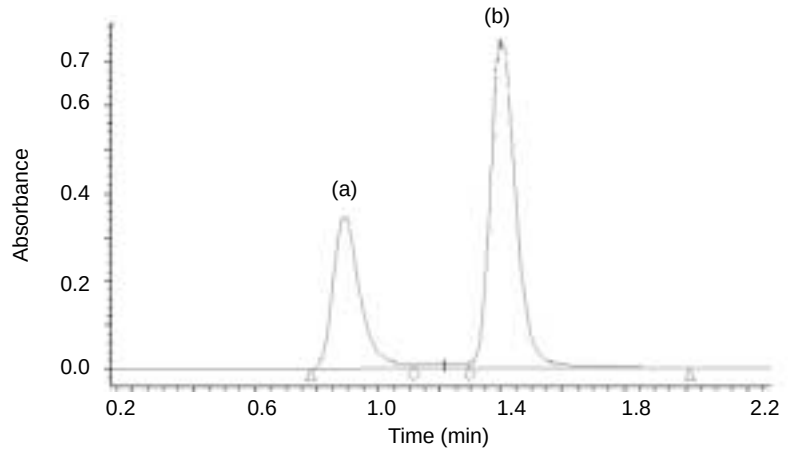

Figure 3. HPLC peaks for salicylic acid (a) and methyl paraben (b) captured from the urine of a subject after 60 minutes of introduction of 600mg salicylic acid suppository from base A

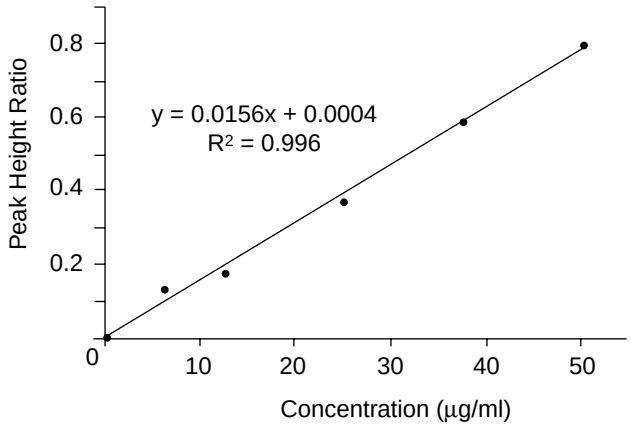

Figure 4. Standard curve for salicylic acid
The results in the graph are the mean values for injections done in the morning, afternoon and evening of three different days where the RSD was less than 2.8%, and the one-way anova proves the equality of the variances ($p>0.05$)

Table 1. Results of HPLC analysis of urine samples spiked with a known amount of salicylic acid

Actual Amount of salicylic spiked into urine (μg/ml)	Peak Height Ratio with internal standard	Amount of salicylic acid detemined by the method employed (μg/ml)	Percentage amount extracted from urine sample	*p*-value determined using the paired *t*-test statistical analysis
60	1.04 ±0.02	60.58 ± 1.17	100.97± 1.94	0.48
90	1.58 ± 0.07	91.47 ± 3.96	101.64 ± 1.44	0.59
180	3.23 ± 0.04	185.69 ± 2.40	103.16 ± 1.33	0.06

Each data is obtained from three repeated tests and expressed as mean ±SD (n=5)

difference between the actual amount spiked and the amount determined through analysis using the same method.

Table 2 shows the results of the amounts of aspirin being quantified from the urine, at certain intervals, of all the subjects involved. Figure 5 shows the salicylic acid concentration in the urine, plotted against time. The two suppository dosages with different bases show similarity in curve patterns with regard to the oral dosage. This indirectly suggests that the absorption and the elimination patterns of aspirin in the two rectal dosage forms and the oral dosage form are similar.

If plasma aspirin level was used in this study with the assumption of similarity in the distribution volume and elimination rate, the area under the curve (AUC) can be directly employed to compare bioavailability since the dosage between the compared preparations is the same (8,9).

$$F = \frac{[F]^A}{[F]^B} = \frac{[AUC]^A}{[AUC]^B} \qquad \text{---------- Eq. 1}$$

F is the bioavailability of product A compared relative to product B. In our case, we quantified aspirin from the urine samples to determine the relative availability

Table 2. Salicylic acid released in the urine of subjects who had taken 600mg salicylic acid orally or rectally

Dosage Form	Amount of salicylic acid in urine determined by HPLC at certain hours of time interval after introduction of dosage form. (mg)								
	0.5 hr.	**1 hr.**	**2 hrs.**	**3 hrs.**	**4 hrs.**	**5 hrs.**	**6 hrs.**	**7 hrs.**	**8 hrs.**
600mg Aspirin Capsules	2.08 ±0.61	5.44 ±0.78	11.27 ±1.42	15.48 ±1.21	18.94 ±0.88	14.20 ±0.77	8.63 ±0.55	5.30 ±1.20	4.25 ±1.18
600mg Aspirin Suppository of Base A	1.58 ±1.81	7.32 ±1.95	15.30 ±10.66	18.46 ±14.41	19.71 ±10.85	18.91 ±12.00	10.85 ±8.77	4.05 ±4.17	2.91 ±2.28
600mg Aspirin Suppository of Base B	2.07 ±0.58	7.95 ±3.24	19.43 ±12.46	23.63 ±4.50	21.19 ±3.40	15.60 ±6.76	13.65 ±7.37	8.40 ±2.02	4.08 ±0.78

Each data is obtained from three repeated tests and expressed as mean ± SD (n=12).

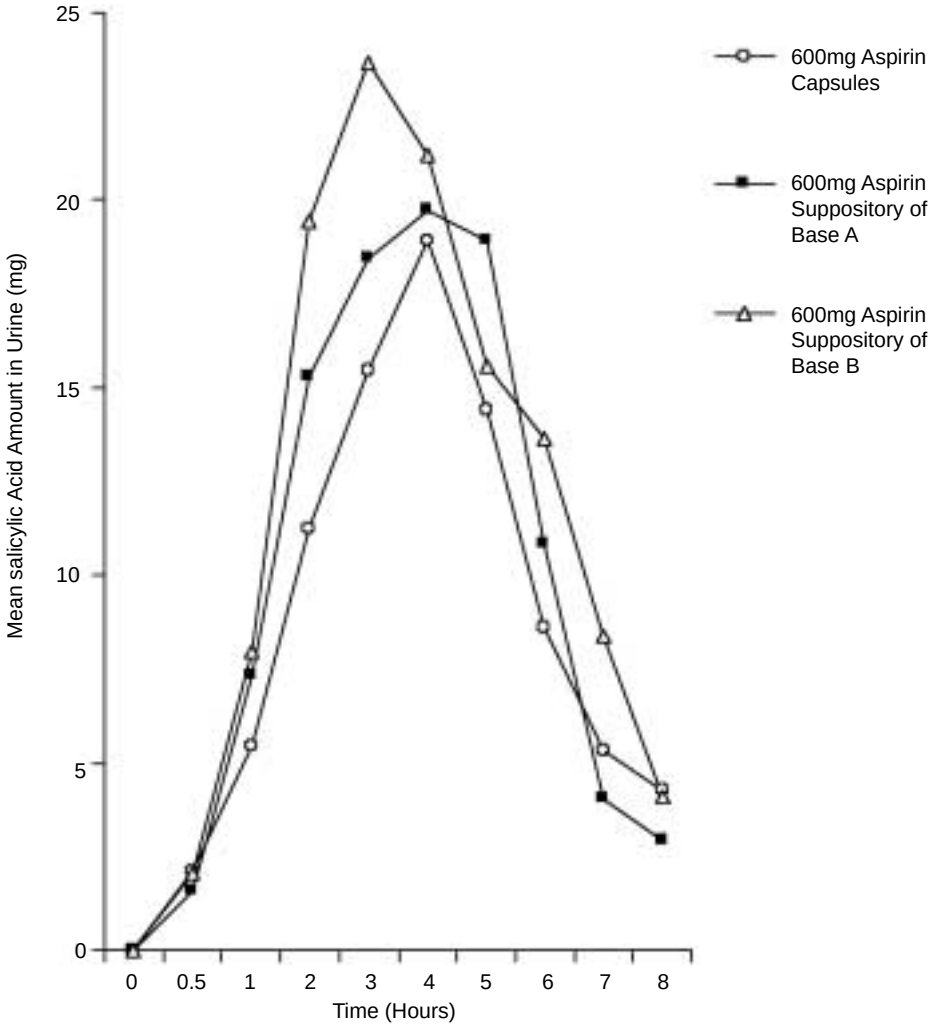

Figure 5. Comparison of plots of mean salicylic acid concentration in the urine against time for the oral capsule and the rectal suppositories made from the two selected palm kernel oil blends each preparation was tested on 12 different subjects (n=12) and the mean values of salicylic acid concentrations in urine were used to plot the curve

of the different suppository preparations relative to the oral dose, so the equation becomes:

$$\text{Relative availability} = \frac{[D_u]^{A\infty}}{[D_u]^{B\infty}} \quad \text{---------- Eq. 2}$$

Where D_u is the cumulative amount of aspirin excreted in the urine. In order to ensure that this equation is valid, we had taken into consideration normal weight with minimal variation when selecting the subjects for our study. Using this consideration, we can safely assume that the volume distribution and elimination of aspirin and absorption are likely to be the same. This will allow us to take the cumulative amount of salicylic acid in the urine from zero hour to eight hours as the relative availability for the particular preparation. Table 2 depicts the relative availability values obtained by comparing the preparation of suppositories from each of the five selected blends with the oral preparation. The aspirin excretion from the urine data collected reflects the absorption of aspirin in the oral and rectal dosage forms. In addition, the different suppository bases proposed in this study were also compared. Tables 2, 3 and 4 depict these results. Based on Shargel and Yu (8), and Gibaldi and Perier (10), we adopted the following pharmacokinetics formula which was suitable in our case where we only had urine data:

$$\frac{dD_u}{dt} = K_e D_B \quad \text{---------- Eq. 3}$$

where ke is the renal excretion rate constant, D_u is the amount of drug excreted in the urine and D_B is the amount of drug in the body at time t. The following equation can be derived taking D_B to be in logarithmic interval:

$$\frac{dD_u}{dt} = k_e D_B^0 e^{-kt} \quad \text{---------- Eq. 4}$$

From the above equation, taking the natural logarithm of both sides and then transforming to common logarithms, the following equation is obtained:

$$\text{Log } \frac{dD_u}{dt} = \frac{-kt}{2.3} + k_e D_B^0 \quad \text{---------- Eq. 5}$$

From the above equation, plotting the excretion rate with the mid-point of urine sampling interval, we determined the elimination constant, k, from the gradient and from here we calculated the half-life, t1/2, of salicylic acid excreted in the urine. Where:

$$t^1/_2 = 0.693k \quad \text{---------- Eq. 6}$$

Table 3 and 4 depict the overall results for these pharmacokinetic data obtained from the graphs (plotted on semi log paper) of the rate of excretion and the midpoint of time intervals.

Table 3. Relative bioavailability of aspirin for each suppository preparation compared to the oral preparation

Suppository of Different Base	Cumulative Amount of Salicylic Acid Excreted in 8 hours (mg)	Cumulative Amount of Salicylic Acid Excreted for oral preparation in 8 hours (mg)	Relative availability of suppository preparation relative to the oral preparation
600mg Aspirin Suppository of Base A	99.09	85.63	1.16
600mg Aspirin Suppository of Base B	118.00	85.63	1.38

Table 4. Elimination rate constant and the salicylic acid half-life calculated for each preparation.

Dosage form	Gradient (-k/2.3)	Elimination Rate Constant (k)	Half-life of Salicylic acid (t1/2=0.693/k) (hr)
600mg Aspirin Suppository of Base A	-0.208	0.479	1.45
600mg Aspirin Suppository of Base B	-0.189	0.435	1.59
600mg Aspirin Capsule	-0.191	0.438	1.58

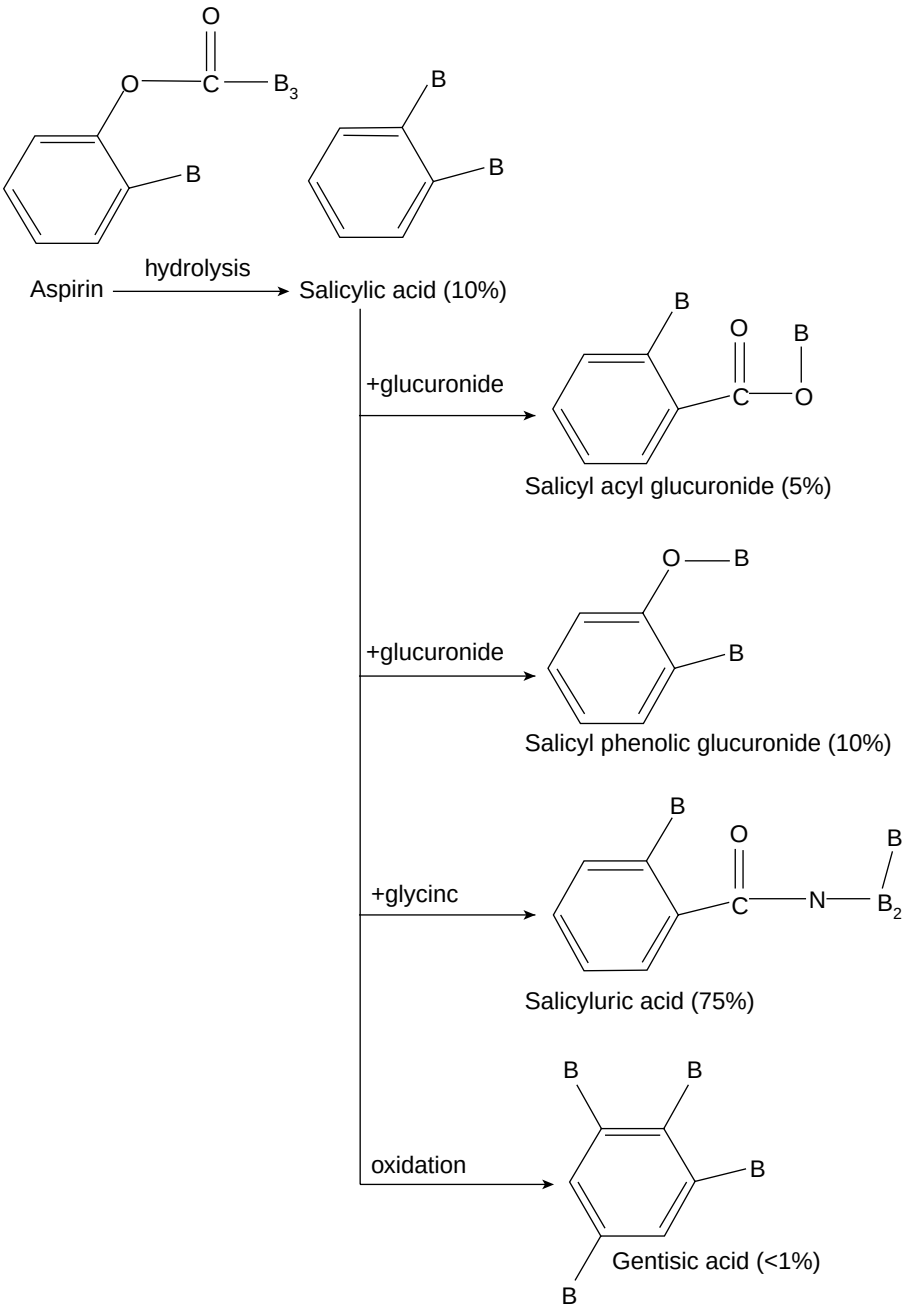

Figure 6. The percentage amount stated for each metabolite was adopted from Insel (II)

The fact that all the graphs plotted show the rate of excretion steadily decreasing linearly in the latter portion shows that excretion followed first order kinetics where as the metabolite's concentration in the body falls, the rate of excretion also falls. This is in agreement with the study by Gibaldi and Perrier (10).

Due to some limitations, we could not determine the full pharmacokinetic profile for each of our preparations. We could only determine the release of aspirin in the form of salicylic acid in the urine, and since we did not have data such as the IV bolus and the plasma level of the drug, we were unable to do a full pharmacokinetic study. But this study indirectly shows that aspirin was released from the proposed suppository bases and was absorbed into the body with steady elimination rates. Table 3 shows the relative availability of all rectal aspirin preparation relative to the oral preparations. The relative availability for each rectal preparation was found to be better compared to the oral preparation. This may be due to the rectal anatomy and its physiological conditions. Drug that is given rectally may be transported by the inferior and middle haemorrhoidal veins and bypass the liver. As such the availability of drug will be different and higher than the oral route.

If we calculate the percentage of salicylic acid released in the urine for the oral and rectal preparations we found that it ranges from 13.7% to 17.1%. The percentage of salicylic acid excreted in urine after ingestion of aspirin is extremely variable and depend upon the dose and the urine pH and the amount can be as low as 0.5% to as high as 30% (11,12,13,14). Figure 6 shows the various aspirin metabolites that can be found in the urine with their reported percentages.

Table 4 depicts the half-life of salicylic acid calculated from the urine data. The half-life of aspirin preparation in the body is very well established as it is not a new drug. Aspirin had been documented to have very short half-life which is less than thirty minutes but the salicylic acid normally shows longer half-life of more than two hours (15). The half-life of salicylic acid in this study was found to range from 1.45-1.58 hours and they are lower than the reported values. This may be due to the small population of subjects where in this study the number were only twelve.

Conclusion

The excretion of aspirin in the urine of twelve subjects taking suppositories made from the two different blends indirectly reflects the drug release ability of these preparations. The bioavailability of the two aspirin suppositories were found to be better than the oral route of administration.

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HIGH DOSE INTRAVENOUS IMMUNOGLOBULIN FOR SYSTEMIC LUPUS ERYTHEMATOSUS WITH LUPUS NEPHRITIS AND ASSOCIATED STUDIES – CASE REPORT

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ABSTRACT: Systemic lupus erythematosus (SLE) is one of the commonest systemic autoimmune diseases that can present with variable clinical manifestations. Intravenous Immunoglobulin (IVIG) has been used as a salvage therapy for severe lupus with encouraging results though there is yet randomised trial to support the usage. This report highlights the efficacy and safety of high dose IVIG in SLE patients with multi-organ involvement particularly lupus nephritis. We also reviewed the literature on the usage of IVIG for lupus nephritis. However, more studies are needed to further clarify the optimal therapeutic dosage and regime for IVIG and to identify the group of patients who might benefit the most from this expensive therapy. *(JUMMEC 2007; 10(2):51-56)*

KEYWORDS: Systemic lupus erythematosus, lupus nephritis, Intravenous Immunoglobulin

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder with variable clinical manifestations that can range from mild clinical findings to life-threatening condition. The conventional treatment for SLE includes steroids and cytotoxic agents such as cyclophosphamide, azathioprine, cyclosporine and newer agent, mycophenolate mofetil. These agents can be very effective in suppressing SLE activity but can also result in severe infection due to immunosuppression. Intravenous immunoglobulin (IVIG) is a standard treatment for various immunodeficiency states and some autoimmune disease such as immune thrombocytopenic purpura (ITP), Guillain-Barre disease, polymyositis and Kawasaki's disease. This expensive drug has been used as a rescue therapy to treat SLE for the past 20 years with encouraging results. We reported three cases of SLE with lupus nephritis and multi-organ involvement that were treated with high dose IVIG with excellent response.

Case Reports

Case 1

Miss NH is a 17-year-old girl who was found to have SLE in 2003 when she presented with autoimmune haemolytic anaemia. She was treated with prednisolone and Azathioprine with satisfactory response. She was diagnosed to have lupus nephritis in April 2005 with renal biopsy confirmed diffuse proliferative glomerulonephritis (DPGN). She then deteriorated with spiking temperature, worsening renal function and severe abdominal pain with profuse watery diarrhea. She developed severe sepsis and was treated empirically as spontaneous bacterial peritonitis in addition to active SLE with multi-organ involvement, i.e., lupus nephritis with renal failure, serositis with pleural effusion and pericardial effusion as well as possible mesenteric vasculitis.

She was managed in the intensive care unit and was commenced on continuous renal replacement therapy. In view of concomitant sepsis and active lupus, IVIG was commenced at 0.4 g/kg/day for five days (total dose of 2 g/kg). Her condition stabilised and she was transferred to the normal ward after one week but was still dialysis-dependent. She developed status epilepticus nine days later which needed multiple anti-epileptic agents to control the seizure. Biochemistry results, CT brain and lumbar puncture excluded infective and metabolic cause of the status epilepticus. She was treated as lupus cerebritis and was commenced on therapeutic plasma exchange. She responded well to the treatment with cessation of the seizure and renal

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function continued to improve till off dialysis after three weeks. She was commenced on mycophenolate mofetil at the dose 2 g per day after completing six monthly cycle of IVIG. She is currently well with complete remission of the SLE. The renal function remained normal with latest serum creatinine of 60μmol/L and she has no residual neurological deficit.

Case 2

Miss NSC was found to have SLE at the age of fifteen when she presented with skin rashes, arthritis, leucopenia and thrombocytopenia. She was initially treated with oral prednisolone and hydroxychloroquine with satisfactory response. Five years later, she developed class IV lupus nephritis. She achieved complete remission after a course of oral cyclophosphamide. She could not tolerate Azathioprine due to leucopenia and was commenced on mycophenolate mofetil (Cellcept) with excellent response.

However, she stopped taking the medications due to financial reasons and was presented with features of active SLE nine months later with leg swelling, facial puffiness, multiple joint pain, fever and thrombocytopenia. She was given pulse methylprednisolone with total dose of 1.5 grams but developed generalised tonic-clonic seizure and acute confusional state. All the electrolytes were normal and CT scan of brain did not reveal any intracranial lesion. At the same time, the renal function deteriorated very rapidly requiring dialysis support. Therefore, diagnosis of active SLE with possible cerebral lupus, lupus nephritis with rapidly progressive glomerulonephritis (RPGN) and thrombocytopenia was made. In view of the spiking temperature and possible concurrent infection, IVIG was started at 0.4g/kg/day for five days (total dose of 2g/kg).

She continued to have high blood pressure with persistent headache and blurred vision. MRI brain revealed sagittal sinus thrombosis. The thrombophilia screen was negative. Anticardiolipin antibody and lupus anticoagulant were also not suggestive of antiphospholipid syndrome. Lumbar puncture was also normal. She was commenced on anticoagulation. Her renal function stabilised after the IVIG and she managed to come off dialysis after one week with serum creatinine ranged 200 - 240μmol/L. The platelet count also normalised later and she was maintained seizure-free with antiepileptics. She continued to receive IVIG for another three monthly cycles before converting to mycophenolate mofetil. She remained well and the serum creatinine continued to improve and ranged 160-180 μmol/L on last follow-up. Renal biopsy which was performed after she completed the warfarin therapy revealed class IV lupus nephritis with evidence of chronicity.

Case 3

Miss NW, 22-year-old lady, was diagnosed to have SLE in 2003 with nephrotic-nephritic syndrome and positive SLE serology. Renal biopsy confirmed focal proliferative glomerulonephritis with membranous changes (Class III and V disease). She achieved remission after prednisolone and Azathioprine. She was advised to have a repeat renal biopsy at the end of 2006 when was found to have increased proteinuria and active urine sediments. Unfortunately, she was not keen and the prednisolone dose was stepped up during the review.

A month later, she presented after being unwell and febrile for three weeks. She developed episodes of seizure and was ventilated for airway protection. Further investigations revealed that she has active SLE with multi-organ involvement which include lupus nephritis with renal failure, pancytopenia, extensive vasculitic lesions over the trunk and limbs and likely cerebral lupus which caused the seizures. MRI revealed cerebral atrophy which was not consistent with her age but no vasculitic lesion in the brain and no evidence of transverse myelitis. Lumber puncture was not performed without the consent from the parents.

Intravenous methylprednisolone was given but was withheld after two doses due to spiking temperature. IVIG was commenced at 0.8g/kg/day for four days (total dose of 3.2g/kg). At the same time, her kidney function worsened and was commenced on continuous renal replacement therapy. She improved very slowly and needed prolonged ventilation for almost a month. Her renal function also started to improve after the second dose of IVIG three weeks later and she managed to come off dialysis after being dialysis-dependent for 36 days.

Unfortunately, she was found to have tetraplegia with no bladder or bowel involvement after being extubated. Nerve conduction study showed axonal peripheral neuropathy which was not conclusive. Her neurological status improved very slowly but was encouraging. At the current state, she is ambulating with support and is independent on activities of daily living. In view of the significance improvement, the IVIG was continued at 3.2g/kg for total of four cycles before changing to mycophenolate mofetil as maintenance therapy. Renal biopsy later confirmed Class IV lupus nephritis with crescent formation. She is currently in complete remission with normal renal function.

Literature Review

Intravenous immunoglobulin (IVIG) has been used to treat Systemic lupus erythematosus (SLE) for various indications for decades which include lupus nephritis, cerebral lupus with encephalitis, neuropsychiatric lupus, immune thrombocytopenia or autoimmune haemolytic anaemia, antiphospholipid syndrome, pneumonitis, serositis and vasculitis. The most extensive experience is with lupus nephritis. However, the usage is mainly based on case reports and case series. We reviewed about 16 reports/series which used IVIG in lupus nephritis of various classes. The overview is presented in Table 1.

The most common indication to use IVIG in most of the reports is as a salvage therapy for severe active lupus when the patients do not response to conventional therapy or when there is concurrent active disease and sepsis. Various IVIG doses and regime has been used in different reports. The commonest dosage regime is 0.4g/kg/day for five days or total dose of 2g/kg which is most probably based on the experience of IVIG in treatment of other autoimmune disorders such as Guillain-Barre syndrome and ITP. The total courses given ranged from one to twenty-four. Overall, there was no conclusive evidence to suggest the optimal therapeutic dosage and regime.

There was only one randomised trial by Boletis and coworkers (1999) who studied the use of IVIG as maintenance therapy in proliferative glomerulonephritis (1). All the patients were treated with prednisolone and cyclophosphamide for six months before being randomised to cyclophosphamide or IVIG as maintenance therapy. Five patients were treated with IVIG 0.4g/kg body weight monthly for 18 months and nine patients were treated with cyclophosphamide 1g/m2 every two months for six months and every six months for one year. IVIG was found to be safe and as efficacious as cyclophosphamide to maintain the disease activity. However, the cost effectiveness of the above approach needs further evaluation.

The first report came from Sugisaki in 1982 who reported the use of IVIG in three patients with lupus nephritis with 100% improvement in proteinuria (2). Most of the experience on use of IVIG in lupus nephritis was reported in 1990s. Monova had the largest clinical experience with IVIG in the recent years involving 116 patients with biopsy-proven glomerulonephritis (3). Among those, fifty-eight patients had lupus nephritis with varying classes from class II to V. Among the eighteen patients with proliferative glomerulonephritis (Class IV), twelve achieved partial or complete remissions, two was dialysis-dependent and five died. Similarly, the IVIG dose used was much lower i.e. 0.255g/kg body weight.

In summary, the above reports suggested that IVIG is a safe and efficacious therapy for lupus nephritis of varying classes. Yet, many questions remained unanswered. Controlled studies on the use of IVIG in SLE and lupus nephritis in particular are very limited. Secondly, the dosage and regime used in various reports has been variable. In view of the high cost of the therapy, further study to determine the appropriate therapeutic indications and the optimal dosage and regime would be very essential.

Discussion

The three patients who were presented above had severe active SLE with multi-organ involvement which include Class IV lupus nephritis, neurological and haematological involvement. Table 2 gives an overview of patients' details, treatment and outcome. One of the main indications for IVIG in these three cases is concomitant sepsis and active SLE because of its immunomudulatory effects. As in other autoimmune diseases, the exact mechanism of action of IVIG in SLE is unclear. Some investigators demonstrated that gamma globulins solubilised glomerular immune deposits in lupus nephritis patients (4). Sugisaki and Lin has reported a marked reduction in immune deposits along glomerular capillary walls on follow-up renal biopsy after IVIG treatment in 1980's (2,5). However, the direct action of IVIG on glomerular immune complexes needs further investigation.

All the three patients showed marked improvement in renal function after IVIG therapy and managed to come off dialysis even though one patient (NSC) was dialysis-dependent for more than one month. The proteinuria started to reduce after the first course with normalisation of the serum albumin. This process usually takes weeks to months. Haematological complications seem to respond faster after IVIG therapy. We used IVIG dose of 2.0g/kg for the first two cases, which is the commonest dosing used in the literature. This experience was extrapolated from usage of IVIG in other conditions such as Kawasaki disease, Guillain-Barre syndrome and immune thrombocytopenic purpura (ITP). Nevertheless, the optimal dose and regime for IVIG in SLE remained unanswered. For patient NW, higher dose of 3.2g/kg was used because she was more ill at presentation.

The three patients tolerated the IVIG therapy well with no commonly reported side effects such as anaphylactoid reactions, low grade fever, backache, nausea, excessive sweating, headache or hypotension. Some has been concerned on the usage in SLE patients when Barron (1992) reported three patients who developed exacerbation or new onset of renal disease after IVIG therapy (6). IVIG induced acute renal failure

Table 1. Literature review of IVIG in lupus nephritis.

Year	Author	Type of study	Pt. No	WHO Class of LN	IVIG regime	Improved renal function	Improved proteinuria
1982	**Sugisaki (2)**	Case report	3	NS	Total dose 30g	NS	3/3
1989	**Lin (5)**	Case series	9	WHO IV 5 WHO IV+V 2 WHO V 2	2g/kg x 1-2 courses	IV- 5/5 IV+V- 2/2 V- 2/2 minor improvement	9/9
1989	**Corvetta (9)**	Case report	1	IV	1.2g/kg x 1 course	Deteriorated due to ATN	NS
1990	**Akashi K. (10)**	Case report	2	WHO IIb x 1 WHO III x 1	0.6-2.25g/kg monthly x 2-3 courses	NS	2/2
1992	**Oliet A. (11)**	Case report	1	IV	2g/kg x 1 course	Normal renal function	1/1
1993	**Winder A. (12)**	Case report	1	V	2g/kg x 1 course	1/1	1/1
1994	**Francioni C. (13)**	Case series	5	III & IV	2g/kg monthly x 6-24 courses	5/5	5/5
1995	**Welch *et al*. (14)**	Case report	1	IV	1g/kg monthly x 6 courses	Normal renal function	1/1
1995	**Welcker and Helmke (15)**	Case series	7	NS	Total dose 30g x 1 and Immunoadsorbtion	NS	NS
1999	**Arahata H. (16)**	Case report	1	IV	Total dose 62.5g	1/1	1/1
1999	**Boletis JN (1)**	RCT	5	WHO III 4 WHO IV 1	0.4g/kg monthly x 18 courses	Maintained remission	Maintained remission
1999	**Levy Y. (17)**	Case series	5	NS	2g/kg x 1-6 courses	NS	4/5
2000	**Levy Y. (18)**	Case series	7	WHO IV- 3 WHO V- 2 No biopsy- 2	2g/kg x 1-6 courses	NS	7/7
2000	**Meissner M. (19)**	Case report	1	NS	2.8g/kg x 1 course	Normal renal function	1/1
2002	**Monova D. (3)**	Case series	58	WHO II 16 WHO III 6 WHO IV 18 WHO V 18	0.255g/kg x 1-28 courses	CR 14 PR 27 Dialysis 8 Death 9	NS
2005	**Sevil Kamali (20)**	Case series	4	NS	2g/kg monthly x 1-6 courses	2/4	2/4

** LN lupus nephritis. ATN acute tubular necrosis. CR complete remission. PR partial remission. NS not specified. RCT randomised controlled trial.*

Table 2. Patients' characteristics, treatment details and outcome.

	NH	NSC	NW
Age	17	29	22
Age at presentation(year)	13(2003)	15(1993)	16(2000)
Race	Malay	Chinese	Malay
Lupus history - Organ involvement	4 years of SLE	4 years of SLE	6 years of SLE
1. Skin rash	Yes	Yes	Yes
2. Arthritis	Yes	Yes	Yes
3. Lupus nephritis	Class IV	Class IV	Class IV
4. Neurological	Cerebral lupus Depression	Sagittal sinus thrombosis	Cerebral lupus
5. Haematological	Autoimmune haemolytic anaemia	Leucopenia, thrombocytopenia	Thrombocytopenia
6. Serositis	Pleural effusion	Nil	Nil
7. Vasculitis	Pericardial effusion Mesenteric vasculitis (possible)	Nil	Skin Vasculitis
Associated antiphospholipid syndrome	Nil	Nil	Nil
Duration of dialysis dependent	21 days	7 days	32 days
Immunosuppression before relapse	Prednisolone & Azathioprine	Prednisolone	Prednisolone & Azathioprine
IVIG regime & dose	2g/kg, completed 6 monthly cycle	2g/kg, completed 4 monthly cycles	3.2g/kg, completing 4 3-weekly cycle
Outcome	Normal renal function Proteinuria resolved No neurological deficit, no depression	Mild renal impairment Proteinuria reduced more than 50% No neurological deficit	Normal renal function Proteinuria resolved Paraparesis (improving) Complete resolution of skin vasculitis
Immunosuppression after IVIG	Prednisolone & mycophenolate mofetil	Prednisolone & mycophenolate mofetil	Prednisolone & mycophenolate mofetil

is rare but potentially serious complication especially in our patients who presented with renal failure. It is also important to note that the renal complication is most probably infusion rate-dependent rather than dose-dependent (7). It was initially thought to be an immunological process when newly formed nephritogenic circulating immune complexes formed by anti anti-idiotype antibody deposit in kidney causing glomerular damage (8). Nowadays, the recognised mechanism of acute renal failure after IVIG therapy is 'osmotic nephrosis'. Large amount of sucrose used as a preservative in some IVIG products is the most probable culprit though the complication might occur even in IVIG not containing sucrose. As in contrast nephropathy, the higher risk is in patients with pre-existing renal failure, elderly, diabetics, volume depletion and concomitant use of nephrotoxic agents or diuretics.

Conclusion

Our report suggested IVIG as a safe and effective rescue therapy for SLE with multi-organ involvement. The decision to use IVIG in SLE patients is easier in severe clinical situations. Higher dosage and prolonged regime might confer more benefits. More studies are needed to determine the group of patients who might benefit the most from IVIG therapy as well as the optimal IVIG dosage and regime.

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AN UNUSUAL PRESENTATION OF A RARE RHABDOMYOSARCOMA OF URINARY BLADDER AND PROSTATE - CASE REPORT

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ABSTRACT: Rhabdomyosarcoma of the genitourinary tract is rare and predominantly affects paediatric patients. We present an unusual case of such a lesion in an adult with extensive occupation of the bladder cavity by the lesion, resulting in bilateral ureteric obstruction, without evidence of ureteric outlet invasion. We outline the unusual CT and macroscopic appearance of this lesion. We also discuss the literature data and management strategies of rhabdomyosarcoma of the genitourinary tract. *(JUMMEC 2007; 10(2):57-59)*

KEYWORDS: Rhabdomyosarcoma, soft tissue sarcoma, prostate, bladder.

Introduction

Rhabdomyosarcoma (RMS) is a malignant tumour of skeletal muscle differentiation, and may affect organs with minimal or absent striated muscles such as urinary bladder, prostate and common bile duct. The bladder and prostate sites account for about 5% of all rhabdomyosarcomas, which is more prevalent in paediatric populations, but rare in adults (1). We highlight an unusual case of adult rhabdomysarcoma of the urinary bladder with an unusual presentation.

Case Report

A 56-year-old man presented with haematuria preceding an episode of acute urinary retention. Initial IVU, during which the renal profile was normal, showed a large filling defect in the bladder with bilateral hydronephrosis and hydroureter (Figure 1). His renal function deteriorated despite catheterisation, and he was treated with haemodialysis and bilateral percutaneous nephrostomy, after which his renal function normalised. Cystoscopy confirmed presence of extensive bladder lesion, which occupied the whole bladder cavity, without room for endoscopic resection. The biopsy revealed a high grade sarcoma. Staging CT scan demonstrated an organ confined lesion, with no lymphadenopathy. The bladder was completely filled with the lesion, interfaced with air filled cavities (Figure 2). The patient subsequently underwent a radical cysto-prostatatectomy with urinary diversion by ileal conduit. The intra-operative findings revealed a urinary bladder densely packed with lesion,

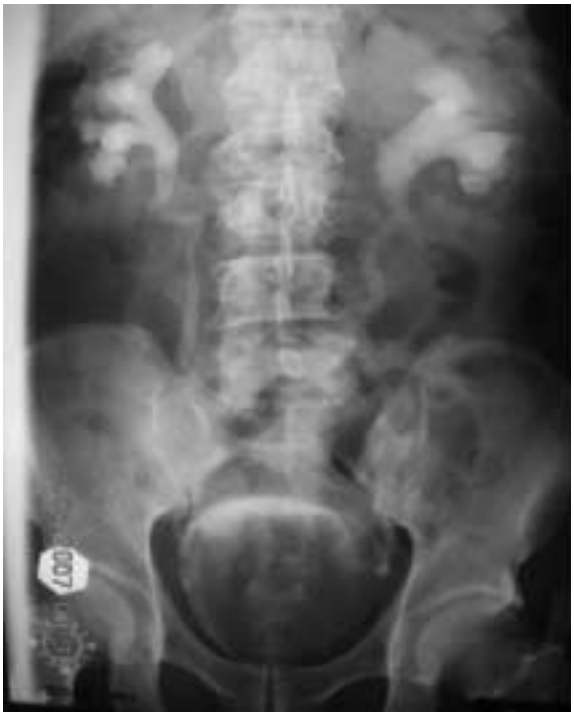

Figure 1. IVU showed a large filling defect in the bladder with bilateral hydronephrosis and hydroureter.

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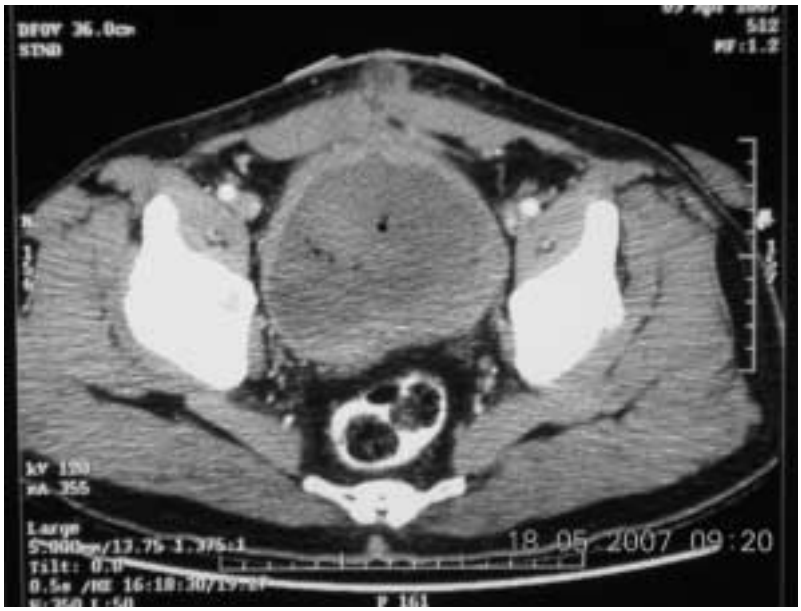

Figure 2. Staging CT scan demonstrated an organ confined lesion, with no lymphadenopathy. The bladder was completely filled with the lesion, interfaced with air filled cavities.

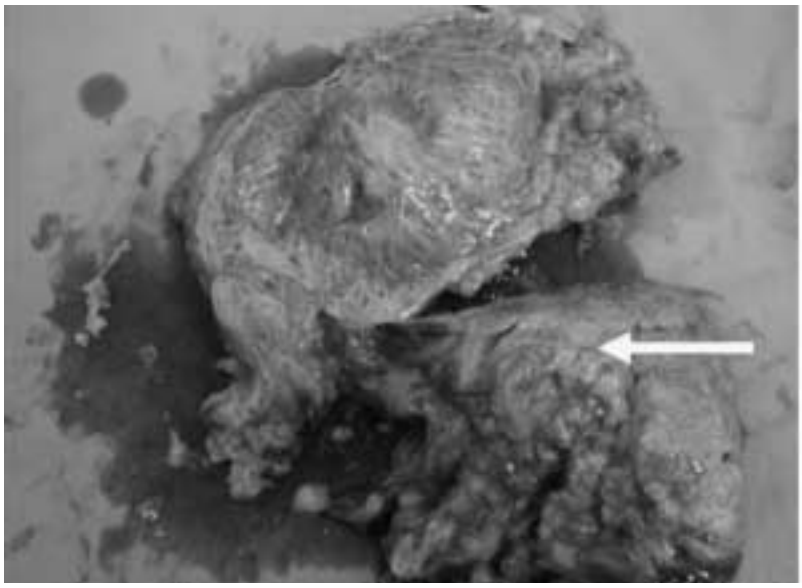

Figure 3. The macroscopic specimen revealed an extensive occupation of the lesion in the bladder cavity and with solitary site of tumour invasion (Arrow).

resulting in bilateral ureteric obstruction, without evidence of ureteric outlet invasion. The macroscopic specimen revealed an extensive occupation of the lesion in the bladder cavity, with solitary site of tumour invasion (Figure 3). The histopathology confirmed highly pleomorphic embryonal type of rhabdomyosarcoma involving the bladder and prostate. Distal end of both the ureters were free of tumour. The patient subsequently underwent adjuvant post-operative IVA regime chemotherapy, i.e., Ifosfomide (3gm/m2), Vincristine (1.5mg/m^2) & Actinomycin D (1.5mg/m^2) for 7 courses followed by 28 and 3 fractions of Radiotherapy to the pelvis and prostate respectively.

Discussion

Primary soft tissue sarcoma of the genitourinary tract in adults is very rare. In the United States, out of ten thousand newly diagnosed cases of soft tissue sarcoma in 2005, only 2.1% involved the genitourinary tract (2). The low incidence of this type of malignancy results in the lack of data available in our extensive literature search.

Leiomyosarcoma is the commonest type, and rhabdomyosarcoma is the least common histological type of soft tissue sarcoma. Bladder and prostate

rhabdomysarcoma also accounts for 0.1% of all the soft tissue sarcoma (3, 4). Rhabdomyosarcoma can be divided into embryonal, alveolar and the pleomorphic types. Embryonal type is the most common, accounting for about 2/3 of cases. Pleomorphic type is very rare and seen only in adults. Prognosis is better in the embryonal type, especially the botyroid and spindle-cell variety (1).

Rhabdomyosarcoma of bladder and prostate predominantly affects the paediatric male patients, and usually present with haematuria and bladder outlet obstruction (3,5). The treatment option largely depends on the stage of the disease at the time of presentation. A well localised disease to the bladder/prostate confirmed by imaging modalities like CT scan is best treated with a radical resection. A complete resection with negative surgical margins (6) gives the best recurrence, progression and survival outcomes (6, 7, 8). The overall prognosis for the genitourinary soft tissue sarcoma is poor compared to the soft tissue sarcoma of other origins (8). The role of adjuvant doxorubicin chemotherapy has not been fully established (9). Although Doxorubicin-based chemotherapy are popular, e.g., VAC regime (Vincristine, Adriamycin and Cyclophosphamide), other regimes like IVA (Ifosfamide, Vincristine and Actinomycin D) and MAID regime (Mesna, Adriamycin, Ifosfamide and Dacarbazine) are also being administered but the success rates needs further evaluation (10).

Conclusion

Rhabdomyosarcoma of the bladder and prostate is a very rare entity and has very poor prognosis. A complete surgical resection in the form of a radical cysto-prostatectomy with negative margins is recommended. This is essential to ensure a good outcome. The use of adjuvant chemotherapy needs further evaluation.

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