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JUMMEC publishes both basic and applied science as well as clinical research studies on any area of medicine that is of interest and relevance to the medical community. This is a peer-reviewed Journal that publishes twice yearly on Review Articles, Original Articles, Short Communications, Clinico-pathological conference abstracts, Case Reports, Letters to the Editor and Book Reviews.

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We welcome journal submissions throughout the year but preferably by **March** and **September**. Articles submitted for publication are understood to be offered only to *JUMMEC* and which have not been sent to other journals for consideration.

Cover

Kompleks Kesihatan Wanita dan Kanak-kanak (Obstetrics & Gynaecology and Paediatrics Building), University of Malaya Medical Centre. Image courtesy of Professor Dr. Thong Meow Keong.

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The **Journal of Health and Translational Medicine (JUMMEC)** publishes both basic and applied science as well as clinical research studies on any area of medicine that is of interest and relevance to the medical community. This is a peer-reviewed journal that publishes Reviews Articles, Original Articles, Short Communications, Clinico-pathological Conference Abstracts, Case Reports, Letters to the Editor and Book Reviews.

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Each manuscript component must begin on a new page in the following sequence: (1) title page; (2) abstract and keywords;

(3) text; (4) acknowledgements; (5) references; (6) figure legends;

(7) tables; and (8) figures. Please submit figures as separate figure files (jpeg or gif) with 300 dpi resolution or better.

Type manuscript double-spaced throughout. Number pages consecutively commencing on the title page.

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The title page should contain a concise title of the article. Names of authors who have contributed to the writing of the manuscript should be written in style of initials followed by surname or preferred name, eg. Saleena VEO, Anita S or Brown J. Add at the bottom of the phrase "Address for correspondence;" followed by full name and address with postal code and email address.

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Limit the number of words to 150. It should state the purpose of the study, a brief description of the procedures employed, main findings and principal of conclusions. At the end of the abstract, please include an alphabetical list of 3-5 keywords and subjects for indexing. Choose the appropriate keywords as these will be used for subsequent retrieval.

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It should consist of an Introduction, Methods, Results, Discussion and Conclusion/Recommendation. Systeme Internationale (SI) Units should be used. Use only standard abbreviations. The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement.

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Number the references in the order of mention in text. References in the text should be indicated by a figure within parenthesis e.g. (1, 2,). Limit references to 30, if possible. Identify references in text, tables and legends.

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Forewords from the Editor

Dear Readers of JUMMEC,

Welcome to the second issue of Journal of Health and Translational Research's *(JUMMEC)* 2012. With the success of our first issue this year, we are now proud to present you another four interesting articles which we hope would be useful in your medical career.

First, let me introduce you to one of our prominent clinician scientists at University of Malaya Medical Center (UMMC), Professor Dr. Thong Meow Keong. Professor Thong has pioneered the field of genetic testing in Malaysian paediatric research. In an article based on his inaugural lecture in 2011, Professor Thong described his view on the development of genetic testing and research in clinical practice in Malaysia. He has witnessed and experienced both the expectation as well as the criticism of this ethically challenging field. In his article, he summarized the achievements and progress in major genetic diseases among Malaysian children. He put forward suggestions and perspectives as how he sees the field should move forward. His many years of experience and success have inspired many budding clinicians to follow his path, and it is with great pleasure and privilege that I share his article with you in this issue.

In this issue, we are also featuring three other medical articles, two of which are on chronic diseases. In any developing and developed countries, including Malaysia, the burden of non-communicable chronic diseases such as obesity and chronic obstructive pulmonary disease (COPD) is rising at an alarming rate. Public awareness on such diseases is crucial; yet, it is unknown which methods are effective in distributing the health information. A study, led by Dr. Tin Tin Su, will describe their investigation on the impact of socio-demographic factors in health information acquisition by the public. The other study by Dr. Hjh, Ayiesah Hj. Ramli, will compare the effectiveness of Feldenkrais method in improving therapy regimen in patients with COPD. Both these studies hopefully will provide more insights on how we, the medical practitioners, combat non-communicable chronic diseases.

Our last article I want to introduce is a result of a randomized clinical trial led by Dr. Koh Peng Soon from Department of Surgery, UMMC. This trial was testing on the effectiveness of preemptive local anaesthetic infiltration to reduce pain in patients undergoing laparoscopic cholecystectomy.

I hope that the articles featured in this issue will inspire you to pursue better research and clinical practice, and I look forward to your continued support and contribution to our journal.

With best wishes,

Associate Prof. Dr. Ivy Chung
Editor,
The Journal of Health and Translational Medicine.

PROFESSOR DR THONG MEOW-KEONG

MBBS (Malaya), M Paeds (Malaya), MD (Malaya), FHGSA (Clinical Genetics), FAMM, FAMS (Hon)

Biography

Dr THONG Meow Keong is a Professor of Paediatrics and Consultant Clinical Geneticist at the University of Malaya Medical Centre, Faculty of Medicine, University of Malaya. He is a board-certified clinical geneticist by the Human Genetics Society of Australasia.

He pioneered and established the first Genetics Clinic in 1995 and the Genetics & Metabolism Unit at the Department of Paediatrics, Faculty of Medicine, University of Malaya. He worked closely with the Ministry of Health Malaysia in developing the counselling module for thalassaemia and clinical practice guidelines on inherited disorders and was invited by the World Health Organization and March of Dimes to prepare a monograph on management of individuals with birth defects and haemoglobinopathies. He also contributed to the Oxford Monograph in Medical Genetics: Genomics and Health in the Developing World, published by the Oxford University Press in 2012

Dr Thong received numerous awards in the past 10 years. He was a Fulbright scholar and past winner of the 8th Royal College of Physicians of London and Academy of Medicine of Malaysia Annual Research Award, recipient of the Australia-Malaysia Fellowship in Research Excellence award by the Australia-Malaysia Institute, as well as Travel Award by the Asian Society for Pediatric Research, Japan. He and his team were gold medallist at the "Biotechnology Asia 2006" and 18th I.TEX Exhibition.

He has served for many administrative roles in University of Malaya. He was awarded the University of Malaya Distinguished Service awards. He was the Head, Department of Paediatrics, University of Malaya from 2009-2011. He is also an Associate Editor for two journals, reviewer for journal manuscripts and research grant applications as well as a theses examiner for national and international examinations.

Currently, he holds many leadership roles in medical associations. Dr Thong is the President of the Asia-Pacific Society of Human Genetics, Vice President of the Medical Genetics Society of Malaysia, Chairman of the Clinical Genetics sub-speciality committee of the National Specialist Register Malaysia and President of the College of Paediatrics, Academy of Medicine of Malaysia.

Dr Thong's current research interests included rare disorders, preventive and curative strategies for genetic disorders, genetic counselling and inborn errors of metabolism. He has published over 60 peer-reviewed publications on genetic disorders that hitherto have not been documented in Malaysia, authored 4 books and 10 book chapters and presented in many national and international conferences. One of his most featured books includes "Rare Journeys of Love", entailing real-life stories of Malaysian patients and their families in coping and living with rare genetic conditions. His passion in improving the quality of life and care for these courageous young children has inspired many younger generation of clinicians and scientists.

GENES, MEDICINE AND SOCIETY: FROM PAEDIATRICS TO GENETIC COUNSELLING AND BEYOND

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ABSTRACT:

The story of Clinical Genetics is a relatively new one, first spearheaded by Paediatrics but increasingly, has taken root in all branches of medicine leading to 'Personalised Medicine'. There are expectations that this revolution in genetics will pave the way to genomic medicine and a cure for all inherited disorders. The development of the field of Clinical Genetics and Genetic Counselling in Malaysia is still in its infancy. Using evidence-based data on genetic disorders such as birth defects, inborn errors of metabolism, genetic syndromes, neurological disorders and hereditary cancers, that hitherto have not been well documented in Malaysia, this review article will focus on findings and issues that will present a unique insight and opportunity to understanding the complex genetic counselling issues related to Clinical Genetics in Malaysia.

Keywords*: Medical genetics, genetic counselling, developing country, genomics*

INTRODUCTION

The story of medical genetics is a relatively new one, emerging with the dawn of the 20th century leading to the successful elucidation of the DNA double helix structure by Watson and Crick about 60 years ago, and witnessing the successful completion of the Human Genome Project in 2003. It is not surprising that there are a lot of expectations that this revolution in genetics will pave the way to genomic medicine and to a cure for all inherited disorders (1).

New Genetics and Personal Genomics

Since then, new information emerged on how individual genes, or groups of genes interacting together with external factors, increased our predisposition to certain diseases such as birth defects, cancers, coronary heart diseases, infertility and psychiatric illnesses. It is also expected that identification of 'good' genes may protect us from these diseases. Pharmacogenomics will lead to more targeted prescribing which is more effectively tailored to the needs of the individual. For example, the US Food and Drug Administration (FDA) released a warning to health professionals and patients that carbamazepine associated Stevens-Johnson syndrome may occur with the use of carbamazepine in patients positive for the *HLA-B*1502* allele and recommended genetic screening for patients of Asian ancestry before initiation of carbamazepine therapy (2). Genetic testing which has becoming faster and more accurate and cheaper and easily available to general practitioners may become an integral part of health care.. In short, genetics has been permeating all fields of medicine (3, 4).

The early perception that medical genetics was a specialty of minor practical relevance changed with the development of new diagnostic and therapeutic possibilities. Paediatrics had largely spearheaded the development of medical genetics. After the completion of the Human Genome Project, many researchers from various medical specialties turned their attention to investigating the role genes play in health and disease.

David Comings, editor of the American Journal of Human Genetics commented in 1980 on a then novel approach for mapping the human genome, "*Since the degree of departure from our previous approaches and the potential of this procedure are so great, one will not be guilty of hyperbole in calling it the 'New Genetics*' (5). Sir David Weatherall in his book 'New Genetics and Clinical Practise 1982 edition' predicted how medical practices will change with new developments but he also lamented "very few genetic diseases can be treated effectively" (6). Fortunately, over the period of 30 years, much has changed. Without a doubt, the greatest advances in translational medicine

over the past 2 decades had been in the area of genetics and now genomics. The range of treatment options available to manage patients with genetic disorders ranged from genetic counselling to organ transplantation. These approaches paved the way for the next wave of advances made in genetic medicine – personalised medicine with the information gained from genomics research (7).

Like any medical conditions, the reduction of the impact of genetic diseases requires both curative and preventive approaches. Treatment of genetic disorders requires the characterisation of the mutations of the genetic diseases and the understanding of the pathophysiology of these changes. With these information made available and validated, effective treatments can be instituted. Therapeutic options include specific dietary manipulation for inborn errors of metabolism, drug therapy to augment gene function such as hydroxyurea in sickle cell anaemia, enzyme or protein replacement therapy and the replacement or removal of abnormal tissues. Recombinant DNA technology has enabled biosynthetic materials such as Factor VII, vaccines and insulin to be produced in large quantities. Stem cell transplantation is successfully used to cure a number of genetic disorders, such as b-thalassaemia major and childhood malignancy. With the curative options steadily increasing, the number of conditions treated in this manner has been increasing (8).

Somatic gene therapy was considered a promising curative option but had remained largely experimental due to a number of technical difficulties (9). The failure of gene therapy to deliver its earlier promise of cure had been due to a number of factors. Firstly, the number of protein variants outnumbers the number of coding genes - one gene may affect expression of many other genes, for example, in Duchenne muscular dystrophy, a dystrophin gene mutation downregulates 327 other genes but upregulates 77 genes. In an apparent successful gene therapy for severe combined immunodeficiency (SCID) patients, insertional mutagenesis caused activation of an adjacent oncogene, resulting the patients to dye later from T-cell acute lymphoblastic leukaemia. Immunological reactions and toxicity continue to be a serious problem, and targeted delivery of the normal gene copy to all affected tissues, including brain and heart had largely been limited.

The failure of gene therapy has forced genetic research to re-focus on the basic issues – the multiple gene effects and the association of specific variations with clinical phenotypes. This has resulted in many new fields of research - epigenetics, micro ribonucleic acids (microRNAs), copy number variations (CNVs) and so on, and coupled with new technologies such as genome-wide association studies (GWAS), microarray analyses and low cost sequencing technology, personal genomics emerged (7).

Yet, the gap between these new discoveries and clinical utility remains huge. Emerging data from recent research showed the public perception towards non-specific genomics-informed personalised medicine has rather been muted. For the clinical genetics community, this is not surprising. Personal genomics (PG) tests provide targeted genetic risk profiles for specific conditions. The tests may include studies on linked or causative single nucleotide polymorphisms, functional assays, and genome sequencing and the clinical utility and validity of PG must be validated before available for personalised medicine (10). Patients, families and society want to continue to be the stakeholders, and retaining ownership of their genetic heritage while obtaining accurate diagnosis for their ailments. Personalised treatment will need to combine the classical medicine - clinical history taking with detailed family medical history, careful physical examination and appropriate diagnostic tests, with genetic counselling and genetic tests, where applicable (8).

In the face of the above transformation, what directions should be taken by the healthcare system in a developing country such as Malaysia? How do low and middle-income countries benefit from this genomics revolution and personalised medicine in view of the high cost of technology? The World Health Organization advocated the role of medical genetics and genetic counselling in the control and prevention of non-communicable diseases such as genetic conditions and birth defects (3, 4). To start on this journey, each country will need to study the epidemiology of its inherited disorders and to under the genotype-phenotype of these conditions before medical intervention using these new developments can be instituted. The following are examples of research on birth defects and genetic conditions in Malaysia that led to new insights on conditions that hitherto not been well documented in Malaysia. This enabled preventive and curative options to be utilised to reduce the impact of genetic diseases (11, 12).

From Paediatrics to Genetic Counselling and beyond

A review of Malaysian health statistics showed the number cause of death in children less than 5 years of age is no longer malnutrition or infectious diseases – it is chromosomal disorders and congenital malformations. In addition, learning difficulties and mental handicap have emerged as pressing medical problems. Adult-onset genetic disorders such as hereditary cancers have become an important target for genetic counselling and early disease detection (13, 14).

It is well-known that prevention of genetic diseases may be achieved through empowering individuals with information on their genetic risks and enabling them to make informed choices about their reproductive options. Genetic counselling is non-directive. It is a process whereby counsellors inform patients about their genetic diseases; discuss whether an inherited disorder is a certainty or just a remote possibility for their future offspring; help families make informed decision about reproductive options; and help patients cope with their grief and finally accepting their conditions (15). Accurate genetic counselling requires population-based epidemiology data as well as careful

genotype-phenotype description of various diseases found in the relevant population. Some of these issues have been studied in detail in Malaysia. Arising from these findings, some important milestones have been achieved.

Birth defects

Birth defects are the leading cause of paediatric disability and mortality in developed and developing countries (3). Most Malaysian data on birth defects come from hospital-based studies (13). Information from these studies may be biased as reported data from tertiary referral hospitals are derived from admission of infants with severe birth defects. Data on minor birth defects are not available as they may not be diagnosed. The epidemiology of birth defects from population-based studies is lacking. One of the first such studies which was jointly undertaken by the University of Malaya and Ministry of Health, focused on the epidemiology of major birth defects in Kinta district, Perak (12). Using a population-based birth defect register, major birth defects were studied in 17,720 births. For the first time, the birth prevalence of major birth defects was found to be 1 in 70. With 600,000 births a year, nearly 9,000 newborns are expected to be born with major birth defects in Malaysia each year. The exact syndromic diagnosis of the babies with multiple birth defects could not be identified in 22.5% of these babies. This finding may has implications for the allocation of healthcare resources for corrective surgery, medical treatment, early rehabilitation and intervention programs in Malaysia for this group of patients (12).

Based on the Kinta district study above, the major organ systems involved in the isolated birth defects were cardiovascular (13.8%), cleft lip and palate (11.9%), clubfeet (9.1%), central nervous system (CNS) (including neural tube defects) (7.9%) and musculoskeletal system (5.5%) (8). Among the cohort of babies with major birth defects, the mortality rate was 25.2% during the perinatal period. Various risk factors were identified in the study that predisposed mothers to having a newborn with birth defects. The consanguinity rate of 2.4% was twice that of the control population. Only 15% of major defects were detected antenatally. It is concluded that a birth defects register is needed to monitor these developments and future interventional trials such as fortification of food with folic acid and genetic counselling for at-risk families are needed to reduce birth defects in Malaysia. Subsequently, the Malaysia National Neonatal Registry was established and birth defects surveillance system was implemented (16).

Another separate study on undescended testes in new-borns was done in which 1,002 consecutive Malaysian male new-borns were examined and 4.8% were found to have undescended testes (UDT). The rate and laterality of the UDT were associated with lower birth weight and prematurity, respectively. Boys with UDT were also more likely to have other congenital abnormalities of the external genitalia, the commonest being hydrocele. Although 76.5% of UDT achieved full spontaneous descent by 1 year of age, 1.1% of all infants whose testes remained undescended required regular long-term follow-up with surgical referral and correction at an appropriate time. This finding highlighted the importance of careful postnatal and follow-up examination of these male infants with UDT to prevent future complications (17).

Beta thalassemia

One of the major life-threatening genetic conditions in Malaysian children is beta thalassaemia major. It is one of the commonest genetic disorders in South-East Asia. Hitherto, all the molecular genetics studies of this condition were done in patients from the Peninsular Malaysia. Yet, the state of Sabah had one of the highest numbers of patients with beta thalassaemia major but the spectrum of beta-globin gene mutations in the various ethnic sub-populations on the island of Borneo was relatively unknown. The first genetic study on the KadazanDusun children from Sabah with a severe beta-thalassemia major phenotype, was done using a combination of Southern analysis, polymerase chain reaction analysis and direct sequencing. For the first time, it was found that the affected children were homozygous for a large deletion, which has a 5' breakpoint at position -4279 from the cap site of the beta-globin gene (HBB) with the 3' breakpoint located in a L1 family of repetitive sequences at an unknown distance from the beta-globin gene. This report showed evidence of a founder mutation - homozygosity of the deletion, caused a severe phenotype. This finding also provided the first information on the molecular epidemiology of beta-thalassemia in Sabah. Since the publication of this report, many similar reports from other parts of South-east Asia had emerged, including studies from Indonesia and the Philippines. This argues that this deletion may be the most common deletion of the beta globin gene, and therefore has implications for the population genetics, counselling and preventative strategies for beta-thalassemia major for nearly 300 million individuals in South-East Asia and world communities with large SEA migrants (18).

Taking the next step forward, the control of beta-thalassaemia major requires a multi-disciplinary approach that includes population screening, genetic counselling, prenatal diagnosis and the option of termination of affected pregnancies. The molecular characterisation of the spectrum of beta-globin gene mutations in each of the affected ethnic groups in Malaysia was necessary to achieve this aim. Using a cost-effective, 2-step molecular diagnostic strategy consisting of amplification refractory mutation system (ARMS) to identify the 8 most common mutations followed by other DNA-based diagnostic techniques, a total of 98.3% of beta-thalassaemia alleles were characterised. A 100% success rate was achieved in studying the Kadazan-Dusun community. The strategy to identify beta-globin gene mutations in Malaysians with beta-thalassaemia was proposed based on the findings above (19).

Distal renal tubular acidosis and hereditary elliptocytosis

In the area of genetic syndromes in Malaysia, the first case report of distal renal tubular acidosis (RTA) and hereditary elliptocytosis (now known as South-east Asia ovalocytosis) was reported in a Malay family with 3 children having both elliptocytosis and distal RTA. The simultaneous occurrence of these two distinct genetic conditions was intriguing and it was postulated then that the mechanism may be due to covariations in the same family, a contiguous gene syndrome or dual function of a single gene. The report emphasised the importance of excluding a renal tubular defect in any child who presents with elliptocytosis and failure to thrive in Malaysia. Following this report, a large number of publications describing this similar syndrome were reported, culminating in the discovery that mutations of *SLC4A1*, in either its cytoplasmic or its membrane portion, may cause abnormalities in red cell morphology or interference with proton secretion by the renal collecting duct, giving rise to distal RTA (20). Subsequently, in one of the biggest studies on this condition, it was hypothesised that these changes in the red cell metabolism caused by these mutations might protect against malaria. This landmark paper was made possible with the participation of multiple centres in South-East Asia, including Malaysia (21).

Al-Gazali syndrome

From a Bidayuh family in Sarawak, two siblings from a consanguineous family with multiple skeletal abnormalities, anterior segment anomalies of the eye and early lethality were reported. These features are consistent with a syndrome first described by Al-Gazali and we provide further delineation of the syndrome. This second report provided evidence to support the proposed new Al-Gazali syndrome (22).

Duchenne muscular dystrophy

Another area of research is on Malaysian children with learning or physical disabilities. A clinical, molecular genetics and functional assessment was performed in a group of Malaysian boys with Duchenne muscular dystrophy (DMD). The study successfully delineated the demographic characteristics, electrophysiological and molecular genetics analyses and reported the outcome of 21 Malaysian males diagnosed with DMD over a period of 10 years. Molecular genetic analysis showed that dystrophin gene deletions were found in 11 of 16 patients (69%). Chief concerns were the delay in diagnosis and only 43% had satisfactory school performances. The majority were classified as having severe to total dependency levels, based on the modified Barthel Index for activities of daily living assessment. DMD is associated with significant medical and social needs for a developing country such as Malaysia. This study resulted in a change of diagnostic approach, where molecular genetic testing is performed before muscle biopsy as latter procedure was invasive. Earlier referral, genetic counselling, and provision of support and rehabilitative services were the main priorities identified for children with DMD (23).

Rett syndrome

A study on Malaysian girls with Rett syndrome (RS) - a severe neurodevelopmental disorder characterised by normal neurological development followed by progressive developmental regression - was done using denaturing high-performance liquid chromatography (DHPLC) to detect mutations in the MECP2 gene. Mutations in the MECP2 gene were detected in 65% of RS patients. On the basis of this study, a suitable algorithm for clinical and molecular genetic assessment was proposed for Malaysian girls with RS (24).

Inborn errors of metabolism

One major area of interest in medical genetics is the study of inborn errors of metabolism (IEM). Issues pertaining to the diagnosis and management of IEM in Malaysia include low awareness of atypical and variable presentations in IEMs leading to delayed diagnosis or treatment, absence of reliable population data on IEMs and involvement of multiple siblings in the same family due to consanguinity. The importance of careful reporting of family history and genetic counselling needs to be emphasized. Selected testing of ill infants and children for IEM yielded a positive 2% (264/13,500) results for IEMs in Malaysia. Out of the 264 patients, the spectrum of IEMs in Malaysia included organic acidurias (n=98), aminoacidopathies (n=78), urea cycle defects (n=54), neurotransmitter conditions (n=12) and lysosomal disorders, mainly mucopolysaccharidosis (n=14). Confirmatory studies of IEMs are an important aspect of management of IEMs. There is a need for more metabolic specialists and funding for diagnosis and treatment of IEMs in Malaysia. Long-term care issues and cost-effectiveness of IEM therapy, supportive and preventive aspects will need further studies in Malaysia (25, 26).

Congenital disorder of glycosylation

A number of first reports of IEM were made in Malaysian children. The first report of congenital disorder of glycosylation (CDG) was identified in a Malaysian infant female at 2 days of life with CDG type Ia. The diagnosis was suspected on the basis of dysmorphic features supported by neuroimaging studies showing cerebellar hypoplasia and presence of coagulopathy, hypothyroidism and severe pericardial effusion. The patient died at 7 months of life. The diagnosis was supported by abnormal serum transferrin isoform pattern. Enzyme testing of peripheral leukocytes showed decreased level of phosphomannomutase (PMM) activity and a normal level of phosphomannose isomerase activity, indicating a diagnosis of CDG type Ia.

Mutation study of the PMM2 gene showed the patient was heterozygous for both the common p.R141H (c.422T>A) mutation and a novel sequence change in exon 7, c.618C>A, that was confirmed to be pathogenic. To the best of our knowledge, this is the first report of CDG in the Malay population. Prenatal diagnosis was successfully performed in subsequent pregnancies for this family (27).

Citrin deficiency

Another emerging IEM in Asia was first reported in two Malaysian siblings with neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD). This was first reported in a six-month-old Chinese girl who presented with prolonged cholestasis and was investigated for biliary atresia. Urine metabolic screen showed the presence of urinary-reducing sugars, and she was treated with a lactose-free formula. NICCD was suspected based on the clinical history, examination and presence of urinary citrulline. Mutation study of the SLC25A13 gene showed the compound heterozygotes, 851del4 and IVS16ins3kb, which confirmed the diagnosis of NICCD in the patient and her three-year-old female sibling, who also had unexplained neonatal cholestasis. Long-term dietary advice, medical surveillance and genetic counselling were provided to the family. The diagnosis of NICCD should be considered in infants with unexplained prolonged jaundice. DNA-based genetic testing of the SLC25A13 gene may be performed to confirm the diagnosis retrospectively. An awareness of this condition may help in early diagnosis using appropriate metabolic and biochemical investigations, thus avoiding invasive investigations such as liver biopsy in infants with neonatal cholestasis caused by NICCD (28). Many other publications on NICCD in Asia and Malaysia were published after this condition was reported (29).

Adult-onset cancer

In adult-onset genetic conditions such as hereditary breast and ovarian cancer syndromes, genetic counseling (GC) and genetic testing are vital risk management strategies. Hitherto, cancer genetic testing amongst Asians has been described only in developed and high-income Asian countries. A long-term collaborative study between University of Malaya (breast surgeons, clinical geneticist) and CARIF (Cancer Research Initiative Foundation) studied the uptake and acceptance of GC and genetic testing services in Malaysian BRCA carriers in a middle-income country. A total of 363 patients were tested by full sequencing and large rearrangement analysis of both BRCA1 and BRCA2 genes in the Malaysian Breast Cancer (MyBrCa) Genetic Study. Of these, 13.5% were found to carry deleterious mutations. GC pre- and post- result disclosures were provided and these groups of patients and their families were studied. GC and genetic testing were accepted by 82% of Malaysian patients at high risk for HBOC syndromes. Only 78% of index patients informed their families of their risks and 11% of relatives came forward when offered free counseling and testing. Even when GC and genetic testing were provided at no cost, there remained significant societal and regulatory barriers to effective cancer genetic services. There is a need for regulatory protection against genetic discrimination. Further studies are needed in the area of increasing awareness about the potential benefits of GC and genetic testing in this region (30).

The lessons learnt from these examples above showed the importance of astute clinical observation, careful documentation and diagnosis, genetic counselling before performing any genetic testing and the importance of multi-institutional collaboration. While these examples emanated from childhood disorders, it was clear there was a wider implication for the family and society - ranging from improved understanding of the basic pathophysiology of the conditions to psychosocial, reproductive, ethical and public health issues and their short and long-term ramifications. There is still much to do in providing an acceptable level of care for patients with hereditary conditions in Malaysia.

Pitfalls, challenges and opportunities

While genetic testing and mutation analyses are increasingly used in medicine, it is crucial that clinicians are aware of their pitfalls and limitations. Genetic testing should be preceded by genetic counselling. There are ethical concerns that mutation studies should not be performed in children or minors unless there are important medical consequences. Many genetic tests are often done on a research basis and are not meant for diagnostic purposes. In addition, a 'negative' molecular result does not exclude a diagnosis. Conversely, a novel DNA variant or polymorphism may be mistakenly regarded as pathogenic by medical staff not familiar with genetics. Biotechnology is rapidly evolving and the sensitivity of the various methodologies of mutation detections may vary with different techniques (31, 32).

On the other hand, the medical genetics community encourages the use of family medical history as a 'front-line' screening tool for genetic disorders. The Center for Disease Control (CDC) Office of Genomics and Disease Prevention in collaboration with National Institutes of Health, USA embarked on a public health initiative to use family history information to asses risk for common diseases and to influence early detection and prevention strategies in 2002 (Family History Public Health Initiative). The American Society of Human Genetics has declared family medical history the 'gold standard' for assessing disease risk. Genes alone do not act in a vacuum and family health history is a better predictor than personal genomics testing. By using an easy to follow "Family History Tool" to assess risk classification for each individual, it is feasible to stratify public health and personalised recommendations for each family. Therefore family doctors and public health practitioners have their roles to play in reducing genetic disorders in the community (33).

The ethical, legal, social and religious implications of 'New Genetics' and 'Personal Genomics' must be carefully evaluated and debated. The Ministry of Health of Malaysia announced plans to screen the population for thalassaemic trait as part of the Thalassaemia Control program. While this is a laudable move, there are a number of considerations that must be taken into account before population screening can be done. For example, will genetic counselling be provided to the population? Which age groups will be screened? Will prenatal diagnosis and termination of pregnancy for affected fetuses be allowed in government hospitals if two thalassaemic carriers decided to start their family? The setting up of genetic support groups such as Malaysian Rare Disorders Society and others are crucial to give a voice for families and patients, to advocate and to allow clinicians to act in the best interest of the patients (34-36).

In conclusion, it is recommended that both suitable curative and preventive aspects be utilised to reduce the impact of genetic diseases in the era of personalised medicine (3, 36). More clinical research into genetic conditions is required in Malaysia. Genetic counselling should remain the mainstay of all genetic services and empowering at-risk families and individuals should be a priority, even in the age of personal genomics and individualised medicine.

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THE DETERMINANTS OF CONSUMER HEALTH INFORMATION ON CHRONIC NON-COMMUNICABLE DISEASE: AN EXPLORATORY STUDY IN PENANG, MALAYSIA

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ABSTRACT:

The objective of the present study is to investigate the impact of socio-demographic factors on the acquisition of health information on Non-Communicable Diseases (NCDs) among Malaysian adults. A robust analysis was conducted on cross-sectional survey data obtained from 398 respondents in Penang (Malaysia) between August to October 2010. An ordered probit model was applied to examine the factors affecting the scale of health information. The results suggest that old individuals, rural dwellers, having chronic disease and history of serious family illnesses are 0.19%, 2.39%, 2.2% and 2.71% less likely to acquire poor health information on NCDs than others, whereas Malays, Chinese, males and those of low educated are 8.76%, 6.22%, 2.94% and 21.62% more likely to acquire poor health information on NCDs than others. Based on these findings, several intervention measures toward increasing the health knowledge among the population are recommended, which include the use of language-based mass media to advertise the information on diseases, designing health awareness campaigns in urban areas and introducing more basic health related subjects and courses into primary and secondary schools.

Keywords: *NCD, health information, Health Literacy, Malaysia*

Introduction

The increasing burden of Non-Communicable Disease (NCDs) has become a serious issue worldwide (1). Disease Control Division reported that approximately 60% of mortality and 43% of disease burden were related to NCDs (2).[1] It was predicted that by the year 2020, NCDs would be responsible for at least 75% of all deaths in the world (2). In Malaysia, the majority of mortality and morbidity were caused by NCDs (2), accounting for more than two-third of total disease burdens (3). Each year, there are at least 70% of Malaysians diagnosed with NCDs, most notably, heart diseases, diabetes and cancers (4). Ministry of Health Malaysia reported that NCDs are the leading factors causing mortality in the government hospital (3).

The risk of acquiring diseases can be reduced if individuals are aware of the symptoms and treatments for the diseases. However, most individuals lack of knowledge on health (5). Hence, individuals tend to seek health care at the late stage of disease, and consequently are less likely to be cured (6). As emphasized by Newhouse and Friedlander, most of the NCDs can be prevented through changes in lifestyle (7), but was not practiced, probably due to the lack of knowledge and/or awareness. To reduce the prevalence of NCDs, essential health information has to be communicated to the society in an effective manner.

[1] Disease Control Division refers to the NCD survey conducted by the Ministry of Health Malaysia to establish the NCD surveillance system which would provide information to determine the extent of NCD risk factors Malaysia (2).

A thorough review of the existing literatures indicates that there are only a few in-depth studies examining the factors affecting the acquisition of health information. This is mainly due to the difficulties in measuring health information. The empirical study on acquisition of health information was first conducted by Pauly and Satterthwaite, but the method used in the study was just a proxy for measuring health information, and thus could not accurately identify the determining factors (8). Another two studies used a direct assessment to measure the scale of health information acquisition (6, 9).[2] These studies observed that socio-demographic factors such as age, gender, education and income could significantly influence the acquisition of health information among population.

In spite of the rising prevalence of NCDs in Malaysia, there is lack of study that investigates factors influencing the acquisition of health information on NCDs (i.e. the symptoms of hypertension and diabetes) among Malaysian adults.[3] The contributions of the present study are two folds. First, the present study takes into account several lifestyle and health factors, in addition to socio-demographic factors, in an effort to examine their impact on acquisition of health information. Two, a better understanding of the factors affecting the acquisition of health information can assist the public policy makers in formulating better intervention measures towards improving the health awareness among population.

Methods

Data

Data used in the present study was a primary cross-sectional survey data of Penang (Malaysia) (10). Given the time, budget and geographical constraints, a non-probabilistic convenience sampling approach was adopted to conduct the survey. Nevertheless, samples were stratified in proportion to the ethnic structure of Penang population (41.6% Malays, 40.9% Chinese, 17.5% Indian/ others). The data was collected at various locations in Penang such as university, shopping malls, offices and cafes, where include individuals with various age, income ranges and education levels. The survey period was conducted between August to October, 2010.

Pretested bi-lingual (*Bahasa Malaysia* and English) questionnaires were distributed to the respondents who were 21 years old and above, and had resided in Penang for at least 12 months. During the survey, the respondents were asked to answer the questionnaires by themselves along with the assistance by the interviewers. Several questions in relation to the general health knowledge on NCDs were addressed to the respondents. Meanwhile, the respondents were asked to self-report on their socio-demographic, lifestyle and health profiles such as age, income, education, ethnicity, gender, marital status and history of serious family illnesses.

The sample size was calculated using OpenEpi software (12). The sample size calculation was based on three criteria: 1) the assumption of 50% (+/- 5%) of population had a high level of health information on NCDs; 2) the level of precision (95% of confidence level); and 3) 1609900 populations of Penang (13). A total of 415 respondents were surveyed (8% above the estimated minimum sample size) and the non-response rate was 4.1%. Data of the remaining respondents (398 respondents) were analyzed using the Stata statistical software (14).

Statistical analysis

The dependent variable of the present study is the scale of health information, that is, the amount of health knowledge that individuals acquire, and is measured as categorical and ordinal outcomes with a clear ordering (low, lower-middle, upper-middle, high). As such, the ordered probit model is appropriate to use for explaining the variations of such variable (15). In general, the ordered probit model can be expressed as below:

$$HealthInformation^* = X'\beta + e$$

$$\begin{aligned}&\text{Health information} = 1(\text{low}) \\ &\text{if } [-\infty < HealthInformation^* < \mu_1] \\ &\\ &\text{Health information} = 2(\text{lower-middle}) \\ &\text{if } [\mu_1 < HealthInformation^* < \mu_2] \\ &\\ &\text{Health information} = 3(\text{upper-middle}) \\ &\text{if } [\mu_2 < HealthInformation^* < \mu_3] \\ &\\ &\text{Health information} = 4(\text{high}) \\ &\text{if } [\mu_3 < HealthInformation^* < \infty]\end{aligned} \quad (1)$$

where, *HealthInformation** is a latent variable for health information, X' is a transposed vector of the independent variables, β is a matrix of the regression coefficients and e is the stochastic error term. μ_1, μ_2 and μ_3 are the corresponding thresholds.

Dependent variables

The approach applied in the present study to measure health information was similar to those of Kenkel and Hsieh and Lin (6, 9). The respondents were given 20 questions concerning the indicators and effects of diabetes and hypertension, and were asked to answer 'yes', if they

[2] Kenkel and Hsieh and Lin used several survey questions about the definitions and symptoms of NCDs to examine the respondents' health knowledge (6, 9).

[3] Since the prevalence of hypertension and diabetes in Malaysia rises tremendously, these two particular NCDs are chosen (11).

knew the answer, otherwise 'no'.[4] Those respondents who answered 'yes' for 16 questions and above were considered as having 'high stock of health information (high)', 11-15 questions were referred as having 'upper-middle stock of health information (upper-middle)', 6-10 questions were denoted as having 'lower-middle stock of health information (lower-middle)', and less than 6 questions were indicated as having 'low stock of health information (low)' (Table 1).

Table 1: Description of variables in the statistical model

Variable name	Descriptions
I. Dependent variables	
STOCK	Amount of stock of health information (High = 4, Upper-middle = 3, Lower-middle = 2, Low = 1)
II. Independent variables	
AGE	Age (in years)
MALAY	Being Malay (yes = 1, otherwise = 0)
CHINESE	Being Chinese (yes = 1, otherwise = 0)
INDOH*	Being Indian/other (yes = 1, otherwise = 0)
MALE	Being male (yes = 1, otherwise = 0)
MARRIED	Being married (yes = 1, otherwise = 0)
INSURANCE	Having medical insurance (yes = 1, otherwise = 0)
RURAL	Living in rural area (yes = 1, otherwise = 0)
CHRONIC	Presence of chronic disease (yes = 1, otherwise = 0)
FAMILL	Presence of history of serious family illnesses (yes = 1, otherwise = 0)
PRIMARY	Having primary school qualification or less as highest level of education (yes = 1, otherwise = 0)
SOMEHIGH	Having some high school qualification as highest level of education (yes = 1, otherwise = 0)
HIGHSCHOOL	Having completed high school qualification as highest level of education (yes = 1, otherwise = 0)
COLLEGE	Having some college qualification as highest level of education (yes = 1, otherwise = 0)
BACHELOR*	Having at least bachelor degree as highest level of education (yes = 1, otherwise = 0)
LOWINC*	Monthly individual income is RM 0 – RM 999 (yes = 1, otherwise = 0)
LOWMIDINC	Monthly individual income is RM 1000 – RM 2999 (yes = 1, otherwise = 0)
UPMIDINC	Monthly individual income is RM 3000 – RM 5999 (yes = 1, otherwise = 0)
HIGHINC	Monthly individual income is ≥ RM 6000 (yes = 1, otherwise = 0)
SMOKER	Being a smoker (yes = 1, otherwise = 0)
DRINKER	Being a alcohol drinker (yes = 1, otherwise = 0)
POORHLT	Self-rated poor health (yes = 1, otherwise = 0)

*Note: *Refers to base/reference category.*

[4] Appendix I demonstrates the survey questions that were used to measure the respondents' health information.

Independent variables

Owing to the paucity of empirical studies examining acquisition of health information in Malaysia, the independent variables of the present study were selected based on Kenkel and Hsieh and Lin (6, 9). In particular, the following variables were hypothesized to have significant impacts on the acquisition of health information: (1) age; (2) ethnicities; (3) gender; (4) marital status; (5) medical insurance; (6) house locality; (7) chronic disease; (8) history of serious family illnesses; (9) education; (10) income; (11) smoking; (12) drinking; and (13) self-rated health (Table 1).

In the present study, the respondents' age (AGE) was included as a continuous variable for analysis. The respondents' ethnicities were categorized into three categories: MALAY (Malays), CHINESE (Chinese) and INDOTH (Indians and those of other ethnic groups).[5] Three health variables were included for analysis: presence of chronic disease (CHRONIC), presence of history of serious family illnesses (FAMILL) and self-rated health (POORHLT).[6] The respondents' education level was categorised into five groups: primary school or less (PRIMARY), some high school (SOMEHIGH), completed high school (HIGHSCHOOL), college (COLLEGE) and bachelor degree or higher (BACHELOR). Four categories were included: RM 0 – RM 999 (LOWINC), RM 1000 – RM 2999 (LOWMIDINC), RM 3000 – RM 5999 (UPMIDNIC) and ≥ RM 6000 (HIGHINC). Two lifestyle variables were included: smoking (SMOKER) and drinking (DRINKER).

Results

Characteristics of the survey respondents

Descriptive analysis for health information is illustrated in Table 2. Of the total respondents, 52% have high stock of health information, 30% have upper-middle stock of health information, 12% have lower-middle stock of health information, and only 6% have low stock of health information. The total sample consists of approximately 38% Malays, 41% Chinese, 21% Indians/others and 44% males. These ethnic and gender compositions closely mirror the population structure of Penang (41.6% Malays, 40.9% Chinese, 17.5% Indian/others, 49.3% males) (14).

Marginal effects of independent variables

Results for ordered probit analysis of acquisition of health information are presented in Table 3. The statistical test is considered significant if the p-values are below 10%, 5% and 1% at 2-sided level. The results show that an additional year of age (AGE) reduces the probability of having low stock of health information by 0.19%, lower-middle stock

[5] Indians and those of other ethnic groups were combined to represent the ethnic minority in Malaysia.

[6] The details about self-rated health were described elsewhere (16).

Table 2: Descriptive analysis for stock of health information

Variables	Mean [standard deviation] or percentage				
	High [n_1=207(52%)]	Upper-middle [n_2=118(30%)]	Lower-middle [n_3=48(12%)]	Low [n_4=25(6%)]	Total [n=398(100%)]
AGE	38.54 [14.20]	34.40 [12.63]	32.63 [12.00]	37.92 [13.33]	36.56 [13.60]
MALAY	30	41	56	56	38
CHINESE	40	47	31	40	41
INDOH	30	13	13	4	21
MALE	42	42	48	68	44
MARRIED	53	43	46	60	50
INSURANCE	66	66	65	56	65
RURAL	23	20	19	12	21
CHRONIC	22	12	19	8	18
FAMILL	57	47	40	36	51
PRIMARY	4	4	6	12	5
SOME HIGH	11	5	2	24	9
HIGH SCHOOL	19	24	31	16	22
COLLEGE	18	19	13	20	18
BACHELOR	49	48	48	28	47
LOWINC	31	37	27	28	32
LOWMIDINC	42	46	52	52	45
UPMIDINC	22	14	19	16	19
HIGHINC	5	3	2	4	4
SMOKER	11	16	23	24	15
DRINKER	29	42	23	24	32
POORHLT	6	3	6	4	5

Note: For age variable (continuous outcomes), the values refer to mean [standard deviation], whereas, for the other variables (categorical outcomes), the values refer to percentage.

of health information by 0.30% and upper-middle stock of health information by 0.32%, but increases the probability of having high stock of health information by about 0.81%.

Malays (MALAY) and Chinese (CHINESE) are found to be 30.45% and 23.67% less likely to have high stock of health information, respectively, than Indians and other ethnic groups (INDOTH). Likewise, the results also indicate that Malays have a 8.76%, 11.65% and 10.05% higher probability of having low, lower-middle and upper-middle stock of health information, respectively, compared to Indian/others. Besides, Chinese are also observed to have a 6.22%, 8.94% and 8.52% higher propensity of having low, lower-middle and upper-middle stock of health information, respectively, than Indian/others.

Our data suggests that males (MALE) have a 2.94%, 4.56% and 4.75% higher probability of acquiring low, lower-middle and upper-middle stock of health information, respectively, than females. Similarly, males were also found to be 12.26% less likely than females to acquire high stock of health information. It is found that rural dwellers (RURAL) have a 11.82% higher probability of having high stock of health information than urbanites. Also, these individuals are 2.39%, 4.16% and 5.27% less likely to have low, lower-middle and upper-middle stock of health information, respectively, compared to urban dwellers.

Individuals who have history of serious family illnesses (FAMILL) are 11.60% more likely to have high stock of health information compared to those without such health background. Similarly, they also have a lower probability of having low (2.71%), lower-middle (4.28%) and upper-middle (4.61%) stock of health information. Individuals who have chronic disease (CHRONIC) have a 2.20% lower probability of having low stock of health information compared to those without chronic disease. The findings of the present study exhibit that individuals with only primary school or less education (PRIMARY) are 38.49% less likely to have high stock of health information than those who have at least bachelor degree (BACHELOR), this is followed by a higher likelihood of having low (21.62%) and lower middle stock of health information (15.72%).

Discussion

Application of simple linear regression models such as ordinary least square (OLS) and linear probability model (LPM) will face a serious problem if the dependent

Table 3: Results for ordered probit analysis of acquisition of health information

Variables	Low	Lower-middle	Upper-middle	High
AGE	-0.0019**	-0.0030***	-0.0032**	0.0081***
	(0.0007)	(0.0011)	(0.0013)	(0.0029)
MALAY	0.0876***	0.1165***	0.1005***	-0.3045***
	(0.0275)	(0.0299)	(0.0229)	(0.0679)
CHINESE	0.0622***	0.0894***	0.0852***	-0.2367***
	(0.0228)	(0.0285)	(0.0250)	(0.0690)
MALE	0.0294**	0.0456**	0.0475**	-0.1226**
	(0.0145)	(0.0216)	(0.0216)	(0.0552)
MARRIED	0.0168	0.0267	0.0289	-0.0724
	(0.0138)	(0.0217)	(0.0235)	(0.0582)
INSURANCE	-0.0127	-0.0199	-0.0207	0.0533
	(0.0143)	(0.0218)	(0.0217)	(0.0574)
RURAL	-0.0239**	-0.0416**	-0.0527*	0.1182**
	(0.0112)	(0.0205)	(0.0295)	(0.0592)
CHRONIC	-0.0220*	-0.0385	-0.0491	0.1096
	(0.0131)	(0.0246)	(0.0360)	(0.0722)
FAMILL	-0.0271**	-0.0428**	-0.0461**	0.1160**
	(0.0123)	(0.0187)	(0.0203)	(0.0489)
PRIMARY	0.2162*	0.1572***	0.0115	-0.3849***
	(0.1126)	(0.0376)	(0.0536)	(0.0914)
SOMEHIGH	0.0253	0.0359	0.0317	-0.0929
	(0.0330)	(0.0420)	(0.0290)	(0.1031)
HIGHSCHOOL	0.0284	0.0413	0.0380	-0.1077
	(0.0227)	(0.0297)	(0.0232)	(0.0741)
COLLEGE	0.0032	0.0051	0.0054	-0.0137
	(0.0165)	(0.0257)	(0.0267)	(0.0689)
LOWMIDINC	0.0130	0.0207	0.0221	-0.0558
	(0.0141)	(0.0221)	(0.0232)	(0.0589)
UPMIDINC	-0.0116	-0.0194	-0.0228	0.0539
	(0.0163)	(0.0283)	(0.0359)	(0.0802)
HIGHINC	-0.0085	-0.0143	-0.0169	0.0398
	(0.0278)	(0.0492)	(0.0631)	(0.1400)
SMOKER	0.0216	0.0316	0.0294	-0.0825
	(0.0222)	(0.0295)	(0.0234)	(0.0741)
DRINKER	0.0065	0.0102	0.0108	-0.0275
	(0.0153)	(0.0237)	(0.0245)	(0.0634)
POORHLT	-0.0063	-0.0105	-0.0121	0.0290
	(0.0296)	(0.0510)	(0.0625)	(0.1430)

*Note: Asymptotic standard errors in parentheses. Asterisks *** indicate significance at the 1% level, ** at the 5% level, and * at the 10% level. Log likelihood = -415.4560, LR χ^2 (19) = 68.10, P > χ^2 = 0.0000, Pseudo R^2 = 0.0757*

variable is measured as categorical and ordinal outcomes. Therefore, in order to improve the degree of reliability, an ordered probit model is used (17). The results of the present study suggest that age, ethnicity, gender, house locality, chronic disease, history of serious family illnesses and education are significantly associated with acquisition of health information. Specifically, individuals who are older, rural dwellers, having chronic disease and history of family illness are less likely to acquire poor health information than others, whereas Malays, Chinese, males and those of low educated are more likely to acquire poor health information compared to others. These findings can provide the public policy makers with the important information on formulating an effective intervention

measure towards increasing health knowledge among the population, which, in turn, reducing the prevalence of NCDs.

Age is positively associated with the probability of acquiring good health knowledge. This finding is in contrast to that of Hsieh and Lin, which concluded otherwise (9). This may be explained by the fact that older individuals tend to encounter more serious deterioration in health (18), and they spend more for using health care services (19). As the consequence, they tend to be more concerned about the symptoms and negative consequences of diseases than their younger counterparts. In view of this finding, an effective public health policy should focus on improving health knowledge among youngsters. It is recommended that detailed information about diseases should be frequently publicised in the social media that have strong influences on youngsters such as Facebook, Twitter and Instagram.

It is interesting to note that Indians and other ethnic groups are more likely to acquire a high stock of health information compared to Malay and Chinese, making these ethnicities to have the greatest awareness of health among all the ethnic groups in Malaysia. However, owing to the limited availability of data, there is a lack of clear definition on the percentage of different ethnicity in the population and the acquisition of subjects from different ethnic groups by chance. Therefore, future in-depth studies which examine the ethnic differences in acquisition of health information are needed. In terms of policy implication, the public policy makers should urgently introduce more nationwide health awareness programmes. We suggest that the government should use various Malay and Chinese language-based mass media such as newspapers, television programmes and radio channels to widely advertise the information about health and diseases.

Women are found to have a higher likelihood of acquiring good health information compared to men. This finding is consistent with the argument of Kenkel that women carry greater responsibilities to look after their family health, whereas men are more inclined to spend their time on paid works, and consequently have a lower priority for family health (6). Hence, in general, women tend to have better health knowledge in relative to men. Conversely however, this finding contradicts that of a study conducted in Burkina Faso (20). The study claimed that females and those individuals living in a female headed household are more likely to report illnesses than males and those individuals living in a male headed household, respectively.

Rural dwellers are found to have a higher likelihood of having good health knowledge than urbanites, which somewhat contradicts the finding of Hsieh and Lin (9). Perhaps, this is because urban dwellers have better access to health care facilities, and may tend to rely heavily on health care professional for treating diseases, whilst people reside in rural areas tend to rely on their health knowledge for preventing diseases. Such explanations, however, need to be confirmed by the future studies using more comprehensive health survey data. An effective intervention measure should be aimed primarily at providing more health information for urban dwellers. This can include designing more health awareness campaigns and seminars in urban areas.

Rather astonishingly, results of the present study suggest that individuals with chronic disease and history of serious family illnesses are more likely to have good health knowledge than their counterparts who without such health background. The notion is that individuals with chronic disease and history of serious family illnesses are likely to be more conscious of their health. Hence, they are highly motivated in acquiring new health information. This is in agreement with the findings of Cheah that individuals who have history of serious family illnesses and self-rated poor health tend to be more health-conscious, and thus are more likely to use health care to prevent diseases (10). Considering this outcome, the present study suggests selection and training of peer educators from individuals with NCDs and who have family members with NCDs. This will be a promising possibility to disseminate health information effectively in the community.

Education is found to be significantly associated with acquisition of health knowledge, as higher educated individuals are more likely to acquire good health knowledge compared to lower educated individuals (6, 9). Well-educated individuals tend to have a better interpreting skill, and thereby can easily obtain more health information than those of less educated. With regard to policy implication, information about diseases should be made more available at school, whereby students can access it since schooling years. For instance, the government can consider introducing more basic health related subjects and courses into primary and secondary schools.

Somewhat surprisingly, the evidence of the present study suggests that income is not significantly correlated with acquisition of health information. This outcome is contrary to the finding of Kenkel and Hsieh and Lin that suggests that income is positively associated with the amount of health information acquired (6, 9). The absence of the causal relationship between income and acquisition of health information may be possible due to limited information provided by the data, as the information about the exact amount of individual and household income of the respondents has not been canvassed.

Given the budget, time and geographical constraints, several inherent limitations are noted. First, the sample size used in the present study could not represent the Malaysia population as a whole. Second, questions used in the present study to measure health information are somewhat limited. Hence, in addition to adding the sample size, questions measuring individuals' health awareness such as use of vitamins, and consumption of green leafy vegetables and fruits are suggested to be taken into account by the future studies.

Conclusion

Findings of the present study suggest that socio-demographic factors are significantly associated with acquisition of health information. Specifically, the elderly, rural dwellers and individuals with chronic disease and history of family illness have a higher likelihood of having good health knowledge than others, whereas, Malays, Chinese, males and those of lower educated are more likely to have poor health knowledge than others. Marital status, income, medical insurance, self-rated health, as well as drinking and smoking do not possess any significant impacts on acquisition of health information.

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A STUDY COMPARING THE EFFECTIVENESS OF THE FELDENKRAIS METHOD VERSUS THE STANDARD PULMONARY REHABILITATION PROGRAM IN IMPROVING THE BORG SCORE AND 6 MINUTE WALK IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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ABSTRACT

INTRODUCTION:

Although the Feldenkrais method of rehabilitating chronic obstructive pulmonary disease (COPD) patients have been suggested, its use among practitioners is not widespread owing to preference of the more familiar standard program presently available. Several advantageous of the Feldenkrais Method have been suggested which includes improving the efficiency of movement, posture and, breathing. However how this compares to the standard rehabilitation protocol or pulmonary rehabilitation program (PRP) have not been previously demonstrated. The present study was thus conducted to compare the effectiveness of the Feldenkrais Method to the standard PRP using Borg score and 6 minute walked distance (6MWD) as outcome measurement tools.

RESULTS:

There were 17 subjects in the Feldenkrais group (FG) and 19 subjects in the pulmonary group (PG), both of which received therapy for 8 weeks and assessed before and after receiving therapy. There were no improvements observed in the Borg score for the FG (after and before; 6.06$\pm$ 1.09 vs. 6.00$\pm$0.94). However, improvements in the PG group could be seen (after and before; 3.58$\pm$ 1.17 vs. 5.84 $\pm$1.01). Improvements in the 6MWD was observed in both groups with no significance differences noted (FG vs. PG; 379$\pm$129m vs. 374$\pm$80m).

CONCLUSION:

The Feldenkrais method does not offer any advantage over the present PRP and in fact the latter offers better improvement in terms of the Borg score. However in view of the small study sample, further study would be needed before a final conclusion can be made.

Keywords: *Borg scale, exercise tolerance, Feldenkrais method, 6 minute walk test, pulmonary rehabilitation program*

Introduction

Pulmonary rehabilitation program (PRP) for chronic obstructive pulmonary disease (COPD) patients is well established (1, 2). It is a widely accepted therapeutic means of enhancing standard therapy to lessen symptoms and optimize function. Such programs have encouraged patients to become more independent in their daily activities, and become less dependent on health professionals and expensive medical resources (2). The problems associated with COPD such as exercise deconditioning, muscle wasting, dyspnoea and weight loss can be overcomed with the attendance to PRPs (3).

The Feldenkrais Method is becoming an increasingly popular treatment modality used by health professionals to assess a range of dysfunctions (4). It was originally developed to explore the relationship between movement, physical experience, and development. This modality helps to decrease the muscular effort that is needed to perform movement and is directed at those people who wish to improve their efficiency of movement, posture and breathing, muscular tension, flexibility and neuromotor functioning (5).

Dyspnoea has been the primary reason for COPD patients seeking medical care. Measurements of dyspnoea provide an insight into the practical effects of treatment on everyday life, reflecting whether or not the patients perceive an improvement in their primary symptom. Mostly, the COPD patients would often decrease their activity to avoid the unpleasant sensation of breathlessness. Several methods have been used to evaluate patient's experience of breathlessness, during daily activities (using of questionnaires) or exercise testing (the Borg scale)(6). These measures have been produced to grade the severity of dyspnoea according to the degree of breathlessness associated with any particular task.

In clinical practice, the 6-minute walk test (6MWT) is commonly used to assess changes in functional exercise capacity following pulmonary rehabilitation. Both tests (6MWT and Borg score) have showed validity, reliability after one familiarization test, and have the ability to detect changes following pulmonary rehabilitation (7). Unlike pulmonary rehabilitation, there is a relatively limited body of empirical evidence on Feldenkrais Method being used among COPD patients. It is therefore the objective of this study to explore the effects of the Feldenkrais Method as compared to the usual pulmonary rehabilitation program (PRP) on Borg score and distance walking. The findings can provide the opportunity for the application of concepts of Feldenkrias Method to be used to complement the existing pulmonary rehabilitation programs and thus benefiting COPD patients.

Methods

Study Design

This study is a continuity of a previous study carried out among COPD patients who had undergone 8 weeks of pulmonary rehabilitation program (PRP) with a control group that no intervention. Only 66 subjects completed attendance to the PRP in phase 1 of the study, and they were then enrolled into the study for the second phase of study, which may see patients enrolled into the PRP program (PG) or to take part in the Feldenkrais Program (FG). However, only 17 (47%) subjects from Feldenkrais group (FG) and another 19 (53%) from the pulmonary group (PG) managed to complete their intervention. Reasons for withdrawal from the study trial includes 5 (17%) subjects that developed exacerbations of COPD whilst the other 25 (83 %) of them voluntary withdrew from the program due to various personal issues such as transportation availability, lack of assistance, failure to get off from work and financial issues.

In phase 1 of the study, recruitment of COPD patients was performed by medical doctors were referred by the physiotherapy department, at University Kebangsaan Malaysia Medical Centre (UKMMC). This was a quasi-experimental study using convenience sampling among a pool of COPD patients who met the inclusion criteria. The study protocol was approved by the medical research and ethics committee of the institution. Written informed consent was obtained prior to enrollment. Eligible patients that met the inclusion criteria included: (1) patients diagnosed as COAD by respiratory physician regardless of their status of disease severity as classified by ATS (2004), (2) able to understand Bahasa Malaysia or English and (3) of aged more than 45 years. Exclusion criteria are patients with malignancy and other severe cardiopulmonary and neurological dysfunctions.

Multidimensional Assessment

In phase 1 of the study, multidimensional assessment was done at week 1 and 8 and in phase 2, assessment was done at week 10 and 16.

Pulmonary Function Testing, 6 minute walk test and Borg test

Spirometry was performed prior and after each rehabilitation session using spirometry COSMED Pony Spirometer Graphic. Values of forced expiratory volume in 1 second (FEV1) were recorded. Patients were asked to repeat the procedure 3 times and the best reading was taken. The 6-Minute Walk Test (6MWT) is an index of functional capacity with subjects walking as far as they could in 6 minutes. The test was performed along a 30 m corridor and the better of 2 repeatable tests were taken and the distance walked was recorded. (8) They were encouraged during the test by the therapist every minute. A mean improvement of 54 m was taken as the cut off point to represent the minimal distance improved among COPD patients (9). With the Borg scale, it allows the patients to grade the intensity of their breathlessness during the walking tests (10). This tool was used as a guide to increase the exercise tolerance among COPD patients.

The intervention carried out was within 45 to 60 minutes, twice per week and for 8 weeks duration. Patients were recruited randomly into the FG or PG programs.

The Feldenkrais Program (FG)

The Feldenkrais Method was based upon the work of Moshe Feldenkrais (11). An "Awareness Through Movement" (ATM) lesson was carried out on COAD patients' with exercise regimens different from the usual PRP, prior to starting the exercises. The focus of the program is the restoration of mechanical properties of the human motion by application of sensory motor control of movement. Some of the foundational principles underlying Feldenkrais concepts include paying attention to the quality of movement, doing the movements slowly with minimal effort, resting frequently between movements to avoid physical and mental fatigue, and avoiding pain and discomfort. This activities included relaxation exercises, breathing exercises, floor activities that included sessions of trunk and pelvic movements (rolling on the floor from side to side, trunk twisting, pelvis rolling forward and backward, sitting cross legged).

Pulmonary Rehabilitation Program (PG)

The exercise sessions in PRP consist of exercise training using bicycle ergometer, lower and upper-extremity training. These patients used an electronically braked bicycle ergometer and they started training at 50% of the maximum workload. The goal of cycle ergometry was to maintain a training duration of 20 minutes and only then was the work cycled increased according to the individual needs of each patient. Upper-extremity training was performed by repetitively raising and lowering a dowel from the height of the waist to the height of the shoulders (using an interval-training regimen with repetitive period of exercise and rest as tolerated by the patient for 10 minute, a weight of 0.5 1b was added to each arm (12).Treadmill was incorporated for another 15 minutes sessions as tolerated by the patient. Stretching of the limbs muscles are performed prior to each exercise session, for warming up.

Statistical analysis

After checking for normal distribution, baseline data from the above outcome measures were analyzed using ANOVA analysis which is a two-way mixed split plot design. A significance level was set at p<0.05. The magnitude of the effect size was judged against the criteria recommended by Cohen to represent small, moderate and large changes (14).

Results

There were uneven numbers of males and females subjects between recruited between groups (Table 1). The mean age is younger (63.53± 9.87) in the FG group as compared to PG group (67.52 ±9.65). History of smoking was presents in both groups, with more smokers than non-smokers among the subjects. According to classification of disease severity (ATS, 2004), most subjects had moderate degree of airflow obstruction (42%, n=15), some had mild airflow obstruction (30%, n=11) while others had severed airflow obstruction (28%, n=10). The demographic profiles were comparable (p>0.05) for gender (p=0.048), age (p=0.459), and smoking history (p =0.535).

Table 1: Patient characteristic between Feldenkrais and Pulmonary Rehabilitation Group.

	Feldenkrais Group (IG) n (%)	Pulmonary Group (CG) n (%)	*p* value
Gender			
Male	7(41.2)	14(73.7)	0.048
Female	10(58.8)	5(26.3)	
Age	63.53± 9.87	67.52 ±9.65	0.459
Race			
Malay	7 (41.2)	11 (57.9)	0.587
Chinese	8(47.1)	6(31.6)	
Indian	2 (11.8)	2(10.5)	
Smoking History			
Non smokers	8 (47.1)	7(36.8)	0.535
Smokers	9(52.9)	12(63.2)	
Classification of Disease Severity in COPD (FEV% predicted)			
<30% (Severe airflow)	4(23.5)	6(31.6)	0.799
31-50 (Moderate airflow)	8(47.1)	7(36.8)	
51-80 (Mild airflow)	5(29.4)	6(31.6)	
FEV1 in % predicted	40.50±9.72	39.44±13.38	0.789
Borg Score	6.00± 0.94	5.84 ±1.08	0.632
6 Minute Walk Test	315.29±117.16	323.68±76.54	0.799

Independent t-test, Significant at *$p< 0.05$;**$p<0.01$*

Evaluation of Lung Function Testing

The FEV1% predicted showed significant differences within-subjects effect, F (1, 34) = 0.447, p < 0.001, partial eta squared = 0.553, in the Feldenkrias groups (FG). The pulmonary group showed similar status of FEV1% predicted, F(1,34)=, p p=0.587 partial eta squared = 0.021, across the time periods (Table 2).

Evaluation of Borg Score

In the Borg score, there are significant difference in the CG within the groups effect F (1, 34) = 0.191, p < 0.001, partial eta squared = 0.809 indicating better lung volume following intervention compared to baseline reading (Table

2). The IG proved to benefit more during the intervention with decreased dyspnea. However, the Feldenkrais group had similar Borg score as in the baseline. These showed no improved perception of dyspnea in the FG. Borg score was assessed when subjects were carrying out the 6 minute walked distance (6MWD).

Table 2: Pre and Post values of Borg scale, 6 minute walked distance and FEV1% predicted following intervention

	Pre exercise		Post exercise		*p* value	
	IG	CG	IG	CG	Within groups effect	Between groups effect
Borg scale (unit)	6.06+ 1.09	5.84+ 1.01	6.00+ 0.94	3.58+ 1.17	<0.000*	0.987
6MWT (m)	302.64± 107.04	277.58± 79.01	356.58± 93.552	282.93± 72.97	<0.001*	0.876
FEV1% preicted	40.50+ 9.72	39.44+ 13.38	42.79+ 13.10	39.93+ 14.66	0.403	0.626

IG= Feldenkais Group, CG- pulmonary rehabilitation group, $p < 0.05$

Evaluation of 6 Minute Walk Distance (6MWD)

The exercise tolerance in COPD patients as measured by 6MWD showed significant differences within-subjects effect, F (1, 34) = 0.447, $p < 0.001$, partial eta squared = 0.553, with both groups showing an increase in 6 Minute Walk Distance (6MWD) across the time periods. The IG proved to benefit more during the intervention with increased distance walked (score differences of 42.46m) compared to CG (score differences of 33.33m). Sessions of Feldenkrais program had enhanced the exercise tolerance of COPD patients much more than the usual PRP. Interestingly it was observed in the FG group, 9 (53 %) subjects had increased more than 54 meters distance walk compared to only 8(42%) subjects who had decreases tolerance of less than 54 m. Unlike the PG, only 3(16%) subjects had an increase of more than 54 meters distance walked (Figure 1). More subjects in the FG group were walking further than 54 meters. An improvement in walking distance of 20% was observed in FG but only 15% in the PG.

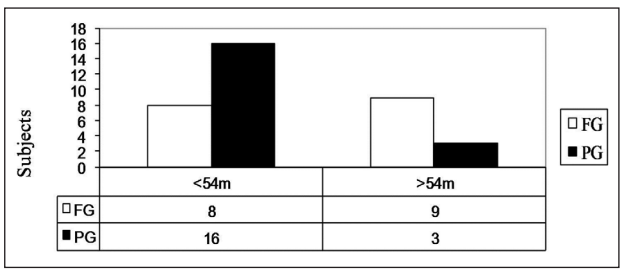

Figure 1: Increase in 6 Minute Distanced Walked Among COPD undergoing Feldenkrais Method and Pulmonary Rehabilitation Program

Discussion

The COPD patients in this study have extended their rehabilitation for 8 weeks duration. Therefore, it is not surprising that 50% of them eventually withdrew from the intervention programs since the duration of the study was long and thus not well tolerated. The withdrawal from the program was disappointing but the difficulty in retaining patients in the outpatient programs is well recognized (14). Similar to other studies, the frequency of exacerbations in COPD is difficult to sustained motivation among COPD patients made worse with the severity of the disease (15). The adherence to pulmonary rehabilitation is a major problem as that being reported previously (16) .

The results of the lung function demonstrate only a low improvement in the exercise tolerance of COPD patients. Measures of FEV1 alone are not sufficient to define the treatment response, as this marker does not fully reflect the pervasive nature and burden associated with COPD. Even though there were changes in the mean scores, this was not large enough to be considered significant. Similarly, the differences between groups, in FEV1 (% predicted) were insignificant to cause any change in the lung function. Therefore, other measures can be used to determine their response to intervention.

Measurements of dyspnoea, for example can provide an insight into the practical effects of treatment on everyday life. This would reflect whether or not the patients perceive an improvement in their primary symptom of COPD since it is a primary reason for them to seek medical care. The significant change in the mean Borg scores have a major influence on the subject. Borg scale have been used to rate perceived dyspnea and exertion. It seems to provides a reliable measure of targeting the training intensity carried out among COPD (17, 18). A subjective rating of 4 to 6 on the Borg scale was appropriate to determine the perception of dyspnoea (19). Those in the PG were observed to be less dyspnea (reduced Borg score) at the later assessment than those in the FG who had almost similar mean score as the initial assessment.

The training in pulmonary rehabilitation involves high intensity exercise and increased cardiovascular endurance. The alteration in the perception of dyspnea in the PG could be an effect of structured physical training. Unlike the FG, the mode of exercise carried out was slow, repetitious and demanded the patients to relax. The exercises were interspersed with breathing naturally and at their own pace. The similar Borg score observed in the initial assessment during the walking tests truly represents an exercise mode-specific desensitization. Throughout the sessions, the physiotherapist was guiding the subjects through a sequence of gentle non-strenuous movements. Attentiveness achieved among the subjects helps them to discover how to move more comfortably and efficiently. There were comments made by the subjects of their experiences with immediate improvements in posture, a feeling of lightness of movement, and freedom from chronic discomforts. The only limitation in this study,

however that is no measurement of minute ventilation (VE) and oxygen consumption (VO2 maximum) was carried out during the course of the intervention.

There were improvements reported in the breathing patterns of subjects undergoing Feldenkrais program. Subjects perceived themselves as always having breathlessness and there is fear of losing control of themselves and in their minds, their Borg score was always similar to what was identified earlier in the initial assessment. The individual's perception of dyspnea is subjected to the subjects' familiarization of what they perceived as being dyspnoea. In using the Borg score, it is important to note that the scoring requires knowledge or quantification of the stimulus among the subjects. Poor subject understanding of how the scores are measured, can be possible reasons for the poor scores perceived by the subjects. This may be difficult to establish because of lack of clear differences between scores. This is consistent with the study of Knox and colleagues (1988), who reported improvements in visual analog scores for dyspnoea over three days of repeated testing but not over four weeks suggesting that the reduced dyspnea was part of a learning effect or related to the changing attitude and beliefs which are known to be among the strong predictors of exercise performance (20).

The 6 minute walking distance is generally believed to be representative of activities of daily living such as shopping, as the level of exertion associated with this test is considered to be maximal (21). Such modest increases in walking distance could therefore be translated into clinically meaningful improvements in quality of life especially if it is accompanied by improvement in symptoms. The improved walking distance in FG is consistent with true physiological training effect. Since the Feldenkrais sessions did not have any structured physical exercise, the improved walking performance in this group presumably occurred because of the improved ventilator capacity which requires adaptations for it to significantly improve the exercise performance (22).

The application of various movement pattern carried out during Feldenkrais sessions indirectly causes a manual stretch of a single or several intercostals spaces which is said to be a therapeutic procedure to improve gas exchange. These techniques have shown to improve regional ventilation, gas exchange, respiratory muscle function, dyspnea, exercise tolerance, and quality of life (23). Compared to spontaneous breathing, pursed-lip breathing reduces respiratory rate, dyspnea, and arterial pressure of carbon dioxide (PaCO2), while improving tidal volume and oxygen saturation in resting conditions (24).

The findings is consistent with an early meta analysis that supports the view of a beneficial effect of relaxation on dyspnoea (25). This was later confirmed by a pilot study that evaluated the role of breathing and relaxation training in patients with severe COPD (26), where patients were randomized either to the intervention or a control (standard care) group. Although, symptoms scored on SGRQ and the MRC Dyspnoea Score appeared unchanged over the test period, there was a significant differences in the walking distance (six minute walking test) between the two groups. The improvements in walking distance occurred without any increase sensation of dyspnoea suggesting the beneficial effect of relaxation in the management of exercise induced dyspnea, which was consistent with our findings.

The implication of our study provides opportunity for a different approach of management to be carried out among COPD patients. This is especially beneficial for severed COPD who tolerates less intense exercise as in PRP but able to progress slowly with Feldenkrais Method. Unfortunately, this study is with limitation as there are reasonably large number of patients who had dropped out of the study recruitment, hence resulting in small number of subjects in the second phase of study. A possible cross over effect of the pulmonary rehabilitation program in Phase 1 could have had an influencing effect on the improvement in Phase 2 of the study. However, further research is warranted to identify possible predictors of improvement with Feldenkrais Method.

Conclusion

Both intervention demonstrated relevance to COPD patients however; the PRP remains the best method to increase patient's tolerance in exercise. Whilst it may be the case that COPD patients may better tolerate the Feldenkrais program, it does not provide better outcomes. Further studies regarding this may be necessary to justify its use in clinical practice since the present study only recruited a small number of subjects.

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SUPERIOR SOMATIC PAIN RELIEF AND IMPROVED VISCERAL PAIN CONTROL IS ACHIEVED USING PRE-EMPTIVE ANALGESIA FOR LAPAROSCOPIC CHOLECYSTECTOMY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

BACKGROUND:

Laparoscopic cholecystectomy, although is less invasive than open surgery, is not completely pain free. The use of local anaesthesia to relieve pain following this procedure is a common practice. However, it remains debatable whether a pre- or post-operative drug administration is more effective. Here, we investigated the role of preemptive local anaesthetic infiltration given pre- or post-incisional, in relieving the pain during laparoscopic surgery.

METHODOLOGY:

A randomized controlled trial was conducted with 96 patients receiving 0.5% Bupivacaine 100mg. Group A (n=48) received post-incisional skin infiltration whilst Group B (n=48) received pre-incisional infiltration. Incisional (somatic) and intra-abdominal (visceral) pain was assessed using Visual Analog Scale (VAS) at day 0, day 1 and day 7 post-operative days.

RESULT:

Baseline characteristics between the two groups were similar. Incisional pain was lower in Group B as compared to Group A at day 0 (P=0.03) and day 1 (P<0.01). Intra-abdominal pain was also lower in Group B at day 0 and day 1 (P= 0.04). VAS score was similar at day 7 although analgesia requirement is higher in Group A (P>0.05).

CONCLUSION:

Administration of pre-incisional local anaesthesia offers better pre-emptive pain relief measure than post-incisional administration by reducing somatic and visceral pain in laparoscopic gall bladder surgery.

Keywords*: laparoscopic cholecystectomy, preemptive analgesia, pain, ethnicity, local anaesthesia*

Introduction

Laparoscopic cholecystectomy is the "gold" standard for gall bladder surgeries today (1). It is well established that minimally invasive surgery is associated with less morbidity as compared to open procedures. In addition, it has been shown that patients undergoing laparoscopic procedures experience less post-operative pain, reduced analgesia consumption and reduced length of hospital stay. However, the procedure is not entirely pain-free as some amount of pain is still associated with laparoscopic procedures (2, 3).

At present, pain management in laparoscopic cholecystectomy has taken a multi-modality approach. The concept of giving pre-emptive analgesia in surgical operations has been widely studied and its use in

laparoscopic procedure such as cholecystectomy is well recognized in various studies (4). It is a common practice for pre-emptive analgesia technique that local anaesthesia to be administered as a post-incisional infiltration. However, how this compares to a pre-incisional local anaesthesia remains, as it is not well studied.

Hence, we compared the pain outcome in patients undergoing laparoscopic cholecystectomy receiving pre-emptive or pre-incisional local anaesthetic infiltration with those receiving a post infiltration local anaesthetic infiltration. We also aim to determine whether pain in patients undergoing laparoscopic cholecystectomy receiving local anaesthetic infiltration is influenced by their demographic profiles such as ethnicity. This study will provide a new perspective for the use of pre-incisional local anaesthesia infiltration in laparoscopic surgeries conducted in University Malaya Medical Centre.

Methodology

Study period, design and sample size

A randomized controlled trial was conducted in the University Malaya Medical Centre (UMMC) for the period of August 2006 to June 2008. This study has been approved by the Medical Ethics Committee (MEC) of University Malaya Medical Center [Ethics committee/IRB reference number: 547]. The patients were randomized into two groups: Group A receiving post-incisional local anaesthetic infiltration and Group B receiving preemptive or pre-incisional local anaesthetic infiltration. All patients enrolled in the study had given their written and informed consent prior to surgery.

During the study period, 96 patients from a total of 103 patients undergoing elective laparoscopic cholecystectomy were recruited for the study. The remaining seven were excluded as these patients were converted to open cholecystectomy during laparoscopic surgery. Except for three patients who had gall bladder polyps, all patients undergoing elective laparoscopic cholecystectomy had underlying cholelithiasis which, is a common symptom for biliary colic. In addition, these patients had previous history of cholecystitis or pancreatitis, which were treated conservatively prior to surgery.

Inclusion and exclusion criteria

Patients between the ages of 18 to 60, who were undergoing elective laparoscopic cholecystectomy with an American Society of Anesthesiologists (ASA) I and II were included in the study. Patients with an ASA of III, emergency laparoscopic cholecystectomy or major perioperative complication were excluded from this study. Patients were admitted one day prior to surgery and were discharged home on the first or second post-operative day.

Anaesthesia

A standard anaesthesia induction was performed using intravenous propofol (2-3mg/kg), fentanyl (1-2mcg/kg) and muscle relaxant atracurium (0.5mg/kg) or rocuronium (0.6mg/kg). Anaesthesia was maintained throughout surgery through the inhalational of sevoflurane and intravenous morphine (0.1-0.2mg/kg). Patients were mechanically ventilated with CO_2 at 35-40 mmHg.

Patients received subcutaneous or oral tramadol 50 mg thrice a day post-operatively and additional tramadol was given in the event of breakthrough pain. Other forms of analgesia were also given to those who experienced nausea and vomiting due to tramadol intolerance. Analgesic requirement were measured both at the first 24 hours post-surgery before discharge and at the end of 7 days post-surgery. The amount of morphine escaped was noted during the immediate post-surgery period.

Surgical technique and local anaesthetic infiltration

The operative procedure was performed using the Hassan or open technique for the initial port placement, with a standard four port technique using two 10 mm ports placed in the epigastrium and peri-umbilical region and two 5 mm ports placed at the subcostal area at the mid-clavicular and anterior axillary line. The abdomen was insufflated with the abdominal pressure maintained at 12-14 mmHg.

We used 0.5% Bupivacaine 100 mg (20 ml) as our choice of local anaesthetic agent (4). About 5 ml or 25mg of 0.5% Bupivacaine were infiltrated in each port site with attempts to infiltrate the local anaesthetic agent at the level of skin, fascia, peritoneum and periportally.

Group A received local anaesthetic infiltration at the end of surgery after removal of the laparoscopic ports which is the standard of practice in UMMC. Group B, received an infiltration of the local anaesthetic agent prior to laparoscopic port insertion. The local anaesthetic was given under direct vision for the first port insertion and the remaining ports are infiltrated under camera vision by first creating a bleb in the peritoneum and withdrawing it into the other levels and periportally.

Pain assessment

Patient's pain score was assessed post-operatively using the Visual Analogue Scale (VAS), which has a score of 0 to 10. A score of 0 is attributed to being no pain and 10 being the worst imaginable pain. Assessment of pain is done by the Acute Pain Service (APS) (5, 6). Nurses were randomized to become independent assessor of patient's pain score with a standard questionnaire. Patients were thoroughly informed on how they would be asked on their pain outcome using the VAS score.

Pain was assessed at two levels, namely:-

- Incisional (somatic) pain – pain is described to patient as a sharp, localized pain arising from the skin and incision site
- Intra-abdominal (visceral) pain – pain is described as a generalized, vague, dull aching, non-localized pain.

The above VAS score were assessed three times. The first assessment was done immediately after surgery or during the first six hours post-surgery when the patient regained full consciousness. The second assessment was performed 1 day post-surgery or prior to discharge. The final assessment was scored after 7-days post-surgery via a telephone call to patients with the same set of questionnaire repeated. Shoulder pain experienced by the patients was also enquired.

In addition, the amount of analgesia consumption or requirement was obtained from the medical record and telephone conversation. The requirement for an escape dose of morphine immediately after surgery was taken into account in patients who complained of severe pain with VAS > 3. No patients were excluded from the study due to major complications resulted from the surgery.

Any major complication that arises post-operatively was also obtained from patients and patients were excluded from study if occurred. So far, we had no reports of major complication from patients enrolled in this study.

Data and statistical analysis

Demographic details such as gender, age, body mass index (BMI), ethnicity, length of operating time and prior endoscopic retrograde cholangiopancreatography (ERCP) were obtained. Both age and BMI was presented as mean $\pm$ standard deviation (S.D.) and was analyzed using the Fisher Exact test. Length of operating time was presented as median (range) and was analyzed using the Mann-U Whitney test as data was presented as a continuous variable with a skewed distribution of the normal curve. The VAS score was determined for Day 0 (immediate post-surgery), Day 1 (the next day post-surgery) and Day 7 (one week post-surgery) as median (range). Statistical analysis was performed using the Mann-U Whitney test for the VAS score for both incisional and intra-abdominal pain respectively during the 3 occasions. Further analysis to determine the co-variates that may have affected the VAS score was performed. Here, Mann-U Whitney test was used for gender, BMI, and ERCP, and Kruskal-Wallis test was used to determine the median differences of age and ethnicity in order to determine whether the above co-variables may affect the outcome of the VAS score.

The amount of escape doses of morphine required at the immediate post-operative period (Day 0) was assessed in both groups and presented as the amount of times required for this treatment. Statistical analysis was done using the Fischer Exact test. The analgesia requirement in both groups was also assessed from the amount of intake in the first 24 hours and at the end of one week, presented as median (range). Statistical analysis was done using the Mann-U Whitney test. A P value <0.05 indicates a statistically significant difference.

Results

Demographic details and baseline characteristics

A total of 103 patients were enrolled for the study from August 2006 to June 2008, out of which seven patients were excluded due to open conversion cholecystectomy. Hence the conversion surgical rate was determined at 6.8%. The remaining 96 patients were equally randomized into two groups with 48 patients in each group.

Among the recruited subjects, 80 (83.3%) were female and 16 (16.7%) were male. These patients presented various gall bladder diseases ranging from cholelithiasis, previous history of cholecystitis, pancreatitis or choledocholithiasis, and gall bladder polyp. Ethnicity analysis showed that 46 (47.9%) were Malay, 30 (31.3%) were Chinese and, 17 (17.7%) were Indian. The remaining 3 (3.1%) were of other backgrounds and ethnicities. Majority of the patients (84 or 87.5%) had no prior Endoscopic Retrograde Cholangiopancreatography (ERCP).

There was no significant difference between Group A and B in relation to the gender, ethnicity, age, BMI, length of surgery and history of ERCP (Table 1). The mean age between Group A and Group B was 45.56 (S.D. $\pm$ 10.82) and 46.08 (S.D. $\pm$ 8.85) respectively whereas the mean BMI was 25.59 (S.D. $\pm$ 5.34) and 26.87 (S.D. $\pm$ 5.14) between Group A and Group B. Length of surgery was found to be 80.00 minutes (range 65.00-97.50) in Group A and 85.00 (range 60.00-105.00) minutes in Group B.

Pain on Day 0 and escape dose with morphine

Assigned APS nurses assessed patients VAS scores during the immediate post-surgery duration, i.e. when patient had regained consciousness and within 6 hours post-surgery period. The median VAS score for incisional pain was significantly higher in Group A was (3.5, range 0.0-5.8), when compared to those in Group B at (0.5, range 0.0-5.0). The VAS score for incisional pain was not affected by gender, ethnicity, ERCP, age, and BMI.

The median VAS score for abdominal pain experienced by patients in Group A was 3.0 (range 0.0-7.0), which was higher than Group B at 1.5 (range 0.0-5.0); however, this was not statistically significant. Similarly, the VAS score for intra-abdominal pain was not affected by patients' gender, ethnicity, ERCP, age, and BMI.

Patients who complained of severe pain as reflected by a high pain score at immediate post-surgery and who received their required escape doses of morphine were also assessed. It was found that the amount was comparable in both groups without significant differences (Table 2). Pain score for incisional and intra-abdominal pain for both groups at Day 0 is summarized in the Table 3.

Table 1 – Baseline characteristic of control and intervention group.

	Group A n=48 (%)	Group B n=48 (%)	*P*-value
Gender			
Male	5 (10.4)	11 (22.9)	0.17
Female	43 (89.6)	37 (77.1)	
Ethnicity			
Malay	21 (43.9)	25 (52.1)	0.59
Chinese	15 (31.3)	15 (31.3)	
Indian	11 (22.9)	6 (12.5)	
Others	1 (2.0)	2 (4.1)	
ERCP done			
Yes	4 (8.3)	8 (16.7)	0.36
No	44 (91.7)	40 (83.3)	
Age *	45.56 (± 10.82)	46.08 (± 8.85)	0.80
BMI *	25.59 (± 5.34)	26.87 (± 5.14)	0.23
Length of operation (mins) #	80.00 (65.00 – 97.50)	85.00 (60.00 – 105.00)	0.97

a. *P*-value in Fischer exact test unless otherwise stated
* values in mean ± s.d. and independent t-test used for p-value
# values in median (range) and Mann-U Whitney test used for p-value

Table 2 – Escape doses of morphine required immediate post-operative period

	Group A n=48	Group B n=48	*P*-value
Escape dose required	31	32	1.00
Escape dose not required	17	16	

a. Fischer exact test used

Table 3 – Pain score at Day 0 and the influence of the co-variates on VAS

	Incisional pain		Intraabdominal pain	
	VAS score	*P*-value	VAS score	*P*-value
Group A	3.5 (0.0 – 5.8)	0.03	3.0 (0.0 – 7.0)	0.47
Group B	0.5 (0.0 – 5.0)		1.5 (0.0 – 5.0)	

a. all values in median (range) and Mann-U Whitney test used for p-value unless otherwise stated.
* Kruskawallis test used for *P*-value

Pain assessment and analgesia requirement on Day 1

The median VAS score for incisional pain in the Group A patients was 5.0 (range 3.0-.6.0), which was higher than Group B at 1.0 (range 0.0-3.0) (*P*<0.01) (Table 4). Again, the VAS score for incisional pain on Day1 was not influenced by gender, ethnicity, ERCP, age, and BMI.

We also observed that the median VAS score for intra-abdominal pain in Group A was 5.0 (range 0.5-6.0), which was higher than Group B at 2.0 (range 0.0-5.0) (*P*=0.04) (Table 4). Similarly, the VAS score for intra-abdominal pain was not influenced by gender, ERCP, and BMI.

Table 4 – Pain score at Day 1 and the influence of the co-variates on VAS

	Incisional pain		Intraabdominal pain	
	VAS score	*P*-value	VAS score	*P*-value
Group A	5.0 (3.0 – 6.0)	< 0.01	5.0 (0.5 – 6.0)	0.04
Group B	1.0 (0.0 – 3.0)		2.0 (0.0 – 5.0)	

a. all values in median (range) and Mann-U Whitney test used unless otherwise stated.
* Kruskawallis test used

In addition, we examined the amount of times that analgesia was given to patients within the first operative day (Table 5). No significant difference was observed in the frequency of analgesic administration between the two groups.

Table 5 – Amount of times analgesia needed at Day 1 and the co-variates

	Amount of times analgesia needed	p-value
Group A	2.00 (1.25 - 3.00)	0.15
Group B	2.00 (1.00 - 3.00)	

a. values in median (range) and Mann-U Whitney test used unless otherwise stated
* Kruskawallis test used

Pain assessment and analgesia requirement on Day 7

On the seventh post-operative day, a telephone call were made by the APS nurses to all patients enrolled in the study and the same question regarding their VAS score for incisional and intra-abdominal pain were repeated. Patients were also asked on the total amount of analgesia used at the end of one week. All patients did not encounter any significant post-operative complication when enquired.

We observed that the median VAS score for incisional and intra-abdominal pain on Day 7 were almost similar without significant difference in both groups (Table 6). The VAS score for incisional and intra-abdominal pain for either group was also not influenced by gender, ethnicity, ERCP, age, and BMI.

However, when reviewing the number of times that analgesia administered, we found a trend that Group A

group required more at 5.0 (range 2.0-14.0) versus Group B at 2.0 (range 1.3-3.0). although not statistically significant (Table 7).

Table 6 – Pain score at Day 7 and the influence of the co-variates on VAS

	Incisional pain		Intraabdominal pain	
	VAS score	p-value	VAS score	p-value
Group A	2.0 (0.0 – 3.0)	0.80	0.0 (0.0 – 2.0)	0.74
Group B	0.0 (0.0 – 2.0)		0.5 (0.0 – 3.0)	

a. all values in median (range) and Mann-U Whitney test used unless otherwise stated.
* Kruskawallis test used

Table 7 – Amount of times analgesia needed at 1 week and the co-variates

	Amount of times analgesia needed	p-value
Group A	5.00 (2.00- 14.00)	0.13
Group B	3.00 (2.00- 8.50)	

a. values in median (range) and Mann-U Whitney test used unless otherwise stated
* Kruskawallis test used

Shoulder pain

Our data shows that shoulder tip pain was not the main complaint of pain among our patients following laparoscopic cholecystectomy. Both groups showed similar complaints of shoulder tip pain following surgery (*P*=0.82).

Discussion

Laparoscopic cholecystectomy is now considered a standard operating procedure for many gall bladder diseases in both developed and developing countries. Laparoscopic cholecystectomy can reduce morbidity, shorten hospital stay and reduce post-operative pain when compared to open cholecystectomy (2, 3, 7). In our study, females represent the majority of patients with gall bladder diseases. In addition, cholelithiasis remains the most common gall bladder disease presented in this group. Our rate of conversion to open cholecystectomy was 6.8%, which was almost similar to that reported in many other established centers around the world (8-10).

The ethnic distributions in our study population were equally distributed in both Group A and Group B, with no significant difference found between the two groups. There was also no difference between the VAS score from these ethnic groups. This is interesting to note, as it has been shown that patients of Indian ethnicity tend to have higher frequency and scoring of pain (11). We believe that pain assessed with an objective and quantitative assessment method such as the Visual Analog Scale (VAS), will not show any differences between these groups, as the expression of pain may differ from one individual to another. This may be due to their different cultural practices and upbringing, an aspect which was not taken into account in our study.

VAS score in assessment of pain is known to be the oldest, easiest and best validated form of measuring pain. (12). The role of using preemptive analgesia in surgical setting has been widely studied and applied in various disciplines by surgeons, obstetrician and gynaecologists (13). Its use ranges from simple administration of oral analgesic to local anaesthetic infiltration and, at times the use of more invasive procedures such as epidural or nerve blocks have been reported. The choice of technique or method aims to improve and reduce pain in patients undergoing any surgical procedures by administrating analgesia prior to surgery (14-16). In our study, we looked into patient pain outcome over a period of a week. This was done since Bisgaard *et al* had suggested that incisional or somatic pain seems to be the most common or dominant pain experienced by patients undergoing laparoscopic cholecystectomy during the first post-operative week (17). Although, laparoscopic cholecystectomy is known to reduce post-operative pain as compared to open cholecystectomy, it does not provide completely pain-free surgery. Pain following laparoscopic cholecystectomy can be considered multifactorial (18,19). Bisgaard *et al* has suggested that pain in laparoscopic cholecystectomy is a combination of three different and clinically separate components, namely incisional pain (somatic pain), intra-abdominal pain (visceral pain) and shoulder pain (referred visceral pain) (20).

The idea for such preemptive use was first mooted by Woolf in 1983 when the idea of central sensitization was first introduced (21). Its application in the field of surgery was found to be most effective. It is worth to note that the perception of pain involves both peripheral and central nervous system. When there is a noxious stimulus such tissue injury in surgery, a cascade of pain pathways occur beginning at the site of injury where pain is relayed via the peripheral nerve to the spinal cord and then to the brain. Based on this knowledge, the use of preemptive analgesia administered prior to tissue injury, prevents central sensitization and reduces or limits the pain experienced by patients (22). In other words, central sensitization is reflected by the increase in pain perception following noxious stimuli and a decrease in threshold of the central nociceptive pathways after peripheral tissue injury or inflammation, which has been implicated in the development of hyperalgesia and maintenance of persistent pain following the noxious stimuli (23). Our findings also concur with many other studies regarding reduced post-operative pain among patients who had preemptive local anaesthetic infiltration at the incisional site. However, our study design was slightly different from others. In one study, the use of local anaesthetic infiltration at the incisional site was compared with placebo. Somehow this seems strange and the outcome would have been obvious since the administration of anaesthesia would undoubtedly provide better pain relief.

In addition, the number of times and amount of analgesia was administered was not mentioned (24-26).

When comparing administration of local anaesthetic infiltration as a pre-incisional versus post incisional procedure, we found that it was a better option to give prior to port insertion. This also concur with findings by Uzunkoy et al (27, 28). Similar finding on the benefits of giving preemptive local anaesthetic infiltration for incision was also shown by Bisgaard et al and Lee et al (17, 29). Both studies examined administration of intraperitoneal local anaesthetic infiltration to provide more pain control and investigated the control of pain in the multimodality or multiregional aspect. Both studies also agreed that incisional or somatic pain was the most dominant pain experienced by patients during the early operative period. However, one study by Sarac et al showed that giving local anaesthetic infiltration provide better outcome in pain management when compared with placebo but further showed that pain score was lower when given post incisionally compared with preemptive administration (30).

Whilst shoulder pain remains the major complain for pain from gall bladder disease and thus, surgeries involving the gall bladder would yield similar complaints, our study does not appear to support this notion. It has been postulated that pain in the shoulder is the result of diaphragmatic stretching resulting in phrenic nerve neuropraxia (31). In order to reduce this, lower insufflation pressure and careful decompression may be the key to lowering pain. But not all studies appear to agree on this (17, 19, 32, 33). Perhaps the absence of shoulder pain in our study is not because of the local analgesia itself, but rather of the skill of the surgeons. However, this needs to be investigated further since we are not able to confirm or refute this hypothesis.

One limitation that we had observed in our study was insufficiency in post-operative pain management. This was not surprising since many studies including that of Rawal *et al.* had shown that there is a lack in the recognition of inadequate treatment of pain and that is continues to be a clinical problem in many hospitals worldwide (34). In our study, this is evident from Day 1 post operatively, when the control group had shown to have a higher pain score and yet analgesia consumption was almost similar to the intervention group. This suggests a limitation contributed by human factor. A survey by Bardiau *et al* found that knowledge of post-operative pain among nurses were lacking thus affecting skills in assessing and managing pain effectively among patients. When clinical guidelines or pain treatment protocols as well as the inception of the Acute Pain Service (APS) were applied, pain relief improved significantly (35).

Our study was not able to demonstrate the effectiveness of local analgesia in comparison to that of other modalities in relieving pain. It has been reported that other various preemptive analgesic techniques were also evaluated by other trials. Some trials have preemptively used dextromethorphan {an NMDA (N-methyl-D-aspartate) receptor antagonist}, NSAIDS, opiods, epidural, and multimodal analgesia with positive results in reducing pain among patients (4, 36, 37). Other trials assessing the role of local anaesthetic given preemptively in the form of intraperitoneal instillation were also conducted where local anaesthetic agent were given intraperitoneally and compared with placebo or groups with instillation at the end of operation (31, 38-40). However, these techniques can only be conducted after extensive literature review and large-scale multi-centre trials since evidence of the use of these modalities does not appear to be supported by large number of evidence-based literatures (4,17).

Conclusion

In conclusion, the use of preemptive pre-incisional local analgesia has been shown in our study to improve visceral and somatic pain more effectively than the administration of post-incisional local anaesthesia. In addition, shoulder tip pain in laparoscopic cholecystectomy was not form the main complaint among patients and that ethnicity does not influence the outcome of pain following surgery in many patients. Based on our findings, we can safely recommend that preemptive local anaesthetic infiltration i.e pre-incisional local anaesthesia, be given as standard practice in patients undergoing laparoscopic gall bladder procedures.

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