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This issue of the Journal has a new cover. This is not merely a change in physical appearance but also a signal of a new era for the Journal. The Journal was conceived as a vehicle to promote a continuation of scientific enquiry among doctors and other healthcare professionals, many of whom had been active in research and publication before entering private practice. It was a unique and bold move as doctors and healthcare professionals in private practice had been seen as leaving for greener pastures and turning their back on research or academic pursuits. The “experiment” was carried out by some of us who had a desire to inject an academic flavour into private practice. The Journal may not have taken off like a rocket, having only five issues since the first one in 2003, but it has been able to attract sufficient interest among us so as to prove that it is a worthwhile endeavour.

The elevation of the KPJ International College of Nursing and Health Sciences to a University College, now known as KPJ Healthcare University College, has given a boost to the Journal. The existence of a medical journal in the Group in turn provides the University College a ready made scientific arm to its academic and research efforts. This issue reflects beautifully the synergy between the academic and professional arms of KPJ Healthcare. Contributions from both arms have given a fresh and significantly more robust face to the Journal, reflected by more varied contents representing both laboratory and clinical works. It is fitting that the Journal now becomes the “Official Journal of KPJ Healthcare Hospitals and KPJ Healthcare University College”.

A prerequisite to further success in our publication efforts is a healthy and active research environment. It is expected that academic staff should do research and publish but there is no obligation to do so by other professionals and staff in the Group. Some encouragement and, perhaps, incentives may be needed for the latter group. Several commitments should be made by all involved for future progress. First, the research machinery must be strengthened and oiled. The work of the Research and Development (R&D) Committee needs continuing support with implementation of a smooth and efficient mechanism of its function. Funding support has been assured. But most importantly the real function of this Committee, which is to promote the development of research, which in turn involves training and hands on assistance on design of research proposals, should be fully appreciated. As most non-academic staff are new in research a lot of time and efforts will have to be invested by members of the R&D Committee to guide them. Success may be slow in coming but patience and hard work will be rewarded in the end. Additionally, an ethical review committee, an essential component of the research organisation, has to be in place and has its function clearly defined.
Finally, there needs to be a clear vision of the direction and focus of our research. For healthcare professionals, the most important purpose of research is to improve patient care. No matter how small an improvement that can be achieved it is always worthwhile. The research that matters is the one that tests a hypothesis that arises from one’s own experience in daily practice. It is too often that researchers are recruited into research, such as trials of pharmaceuticals that promise monetary and other rewards, but they are only involved in conducting a small portion of the study without any say or input into design or analysis. While not wanting to discourage this kind of research altogether, it is my opinion that developing one’s own hypothesis to answer one’s own clinical or scientific question, then designing and conducting the research as the principal researcher and finally publishing it is the most rewarding experience in a researcher’s life. There are myriad questions to be asked and answered through research at our work place ranging from clinical issues to management ones such as cost-benefit analysis of services and marketing strategies. Questions on aspects of quality and safety in patient care need special attention as answering them gives us tools to provide the best of what is expected of us by our patients. In short, our research philosophy should be in line with our current drive to improve patient care and customer service.

Azizi Haji Omar, MMedSc, FRCP, FAMM
HEALTH EDUCATION AND HEALTH SERVICES – A NEW ORGANIZATIONAL MODEL …
A New Concept in Delivery of Innovative, Effective and Integrated Health Services and Health Education

Lokman Saim, MD, FRCS, MSurg ORL

BACKGROUND

Medicine as it is practiced today developed throughout the thousands of years of human civilization. It is the culmination of efforts of thousands or perhaps millions of people, some we know and others we do not. They practiced the art of medicine with compassion, passed down the knowledge through dedicated teaching and improved the profession through research. Before the era of the Renaissance in Europe, the main contributors to the development of modern medicine were the doctors and scientists of the Islamic Empire in Persia and Spain. The practice of medicine was regulated and medical education was a ‘serious and systematic discipline’. The Muslims regarded the study of medicine as ‘fardh kifayah’. Funding was provided by the state, to build hospitals to provide excellent services as well as facilities for medical education. The ablest of physicians such as Al Razi (Al-Razes), Ibn-Sina (Avecenna) and Ibn Zuhr (Avenzoar) worked both as the hospital directors and the deans of medical schools. Curiously, over the time of immense development in medical services and medical education, the organizational structures of these two missions were separated. This could be partly due to the advent of managed health care and changes in reimbursement systems for patient care, which resulted in the perception that business effectiveness and efficiencies could best be achieved by separating the clinical service enterprise from the education mission. Nowadays, the organizational structures of teaching hospitals and medical faculties are separated and in most countries the hospitals are administered under the Ministry of Health while the faculty of medicine is under the Ministry of Education or Higher Education, as in Malaysia.

CURRENT TREND

There has been a changing trend in the organizational structures of health services and health education. The trend is towards partnership approach in health services and health education. There is greater emphasis on stronger cooperation between the academic enterprise and the health-care sector. These two areas are obviously closely related. This has led to the evolution of academic health centers where medical and health services, education and research are integrated and managed by a single systematic organizational structure. When these partnerships are done properly, it is believed that both the academic and the clinical enterprises are enriched significantly.

WHAT IS AN ACADEMIC HEALTH CENTRE?

An academic health center is defined as an institution that integrates a medical school, one or more other health professional schools or programmes and one or more teaching hospitals or health systems. An academic health center offers comprehensive, cutting edge patient care to the communities that they serve and have large research programmes that explore new concepts, treatments and cures, as well as train the health care professionals of the future. This integrated centre serves the tripartite mission of excellence in medical and health services, research and education.

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THE CONCEPT ACADEMIC HEALTH CENTRE

In Malaysia, both the medical schools, as the major institutions in the training of medical and health care professionals and the government hospitals are expected to progress as the leaders in the development of innovative, efficient and effective health care educational programmes and healthcare delivery. One of the most important factors for this mandate is the provision and development of an organizational structure that is able to support both missions.3 There is a dire need for development of integrated Academic Health Centre. This centre will not only integrate the teaching, research and health services of the medical sector but also the other health sectors namely, pharmacy, dentistry, nursing and public health.

The new organizational model of academic health centre will demonstrate the platform and extent of integration between all the faculties, teaching hospital and research facilities. This is to be achieved through the creation of integrated, interdisciplinary and modern teaching health centers with laboratories and health clinics that will support the developing and demanding needs of undergraduate, graduate, clinical and research work. The new academic health centers should be able to sustain programme integration and interdisciplinary health care in an environment of team health care delivery.

Therefore the new academic health center should be able to provide all the facilities to achieve the following expected outcomes:

a. A new emphasis on interdisciplinary teaching and learning, including undergraduate and graduate programmes and continuing education.
b. A strengthened process of learning through enhanced relations between academic (theory) and clinical activities.
c. Increased attention to health and wellness of the community.
d. Enhanced opportunities for collaborative research, including integrated laboratory research centres.
e. Reconfiguration of student teaching space and facilities, with emphasis on the use of information technology in teaching and training, integrated student hostels, interdisciplinary teaching, problem-based learning and delivery of personal and professional development curriculum.
f. A new concept of administrative and organizational structure with a view towards emphasizing interdisciplinary scholarship and support to facilitating interaction between faculties, schools and across disciplines.

ACADEMIC HEALTH CENTRE ORGANIZATIONAL MODEL AND TRANSFORMATION OF MEDICINE

Many countries, including the USA, UK, Singapore, the Netherlands and Canada have reorganized the health and education management into an academic health centers to improve health locally and compete globally.4 US institutions that have begun to develop models of integrated translational research and care-delivery systems include the University of Pennsylvania, John Hopkins University and Harvard University – Partners Healthcare. The UK is also creating academic health centers through integration of academic institutions and national Health Services trusts such as Imperial College Academic Health Science Center in London. To transform health care, it is believed that academic health center should evolve as integrated health-care delivery systems that not only include the traditional medical centre but also a network of community hospitals and practices. To catalyse the needed transformation, academic health centers should focus on organizational structures, external partnerships, research translation, models of care delivery and new educational models.

The new organizational model for these changes and challenges has been a trend towards more “corporate” management. It is characterized by reorganization along non-disciplinary lines towards an administrative structure that spans conceptually and operationally the totality of the academic health center enterprise and encompasses all mission areas. Therefore a single leader and a single board of managers is now the trend. The ideal choice of governance method is perhaps an integrated model with a single organizational structure, but other affiliated models may be considered to make this major change more achievable.

THE CHALLENGES

Advocating the creation of academic health centers in Malaysia has many challenges. But in order to build centers of world-class excellence in medical and health services, education, translational and clinical research, we should recognize the challenges and have strategies to overcome them. First, there is a “culture” differences between Ministry of Higher Education universities and Ministry of Health hospitals which are currently managed as a separate conglomerate with different priorities. This results in some ‘tension’ between universities and hospitals over their diverse missions, priorities and operational frameworks which can frustrate attempts to bridge the gap. The second barrier is that the three missions of an academic health centers,
namely research, education and health care are overseen by three separate ministries and thus three separate ministers. Third, there are other government departments that play an important role in the medical and health sector such as the Economic Planning Unit, the Legal Department and many others that may not be supportive of integration of the missions.

However, none of these issues is unique to Malaysia or insurmountable, especially when one considers the complexities of the US health care environment where academic health centers began. The real challenge will be winning the hearts and minds of the administrators and perhaps the politicians. They will need convincing of the economic benefits of linking health services to teaching and research.

CONCLUSION

The Ministry of Health is planning 1–Care health system in line with the government’s transformation plan. The time is ripe for Malaysia’s health systems to grasp this opportunity to move from good to great and establish world-class academic health centers. The proposed academic health center should have a new organizational model – one that can focus principally on the need for greater integration of learning, research, and health-care practice. In this way, we will not only provide the best health services, but will be training health-care professionals for the integrated, complex, and information-rich world in which they will be working upon graduation. Nevertheless, we should not underestimate the challenges of change management, which will require both top-down and bottom-up approaches to unite hospitals and universities, primary care and medical research institutes in a single mission.

REFERENCES

Local Experience of Weight Loss in Bariatric Surgery

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ABSTRACT
Objective: To analyze the weight loss results from laparoscopic sleeve gastrectomy (LSG) against laparoscopic Roux en Y gastric bypass (LRYGB) over time.
Summary Background Data: Malaysian data regarding weight loss outcome in bariatric surgery is extremely scarce. To our knowledge this is the first comparison between the 2 procedures locally.
Methods: Retrospective data of 78 morbidly obese patients, with body mass indices (BMI) between 29.3 kg/m² to 81.8 kg/m² were analyzed. 45 underwent LSG and 33 underwent LRYGB from April 2008 until June 2012.
Results: The mean pre-operative BMI was 44.98 kg/m²; ranging from 29.3 kg/m² to 81.8 kg/m². The difference in the percentage of excess weight loss (EWL) is significant between the two groups at postoperative week 2, month 3 and month 6 (p = 0.02, 0.042 and 0.013 respectively), favoring LSG.
Conclusion: This study demonstrates that laparoscopic sleeve gastrectomy (LSG) is superior to laparoscopic Roux en Y gastric bypass (LRYGB). Significant differences were demonstrated in the percentage of excess weight loss and percentage of BMI loss at postoperative week 2, month 3 and month 6. KPJ Medical Journal 2012; 5:6–9

Key words: Bariatric surgery, laparoscopic sleeve gastrectomy, laparoscopic Roux en Y gastric bypass.

INTRODUCTION

The prevalence of obesity has increased markedly in the last thirty years. A systematic review of 199 countries in 2008 estimated that 502 million people worldwide were obese. The World Health Organization projects this number to increase to 700 million by the middle of this decade.1 Of all the Southeast Asian countries, Malaysia leads in the prevalence of obesity with almost one in two Malaysians are either overweight or obese.2

Obesity directly contributes to many chronic, debilitating and life-threatening diseases. These include type-2 diabetes, ischemic heart disease, stroke, hypertension, dyslipidemia, sleep apnoea, degenerative joint diseases and several common cancers. Currently there is no non-surgical method for predictably achieving major weight loss in the obese and maintaining that weight loss for an extended period of time. Programs involving diet, behavioral modification, exercise, with or without drug supplementation, are able, at best, to achieve a modest weight loss which is generally sustained only throughout the duration of the program.

Surgical methods however have been known to achieve substantial and durable weight loss for more than half a century; yet initially they have not achieve a significant impact on community health. However the introduction of laparoscopy in bariatric surgery has led to a major rise in these procedures. In the United States the estimated total bariatric procedures in 1990 was 30,000. The total for 2008 was estimated to be 220,000 case.3

Malaysian data regarding weight loss outcome in bariatric surgery are extremely scarce. The objective of our study is to analyze and compare the experience of a

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single institution (Advanced Laparoscopy and Weight Management Centre of Damansara Specialist Hospital) with the two procedures and their impact on weight loss over time.

MATERIALS AND METHODS

Retrospective data of 45 patients who underwent LSG and 33 patients who underwent LRYGB surgery in this hospital from the year 2008 until June 2012 were analyzed.

Primary outcomes measured were the percentage of excess weight loss (EWL) and percentage of excess BMI loss (EBMIL) at specific time points.

The ideal weight for each patient is calculated based on the BMI of 23 kg/m² (ideal BMI for Asians)\(^4\).

The following formulas were used to calculate EWL and EBMIL:

\[
\text{Excess weight} = \text{Actual weight} - \text{Ideal weight}
\]

\[
\%\text{Excess weight loss (EWL)} = \frac{\text{Pre-operative weight} - \text{follow-up weight}}{\text{Excess weight}} \times 100
\]

\[
\%\text{Excess BMI loss (EBMIL)} = \frac{100 - \left(\frac{\text{follow-up BMI} - 23}{\text{pre-operative BMI} - 23}\right)}{100}
\]

The patients’ EWL and EBMIL were measured at week 1 and 2, then at 1, 2, 3, 6, 9 and 12 months, and finally at 2 year follow up.

DATA ENTRY AND STATISTICAL ANALYSIS

Data were analyzed using SPSS version 19. Independent t-test and Levene’s test were used for statistical analysis. \(p < 0.05\) was taken as indicator for significant difference between the two groups.

RESULTS

78 cases were included in the analyses; 45 patients had LSG and 33 patients had LRYGB. There were 25 males and 53 females. The racial distribution constituted 60 Malays, 9 Indians, 4 Chinese and 5 from other races. The patients were between the ages of 18 and 71 years old with the mean age being 39 years.

The mean pre-operative BMI was 44.98 kg/m² ranging from 29.3 kg/m² to 81.8 kg/m². The mean EWL and EBMIL at specific time points are shown below.

There were significant differences in the EWL and EBMIL between the two groups of patients, where patients with LSG obtained significantly greater weight loss compared to LRYGB. (Fig 1, Table 1)

EWL for LSG were greater than LRYGB at week 1, week 2, month 1, 2, 3, 6 and 9 and year 2 post surgery.

There were significant differences in EWL between the two groups at week 2, month 3 and month 6 (\(p=0.02\), 0.042 and 0.013 respectively).

Table 1 — Mean (SD) EWL for patients who had LSG and LRYGB, showing the pertinent statistical parameters

<table>
<thead>
<tr>
<th></th>
<th>LSG</th>
<th>LRYGB</th>
<th>t value</th>
<th>Df</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 weeks</td>
<td>18.576 (8.09)</td>
<td>12.220 (3.56)</td>
<td>-2.504</td>
<td>23</td>
<td>0.020</td>
</tr>
<tr>
<td>3 months</td>
<td>46.220 (16.46)</td>
<td>34.345 (12.06)</td>
<td>-2.145</td>
<td>25</td>
<td>0.042</td>
</tr>
<tr>
<td>6 months</td>
<td>63.872 (17.59)</td>
<td>46.220 (14.74)</td>
<td>-2.683</td>
<td>23</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Similar pattern of weight loss for LSG compared to LRYGB was demonstrated in the EBMIL data. (Fig 2, Table 2) Data for EBMIL demonstrated similar significant differences at week 2, month 3 and month 6. At 2 years however, patients with LSG had comparable weight loss compared to those who underwent LRYGB.

**DISCUSSION**

Current methods in bariatric surgery include laparoscopic adjustable gastric banding (LAGB), Roux-en-Y gastric bypass (LRYGB), bilipancreatic diversion / duodenal switch (BPD / DS), sleeve gastrectomy (LSG) and gastric plication (LGP). Historically it is believed that bariatric surgery promotes weight loss via a combination of the surgery being restrictive on food intake as well as there being induced malabsorption. This narrow dichotomous concept has now faded as better research has led to a much broader understanding of the mechanistic options. Possible mechanisms of weight loss following bariatric surgery include the following:

- Induce satiety, reduce appetite, control hunger
- Change of taste preference - less sweet foods; lower fat content;
- Restrict intake
- Diversion from upper GI tract
- Mal-absorption of macronutrients
- Increased energy expenditure; Increased diet-induced thermogenesis
- Aversion to food through side-effects
- Inhibition of the metabolic adaptation to weight loss
- Changes to the gut micro-flora
- Changes in gut hormones: candidates include the incretins (GLP-1; GIP), ghrelin, CCK, Peptide YY,
- Central mechanisms: Modify hedonics; central appetite control; altered liking and wanting

Currently there are no long term data on outcomes following laparoscopic sleeve gastrectomy (LSG) with few medium-term data. Brethauer et al provided a literature review of the 36 published reports involving 2570 patients that were available in 2009.5 Only one report gave data beyond 3 years. There was a mean weight loss for the full group of 55% EWL.

The only study exceeding three years showed a weight regain of approximately 40% from 3 - 5 years.
Weiner et al has the largest series with longer follow up. He reported the outcomes of 746 patients with up to 8 year follow up. The %EWL was 59% at 2 yr, 45% at 5 yr and 36% at 8 yr.

We attempted to look at our own experience with sleeve gastrectomy compared to a more established procedure in the form of laparoscopic Roux-en-Y gastric bypass (LRYGB).

Laparoscopic sleeve gastrectomy is a restrictive whereas gastric bypass is a mal-absorptive bariatric surgery. LSG is a procedure involving resection of most part of the stomach along the greater curvature, leaving behind a sleeve of stomach that runs from the gastro-oesophageal junction until the pylorus. The continuity of gastrointestinal tract is not altered, thus endoscopic procedure can be done without complexity. In Asia, prevalence of gastric cancer is high especially in Japan, thus ability to conduct endoscopic procedure without any problem is a credit to LSG. Weight loss in LSG is attributed by smaller stomach size and alteration in GIT hormones. Reduced stomach distensability will limit the amount of food intake. GIT hormones are altered as when most part of stomach is resected, ghrelin-producing cells in the gastric fundus are also removed. This potentially will reduce the appetite.

Restrictive and malabsorptive bariatric surgery such as Laparoscopic Roux-en-Y (RNY) Gastric Bypass is the other commonly performed type of gastric bypass surgery. LRYGB rearranges the stomach, duodenum and other parts of intestines in a sort of Y configuration. This allows the small portion of the stomach to absorb nutrients and still derive nutritional benefits from food. The surgery does not involve removal of the stomach, which is still able to produce digestive juices. Consequently, LRYGB patients will quickly feel full after eating only a small amount of food.

Compared to LRYGB, LSG has several advantages and these are:
(a) Shorter surgery duration and fewer complications.
(b) Pylorus of stomach is preserved in GIT, thus patients are less likely to develop dumping syndrome.
(c) In LSG, small bowel and mesentery are not altered, therefore there is no added risk of internal hernia and the nutritional deficiencies are less pronounced.
(d) Entire GIT remains accessible to endoscopy.

However, there are some negative points against LSG and these are:
(a) There is risk of gastric stenosis requiring treatment with dilators.
(b) The gastric sleeve may become permanently dilated with overeating.
(c) A second malabsorptive procedure such as LRYGB may have to be conducted in order to promote further weight loss.
(d) The most significant complications associated are leakage because a portion of stomach is removed and the surgeon staples the edges of the stomach to fix them together.

CONCLUSION

LSG is a technically simpler procedure compared to LRYGB. Our data demonstrated that LSG gave significantly better weight loss outcome in the short term compared to LRYGB.

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Antibacterial Activity of *Tamarindus Indica* Extracts Against Isolated Upper Respiratory Tract Pathogens

Anita Gnana Kumari M.Sc., M.Phil., Ph.D.

**ABSTRACT**

**Objective:** The aim of the present study was to evaluate the antibacterial potential of various extracts of *Tamarindus indica* against isolated upper respiratory tract pathogens.

**Methods:** *T. indica* fruits extracts such as pet ether extract, methanol extract and aqueous extract at a concentration of 200 mg/ml were screened against three gram-positive bacteria viz as β-haemolytic streptococcus, *Pneumococci* and *Staphylococcus aureus* and three gram-negative bacteria such as *Klebsiella*, *E. coli* and *Pseudomonas aeruginosa*. The agar well diffusion method was adopted to examine antibacterial activity and minimum inhibitory concentration (MIC) values of most effective extracts against the susceptible bacteria. Erythromycin was used as positive control to determine the sensitivity of the strains.

**Results:** Out of the six bacterial species tested, β-haemolytic streptococcus was the most susceptible. The methanol extract exhibited maximum antibacterial activity against all the tested microorganisms while aqueous extract showed maximum activity against *P. aeruginosa*. The MIC values ranged between 40 to 50 mg/ml for all the selected organisms.

**Conclusion:** From the studies, it can be concluded that the *Tamarindus indica* is a potential source of antimicrobial agents against the isolated upper respiratory tract pathogens. **KPJ Medical Journal 2012; 5:10–13**

**Key words:** *Tamarindus indica*, URT pathogens, antibacterial activity, minimum inhibitory concentration.

**INTRODUCTION**

Upper Respiratory Tract Infection (URI) is a nonspecific term used to describe acute infections involving the nose, the paranasal sinuses, pharynx, larynx, trachea and bronchi. Respiratory tract infections are extremely common and are primarily due to viral infections, those which are more severe and prolonged usually indicate secondary bacterial infection. Successful treatment of the bacterial infection can make the patient more comfortable, shorten the period of illness and reduce the chances of serious complications. Some infections are often related to specific bacterial pathogens such as sore throat due to *Streptococcus pyogenes*, lobar pneumonia due to the *Pneumococcus*. Most upper respiratory tract infections occur more frequently during the cold winter months. Acute pharyngitis accounts for 1% to 2% of all visits to outpatient and emergency departments, resulting in 7 million annual visits by adults alone. It is estimated that 31 million to 35 million US citizens have sinus disease. About 12 million individuals are diagnosed with acute tracheobronchitis annually, accounting for 1/3 of patients presenting with acute cough. Most of the surfaces of the upper respiratory tract (including nasal and oral passages, nasopharynx, oropharynx and trachea) are colonized by normal flora. The most common normal flora found in upper respiratory tract are *Staphylococcus aureus*, *Staphylococcus epidermidis*, Corynebacteria, *Streptococcus pneumoniae*, Neisseria meningitidis and *Haemophilus influenza*.

*Tamarindus indica* is a plant tree belonging to the family Leguminosae. In Indonesia and Malaysia, *tamarind* is commonly known as the *asam* (or *asem*). It is widely cultivated as an ornamental tree and for its acidic fruits used in making drinks and a popular component of many decoctions used as health remedies. In Indonesia, Malaysia, Philippines and Javanese traditional medicine, *asem* leaves are used as a herbal infusion for malarial fever, the fruit juice as an antiseptic, and for sore throat and cough cure. The various parts of *T. indica* was reported for hepatoprotective, anti-asthmatic and anthelmintic activities. The antimicrobial activity of extracts of *Tamarindus indica* has been reported. Because of its wide usage and availability, this study was carried out to scientifically investigate the antimicrobial potential of *Tamarindus indica* fruit against upper respiratory tract pathogens.

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Materials and Methods

Plant materials

*Tamarindus indica* fruits were purchased from local market, Nilai, Malaysia. The fruits were cleaned, dried and ground to coarse particles.

Preparation of extract

100 of *Tamarindus indica* fruits were soaked separately in 500 ml of pet. ether, methanol and distilled water for 7 days. The mixture was filtered using Whatman No 1 filter paper and collected separately. The excessive solvent in the filtrate was evaporated and concentrated under vacuum at 40°C to get the extract.

Collection of test organisms

The isolates were obtained from the patients with upper respiratory tract infection (30 cases) from different clinics in Negeri Sembilan, Malaysia. Throat and mouth specimens were collected according to the standard procedures described by Cheesborough. All the isolated bacteria were cultured and properly identified following standard methods. All the isolated bacteria were maintained in a refrigerator at 4°C on Mueller Hinton agar slants until required.

Antibacterial testing

The antibacterial activity of different extracts was determined by agar well-diffusion method. The prepared Mueller Hinton agar plates were inoculated with different isolated strains of bacteria using streak plate method. A cork borer (6 mm diameter) was used to punch wells in solidified medium and filled with extracts of 45 μl of 200mg/ml final concentration of extracts. Sterile water was used as negative control. The efficacy of extracts against bacteria was compared with the standard drug, erythromycin (positive control). The plates were incubated at 37°C for 24 h in BOD incubator and the diameter of the zone of inhibition was measured in millimetre. Each sample was assessed in triplicate and the mean value was tabulated. The antibacterial activity was interpreted from the size of the diameter of zone of inhibition measured to the nearest millimetre (mm) as observed from the clear zones surrounding the wells.

Fig. 1. *Tamarindus indica*.

Fig. 2. Specimen collection from throat and mouth.

Fig. 3. Percentage of isolated pathogens from upper respiratory tract infected patients.
Determination of minimum inhibitory concentration (MIC)

Broth dilution test was used to determine the Minimum Inhibitory Concentration (MIC) of the antimicrobial drugs. The MIC of most effective extract (methanol extract) was performed by agar well diffusion method for all selected test pathogens (Table 2). Concentrations of 200, 100, 75, 50, 40, 30, 25 and 20 mg/ml of the methanol extract were constituted in different sets of test tubes, and 1 ml of nutrient broth was added. To this, a loopful of the test organism previously diluted to 0.5 McFarland turbidity standard was introduced. The procedure was repeated on the test organisms using the standard antibiotic erythromycin. A set of test tubes containing nutrient broth only were seeded with the test organisms as described above to serve as control. The test tubes were then incubated at 37ºC for 24 h. The concentration that showed no visible growth of the test organism was taken as the minimum inhibitory concentration.

RESULTS

The table 1 illustrates the broad spectrum antibacterial activity of T. indica fruits extracts. Aqueous, methanol and petroleum ether extracts of T. indica exhibited antibacterial activity against all the isolated upper respiratory tract pathogens and found to be less effective as compared to erythromycin. In case of β-haemolytic streptococcus, S. aureus, Pneumococcus and Klebsiella, the methanol extract exhibited the highest degree of antimicrobial activity as compared to aqueous, and pet. ether extracts. The maximum inhibition by methanol extract was found against β-haemolytic streptococcus, Pneumococcus, S. aureus and E. coli, was 17mm, 15mm, 14mm and 13mm respectively. While in case of Klebsiella, P. aeruginosa and E. coli, the aqueous extract was most active and showed maximum inhibition (12mm) following by methanol and petroleum ether. Further MIC was determined against the isolated upper respiratory pathogens that showed positive inhibition.

<table>
<thead>
<tr>
<th>Isolated Pathogens</th>
<th>Pet. Ether extract</th>
<th>Methanol extract</th>
<th>Aqueous extract</th>
<th>Positive Control (Erythromycin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-haemolytic Streptococcus</td>
<td>9</td>
<td>17</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>S. aureus</td>
<td>8</td>
<td>14</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>11</td>
<td>15</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>E.coli</td>
<td>8</td>
<td>13</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>9</td>
<td>11</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>n=3</td>
<td></td>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Concentration (mg/ml)</th>
<th>β-haemolytic Streptococcus</th>
<th>S. aureus</th>
<th>Pneumococci</th>
<th>Klebsiella</th>
<th>E.coli</th>
<th>P. aeruginosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
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<td>-</td>
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<td>75</td>
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<td>50</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

(-): Absence of growth, (+): Presence of growth
and found that the lowest inhibitory value was exhibited by β-haemolytic streptococcus, Pneumococci and Klebsiella at 40mg/ml and S. aureus, P. aeruginosa and E. coli at 50 mg/ml concentrations. The study reveals that the extracts of T. indica possess a significant antibacterial activity against isolated URT pathogens.

CONCLUSION

The findings conclude that Tamarindus indica extracts have potential antibacterial activity against microorganisms which are responsible for upper respiratory tract infections. Also, the folkloric claim of T. indica against upper respiratory tract infections has been scientifically proven. This plant may lead to develop new antibacterial agents to meet therapeutic needs. Further investigation is in progress to isolate and characterize the active principles, since compounds of biological origin are known to possess minimal residual effect. Hence, in the present study, the antibacterial activity of T. indica has been demonstrated for the first time and suggests the possibility of using this plant in the management of upper respiratory tract infections.

ACKNOWLEDGEMENTS

The authors are grateful to the Vice-chancellor, the Executive directors and the Management of KPJ University College, Kota Sereimes, Nilai, Malaysia, for their continuous encouragement and support.

REFERENCES

INTRODUCTION

Peptic ulcer is a benign lesion of the gastric or duodenal mucosa, which occurs at a site where the mucosal epithelium is exposed to acid and pepsin. Stress, smoking, nutritional deficiencies and ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) can all increase the incidence of gastric ulcers. The treatment of peptic ulcer is generally based on the inhibition of gastric acid secretion by H2-antagonists, such as omeprazole and antimuscarinics, as well as acid-independent treatment by sucralfate and bismuth. However, one of the major problems in the treatment of gastroduodenal ulcer is that, despite a healing rate of 80–100% after 4–8 weeks of therapy with H2-antagonists and proton pump inhibitors, the rate of ulcer recurrence within one year after suspending the treatment is between 40 and 80%. Furthermore, most of these drugs produce several adverse reactions. A search for new therapeutic antiulcer agents is therefore essential.

The use of Melastoma species in the treatment of various diseases including ulcer, wounds, diarrhoea, microbial infections etc are extensive in east Malaysia. Plants belonging to the Melastomataceae family are widespread throughout the world. The leaves, flowers and roots of some Melastoma species are used in traditional medicine due to their analgesic, anti-inflammatory, anti-diarrhoeal and antiulcerogenic activities. Several species of that family have been cited as displaying antiulcer activity. In Malaysia, Melastoma borneense is one of the important plants in folk medicine, to treat stomach ulcers, and very well adapted to east Malaysia. However, there have been no reports regarding the antiulcer activity of M. borneense extract. Therefore, this study was carried out to evaluate the antiulcer property of the aqueous extract of M. borneense leaves.

MATERIALS AND METHODS

Plant material

The leaves of Melastoma borneense (Fig.1) were collected from Kota Seriemas, Nilai, Negeri Sembilan, Malaysia in the month of April 2011 and identified by Pharmacognosist, KPJ International University College, Kota seriemas, Nilai, Negeri Sembilan, Malaysia. A voucher specimen was deposited at School of Pharmacy, KPJUC/SP/H12/11A.

Correspondence: Dr J. Anbu Jeba Sunilson, Dean, School of Pharmacy, KPJ Healthcare University College, Kota Seriemas, 71800 Nilai, Negeri Sembilan, Malaysia.
Preparation of extracts

*Melastoma borneense* leaves were washed thoroughly with water and dried under air circulation. The dried leaves (500 g) were ground into coarse powder and macerated with distilled water at room temperature for 7 days. The macerated leaves were filtered and concentrated under reduced pressure, yielding 13.2% of crude aqueous extract.

Preliminary photochemical study

Preliminary phytochemical analysis was conducted by the standard methods to establish the phytochemical profile such as alkaloids, carbohydrates and glycosides, amino acids and proteins, fixed oils and fats, phenolic compounds and tannins, triterpenoids, saponins, gums and mucilage, flavones and flavonones which might be responsible for pharmacological activity in *Melastoma borneense*.

Animals

Male Wistar rats, weighing 200–250 g, were used for the experiment. The animals were procured from animal house, UPM, Malaysia and housed in groups of six animals, in standard cages, at room temperature (25 ± 3 °C), with 12 h dark/12 h light cycles, and food and water *ad libitum*. Twelve hours prior to the experiments they were transferred to the laboratory and given only water *ad libitum*.

Antiulcer activity

The antiulcer assays were performed using the following protocols aqueous-induced ulcer, nonsteroidal anti-inflammatory drug (NSAID)-induced ulcer and stress-induced ulcer. Since traditional uses of this plant is based on oral administration of a decoction prepared from 10g of dry and pulverized leaves in approximately 500 ml of water, taken by people two times a day, Based on this traditional preparation and use, the extract was administered by oral route at 50, 250 and 500 mg/kg.

Ethanol-induced ulcer

The experiment was performed according to the method of Morimoto. After 12 h of fasting, the rats were randomly divided into five groups of six animals each. 1 ml of vehicle (1% Tween-80 aqueous solution) was given to the first group and the second group was treated with omeprazole (30 mg/kg). The remaining three groups received 50, 250 and 500 mg/kg of *Melastoma borneense* extract, respectively. All the drug/extracts were administered orally. One hour after treatment, all the rats received 1 ml of 99.5% ethanol to induce gastric ulcer. One hour later, the animals were sacrificed by cervical dislocation, and the stomachs were removed and opened along the greater curvature. The stomachs were gently rinsed with water to remove the gastric contents and blood clots, for subsequent scanning. The images obtained were analyzed using specific “EARP” software to measure each lesion point. The ulcers were classified as level I, ulcer area <1 mm²; level II, ulcer area 1–3 mm²; and level III, ulcer area >3 mm². The parameters such as Ulcerative Lesion Index (ULI) as \[ C = 100 - \left( \frac{IUtreated \times 100}{IUcontrol} \right) \] total area of lesion and percentage of lesion area in relation to total stomach area were determined.

Non-steroidal anti-inflammatory drug (NSAID)-induced ulcer

The experiment was performed according to the method of Nwafor with few modifications. After 12 h of fasting, the rats were randomly divided into five groups of six animals each. The first group was given 1 ml of vehicle (1% Tween-80 aqueous solution), and the second group was treated with cimetidine (100 mg/kg). The remaining three groups received 50, 250 and 500 mg/kg of *Melastoma borneense* extract, respectively. All the drug/extracts were administered orally. One hour after treatment, all the rats received indomethacin (100 mg/kg) to induce gastric ulcer. Four hours after treatment with indomethacin, the animals were sacrificed by cervical dislocation. The stomachs were removed, and opened along the greater curvature. The stomachs were gently rinsed with water to remove the gastric contents and blood clots, for subsequent scanning. The images obtained were analyzed using the parameters previously described.

Stress-induced ulcer

The method described by Basile was used in this assay. Groups of six animals were treated as previously described, and 30 min later, each animal was placed in a tube and immersed vertically until the water reached the neck region in a tank with current water at 25 °C for 17 h. After this period, the rats were sacrificed by cervical
RESULTS

The preliminary phytochemical analysis of *M. borneense* aqueous extract showed the presence of flavonoids, carbohydrates, glycosides, phenols and triterpenoids.

In ethanol-induced ulcer model, it was observed that the treatment with *Melastoma borneense* aqueous extract (50, 250 and 500 mg/kg) and omeprazole (30 mg/kg) significantly reduced the lesion index, the total lesion area and the percentage of lesion, in comparison with negative control group (*p* < 0.05). The percentages of inhibition of ulcers were 75.7 ± 6.3, 85.4 ± 8.2, 87.5 ± 7.3 and 76.8 ± 4.8 for the treated groups with 50, 250 and 500 mg/kg of *Melastoma borneense* and positive control (omeprazole) respectively.

The treatment with *M. borneense* aqueous extract (50, 250 and 500 mg/kg) and cimetidine (100 mg/kg) significantly reduced all the evaluated parameters in comparison with control group (*p* < 0.05) in indomethacin-induced ulcer model. In this model, the percentages of inhibition of ulcers were 66.8 ± 6.2, 67.1 ± 7.3, 68.2 ± 4.2 and 96.3 ± 4.7 for groups treated with 50, 250 and 500 mg/kg of *M. borneense* and positive control (cimetidine) respectively.

In the stress-induced ulcer model, it was observed that a significant reduction in lesion index, total lesion area and in the percentage of lesion in animals treated with *Melastoma borneense* aqueous extract (50, 250 and 500 mg/kg) and cimetidine (100 mg/kg), in comparison with negative control group (*p* < 0.05). The percentage of inhibition of ulcers were 70.7 ± 4.3, 72.3 ± 4.6, 78.4 ± 8.1 and 90.7 ± 6.3 for the groups treated with 50, 250 and 500 mg/kg of *Melastoma borneense* extracts and positive control (cimetidine), respectively. These results are summarized in Fig. 2, Fig. 3 and Fig. 4.

Determination of gastric secretion

The assay was performed using the method of Shay with few modifications. The animals were divided into groups (*n* = 6), according to the treatment used, as previously described. After 24 h of fasting, the animals were anesthetized with thiopental sodium (10 mg/kg, i.p.) the abdomen was incised and the pylorus was ligated. Immediately after pylorus ligature, *Melastoma borneense* extract was administered at doses of 50, 250 and 500 mg/kg, respectively. Cimetidine (100 mg/kg) was used as positive control, and 1 ml of vehicle (1% Tween-80 aqueous solution) was administered as negative control. All the samples were administered intraduodenally. Four hours later, the animals were sacrificed by cervical dislocation; the abdomen was opened and another ligature was placed at the oesophageal end. The stomachs were removed and the gastric contents were collected and centrifuged at 3000 rpm for 10 min. The amount of gastric acid (ml) and the pH values were determined. The total acid secretion was determined in the supernatant volume by titration to pH 7.0 using 0.01 mol−1 NaOH solution, and phenolphthalein as indicator.

Statistical analysis

Data are reported as mean ± standard error of the mean (S.E.M.) and were compared using one-way analysis of variance (ANOVA), followed by Dunnet’s pairwise test, and p values < 0.05 were considered as significant.

![Fig. 2. Effect of *Melastoma borneense* aqueous extract on ulcer index (UI), total area of lesion, percentage of lesion and inhibition of ulcers in aqueous-induced ulcer model. The results are mean ± S.E.M. for six rats. Statistical comparison was performed using ANOVA followed by the Dunnet’s test. *p* < 0.05 in comparison with the control group.](image-url)
Melastoma borneense Bakh.f. : A Potential Alternative Antiulcer Agent

aqueous extract (50, 250 and 500 mg/kg) and cimetidine (100 mg/kg), respectively, reduced the volume of gastric juice, total acidity and raised gastric pH significantly (p<0.05) in comparison with the control group (Table. 1).

The results are mean ± S.E.M; n=6. Statistical comparison was performed using ANOVA followed by the Dunnet’s test (*p<0.05) in comparison with the control group.

Table 1 — Effect of Melastoma borneense aqueous extract, administered intraduodenally, on the biochemical parameters of gastric juice obtained from pylorus ligation in rats

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Dose (mg/kg)</th>
<th>pH</th>
<th>Gastric juice volume (ml)</th>
<th>[H+] mequiv./1/4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>–</td>
<td>1.69 ± 0.18</td>
<td>2.94 ± 0.32</td>
<td>119.51 ± 10.09</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>100</td>
<td>3.11 ± 0.21*</td>
<td>0.73 ± 0.16*</td>
<td>50.47 ± 3.42*</td>
</tr>
<tr>
<td>Melastoma borneense</td>
<td>50</td>
<td>2.56 ± 0.18*</td>
<td>0.99 ± 0.23*</td>
<td>65.23 ± 5.41*</td>
</tr>
<tr>
<td>aqueous extract</td>
<td>250</td>
<td>3.06 ± 0.18*</td>
<td>0.92 ± 0.13*</td>
<td>60.54 ± 2.33*</td>
</tr>
<tr>
<td></td>
<td>500</td>
<td>2.98 ± 0.54*</td>
<td>0.82 ± 0.02*</td>
<td>59.71 ± 3.91*</td>
</tr>
</tbody>
</table>

aqueous extract (50, 250 and 500 mg/kg) and cimetidine (100 mg/kg), respectively, reduced the volume of gastric juice, total acidity and raised gastric pH significantly (p<0.05) in comparison with the control group (Table. 1).
DISCUSSION AND CONCLUSION

There are several factors that may induce ulcer in human beings, such as stress, chronic use of anti-inflammatory drugs and continuous alcohol ingestion. Although in most cases the aetiology of ulcer is unknown, it is generally accepted that it is the result of an imbalance between aggressive factors and maintenance of the mucosal integrity through the endogenous defense mechanism. The candidate for an effective drug against peptic ulcer should basically act either by reducing the aggressive factors on gastroduodenal mucosa or by increasing mucosal resistance against them.

Exposure to aqueous increases the extension of cellular damage in a dose-dependent way. Ethanol is metabolized in the body and releases superoxide anion and hydroperoxy free radicals. It has been found that oxygen-derived free radicals are involved in the mechanism of acute and chronic ulceration in the gastric mucosa. Furthermore, disturbances in gastric secretion, damage to the gastric mucosa, alterations in permeability, gastric mucus depletion and free-radical production are observed after the administration of ethanol. These data suggest that antioxidant compounds could be active in this experimental model, producing antiulcer effects. This effect is known as cytoprotection.

In the present study, the group administered orally with ethanol clearly produced the expected characteristic zone of necrotizing mucosal lesions (Fig. 5b) when compared with normal rat stomach (Fig. 5a). On the other hand, the treatments with Melastoma borneense extract significantly decreased the lesion index, the total lesion area and the percentage of lesion (Fig. 5c-e).

Fig. 5a. Normal control rat stomach; 5b. Rat stomach induced by ethanol; 5c. Rat stomach treated with 500 mg/kg of Melastoma borneense aqueous extract; 5d. Rat stomach treated with 250 mg/kg of Melastoma borneense aqueous extract; 5e. Rat stomach treated with 500 mg/kg of Melastoma borneense aqueous extract; 5f. Rat stomach treated with standard drug, cimetidine

These results indicate that M. borneense aqueous extract displays an antiulcer effect related to cytoprotective activity, since it significantly reduced the ethanol-induced ulcer.

Non-steroidal anti-inflammatory drugs (NSAIDS) like aspirin and indomethacin, are known to induce ulcers during the course of anti-inflammatory therapy, by inhibiting prostaglandin synthetase through the cyclooxygenase pathway. In the stomach, prostaglandins play a vital protective role, stimulating the secretion of bicarbonate and mucus, maintaining mucosal blood flow, and regulating mucosal cell turnover and repair. Thus, the suppression of prostaglandin synthesis by NSAIDS results in increased susceptibility to mucosal injury and gastroduodenal ulceration. It was observed that M. borneense aqueous extract displayed significant reduction of the mucosal damage in the indomethacin-induced ulcer model. These results suggest the possible involvement of prostaglandins and/or mucus in the antiulcer effect of the extract.

Besides, gastric stress ulceration is probably mediated by the release of histamine. It not only enhances the gastric secretion, often called the aggressive factor, but also causes disturbances of the gastric mucosal microcirculation and abnormal motility, and reduces mucus production, known as the defensive factor. Moreover, stress-induced ulcer in animal models may be partially or entirely prevented by vagotomy, since increased vagal activity has been suggested as the main factor in stress-induced ulceration. In the current study, M. borneense aqueous extract inhibited the production of stress-induced ulcers. These findings indicate that Melastoma borneense aqueous extract may enhance gastric mucosal defensive factors.
In the present work, the gastro ulcero protective activity of *Melastoma borneense* extract on gastric secretion in the ligature pylorus model was also evaluated. A significant decrease in gastric fluid volume, and a decrease in acid output with an elevation in gastric pH, were observed after intraduodenal administration of *M. borneense* extract, when compared with the respective control, indicating that it possess antisecretory potency. Moreover, these results showed that the antulcer activity of this extract was not only related to a local neutralization of gastric content, but also that it was effective after the absorption of the extract, indicating a systemic effect. This effect is also indicative of antihistaminic activity.

In conclusion, the results of the present study illustrate that the aqueous extract of *Melastoma borneense* leaves displays gastroprotective activity, as demonstrated by its significant inhibition of the formation of ulcers induced using different models, as well as its ability to decrease gastric secretion.

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The author would like to thank the Vice-chancellor, the Executive directors and the Management of KPJ University College, Kota Seriemas, Nilai, Malaysia, for their continuous encouragement and support.

REFERENCES

Antibacterial Activity of 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]-N-[(substituted amino) methyl] Acetamides

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ABSTRACT

Introduction: Hetero aromatic compounds have attracted considerable attention in the design of biologically active molecules.

Objective: The present study was aimed to synthesize a series of novel mannich bases and evaluate their antibacterial activity.

Methods: 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]-N-[(substituted amino) methyl] acetamides (CPF 01–06) were synthesized using 2,2-dichloro-N-(1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl) acetamide, formaldehyde and compounds bearing secondary amine by Mannich reaction. The reaction progress was checked by TLC. The difference between the melting point and IR spectral data of the each synthesized compounds indicted the formation of new chemical analogues. All the newly synthesized mannich bases were screened for their antibacterial property.

Results: All compounds showed moderate anti-bacterial activity against gram positive (+ve) organisms such as Bacillus subtilis, Staphylococcus aureus, Streptococcus pyogenes and gram negative (-ve) organisms such as Escherichia coli, Proteus mirabilis, Klebsiella aerogenes, by cup plate method against the tested organisms when compared with standard drug, chloramphenicol at 30mcg/ml.

Conclusion: The findings of the present study revealed that the title compounds have antibacterial activity even with minor change in their chemical structure. KPJ Medical Journal 2012; 5:20–23

Key words : Mannich reaction, formaldehyde, chloramphenicol, antibacterial.

INTRODUCTION

The exploitation of a simple molecule with different functionalities for the synthesis of new compounds is a worthwhile contribution in the medicinal chemistry. Mannich bases have attracted considerable attention in the design of biologically active molecules and great interest in synthetic organic chemistry and medicinal chemistry. Mannich bases are generally formed by the reaction between a compound having a reactive hydrogen atom, a secondary amine and an aldehyde. This reaction is useful in making N-methyl and C-methyl derivatives of many drug molecules.

There is still interest in the synthesis of mannich bases for obtaining new biologically active compounds because of their diverse biological activity. The N-methyl mannich bases were found to possess wide range of biological activities such as analgesic1, anti-inflammatory2, anti-convulsant3, antiviral4, antifungal5, anti-microbial6 and anthelmintic7 activities.

Chloramphenicol, chemically 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl] acetamide is used as broad spectrum antibiotic. There was no scientific report available for the antibacterial activity on the modification of the secondary amine in chloramphenicol. The invention of new molecules from lead compounds is used to design effective and safe drugs and also to reduce drug toxicities. These observations lead the present investigation to synthesis some new 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]-N-[(substituted amino) methyl] acetamides by mannich reaction using some selected compounds having secondary amine and formaldehyde and tested for their antibacterial activity.

EXPERIMENTAL

General

Starting materials and reagents used were laboratory grade and procured from commercial suppliers. Melting points were determined by open-ended capillary tube on Veego electrical melting point apparatus and were
Antibacterial Activity of Substituted Chemical Structure of Chloramphenicol

The purity of the compounds were checked by TLC using Silica Gel as stationary phase and chloroform-methanol (9:1) as eluent and the spots were visually detected in an Iodine chamber. The structure of the synthesized compounds was elucidated by IR spectra in $\nu_{\text{max}}$ (cm$^{-1}$) on FT-IR (Shizmadu-8400 series) using KBr disc technique and $^1$H NMR spectra in $\delta$ units (ppm) relative to an internal standard of tetramethylsilane on $^1$H NMR (Bruker 400 MHz) in DMSO-d$_6$. The synthetic method is depicted in Fig. 1.

**Experimental Procedure for the synthesis of novel 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-y1]-N-[(substituted amino) methyl] acetamides (CPF01-06)**

Equimolar quantities (0.01mol) of 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl] acetamide (CP) and the respective compounds having secondary amine were dissolved in methanol (30 mL) in a beaker under perfect ice-cold condition and stirred constantly. To this solution, formaldehyde (0.01mol) was added slowly and heated to reflux for 3h. The content was kept overnight in the freezer. The corresponding crystals of manich base of novel 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]-N-[(substituted amino) methyl] acetamides.$^1$

**Microorganisms Used**

Gram (+ve) organisms such as *Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus pyogenes* and gram (-ve) organisms such as *Escherichia coli*, *Proteus mirabilis*, *Klebsiella aerogenes* were used for this study.

**Antibacterial activity**

The antibacterial activity was performed by cup-plate method developed by Rajasekaran.$^8$ The protocol has been approved by KPJ Healthcare University Research and Ethics Committees. All the synthesized compounds were dissolved in 2 % v/v Tween 80 at a concentration of 30mcg/mL. The respective bacterial culture was spread (swabbed) into the nutrient agar plates for uniform distribution of colonies. Using a sterile cork borer, 6 mm wide well was made on each agar plates. All the synthesized compounds (30mcg/mL) were poured into each wells using a sterile micropipette and chloramphenicol (30mcg/mL) were used as standard. The plates were incubated for 24 h at 37°C. The antibacterial activity was assessed by measuring the diameter of zone of inhibition (mm). All the experiments were triplicate. The results were tabulated in Table 2.

![Fig. 1. Chloramphenicol Synthetic Method](image-url)
A series of 6 novel manich bases of 2,2-dichloro-N-[1,3-dihydroxy-1-(4-nitrophenyl) propan-2-yl]-N-[(substituted amino) methyl] acetamides were synthesized using manich reaction by the reaction between compounds having secondary amine and formaldehyde. The formation of new chemical analogues was indicated by the melting point and Rf value (Table 1). The structure of the synthesized compounds was established by spectral methods such as IR and 1H NMR spectra. Among the compounds tested, all the compounds showed moderate antibacterial activity at a concentration of 30mcg/mL when compared to standard drug, chloramphenicol (Table 2). Compound CPF01 and CPF06 showed good antibacterial activity against E. coli. All the title compounds exhibited good antibacterial activity against K. aerogenes (Fig. 2).
DISCUSSION

The NH band (3314 cm⁻¹) and NH proton signal (4.78 ppm) of CF in IR and ¹H NMR spectrum respectively were absent in all the newly synthesized compounds confirmed that the reaction was taken at N position. The NH band (3264 - 3382 cm⁻¹) and NH proton signal (4.52 – 5.64 ppm) in IR and ¹H NMR spectrum respectively were noted in all the newly synthesized compounds. Together with the presence for CH₂ stretching (1436 - 1458 cm⁻¹) and CH₂ proton signal (3.26 – 3.78 ppm) in IR and ¹H NMR spectrum respectively confirmed the formation of the titled compounds.

The prediction of molecular and drug-likeness properties was based on the description of “Rule of 5”. The rule states that most “drug-like” molecules have log P ≤ 5 and molecular weight ≤ 500. Molecules violating more than one of these rules may have problems with bioavailability. Based on this, the log P value of each compound synthesized found that all the newly synthesized compounds have molecular and drug-likeness properties (Table 1).

CONCLUSION

The findings of the present study revealed that considerable variation in these effects were seen with each structural change, varying from agents that had antibacterial activity to those with high potency and significant changes in potency resulted even from minor change in chemical structure. The present investigations suggest that the experimental procedures make this a better methodology for the synthesis of title compounds as good antibacterial agents. Further investigations such as toxicity studies on these compounds are needed to standardize the pharmacological profile.

ACKNOWLEDGEMENTS

The authors are thankful to the Vice-chancellor, the Executive directors and the Management of KPJ University College, Kota Seriemas, Nilai, Malaysia, for their continuous encouragement and support.

REFERENCES

Cyclin D1 Expression in Nasopharyngeal Carcinoma

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ABSTRACT

Objectives: TNM staging and histopathology type are the main factors used to predict local recurrence and metastatic risk in nasopharyngeal carcinoma (NPC). However, to date no satisfying laboratory parameters predicting response to treatment and subsequent prognosis of the disease is available. The aim of this study is to determine cyclin D1 expression in NPC by using the immuno-histochemical method.

Methods: This is a retrospective study carried out from January 1998 till June 2003. A total of 100 cases of NPC were taken into the study. The slides and paraffin blocks were collected from the storage room and immunohistochemical test performed.

Results: High cyclin D1 was expressed in 59% patients and low cyclin D1 in 41% of patients. Statistically high cyclin D1 was associated with a high recurrence rate (77.1%) whereas patients with low cyclin D1 had a lower recurrence rate (49.1%) and better response to treatment (54%). Other known prognostic factors i.e. TNM staging, grading, parapharyngeal extension, lymph node size and supraclavicular lymph nodes involvement did not prove to be statistically significant to the level of cyclin D1 (p>0.05). An overall five years of survival was higher in patients with low cyclin D1 expression than for those with high expression of cyclin D1 (p<0.05).

Conclusion: Level of cyclin D1 is a good predictor of a high risk patient developing poor response and recurrence and this knowledge will assist in selecting and planning treatment. KPJ Medical Journal 2012; 5:24–27

Key words : Cyclin D1, Nasopharyngeal carcinoma, radiotherapy, recurrence.
from the bcl-1 gene on chromosome 11q13 which is important in the transition of cells from G1 phase to S phase. In the G1 (resting) phase of the cell cycle, cyclin D1 together with cyclin dependant kinase (cdk) is responsible for transition to the S phase (DNA synthesis) by phosphorylating selected proteins which then releases transcription factors important in the initiation of DNA multiplication. Over-expression of cyclin D1 protein releases a cell from its normal controls and causes transformation to a malignant phenotype.

MATERIAL AND METHODS

This was a cross sectional study using a retrospective material and data. This study included cases diagnosed with nasopharyngeal carcinoma from January 1998 till June 2003. The cases were collected from the files of the Department of Pathology, UKM Medical Centre. The slides and paraffin blocks were collected from the storage room. A number of 100 cases of NPC were taken into the study. Patient who had been treated with radiotherapy or chemotherapy, with recurrence, missing block or no tissue left on the block for sectioning were excluded from the study.

The primary anti-cyclin D1 antibody is a monoclonal antibody supplied by DAKO Company Ltd with the dilution 1:100. The selected paraffin blocks were sectioned at five micron thick and placed on Poly-L-Lysine coated slides. Sections were deparaffinized through series of xylene and alcohol at decreasing concentration. The slides were placed in microwave immersed in zinc sulphate for ten minutes followed by 20 minutes at room temperature for antigen retrieval purposes. The sections were then immersed in 3 percent hydrogen peroxide to block endogenous peroxidase followed by incubation in diluted goat serum 1:4 with tris buffer for 5 minutes to block non specific binding of tissue section. Sections were then incubated in primary antibody with a dilution of 1: 100 for 45 minutes. After washing several times with buffer, three drops of link antibody was applied to the sections for 20 minutes. Incubation with an avidin-biotin complex conjugated to horseradish peroxidase followed by 3, 3-diaminobenzidine as a chromogen was performed. The slides were counterstained with haematoxylin, dehydrated, mounted and examined under light microscopy. A normal human tonsil known to express cyclin D1 expression was used as positive control (Fig. 1). For negative control, the same tissue control was used but with primary antibody omitted.

A representative area with at least 500 tumour cells was counted simultaneously at ten high power fields (X40) for the presence or absence of staining by two pathologists. The number of positive cells by light microscopy was scored as no staining of tumour cells as negative result. 1 - 10% of tumour cells stained were interpreted as 1+, 11 - 50% of tumour cells stained were 2+ and 51 - 100% of tumour cells stained were scored as 3+. Equivocal result was re-stained and if equivocal result again obtained, it was considered as negative. Only nuclear staining was taken as positive staining whereas cells showing exclusive cytoplasmic staining were regarded as negative. The results were further categorized into negative and 1+ as low level whereas 2+ and 3+ as high level (Fig. 2 and Fig. 3).
The patients’ data on the age, sex, stage and size of the tumour, histological grading, dose of radiation therapy, chemotherapy, response and recurrence of the tumour were collected. WHO categorized the nasopharyngeal carcinoma into keratinizing squamous cell carcinoma (WHO class I), non-keratinizing squamous cell carcinoma (WHO class II) and undifferentiated carcinoma (WHO class III).5 The workup included nasopharyngoscopy, computed tomographic or magnetic resonance imaging scan from the skull base to the whole neck, chest radiography, whole-body bone scan, abdominal sonogram, complete biochemical profile. Chest computed tomographic scans and bone marrow biopsies were not routine but were selectively performed when lung metastasis was suspected on the basis of chest x-ray and an abnormal blood count was noted. Staging were determined according to the 1998 American Joint Committee on Cancer criteria (AJCC) TNM staging. SPSS 11.5 were adopted for data analysis. A Chi square test and Kaplan Meier survival analysis were used.

RESULTS

A total number of hundred patients were included in this study. There were 74 (74%) males and 26 (26%) females. 30% were Malays, 68% Chinese and only 2% Indian. The peak incidence of NPC occurs between 20 to 40 years old. Stage T1 was found in 34%, T2 in 20%, T3 in 11% and T4 in 31%. Regional lymph node involvement revealed N0 in 29%, N1 in 32%, N2 in 28%, and N3 in 7%. Metastasis occurred in only 8 patients at presentation (8%) with involvement of the bone in 4 patients, lung in 3 patients and liver in 1 patient. Tumour grading of WHO type 1 present in 3%, WHO type 2 in 1% and majority of cases were WHO type 3 (undifferentiated type) in 96%. 59 (59%) of patients with NPC showed a high cyclin D1 and 41 (41%) showed a low cyclin D1. Eight patients had a history of cancer in the family in which 5 nasopharyngeal carcinomas. A study of 115 patients with head and neck squamous cell carcinoma showed that overexpression of cyclin D1 was an independent prognostic variable hypopharyngeal and laryngeal carcinomas. A study of 115 patients with head and neck squamous cell carcinoma showed that overexpression of cyclin D1 was an independent prognostic variable hypopharyngeal and laryngeal carcinomas. Lai et al found that 55% of NPC patients had overexpression of cyclin D1 within the primary tumor were associated with high recurrence rate and a shorter survival time. Similar reports documented in breast cancer, esophageal carcinomas, myeloma, colorectal cancer. However in contrast another study showed that high levels of cyclin D1 was associated with longer survival time where as low level correlated with recurrence in breast tumor. In our study 59% of patients had high cyclin D1 and 41% low cyclin D1 within the primary tumor. High tissue level of cyclin D1 had a higher recurrence rate, low cyclin D1 lower recurrence rate. A high tissue level of cyclin D1 had a higher incidence of partial response, low cyclin D1 complete response. Other known prognostic markers like TNM staging and grading did not correlate with initial tissue level of cyclin D1. A high level cyclin D1 had a shorter survival, low cyclin D1 better survival time. Our result indicate that it might be possible to predict response, recurrence and survival by measuring tissue level of cyclin D1 in primary tumor before commencing therapy.

DISCUSSION

NPC is one of the most prevalent malignancies with high incidence of recurrence and treatment failure. Advances in understanding molecular basis of head and neck cancer helps in identification of new markers which are used to predict prognosis, treatment response and survival. Cyclin D1 overexpression has been shown to be valuable prognostic markers in numerous cancers. Overexpression has been associated with a more aggressive tumor and reduced survival in head and neck squamous cell carcinoma. A study of 115 patients with head and neck squamous cell carcinoma showed that overexpression of cyclin D1 was an independent prognostic variable hypopharyngeal and laryngeal carcinomas.6 Lai et al found that 55% of NPC patients had overexpression of cyclin D1 within the primary tumor were associated with high recurrence rate and a shorter survival time. Similar reports documented in breast cancer, esophageal carcinomas, myeloma, colorectal cancer. However in contrast another study showed that high levels of cyclin D1 was associated with longer survival time where as low level correlated with recurrence in breast tumor. In our study 59% of patients had high cyclin D1 and 41% low cyclin D1 within the primary tumor. High tissue level of cyclin D1 had a higher recurrence rate, low cyclin D1 lower recurrence rate. A high tissue level of cyclin D1 had a higher incidence of partial response, low cyclin D1 complete response. Other known prognostic markers like TNM staging and grading did not correlate with initial tissue level of cyclin D1. A high level cyclin D1 had a shorter survival, low cyclin D1 better survival time. Our result indicate that it might be possible to predict response, recurrence and survival by measuring tissue level of cyclin D1 in primary tumor before commencing therapy.

Table 1 — Tumour recurrence and cyclin D1

<table>
<thead>
<tr>
<th>Tumour Recurrence</th>
<th>cyclin D1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPC recurrence</td>
<td>24(72.7%)</td>
<td>27(54%)</td>
</tr>
<tr>
<td>No NPC recurrence</td>
<td>28(50.9%)</td>
<td>36(49.1%)</td>
</tr>
<tr>
<td>Total</td>
<td>52(59.1%)</td>
<td>88(100%)</td>
</tr>
</tbody>
</table>

Chi square test < 0.05

Table 2 — Response to the radiotherapy and cyclin D1

<table>
<thead>
<tr>
<th>Response to the Radiotherapy</th>
<th>cyclin D1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>27(77.1%)</td>
<td>35(41.2%)</td>
</tr>
<tr>
<td>Complete</td>
<td>23(46.0%)</td>
<td>50(58.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>50(58.8%)</td>
<td>85(100%)</td>
</tr>
</tbody>
</table>

Chi square test < 0.01
CONCLUSION

In this study we demonstrate that high initial tissue levels of cyclin D1 might be an important indicator response to radiotherapy. Recurrent of tumor might also be predicted in high cyclin D1 patients with a lower survival rate. It might be possible that a pre-therapeutic lowering of cyclin D1 levels in patients with NPC might increase the radio-curability of the disease. Selected patients who may benefit with early aggressive treatment may improve treatment outcome.

REFERENCES

A MRI Study of the Anatomy of Femoral Condyles Sizes: Refining the Surgical Anatomy of Anterior Cruciate Ligament Reconstruction

Sreeja Dinesh MSc,1 Anita Hanapi BSc,1 and Wan Hazmy Che Hon MD, MSO Ortho2

ABSTRACT

Anthropometric measurements of femoral condyles are compared among different races of Malaysian population including both genders. The study was completed using data collected from three leading private hospitals of Malaysia. A total of 157 MRI knee images were analysed, including those of 118 males and 39 females. The sagittal, coronal, and axial images were measured for medial condylar width (MCW), lateral condylar width (LCW), as well as epicondylar width (ECW). There were significant differences between males and females for all the condylar size readings (p<0.0001), but there were no significant difference among different races of Malaysian population (p>0.0001). Comparative data of the measurements was obtained from the study of one of the currently used knee replacement prosthesis, NexGen® High-flex implants. The results may help the surgeon in choosing the appropriate tunnel length and interference screw size in anterior cruciate ligament reconstruction for Malaysian population. KPJ Medical Journal 2012; 5:28–31

Key words: MRI, femoral condyle, ACL reconstruction, anthropometry.

INTRODUCTION

The anterior cruciate ligament (ACL), which is located in the inter-condylar notch of the femur, is one of the major stabilizing intra-capsular ligaments in the knee joint.

The anterior and posterior cruciate ligaments as resistors of anterior and posterior tibial translation respectively.1

Conventional radiographs have limited value in the diagnosis of acute ACL injury. Magnetic Resonance Imaging (MRI) has emerged as the modality of choice to evaluate the status of ACL and other associated structures in the knee. Sagittal MR images have been commonly used in the evaluation of ACL.2 However, coronal and axial imaging planes can add useful information about ACL injury3 (Fig. 1 and Fig. 2)

Fig. 1. Knee with ACL tear

Fig. 2. Sagittal Proton Density MRI Knee with normal and torn ACL

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SIGNIFICANCE OF THE STUDY

Anthropologists have established that men and women are morphologically different, and have proven variation among Eastern and Western population as well.4,5,6 Knowledge of the size of femoral condyles and the inter-condylar notches is helpful in choosing the type of reconstruction to be done (using autograft or allograft).7 This would be helpful in choosing the appropriate femoral tunnel length and the correct size of implants for different communities who differ in their body built rather than using the universal tunnel length and implants size and thus avoiding further problems which may arise in the future.

As for total knee replacement, the available implant and measurement were based on the morphometric of the Caucasian knee.5 In ACL reconstruction, particularly using the Bone-Patella-Tendon-Bone (BPTB) graft involves the introduction of a interference screw9,10 into the femoral tunnel in order to stabilize the graft (Fig. 3). Therefore the measurement of size of femoral condyles is helpful in choosing the appropriate tunnel length and further the correct length of an interference screw.

MATERIALS AND METHODS

The study was conducted using 157 samples of MRI images of knee in both males (n=118) and females (n=39) including different races of Malaysian population. Subjects with muscle soreness, cruciate or collateral ligament injury, contusion around the knee were included. Subjects with any co-morbid condition such as deformity or mal-alignment, previous surgery, arthritis, bone loss, or tumor around the knee were excluded from the study.

The images were measured for medial condylar width (MCW), lateral condylar width (LCW), as well as epicondylar width (ECW) using sagittal, coronal and axial MRI images of each knee joint (Fig. 4).

STATISTICAL ANALYSIS

The GraphPad Prism 5.01.336 software (La Jolla, CA, USA) was used for statistical analysis. Non-descriptive statistics was used since some of the measurements were unable to pass normality test. One-way ANOVA used for comparison among races.
RESULTS

The summary of the results are displayed in Table 1 to Table 4.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Malay (n=86) Mean +/- SD (mm)</th>
<th>Chinese (n=6) Mean (mm)</th>
<th>Indian (n=26) Mean (mm)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCW (S)</td>
<td>63.12 +/- 3.7</td>
<td>63.88</td>
<td>63.09</td>
<td>0.8848</td>
</tr>
<tr>
<td>MCW (C)</td>
<td>29.73</td>
<td>28.90</td>
<td>29.03</td>
<td>0.6482</td>
</tr>
<tr>
<td>ECW (C)</td>
<td>81.76</td>
<td>82.86</td>
<td>81.05</td>
<td>0.6334</td>
</tr>
<tr>
<td>LCW (C)</td>
<td>32.46</td>
<td>31.01</td>
<td>33.18</td>
<td>0.5238</td>
</tr>
<tr>
<td>MCW (A)</td>
<td>28.46</td>
<td>27.31</td>
<td>28.47</td>
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</tr>
<tr>
<td>ECW (A)</td>
<td>82.07</td>
<td>83.16</td>
<td>81.92</td>
<td>0.8049</td>
</tr>
<tr>
<td>LCW (A)</td>
<td>29.88</td>
<td>28.33</td>
<td>30.70</td>
<td>0.5545</td>
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</table>

<table>
<thead>
<tr>
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<th>Malay (n=28) Mean (mm)</th>
<th>Chinese (n=5) Mean (mm)</th>
<th>Indian (n=6) Mean (mm)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCW (S)</td>
<td>56.33</td>
<td>58.36</td>
<td>52.66</td>
<td>0.0560</td>
</tr>
<tr>
<td>MCW (C)</td>
<td>23.97</td>
<td>24.16</td>
<td>23.06</td>
<td>0.8091</td>
</tr>
<tr>
<td>ECW (C)</td>
<td>70.47</td>
<td>74.54</td>
<td>68.91</td>
<td>0.0763</td>
</tr>
<tr>
<td>LCW (C)</td>
<td>27.11</td>
<td>25.28</td>
<td>24.60</td>
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<tr>
<td>MCW (A)</td>
<td>22.87</td>
<td>23.26</td>
<td>21.53</td>
<td>0.5666</td>
</tr>
<tr>
<td>ECW (A)</td>
<td>70.48</td>
<td>74.02</td>
<td>66.83</td>
<td>0.0049</td>
</tr>
<tr>
<td>LCW (A)</td>
<td>24.90</td>
<td>23.92</td>
<td>22.80</td>
<td>0.5477</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NexGen® Male</th>
<th>NexGen® Female</th>
<th>Study Male</th>
<th>Study Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ML width (ECW-C) mm</td>
<td>77</td>
<td>64</td>
<td>81.63</td>
<td>70.75</td>
</tr>
<tr>
<td>Mean AP width (LCW-S) mm</td>
<td>67.5</td>
<td>63</td>
<td>63.11</td>
<td>56.03</td>
</tr>
</tbody>
</table>
DISCUSSION

Many studies have shown statistically significant difference between male and female population for all condylar measurements ($p<0.0001$)\(^{11,12,13}\). A local study conducted also found that there is no significant difference seen among different races of Malaysian males as well as females ($p >> 0.0001$).\(^8\) Both findings conform with our study. However more attention should go in addressing the mean measurement because this will determine the most suitable tunnel & interference screw length & size during ACL reconstruction, given the relatively smaller size of the condyles as compared to other overseas studies.

For this purpose we have compared our findings with a study of one of the leading manufacturers of bioprosthetic system, the NexGen®.\(^{14}\) Their study showed the mean AP width of lateral femoral condyle (LCW-S) as 67.5 mm for males and 63 mm for females. The mean ML width (ECW-C) for NexGen® Group was smaller in both male as well as female Malaysian populations as compared to the study group. A relook of the measurement parameter will be beneficial for a better comparative conclusion.

Comparison between the measurement of the AP width of lateral femoral condyle (LCW-S) and mediolateral width (ECW-C) was done since these two are the most important measurements when considering the tunnel length & interference screw size during ACL reconstruction, taking note that the femoral tunnel orientation lies in both axis.

CONCLUSION

This study has contributed to refining the knowledge on ACL reconstruction particularly in deciding the appropriate femoral tunnel length & interference screw size & length to tally with the local population anthropometry without compromising the fixation strength & orientation.

ACKNOWLEDGEMENTS

The authors are thankful to the management of KPJUC as well as the members of research and development committee of KPJUC for their enormous support in fulfilling this project. Apart from that the co-operation of colleagues should also be highly appreciated.

REFERENCES

A MRI Study on the Anatomy of Patella and Patellar Tendon: Refining the Surgical Anatomy in Anterior Cruciate Ligament Reconstruction

Izdihar Kamal BSc,¹ Norhayati Mohd Zain BSc,¹ and Wan Hazmy Che Hon MD.MSOrtho²

INTRODUCTION

Anterior cruciate ligament (ACL) reconstruction is one of the commonest procedures performed in the field of sports surgery. Despite the increasing usage of hamstring tendon as a graft option, Bone Patellar Tendon Bone (BPTB) graft, previously known as the ‘gold standard’ is still popular among the sports surgeon. Understanding the anatomy of the patella and patellar tendon is very important towards achieving excellent ACL reconstruction. The aim of this study is to provide a normative data of geometry of patella and patellar tendon of knee measured on Magnetic Resonance Imaging (MRI) in the local population. MRI images of a total of 143 subjects (107 males and 36 females) constitute of 106 Malays, 11 Chinese and 26 Indians were studied. On sagittal and axial MRIs images of the knees, the morphological parameters of the patella and patellar tendon were measured. As for the patella, the mean longitudinal length of the whole patella is 41.55mm, while the mean longitudinal length of the articulating surface is 26.91mm, the mean thickness of the patella is 21.17 mm and the width is 42.39 mm. For the patellar tendon, the longitudinal length of the whole patellar tendon is 44.91mm, the proximal width is 27.42mm, the distal width is 24.20mm, the proximal thickness is 5.02mm and the distal thickness is 5.26mm. There is a significant difference between male geometry of the patella and patellar tendon compared to the female geometry of the patella and patellar tendon (p<0.001). However there is no significant difference of geometry of the patella and patellar tendon between races. These findings will help the surgeon to choose the appropriate graft size in order to prevent graft-tunnel mismatch and to avoid complications of excessive graft harvesting without compromising the ACL reconstruction.

METHODOLOGY

We assessed MRI of the knees of 143 subjects (107 men and 36 woman) with a mean age of 32 years (11 to 79 years) who had underwent MRI knee scanning at KPJ hospital in the Klang Valley. Subjects were from Malay, Indian & Chinese ethnic group and convenient sampling method was used. Subjects with muscle soreness, cruciate or collateral ligament injury and contusions around the knee were included. Subjects with any morbid condition such as deformities or mal-alignment, bipartite patella, old or new patellar fracture, previous sepsis or surgeries, tumours around knee were excluded.

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Key words : bone-patella-tendon-bone graft, geometry, graft-tunnel mismatch.
A MRI Study on the Anatomy of Patella and Patellar Tendon

Measurements were done on the sagittal and axial MRI images of the knees. In total 10 morphological parameters of the patella and patellar tendon were measured. With reference to Fig. 1, the longitudinal length of the whole patella (a) and the longitudinal length of the articulating surface of patella (b) were measured on sagittal image. The thickness of the patella (c), mediolateral width of the patella (d), and the location of the central ridge from the medial border of the patella (e), were measured on axial image.

As for patellar tendon, the longitudinal length of the whole patellar tendon (A) was measured on sagittal image. The width of proximal (B) and distal (D) part of patellar tendon and thickness of proximal (C) and distal (E) part of the patellar tendon were measured on axial image (Fig. 2). The proximal part was defined as the area where the patellar tendon attaches to the inferior pole of the patella, and the distal part as the area where it attaches to the tibial tuberosity. All the measurements were performed on the images, which showed the largest value.

**STATISTICAL ANALYSIS**

All data were entered in a statistical program (SPSS, version 18), and the results were given in means and standard deviations (SD). The geometry of patella and patellar tendon was compared between male and female subjects by t test and confidence interval (p) was set at 0.01. The data also were analyzed between races Malays, Chinese and Indians with ANOVA. Correlation were also done between thickness of patella and age as well as between length of patellar tendon and age.

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**Fig. 1. Measurement For patella**

**Fig. 2. Measurement For patellar tendon**
RESULTS

Table 1 shows the mean longitudinal length of the whole patella (a) is 41.55±5.4 mm. For males it is 43.27±3.6 mm and for females it is 36.46±6.6 mm. The mean articulating surface of the patella is 26.91±3.9 mm. For males it is 27.97±3.3 mm and 23.76±3.7 mm for females. The mean thickness of the patella is 21.16±5.6 mm. For males it is 22.03±5.6 mm and for female it is 18.59±4.7 mm. The mean width of the patella is 42.38±5.6 mm. For male it is 43.86±5.1 mm and for female it is 38.01±4.4 mm. The mean location of the ridge from the medial border of the patella is 19.61±3.3 mm. For male it is 20.43±3.1 mm and for female it is 17.20±2.7 mm.

As for patellar tendon the mean longitudinal length of the whole patellar tendon is 44.91±5.9 mm. For male is 46.28±5.3 mm and for female is 40.82±5.8 mm. The mean width of proximal patellar tendon is 27.42±3.2 mm. For male is 28.05±3.2 mm and for female is 25.55±2.3 mm. Meanwhile the mean thickness of proximal patellar tendon is 5.02±2.5 mm. For is 5.38±2.6 mm and for female is 3.92±1.72 mm. The mean thickness of distal patellar tendon is 5.26±1.3 mm. For male is 5.52±1.2 mm and for female is 4.44±1.2 mm. The mean width of the distal patellar tendon is 24.20±2.7 mm. For male is 25.04±2.4 mm and for female is 21.7±2 mm. The results were summarized in Table 1.

The geometry of patella and patellar tendon has a significance difference between male and female because the p value for each measurement is <0.001. However the geometry of patella and patellar tendon has no difference between races because the p value for each measurement is >0.001. There is no correlation between length of patellar tendon and age as the coefficient of determination is r = -0.263 as well as correlation between thickness of patella and age as the r value = -0.16. Both correlation were weak (Fig. 3 and Fig. 4).

Table 1 — Patella and patellar tendon geometry

<table>
<thead>
<tr>
<th>Patella</th>
<th>Total (143)</th>
<th>Male (107)</th>
<th>Female (36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longitudinal length of the whole patella (a)</td>
<td>41.55 (5.39)</td>
<td>43.26 (3.62)</td>
<td>36.46 (6.55)</td>
</tr>
<tr>
<td>Longitudinal length of the articulating surface of the patella (b)</td>
<td>26.91 (3.9)</td>
<td>27.97 (3.31)</td>
<td>23.76 (3.73)</td>
</tr>
<tr>
<td>Thickness of patella (c)</td>
<td>21.16 (5.61)</td>
<td>22.03 (5.64)</td>
<td>18.59 (4.71)</td>
</tr>
<tr>
<td>Width of patella (d)</td>
<td>42.38 (5.57)</td>
<td>43.86 (5.15)</td>
<td>38.01 (4.39)</td>
</tr>
<tr>
<td>Location of the ridge from the medial border of the patella (e)</td>
<td>19.61 (3.30)</td>
<td>20.43 (3.09)</td>
<td>17.20 (2.70)</td>
</tr>
<tr>
<td>Longitudinal length of the whole patellar tendon (A)</td>
<td>44.91 (5.93)</td>
<td>46.28 (5.33)</td>
<td>40.8 (5.8)</td>
</tr>
<tr>
<td>The width of proximal patellar tendon (B)</td>
<td>27.42 (3.21)</td>
<td>28.05 (3.23)</td>
<td>25.55 (2.31)</td>
</tr>
<tr>
<td>Thickness of the proximal patellar tendon (C)</td>
<td>5.02 (2.49)</td>
<td>5.38 (2.61)</td>
<td>3.92 (1.72)</td>
</tr>
<tr>
<td>Width of the distal patellar tendon (D)</td>
<td>24.20 (2.70)</td>
<td>25.04 (2.36)</td>
<td>21.70 (2.02)</td>
</tr>
<tr>
<td>Thickness of the distal patellar tendon (E)</td>
<td>5.26 (1.29)</td>
<td>5.52 (1.20)</td>
<td>4.44 (1.20)</td>
</tr>
</tbody>
</table>

Fig. 3. Correlation between thickness of patella and age
DISCUSSION

Magnetic Resonance (MR) Imaging has become the imaging modality of choice for evaluation of knee. Knowledge and recognition of variants are important for accurate analysis of MR images. Incorrect interpretation may lead to unnecessary additional imaging and overtreatment. MRI had proved superior in measuring the patellar tendon and patella, the fact that during MRI the patient is immobilized and in natural position, making it appropriate to measure the whole geometry of patella and patellar tendon. Historical measurement with caliper increases fault caused by the soft tissue in front of the patella. The flexion and eversion of knee also contribute to the inaccuracy of the measurement. Sonography was found to have limited measurement accuracy for perioperative determination of patellar tendon width. MRI despite its cost has been proven to measure width of patellar tendon accurately.

Several authors have reported patellar tendon length, the summary of which is given in Table 2. From our result the length of patella was comparable with other previous reports. Accurate length of patellar tendon is very important to minimize the graft tunnel mismatch. Graft-tunnel mismatch may be estimated preoperatively using magnetic resonance imaging. However, its accuracy can be affected by the knee’s position.

The thickness of patella is important to maintain the extensor lever arm, which is believed to be the primary role of patella itself. In Total Knee Arthroplasty (TKA) the patellar resurfacing is performed by removing the arthritic portion of patella, and substituting polyethylene implant. Restoring the original thickness is mandatory to maintain the patella-femoral mechanics. The morphometry of normal thickness of patella is the basic data not only for designing the implant, but for doing the operation. In ACL reconstruction the thickness & the length of the bony part of the patella taken as a graft can be affected by the anatomic variant among individual and gender.

Table 2 — Length of patellar tendon

<table>
<thead>
<tr>
<th>Author</th>
<th>Patellar Tendon Length (mm)</th>
<th>Subject</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carroll C.C</td>
<td>48±1.2</td>
<td>MRI measurement 22 males &amp; 15 females</td>
<td>DATA??</td>
</tr>
<tr>
<td>Kim et al</td>
<td>40.2</td>
<td>MRI measurement of 165 adults (100 males, 65 females)</td>
<td>29</td>
</tr>
<tr>
<td>Luk MS et al</td>
<td>42.6</td>
<td>109 males &amp; 11 females underwent ACL</td>
<td>25</td>
</tr>
<tr>
<td>This study</td>
<td>44.91</td>
<td>MRI measurement of 143 (107 males 36 females)</td>
<td>32</td>
</tr>
</tbody>
</table>
Table 3 — Comparison data of this study with Jae Ho Yoo et al.

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>JAE HO YOO et al (mm)</th>
<th>THE STUDY (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patella Whole longitudinal length</td>
<td>44.6</td>
<td>41.55</td>
</tr>
<tr>
<td>Longitudinal length of the articulating surface</td>
<td>32.9</td>
<td>26.91</td>
</tr>
<tr>
<td>Thickness</td>
<td>22.3</td>
<td>21.16</td>
</tr>
<tr>
<td>Width</td>
<td>45.8</td>
<td>42.38</td>
</tr>
<tr>
<td>Distance from medial edge of patella (md)</td>
<td>19.9</td>
<td>19.61</td>
</tr>
<tr>
<td>Patellar tendon Longitudinal length</td>
<td>40.2</td>
<td>44.91</td>
</tr>
<tr>
<td>Proximal width</td>
<td>30.3</td>
<td>27.42</td>
</tr>
<tr>
<td>Proximal thickness</td>
<td>3.2</td>
<td>5.018</td>
</tr>
<tr>
<td>Distal Width</td>
<td>24.0</td>
<td>24.2</td>
</tr>
<tr>
<td>Distal thickness</td>
<td>5.0</td>
<td>5.26</td>
</tr>
</tbody>
</table>

Comparative analysis from this study showed similar results with the study done by Jae Ho Yoo et al (Table 3) since both studies used the MRI knee images to collect data. However there are a few differences in measurement possibly due to the locations of population, mean age and type of machine used.

The present data showed significant differences between the sexes similar to the results of the other previous studies. The average anatomic difference between male and female knees can be explained by the average smaller height and size of woman compared with men and not by the gender.7

The patellar tendon is wider proximally than distally because the fascicles tend to converge toward the midline. A study found a moderate correlation exists between patella width and patellar tendon.8 The patellar tendon width has been reported to be a predictor of recovery speed and success following BPTB-ACL reconstruction.9

This study shows no correlation between length of patella and age. This correlates with other study10 that discovered that the patellar tendon length was unaffected by the aging process despite that it was 11% greater (p< 0.05) in men compared with women. Aging does not alter maximal tendon stiffness or elastic modulus of the patellar tendon however tendon stress and strain at peak force output are reduced with aging. These differences, however, appear to be more related to force output rather than age effect.

This study is not without its limitations. First, even though the MRI-based data cannot be directly extrapolated to the surgical situation such as patellar resurfacing in knee arthroplasty or BPTB graft harvesting in ACL reconstruction, our data nonetheless, is important as the normative information. The thickness of patella matters not only for arthroplasty but also for patella-femoral biomechanics before or after ACL reconstruction. Second, the male dominant gender of this research led to uneven distribution of gender and might be the confounding factor in statistical analysis.

The results of this study were not much different from the previously reported studies. However it gave a good overview of the local knee anthropometry, describing the geometry of patella and patellar tendon, which is the fundamental data in understanding various knee conditions and performing reconstructive surgeries.

REFERENCES

The Qualities of an Effective Mentor: From the Operating Department Practice Students’ Perspective

Puziah Yusof and Rasidah Mohamed

ABSTRACT

Context: Developing clinically competent healthcare professionals is probably the principal objective of all healthcare education. However, training for clinical competence is a complex process requiring the involvement and commitment of all stakeholders including students and administrative personnel in the clinical areas as well as the faculty and college. This study explores the qualitative perceptions of the Operating Department Practice (ODP) students of a private Health Education Provider (HEP) on their perceptions of the quality of mentors in meeting the features of an effective supervisor in the clinical areas.

Methods: The study focused on how ODP students developed their professional knowledge while working in the clinical areas. The sample consisted of 10 final year students from an ODP programme who were interviewed individually. Students were requested to reflect on previous experiences starting from their first clinical placement based on their reflective diaries. The in-depth interviews were taped with immediate verification made when necessary. This approach allows the author to interpret emerging themes instantly which essentially forms the basis of data analysis. Hence data collection and initial analysis took place simultaneously.

Findings: During data collection and analysis it became evident that the influence of the clinical mentor and the nature of the relationship were central to students’ knowledge and skills development. By undertaking a content analysis for the relevant data and using an inductive approach, five key elements of the student-mentor relationship emerged. These five aspects will be presented and discussed along with the implications for ODP education and the mentoring role of the clinical staff. KPJ Medical Journal 2013; 5:37–43

Key words: ODP students, effective clinical supervision, quality of mentor, clinical education, clinical experience.

BACKGROUND

The HEP is constantly striving to improve student’s learning experiences to provide a legacy for the next generations of healthcare practitioner in the clinical and academic areas.

The primary author was a new academic member to the ODP program who believes in the importance of bridging theory-practice gaps to enrich student’s clinical experience. Among the important element was identifying explicit role of mentors to the students. Mentors must be aware of the ethical codes in supervision.1 The ODP program requires students to have more than 50% hands-on practice in the operating theatre. Essentially, learning within a mentor-mentee relationship involves two parties and both have important roles to play.2,3,4,5 In other words, not only the mentor has an important role to play but so does the student in order to achieve the targeted learning outcomes.

The Mentorship role

A mentor requires robust preparation to be effective in their role, not only for students learning but also for the quality of that learning, which includes assessment of competencies to demonstrate the extent to which learning outcomes were met.6 The mentorship concept was a new phenomenon within the Malaysian Nursing and Allied Health profession, having started only in the last couple of years. As such, only a small number of studies investigating the experience of both mentors and mentees undergoing the processes were identified.

Students of the ODP program were guided or mentored by their Work-Based Assessors (WBA’s) for their clinical experience. According to the program guidelines, the WBAs were expected to provide support

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for students’ learning in practice and acts as mentor in the clinical areas. However, their performance will be monitored by the HEP and reported to the collaborative university Link-Tutor. The preparation for the WBA to play the mentoring role was carried out according to the program’s guidelines which were reported to be very minimal. These anomalies provoke the interest of the authors to obtain students’ insights pertaining to their clinical experience and expectation towards their mentor as a role model and more significantly identifies the expected qualities of mentor as teachers in the clinical area.

The finding of a study on the lived experience of mentoring nurses in Malaysia suggests the critical need of training and support to improve mentorship program in the country. Even though this study was limited within the nursing scope, the authors believe that obtaining insights from the ODP students would provide for greater knowledge to enhance the understanding of such experiences. The study aimed was to support improvement in mentorship program within the Malaysian Healthcare Educational System. Though it was acknowledged that the results of this study might not have a major effect on the overall performance of the students, there could possibly be some changes made to the proposed formal mentoring program using the WBA. More importantly, the research also aimed at discovering ways in which to adapt management styles or organisational structures in order to reduce any adverse effects on student’s learning in the clinical areas.

Within the research context the WBA or clinical mentors were part and parcel of the hospital staffs as such teaching and assessing students were additional responsibilities and not their primary functions. In addition, the WBA or mentors for the ODP students were not provided with a structured training for supervising and were not reimbursed for their additional role.

Literature review

The mentor’s concept of practice in the current era of globalization was commonly used as an organizational development strategy and was viewed as an integral part of learning and psychosocial support in the workplace. The aim was to increase groups and/or individuals performance to carry out their daily duties and responsibilities, inclusive of familiarizing staff with new core techniques.

Factors that affect the implementation of mentoring depends whether it was formal or informal. It was also dependent on the differences and uniqueness of the organizations in terms of their beliefs, values, strength and weaknesses. The formal mentoring programs were often viewed in literatures as a structured and coordinated relationship between mentor and mentee. Conversely, informal mentoring was seen as the process and systems of relationship between mentor and mentee to achieve specific demands and has been widely implemented to complement and strengthen the formal mentoring program. The relationships between the informal mentor and mentee often last for many years as students choose their own mentor. The positive characteristic of the mentor was defined as someone being knowledgeable, a role model and a teacher, a motivator, counsellor and friendly to the mentee.

Darling identified the characteristics of poor mentors as being toxic, avoiders, dumpers, blockers and destroyers or criticizers. Avoiders were mentors who made themselves ‘invisible’ when involved with students. Dumpers were mentors who make the students ‘swim’ on their own in the process. Mentors with blockers attitude were always reluctant to meet the students and provide all kinds of excuses when asked for supervision. These types of mentors can inhibit student’s development. Finally, mentors who were destroyers or critics either do so subtly or overtly.

Even though numerous studies have been carried out, little has been reported on the effectiveness of the mentoring program in Malaysia to support students in clinical areas. Report by Ismail, et al. on a mentorship program in the Malaysian context revealed that mentoring programs do act as effective predicting variables of individual’s advancement in an organization. As the study was limited only to one organization, their recommendations were to conduct a qualitative study focusing on specific variable to generalize the applicability of these dimensions of mentoring program in other professional areas. The findings by Enrico & Chapman, indicated that unstructured mentoring program challenged the mentors to find their own strategies throughout the mentoring process. This study explored the lived in experiences of qualified nurses mentoring new registered nurses at one major public hospital in East Malaysia. Participants in that study described their challenges to include their unpreparedness to be mentors and the lack of knowledge and skills about mentoring. Their proposed recommendations include providing them with proper mentoring training before committing themselves into the mentoring role. However, the lack of any study exploring the lived in experiences of the mentee from the perspectives of the students particularly in understanding their role and its implication formed the basis of this study. In this case it was to the ODP students.

Research Objectives

The need to examine the effectiveness of the current supervisory process from the mentee’s perspective within the ODP has become imperative. This was mainly to extend the present knowledge on the required nurturing for the development competence and skills of the healthcare practitioner, whilst recognizing ODP as a profession. This qualitative exploratory research was focused on identifying the mentee’s point of view as regards to effective mentorship characteristics.
METHODOLOGY

Research design

This qualitative exploratory and interpretive research design was based on hermeneutic phenomenological approach by Mark van Manen.22 The combination of hermeneutic phenomenology within the process of interview was entirely justified for this study because the authors were unable to fully separate their own feelings gained from clinical experience from that of the participants. This shortcoming however was positively used to interpret and foster further exploration of the participants. The understanding showed in each session could enhance the relationship between both parties and increased the level of trusts, thus encouraging the outcomes of richer and in-depth data. Semi-structured interview consisting of a list of open-ended questions used provide opportunities for both the researcher and participants to discuss topics in more detail. The researcher also used probing questions when the participants have difficulty answering.

Study setting

The individual interview approach was undertaken in a place where privacy and minimized interruptions were ensured. This was to facilitate the process of listening and probing. However, interviews could potentially reveal views, beliefs, attitudes and behaviours that could cause “damage” to participants were always kept in mind.22 Participants were ensured confidentiality of their disclosure. Each interview session lasted about an hour.

Sample

A purposive convenient sampling was used to recruit volunteers for this study. Demographic characteristics such as gender, age, status and previous experience were taken into account as people with different attributes may have different views.23 In this study however, students who volunteered also had to be available on the days allocated for the data collection.

Data collection

Data were collected using face-to-face interviews using semi-structured questionnaires. Examples of questionnaires include: Please share with me clinical experiences which you found as most anxiety provoking?; Which clinical experiences you find most enjoyable?; Can you share with me your experience of working with your mentor?; What was your expectation of working with your mentor?; How do you think these can be improved?; What do you expect from your clinical experience as a whole?

In order to enhance data validity, the interviewer tried to obtain depth perspectives from participants by ensuring ongoing clarification process were made throughout the session, using a method supported by Barriball & While.24

The in-depth interviews were taped, recorded and the researchers took notes of data to be used as cues and links to the participants for clarification processes. The immediate verification by reacting to the responses during the interview gave the opportunities for the authors to interpret emerging themes instantly and this essentially forms the basis of data analysis. Hence data collection and initial analysis took place simultaneously. The presence of the co-researcher during the interview helped to reduce the research biasness and enhanced the validity and rigour of the data collection and interpretive process. At the end of each interview sessions, the author debriefed the participants and assured them the confidentiality of their responses. This session also served as a platform for the authors to express appreciation to the important contribution made by the participants for the research.

Sample size

The samples were the final year of one cohort of ODP students. There were a total of seventeen students but only ten students were available within the data collection days.

Ethical consideration

Approval for this study was obtained from the Research and Development Ethics Committee of KPIJUC. The Program Coordinator and student’s cohort leader were informed that all students’ involvements was on a voluntarily basis.

Data analysis

The thematic analysis was undertaken manually by highlighting the narratives with open coding method for each theme that emerged. The transcripts were read and re-read to identify statements and phrases that revealed what the perceptions of students were like. The emerging themes were highlighted and coded using the words from their statement. As themes repeated and became common amongst participants, main themes were developed in order to grasp the true meaning of their experience and expectation of mentoring process.

There were two major sources of data involved; audio taped interviews and field notes. All audio taped data were transferred verbatim for analysis. Following transcription responses were grouped under related interview questions. Similarities and differences of individual responses were examined.
Findings

Demographic data

There were ten participants in this study. The mean age of participants was 29.1 years with a range of 19 – 40 years.

Themes

Five main categories of findings were identified and each category will be discussed separately. The major emergent themes were:

1. Students’ perception on the importance of mentoring role
2. Differences between a good and a bad mentor
3. Mentoring and role modelling
4. Teaching and learning support
5. Clinical educator

Students’ perception on the importance of mentoring role

During the interviews, students had developed self-perceptions on the characteristic of effective mentors. The last theme evolved as participants were on the thinking mode of what to expect from their clinical experience as a whole for future clinical experience to be successful. The following were related comments from participants;

“...as students, we should get guidance, supports and mutual respects rather than breathed down our neck...”

“...students should be allowed to participate more in practice, they (mentors) just have to trust our abilities to perform...slowly and as we go on...until we can practice unsupervised...”

“...creates a form of relaxed relationship and flexibility...so students do not feel so stress...and lead to more mistakes...”

“I learn well when my mentor had initial discussion prior to any procedure...and provide me with feedback at the end...”

“...students rely so much on mentors...if we get good mentor, we’ll learn better and if I have any problem, I know where to turn to...”

Essentially, the students’ views incorporate important points developed through reflective practice during their mentoring session within the course of study. In essence, their view reflects the attributes of a quality mentor and otherwise.

Differences between a good and a bad mentor

The students described a good mentor as being approachable, friendly, patient and having a sense of humour to minimize stress. They further stressed that a good mentor must be a good role model, professional, caring, enthusiastic, self-confident and, most importantly, knowledgeable with good communication skills. She must be knowledgeable of the ODP course and have the required skills that students should achieve.

One student commented;

“...my opinion of good mentors, (pause) ...they must be able to teach properly ...I mean she/he should know how to guide students to build their confidence from being an observer to a doer... and always make the effort to spend time with students to provide regular feedback...”

Students who had been exposed to what they felt was poor mentors, described these mentor’s as lacking in knowledge, had no structure in their teaching, never kept to their promises and underestimated students’ capability. Some poor mentors tend to ‘over protect’ the students and tried to limit their involvement in the operating theatre activities. Students described these experiences as;

“...very sorry to say that some mentors ...I feel are not fit to be mentors ...why I said that...because I experienced once when my mentor was not very sure about developing portfolio... and ended in me asking help from another senior ODP students...it happened many times.

The effect of having a poor mentor was also well expressed by students;

“...during my second semester placement in hospital...the staff were not so friendly and often disliked me and in fact they invariably used students to do their 'unwanted jobs' in the OR...”

“...I had one experience with a bad mentor...she liked to give bad remarks to students such as ‘very slow’ and ‘blurred’ ...and talked about it during breaks ...that make us feel very down...”

Mentoring and role modelling

Prior to their first placement, the students viewed their mentor positively and placed high expectation for their expected guidance and ‘protection’. The students’ belief was that their mentor would be there exclusively for them individually, teaching and assessing; and as a supervisor to provide guidance in clinical learning. They also felt that the mentor would be nice, approachable, understanding and communicating well with others.

“...I felt more comfortable; actually...at least I have someone to be with me while trying to get familiar with the new surroundings...”

“...my first day in the operating theatre, I felt like an alien...the only time the staff talked to me was when I almost contaminated the ‘green’ trolley...lucky my mentor was there...”
Students experience in their placement indicated that having a mentor was important. They believed that having a mentor was crucial for their learning, whilst they were aware that their mentor had competing priorities at the same time. However, all participants expressed the need to maintain a one to one ratio between mentor and student as other nurses were not familiar with their learning objectives. When the number of mentors were not adequate during clinical posting they spend most of their time doing routine menial tasks, as they were not delegated according to their level of training or scope of practice. This negatively affects their learning opportunities in the clinical area.

“...mentor and I do not always work together in the same operating room...I don’t know why...she said students can get experience from other staff...yes...but other staff means...they just ask us to do routine work like recording patient’s vital signs and push patient to recovery...and they were busy with their own work...so no choice we get help from senior ODP students....”

“...in one hospital, I worked in recovery for one day only...Sister asked me to help circulate for cases in the operating room....she said there was not enough staff in OT....”

A few students indicated that there were staff members who were reluctant to serve as mentors for the ODP students. These findings were in contrast with the fundamental principles of learning in the clinical setting that qualified staff should be willing to teach and act as mentors, supervisors, assessors and preceptors for students in the clinical environment.25

“Sometimes we were ‘passed around’ like a ball....when I request to tag with them to scrub; she (OT staff) gave all the excuses.....”

Teaching and learning support

The ODP was a competency-based program with a ratio of 50% theory and 50% clinical practice. Therefore the need for students to be actively involved in their teaching-learning process in clinical areas was critical. Students’ clinical practice experience and thoughts could lead to new self-knowledge and deeper learning.26 Students believed that support required from the clinical placement to gain the best from their learning experiences could not be under estimated. Therefore, they further emphasized their right to expect input and support from key individuals namely their mentors to enable them to identify learning opportunities within their placement.

A good mentoring depends upon well planned learning opportunities and the provision of support and students’ supervision. However, the participants stated that in reality many of them have a ‘hit and miss’ experience and considered themselves lucky if they got a good mentor. The following quotations denote a “hit and miss” experience with their mentors.

“...experience with the WBA..... (pause), it depends...my WBA in the previous hospitals was quite good but not always I get like that...”

‘...my WBA was away on medical leave, no one replaced her for about two weeks...then the unit manager ‘took care’ of us...but she was also busy with her own work....”

Clinical educator (CE)

Students stated that the presence of clinical educators in the operating theatre who were dedicated for teaching can help ensure consistent support for their learning in clinical areas. One student commented;

“......I gained more experience in hospital....because Ms W. ..... (Clinical Instructor in OT) was there...she would brief us before any case...so we learnt better...”

“...the clinical educator in hospital.... was very approachable and always willing to answer my doubts.... and I didn’t feel scared at all....”

All students were consistent in raising the need of having a dedicated CE for the operating department practice education as having support from someone who was always available in clinical practice and able to remains ‘cool and calm’ even on busy days as a necessity. Students voiced that the constant guidance were reassuring specifically when provided with continued assessment. This was consistent with the finding of Cope, et al. who identified the importance of immediate practice and continuous assessment as skills learned in isolation and out of the context could be lost as students will not be able to make sense of their learning.27

The students basically wished to have support from someone familiar to them. This was consistent with findings from Prescott, who described support as being from someone with a “friendly face” in the busy clinical setting.28 Familiarity with the surrounding environment was an enabling factor in work-based learning.29,30,31 Participants of this study commented that there was no CE in the majority of clinical placements that the availability of CE in the operating theatre was critical for their learning experience. This was described as “the cornerstone of clinical practice.”32 The following were comments from participants regarding the lack of clinical educator.

“we see other students...like physiotherapy...they have evaluation and presentation at the end of postings.....so they can share what they have learnt, discussed and ask questions...from others...because they have the preceptor to do all that...why can’t we?...”
DISCUSSION

Generally, all students experienced what they viewed as a good mentor in at least one of their placements. Students’ description of a good mentor includes the characteristics of being approachable, knowledgeable, with good personality, professional, enthusiastic, friendly and having a sense of humor. These characteristics demonstrate the qualities of a good mentor required to by students to achieve effective clinical supervision. Additionally, the characteristic of a good mentor includes enthusiasm in their role, yet realistic in their expectation of students. A quality mentor also has good teaching skills, able to meet students’ educational needs and spends quality time to develop their learning. Students added that good mentors were good role models and this could be observed from the respect they gained from peers.

In comparison, poor mentorship experience makes them lose interest in their study, feel demoralised, lose confidence and causes them to be stressful. Students described poor mentors as lacking in knowledge and skills made worst by poor attitudes. The findings of this study indicate that all students experienced a toxic mentor at least once and they coped by keeping a low profile.

This study is limited by a small sample size. A bigger study is proposed for the future.

RECOMMENDATIONS

This study provides the authors with valuable information for guiding practice and identifying alternative ways of supporting both students and the WBAs’ to achieve positive outcomes in supervision. Strategies need to be developed by both faculty and the hospital management to improve support for ODP students within the clinical areas. Recommendations based on the study findings are the following:

- The mentor WBA should receive financial remuneration for their role as mentors/WBA by the University College
- Collaboration between the university and hospital management needs to be strengthened in order to facilitate open communication and information sharing to improve the quality of mentorship and supervision.
- The provision of a structured and formal mentorship program needs consideration for preparing the WBAs for their role of supervising students in the clinical areas thus enhancing student’s performance.
- Careful planning is required to protect the welfare of clinical staff as well as students through agreed guidelines for clarity of supervising roles amongst staff in clinical practice and appropriate preparation of students prior to clinical placements.
- Workloads of clinical staff participating as mentors/WBA need to be reduced due to their supernumerary status. This could include a permanent promotional position as Perioperative Nurse Educator dedicated to the operating theatre.
- There should be a set of guidelines for the selection of WBAs’ or mentors.

CONCLUSION

Overall, this study has highlighted the ODP students’ experience with their mentors in clinical placement. Students viewed their mentors as someone who can provide them with guidance, support and assess them throughout the placement but in many occasions it occurred otherwise. In this situation the students experienced anticipatory fear when associated with poor mentors. However, in such situations students learnt the importance of developing relationship with other clinical staff to support them in clinical placement. As for the future, students expressed hoped for the improvement and better quality supervision for effective clinical supervision plays an important role in the achievement of quality student leaving in clinical practice.

REFERENCES

A Study of Dropouts Amongst Student Nurses

Azlina Azmi and Rasidah Mohamed

ABSTRACT

Background: Despite the long history of research into student nurses discontinuation; it has yet to yield effective ways of reducing national attrition rates. Attrition from nursing programmes is of international concerns in both the public and private sector, as such institutions need to analyse these issues.

Aims: The aim of this study was to identify the most common reasons for nursing students’ attrition in a private learning institution so as to develop specific recommendations. Specific objective was to determine the attrition rates according to students’ gender, state of origination and the reasons for attrition.

Method: Retrospective study.

Finding: The main reason for the students drop out was found to be joining other colleges or courses. The finding also showed that some students lost interest in continuing their studies with a high percentage citing personal/family problems.

Conclusion: To reduce the attrition rate it was recommended to consider continuous multi level supports from educators and that the identified factors associated with student drop out be addressed the soonest possible.

INTRODUCTION

Attrition, or people dropping out of professions, careers and courses of study, occurs in all settings and sectors. Indeed, it is becoming common for individuals to have more then one career or even more than one type of job in one’s life. Due to global shortage of nursing professionals and the ageing population, attrition at all points in the profession is of a serious concern. However, reports on the levels of attrition in nursing were at times misleading, inaccurate and out of context. The terms “attrition” were interchangeably used with “dropping out”, “leaving” and “withdrawing” but in this research we focused on students voluntarily leaving their studies and not on those expelled or terminated.

There are many reasons for students to leave their studies. Reasons include changing courses, deferring or moving into vocational programmes, education or the training sector. They may drop out from the programme for personal reasons or due to external factors like leaving for paid work. This part of the paper undertakes a literature review to explore the elements and reasons behind students’ drop out or attrition. The review would also include recommendations and suggestions on methods used to monitor and control students’ attrition.

In this private higher education provider (HEP) the students comprised of local and international school leavers with appropriate grades from the High School National Examination or the Sijil Pelajaran Malaysia or its equivalent. Most were below 20 years of age. All students were given hostel facilities throughout their study.

By 2010 the HEP has doubled its capacity with the number of intake increasing to over 300 students per year. The first intake of male students started in the year 2005.

BACKGROUND

Despite the long history of research into student nurses drop out, it has yet to yield effective ways of reducing attrition. Although there has been a decline from the high attrition rates of the 1960s, it has since stabilized in the 1990s to around 20%.1

The consequences of student attrition affect students, the HEP, the nursing profession and the public at large. For the students there are the psychological effect of failure and the financial consequences of early repayment of their study loan. To the HEP, they will experience lower financial income with every drop out. For the nursing profession, the consequences of student attrition result in the lack of available nurses to meet the public health care needs of the society. To address this, the UK higher education institutions are required to maintain an attrition rate of below 13%.2

Statistics on attrition rates appear to be inconsistent between organizations, possibly due to the definition of attrition adopted.3 This lack of a common definition of attrition means that it has been difficult to make valid
comparisons of attrition rates, over time or between schools.

Nonetheless, available data on overall attrition rates appear to have varied from 23–34% in the 60s, decreasing to 15–20% in the 80s. In the 80s and 90s, rates remained between 15 - 20%. Braithwaite et al showed a decrease in attrition rates between initial and later cohorts. This was also confirmed by the Department of Education, Science and Training of the Australian Government’s report on Higher Education Attrition Rates of 1994 to 2004.

Focus of project

Attrition occurs in all settings and sectors and this is inclusive of the nursing students in this private HEP. Occurrence of attrition at any point in the profession is of serious concern and reports on the level of attrition were sometimes misleading and out of context. As such this retrospective research intends to identify the accurate reasons for students’ attrition in order to institute remedial actions.

Literature review

Extensive research has been conducted on the attrition of students in colleges of nursing education using different methods and approaches. These studies often focused on particular areas of research such as the effects of student expectations, career decision-making, student financial aid, or the institutional environment.

Some researchers have concentrated their efforts on special student populations such as older adults or minorities. Institutional researchers have also evaluated several factors simultaneously in an effort to predict student retention or to examine the relationships among several variables using conceptual models of student attrition. Finally, researchers have assessed whether specific intervention strategies reduce drop-out rates among college students.

Attrition factors

A diversity of factors contributing to student nurses attrition has emerged from the literature. Deary noted that many reasons for attrition have remained similar despite different approaches in gathering information on reasons for leaving.

Several authors discussed factors and reasons contributing to students’ attrition. Wells, focussed more on primary, secondary, tertiary approaches for the prevention of attrition by identifying intervention critical points. Jeffreys, focussed on student retention and success (graduation and licensure) with the goal of preventing withdrawal or dismissal from institutions.

The majority of authors identified course pressures/difficulties as the main factor contributing to student attrition. Other factors generalised by the authors include personal/family problems and wrong career choices, homesickness and difficulties in settling in. Yorke noted that female students were more likely to experience personal and family problems being away from home. Lack of ability to build strong social network early in their studies worsen the situation.

Meanwhile, lack of support and inadequate knowledge/skills have also been identified as minor factors contributing to student attrition. Students felt that they had insufficient tutorial support whilst on placements. With the increase in student numbers it had become very difficult for mentor/preceptor to support each individual student nurse. Some students were not clear about their mentor’s role. Due to obvious reasons, first year students need more direction and support.

Other causal factors of attrition identified were financial problems and ill health with a weighting of below 25%. Financial problems tend to be mutually exclusive to other reasons of leaving especially with family problems. The most common reason used was lack of financial support from their families or support was withdrawn midway through the year. Some students have to work part time to make ends meet simultaneously causing increased pressure on their academic performance.

Illness at critical times during the academic year can have disastrous consequences for students. Critical times include not only examination weeks but also during time of peak coursework. During the latter, the students felt overwhelmed by the volume of work which they must catch up on. However, it was noted that although the incidence of illness was almost equal to those with financial problems, the perception amongst authors on its impact as a contributory factor was considerably lower.

Glossop and Ehrenfield et al found that academic factors contribute to attrition at 77%, 64% and 39% respectively. Student dissatisfaction (5%), family (8.4%) or health problems (4%) were cited as minor causal factors. Social pressures from peers, friends and families were also identified as contributory factors.

The reasons for leaving

The reasons for leaving used in most studies tend to be generalised. Some categories were broadly defined and may be open to interpretations. For example, academic difficulties could mean repeated failure of an assignment or exam, or a student experiencing difficulties with a particular aspect of academic work, despite passing assignments. Failure of clinical competencies was normally classified as academic failure, yet very different skills may be required to achieve clinical competence.

Reports citing “personal reasons” suggest that students might not have wished to share information which was much too private to be disclosed. This category could represent one of a number of factors of family problems or wrong career choice. Thus students
citing this category would have contributed to the high number of students on whom there was limited information.8

Similarly, the reporting of health problems could be based either on physical medical ailment or mental disabilities. They could be caused by pregnancy or migraine attacks from stress at work.3 The health problems could also be related to the student’s parents, relatives or dependants. These kinds of attrition create questions on the manner of withdrawal whether it was voluntary or involuntary.8

The different categories or reasons for leaving were not mutually exclusive, and it was possible that there were causal relationships between them. For example a student’s family difficulties might have resulted in exam failure or, conversely, stress arising from the course might have contributed to family problems. Students may have experienced a number of interrelated difficulties which may ultimately lead to their discontinuation, whether voluntarily or involuntarily because of academic failure.6 Quality assurance and course review also could help to make learning experiences to ensure less distressing and uplifting.1

**General and Specific Objectives of this Project**

The aim of this study was to identify the common reasons of nursing students’ attrition so as to develop suitable recommendations. Specific objectives were to determine the attrition student’s gender, the state of origination and the reasons for attrition.

**Problem Statement**

The private HEP experiences an overall 1.3% drop out rate of nursing students within a 5 year period. Most of these cases occurred during the first year of training with students citing wrong career choice, health, personal and financial difficulties as reasons for attrition. These categories of reasons were broad and subjective. In writing to the HEP in order to withdraw, students would state one of the above or a combination of reasons for quitting. At times the students offer no reasons at all.

Currently, studies undertaken reveal lack of concrete ways to fight attrition. Even though the private HEP attrition rate has been low, the seriousness of student attrition’s exists.

**METHODOLOGY**

A retrospective study of student records from the year 2007-2011 was made from 12 groups of the Diploma in nursing programme. Data were gathered from students’ document with permission from Head of Student Affairs of the private HEP involved. The Research and Development Committee of the HEP approved this project. Data was analysed using basic Excel Microsoft spread sheet.

**RESULTS**

From the year 2007-2011 there were a total of 147 student drop outs from the programme. Total student population was 1576 (Fig. 1).

Students originating from the Negeri Sembilan state have the highest attrition rate (16%), followed by Selangor and Johor (12%), Kuala Lumpur, Perak and Kedah (10%), Kelantan and Pahang (9%). The lower percentages of drop outs were among students from Terengganu (4%), Pulau Pinang (3%), Perlis (2%), Sabah, Sarawak and Melaka (1%) (Fig. 2).

The main reasons for drop-out were students joining other colleges or courses (45%), not being interested to continue their studies (27%), personal/family problems (17%), wrong career choice, wanting to choose other careers (7%), health problems (3%) and financial problems (2%) (Fig. 3).

The percentage of male students’ attrition rate was considerably high considering that they made up less than 20% of the total nursing students’ population. Adding up the three related reasons for dropping out namely; joining other college (33%), not interested (33%) and wrong career choice (11%), resulted in a total of 77% of male students leaving the programme. This gives rise to the assumption than the nursing program was not seen as a correct career choice to them. This result highlighted the need to develop a concerted effort to reduce the high rate of male nursing students’ attrition. Factors contributing to students’ withdrawal by gender are presented in Fig. 4.

**DISCUSSION**

**Reasons for withdrawal**

Prior to 2006, students in this HEP were either self sponsored or sponsored by private hospitals. Since the year 2006, financial sponsorship has come from the Ministry of Higher Education’s Study Loan (PTPTN -in its Bahasa acronym), private hospital loans and from the Ministry of Health sponsorship programme. Within the same time span, this HEP recorded a high rate of 9% dropout. This is a significant factor as the HEP uses student progression and attrition rates as an indicator of programme and curriculum quality.

Fig. 2 showed that students from Negeri Sembilan had the highest number of attrition (16%) as compared to students from other states. This could be partially due to a high number of students in this HEP originate from the Negeri Sembilan state itself.

As earlier mentioned the highest female student attrition was due to personal and family problems (17%) but the actual personal and family problems were not stated. The highest stated cause of attrition was joining other colleges and the least stated cause was financial problems.
Fig. 1. Students Enrollment 2007-2011

Fig. 2. Total Percentages of Students Dropout by State

Fig. 3. Factors Contributing to Dropout

Fig. 4. Factors Contributing to Students Withdrawal (by Gender)
Strategies to reduce attrition

Authors who examined students’ attritions have suggested improving the nursing program in order to reduce the rates. Wells recommended that the greater the interaction between academic and the social systems of the institution, the greater the probability of students finishing the course. A lack of social integration in the campus environment results in a lack of commitment to the institution and increases in the likelihood of withdrawal, even by students with satisfactory academic performance. Indeed, personal tutor system for all students and need to support the students. Targeting more mature students and increasing the level of qualification is required and combination of course structure and student support is very important. Moreover, functional support, facilities learning, psychological support and also orientation program prior to the first semester could provide caring environment of learning to students. Authors recommended for minimizing attrition in nursing by using emotional intelligence (self – awareness, self – regulation, motivation, empathy and social skill). Enquiry –based learning (EBL) is recommended as one positive way to enhance student experience and reduce the theory – practice gap contributing to stressful practice experience.

Wells, also recommended primary and secondary prevention strategies to reduce attrition. Primary prevention strategies include more public awareness, ongoing continuing education program, and development of an institutional think tank group on student retention. The secondary prevention strategies were to focused on early detection by conducting student satisfaction surveys, develop objective criteria to identify attrition risks, conduct trend analysis on attrition numbers and promote faculty development on cultural diversity. The use of an exit interview has proven to be successful in improving the quantity and quality of the information collected. Researchers who are concerned and focusing on male student attrition also have recommended that male role models are available in the teaching and clinical context and they also reinforce that nurse educators need to be cognizant of gender differences in their learning environment.

A screening programme is a necessity during intake to determine the right candidates. Written essays, individual and group interviews including short entry exam is currently the practice in the HEP for selection of candidates into the diploma programmes. An exit interview using a structured format could be made as part of student’s withdrawal process. The interview could be conducted either by the lecturer-in-charge or a designated lecturer or counsellor. It is noted that generalising the reasons for leaving would only restrict knowledge on the actual reason(s) for leaving. Students should be encouraged to write their reasons for leaving and an interview session would serve as an understanding point on behalf of the HEP.

Beneficiaries of Research Results

This retrospective study of major causes of students’ attrition may help the HEP to come up with appropriate solutions to reduce the attrition rate. Indeed, this is in line with the government’s objectives to reduce shortage of qualified nurses nationally and internationally. Appropriate interventions will help lecturers, clinical instructors and management to understand student nurses problems. Each dropout case would be a loss to the individual, the HEP, the profession and the nation as a whole. The student must repay financial loans they received. So, before they decided to drop out concerted efforts must be made to help them make the correct and beneficial decisions.

Limitations of the study

This study only examined the nursing students drop out rates and did not include any the other programmes in the HEP. As such the result this study finding is limited only to the nursing programme. Future studies should focus on the reasons and attrition rates of all programmes provided by the HEP and on identifying elements that motivate the students. These positive elements can be used to help increase overall student’s performance. Such a study would help the HEP to understand why students choose to change courses, drop out or simply stop learning despite the good nursing job prospects.

CONCLUSION

Factors causing nursing students attrition in this HEP can generally be summarised into academic difficulties, personal or family problems, health problems, wrong career choices and financial problems. The literature the seriousness of student attrition’s problem as it contributes to the shortage of nurses. Studies have also revealed the lack of concrete ways to fight attrition and it appeared as though attrition was a natural part of the education process itself.

While the main reason for the student drop out was them joining other university colleges or programmes, the findings also show that students who were not interested to continue their studies had a high percentage of personal/family problems.

To improve the situation the HEP is recommended to consider targeting the mature candidates who could make a final decisions for their chosen career. Mature candidates were found to be able to focus on their own development and live more independently of outside influences. Strong support from educators in improving student teacher interaction and in increasing cultural understanding is also required to reduce student drop out in the future.

Indeed for further improvement the HEP is also recommended to refer students promptly for counselling.
The on call counsellor system should be developed to immediately counsel students who wish to dropout.

REFERENCES

5. BRAITHWAITE (1994).
17. Ramsburg L. Strive for success: A successful retention program for Associate of Science in Nursing students. Teaching and Learning in Nursing. 2007; 12-16.
INTRODUCTION

Antibiogram or antibiotic sensitivity report is a periodic summary of antimicrobial susceptibilities of local bacterial isolated in clinical microbiology laboratory. Antibiograms are often used by clinician to assess local susceptibility rates, as an aid in selecting empiric antibiotic therapy, and in monitoring resistance trends within the organization. Antibiograms are also used to compare susceptibility rates across institutions and track resistance trends. The recommendations of many professional societies and national agencies such as World Health Organisation (WHO) and Center for Disease Control (CDC) for addressing the growing problem of antibiotics resistance include monitoring of antimicrobial resistance.

A standard reporting format has been established and used to ensure the report presented is identical and comparable among the KPJ Groups of hospitals. The antibiotic use and resistance pattern can be analyzed and shared among the hospitals as a guideline in antibiotics selection and used by healthcare professionals for patient care.

OBJECTIVE

The objective of this report is to present the overall antibiotic resistance pattern of the selected antibiotics against selected organisms isolated in the KPJ Hospital medical laboratories for the year 2011.

METHODOLOGY

The data were collected from 15 KPJ Hospitals from January to December 2011. A total of 9,452 isolates (Fig. 1) of six selected organisms were included for the analysis. These organisms were four gram-negative organisms (Acinetobacter sp., E. coli, K. pneumonia and P. aeruginosa), and two gram-positive organisms (S. aureus and MRSA).

Fourteen antibiotics from different classes were selected against the organisms (Fig. 2 and Fig. 3).

RESULTS

Resistant Pattern for Gram-negative Organism

Overall, Amikacin, Cefepime and Imipenem produced the lowest resistant rate for gram-negative organism in 2011 with less than 10% resistant (Table 1). Gram negative organisms were highly resistant against Cefixim, Cefuroxime, Augментin and Unasyn (resistant rate more than 50%).

<table>
<thead>
<tr>
<th>Organism</th>
<th>Year 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter sp.</td>
<td>748</td>
</tr>
<tr>
<td>E. coli</td>
<td>2970</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>2384</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>1198</td>
</tr>
<tr>
<td>S. aureus</td>
<td>2005</td>
</tr>
<tr>
<td>MRSA</td>
<td>147</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9452</strong></td>
</tr>
</tbody>
</table>

Fig. 1. Total number of Organism Isolated for the Year 2011

1Lablink (M) Sdn Bhd.
2Consultant Pathologist, Lablink (M) Sdn Bhd.
3Consultant Physician, KPJ Perdana Specialist Hospital.

Correspondence: Abd Latif Ghazali, Ruang 1, Tingkat 3, Bangunan Pharmcare, 14(129) Jalan Pahang Barat, Off Jalan Pahang, 53000 Kuala Lumpur, Malaysia,
Table 1 — Overall Resistance Pattern of Gram-negative organism (2011)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Amikacin</th>
<th>Ceftadizime</th>
<th>Cefepime</th>
<th>Ceftaxime</th>
<th>Ceftriaxone</th>
<th>Ciprofloxacin</th>
<th>Imipenem</th>
<th>Peflloxacin</th>
<th>Sulperazone</th>
<th>Tazocin</th>
<th>Augmentin</th>
<th>Unasyn</th>
<th>Total Isolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter</td>
<td>22.3</td>
<td>39.2</td>
<td>30.8</td>
<td>87.2</td>
<td>35.3</td>
<td>82.8</td>
<td>82.2</td>
<td>30.4</td>
<td>28.0</td>
<td>20.7</td>
<td>50.8</td>
<td>34.5</td>
<td>30.9</td>
</tr>
<tr>
<td>E. coli</td>
<td>0.2</td>
<td>3.8</td>
<td>2.0</td>
<td>15.1</td>
<td>8.6</td>
<td>7.7</td>
<td>17.4</td>
<td>55.8</td>
<td>31.9</td>
<td>3.6</td>
<td>9.8</td>
<td>61.3</td>
<td>63.5</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>1.0</td>
<td>2.9</td>
<td>1.2</td>
<td>11.1</td>
<td>4.9</td>
<td>3.9</td>
<td>12.0</td>
<td>7.0</td>
<td>1.3</td>
<td>1.1</td>
<td>8.7</td>
<td>18.6</td>
<td>39.9</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>6.6</td>
<td>12.8</td>
<td>9.0</td>
<td>100</td>
<td>40.6</td>
<td>90.7</td>
<td>90.7</td>
<td>13.4</td>
<td>11.8</td>
<td>45.1</td>
<td>51.2</td>
<td>25.5</td>
<td>99.3</td>
</tr>
<tr>
<td>OVERALL</td>
<td>7.5</td>
<td>12.2</td>
<td><strong>10.8</strong></td>
<td>53.4</td>
<td>22.4</td>
<td><strong>27.5</strong></td>
<td>50.6</td>
<td><strong>19.2</strong></td>
<td><strong>10.5</strong></td>
<td>27.3</td>
<td>26.7</td>
<td>19.6</td>
<td>52.5</td>
</tr>
</tbody>
</table>
Antibiogram of *Acinetobacter* sp.

Overall *Acinetobacter* sp. was highly resistant against Cefixim and Cefuroxime. Based on the data collected, Sulperazone was not the best antibiotics for *Acinetobacter* sp. as compared to other third generation cephalosporin (Fig. 4).

Antibiogram of *E. coli*

Amikacin and Imipenem produced the best result against *E. coli* (< 1% resistance) for almost all of the KPJ hospitals. For cephalosporins the resistant rate was below 20%. For beta lactam penicillin, *E. coli* was highly sensitive against Piperacillin/Tazobactam (Tazocin) (10% resistant rate), but it was highly resistant against Augmentin and Unasyn (resistant rate of 61% and 64% respectively) (Fig. 5).
Antibiotic Use and Resistance Pattern in KPJ Hospital

**Antibiogram of K. pneumoniae**

Unasyn was least useful against *K. pneumoniae* with 40% resistance rate followed by Augmentin (19%), Cefuroxime (12%), Pefloxacine (11%) and Cefixim (11%). The rest of antibiotics recorded below 10% resistant rates against *K. pneumoniae*. The best antibiotics responses are Amikacin, Cefepime, Imipenem and Sulperazone with only around 1% resistant rate (Fig. 6).

**Antibiogram of P. aeruginosa**

*P. aeruginosa* is 100% resistant against Cefixime. Augmentin, Unasyn and Cefuroxime are also considered insensitive against *P. aeruginosa* whereas *P. aeruginosa* was highly sensitive to Amikacin and Cefepime (resistant rate 7% and 9% respectively) (Fig. 7).
Resistance Pattern for Gram-positive Organism

*S. aureus* is highly sensitive to selected antibiotics except Fusidic Acid (less than 10% resistant rate) (Table 2). Teicoplanin has the most effective rate (zero resistant). Vancomycin resistant *S. aureus* was reported in 2 of the KPJ hospitals. Teicoplanin and Vancomycin is 100% sensitive against MRSA.

**Antibiogram of S. aureus**

The best performing antibiotic against *S. aureus* was Teicoplanin with 100% sensitivity. Carbapenem (Imipenem) was highly effective. Except for Fusidic Acid, the rest of reported antibiotics had less than 10% resistant against *S. aureus*. Only two out of 15 KPJ Hospitals recorded Vancomycin resistant *S. aureus* (Fig. 8).

**Antibiogram of MRSA**

MRSA were highly resistant against most antibiotics except for Vancomycin and Teicoplanin (zero resistant rate) (Fig. 9).

### Table 2 — Overall Resistance Pattern of Gram-positive organism (2011)

<table>
<thead>
<tr>
<th>Specimen</th>
<th>% Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amikacin</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>7.2</td>
</tr>
<tr>
<td>MRSA</td>
<td>47.5</td>
</tr>
<tr>
<td>TOTAL AVERAGE</td>
<td>27.4</td>
</tr>
</tbody>
</table>

![Antibiogram of S. aureus (2011)](image-url)
Fig. 9. Antibiogram of MRSA (2011)

**CONCLUSION**

Overall, the antibiogram results did not show any alarming trend however the increased Cephalosporins usage among KPJ Hospitals has resulted in increase in resistant rates of some organisms.

Amikacin recorded better results against the common organism isolated in 2011. Most of the selected organism in 2011 recorded high resistant rate against beta lactam penicillin (Augmentin and Unasyn). The drugs of choice for specific organisms still recorded acceptable resistant patterns and could still be used for treatment except for Cefoperazone/Sulbactam (Sulperazone), against which *Acinetobacter sp.* showed a 50% resistant rate.

Constant monitoring of antibiotics use and adherence to antibiotic policy formulated by Infection Control Committee could improve the resistant patterns of antibiotics in the KPJ Hospitals.

**REFERENCES**

Neoadjuvant Concurrent Chemo-radiation in Anal Sparing Surgery from Years 2011–2012 in KPJ Damansara Specialist Hospital

Lum Wan Heng, MBBS, FFR RCSI

ABSTRACT
Rectal cancer adjacent to or invading the levator ani and sphincter muscles can only be cured by removal of these structures using abdominal perineal resection technique and construction of a permanent colostomy. Concurrent chemo radiation is used to downstage and downgrade disease for anal sparing surgery. Cases receiving this modality of treatment from 2011 to 2012 were reviewed. KPJ Medical Journal 2012; 5:56–58

Key words : Rectal cancer, anal sparing surgery, concurrent chemo-radiation.

INTRODUCTION
The rectum is a tubular structure 12cm long, connecting the sigmoid colon to anal sphincter muscles. It functions as a temporary storage for faecal matter. The incidence of colorectal cancer in Malaysia according to the NCR (National Cancer Registry) in 2006 was the highest in males and the second most common in females after breast cancer. In males the incidence was 21.6 per 100,000 population and in females was reported as 15.4 per 100,000 population.

AJCC STAGING SYSTEM FOR COLORECTAL CANCER

<table>
<thead>
<tr>
<th>Primary tumour (T)</th>
<th>Stage 0</th>
<th>T1s</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumour cannot be assessed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T0 No evidence of primary tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1s Carcinoma in situ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 Tumour invades submucosa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Tumour invades muscularis propria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumour invades through the muscularis propria into the subserosa, or into non-peritonealized pericolic or perirectal tissue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumour perforates the visceral peritoneum or directly invades other organs or structure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regional lymph node (N)</th>
<th>Stage 1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX Regional lymph nodes cannot be assessed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 No regional lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 Metastasis 1 to 3 pericolic or perirectal nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2 Metastasis in 4 or more pericolic or perirectal lymph nodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3 Metastasis in any lymph node along the course of a named vascular trunk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Any T</td>
<td>N2, N3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Fig. 1. Stage grouping

Correspondence: Dr Lum Wee Heng, Consultant Oncologist, KPJ Damansara Specialist Hospital, 119, Jalan SS20/10, Damansara Utama, 47400 Petaling Jaya, Selangor, Malaysia.
The publication above show pre operation concurrent chemo-radiation improves survival in addition to increasing the chance of sphincter preservation for patient with low lying rectal tumor where an abdominal perineal resection would conventionally be used. The chances of CR (Complete Response) increases with concurrent chemo-irradiation.

### Material and Methods employed in KPJ Damansara Specialist Hospital

From 2011 to 2012 ten (10) patients were referred for concurrent chemo-radiation in view of high chances of abdominal perineal resection for a low lying rectal cancer. All patients underwent endoscopy to assess the tumor with biopsy done. All patients had tissue confirmation of adeno carcinoma. Patients were selected irrespective of age, sex and performance status. Radiological staging was done with CT scan of thorax, abdomen and pelvic. PET/CT was also accepted for radiological staging. All initial staging was based on radiological findings as surgery had not been performed yet. Most patients were scheduled for colonoscopy again at 7-8 weeks with surgery soon after depending on surgeons’ preference. Eight (8) weeks was chosen to give adequate time for maximum response.

All patients received chemotherapy with Oxaliplatin infusion on D1 and D22 with oral Xeloda 1 gram twice a day on the days of radiation. Radiation was given using “3 field technique” with 2 Lateral opposing and one Posterior field.

### DISCUSSION

Out of the ten (10) patients only one failed treatment and had to progress to abdominal perineal resection; the tumor did shrink but not adequately enough for anal sparing surgery. The other nine (9) patients had excellent response but the result was hampered by two patients who defaulted surgery after colonoscopy. The rest of the 7 patient who undergone TME (Total mesorectal resection) showed excellent results, with three having complete response. The advice for chemo was advocated for patient Number 10 even with a complete response as she presented with deep vein thrombosis from the iliac nodes (3cm) with nodal biopsy confirmation of cancer and anorectal carcinoma.

Patients with radiological diagnosis of nodes positive Stage III was not given further chemo unless proven pathologically to be metastasis as nodes enlargement may be reactive and lack of survival or clinical data to support the use of further chemo in good responder.

In KPJ Damansara high rectal, operable and mobile tumor will receive a short course of radiotherapy

---

**Fig. 2. Preoperative radiotherapy or chemo-radiation (with 4 to 5 weeks fraction schedule)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>CR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation alone&lt;br&gt;45Gy (hyperfractionated)</td>
<td>8.5</td>
<td>Bozzetti et al (1999)</td>
</tr>
<tr>
<td>45Gy</td>
<td>4</td>
<td>Ahmad and Nagle (1997)</td>
</tr>
<tr>
<td>36Gy in 12 fraction</td>
<td>4</td>
<td>Corsa et al (1997)</td>
</tr>
<tr>
<td>Radiation +&lt;br&gt;5-FU/FA&lt;br&gt;Daily during Week 1 and 5 (+hyperthermia)</td>
<td>7</td>
<td>Kaminsky-Forrett et al (1998)</td>
</tr>
<tr>
<td>Radiotherapy +&lt;br&gt;MitoC day 1+&lt;br&gt;Infusion 5FU days 1-5</td>
<td>9</td>
<td>Valentini et al (1997)</td>
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<tr>
<td>40Gy</td>
<td>20</td>
<td>Burke et al (1998)</td>
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<td>40-60Gy</td>
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<td>Ch’ang et al (1998)</td>
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<td>50-54Gy</td>
<td>30</td>
<td>Meterissian et al (1994)</td>
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<td>Infusion 5FU</td>
<td>13</td>
<td>Videtic et al (1998)</td>
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<tr>
<td>Infusion 5FU</td>
<td>27</td>
<td>Chari et al (1995)</td>
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**Note:**
- 5FU: Flurouracil
- MitoC: Mitomycin C

**Radiation Field Borders:**
- Superior border – between L5 and S1
- Inferior border – 1 cm below the anus
- Lateral border – 1.5 cm from pelvic brim
- Anterior border – 3 cm from sacral promontory
- Inferior border – cover the whole sacrum

Dose prescription: 45Gy/25 Fraction/5 weeks
Patient Initial Radiological Report Colonoscopy and Biopsy at 7-8 Weeks Post Chemo RT Pathology Report After TME (Total mesorectal excision)

1. Carcinoma of rectum associated with local infiltration to ischiorectal fossa and regional lymphadenopathy No viable tumor seen Small rectal ulcer but one pararectal node was involved, hence surgically AJCC Stage III. Chemotherapy was advised.

2. Carcinoma of rectum. No lymph nodes No carcinoma seen. Non specific inflammation Pt refuse surgery and defaulted.

3. Rectum carcinoma. No evidence of metastasis Reduction in size but still present. Nodal involvement with failure to downstage. Hence abdominal perineal resection performed and chemotherapy advised. AJCC Stage III

4. Rectum carcinoma No mass seen Microscopic focus of Adenocarcinoma. AJCC Stage I

5. Rectum carcinoma with regional lymphadenopathy No mass seen. No residual disease in pathological specimen.

6. Anorectal junction carcinoma with local nodal metastasis and possible vaginal infiltration Ulcer with slough. No mass seen. Pt refuse surgery and defaulted.

7. Carcinoma of rectum No mass seen Microscopic 1mm tumor. AJCC Stage I

8. Carcinoma of rectum Not done Ulcerated Adenocarcinoma. AJCC Stage I

9. Rectal carcinoma with left iliac, presacral and inferior mesenteric nodes Not done No evidence of malignancy.

10. Rectal Ca with 3cm left iliac node metastasis. Not done No evidence of malignancy.

25Gy/5F/5days follow by surgery one week later for increase overall survival and reduction in local recurrence. Long course concurrent chemo-radiation is reserved for low rectal tumor with intention for anal sparing surgery, reduction in local recurrence and increase in overall survival.

CONCLUSION

Our result of concurrent chemo-radiation is comparable with best published results but statistically weaken by low number of patients. Hopefully more surgeons will adopt the above practise for patient benefit.

REFERENCES


A 12 Month Study of Patients’ Complaints at KPJ Tawakkal Specialist Hospital from July 2010 till June 2011

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ABSTRACT

Background: Today, monitoring of patient complaints in healthcare services is being used as a tool for quality assurance systems and in the future development of services. As a result of an increase in the number of informed consumers, complaints regarding the quality of health care have increased extensively (MOH-PBM 2004). This study is done on all in-patient’s complaints or negative feedback processed at the customer service unit at KPJ Tawakkal Specialist Hospital. The negative feedback obtained was analyzed retrospectively for a 12 months study of in-patient’s complaints from July 2010 till June 2011.

Objective: This study aims to investigate the nature and resolutions of patient complaints and further to explore the use of complaints to drive quality improvement.

Study design: A retrospective cross sectional review of 327 inpatient patient’s negative feedback over 12 months from July till December 2010 and January till June 2011.

Conclusion: This study revealed the tendency of hospital to respond to patient complaints in a reactive manner. By comparing the spectrum of inpatient complaints, this study does suggests that some of the types of complaints collected can be used as indicators to improve quality.

INTRODUCTION

Monitoring of patient complaints in healthcare services is being used as a tool for quality assurance systems and as a source of information for development and reengineering of business processes. As a result of an increase in informed consumers, complaints regarding the quality of health care have increased extensively. This study was carried out using inpatient feedback questionnaires distributed by customer service unit to all inpatient from July 2010 till June 2011. All in-patient’s complaints or negative feedback were processed at the customer service unit at KPJ Tawakkal Specialist Hospital (KPJTSH), the negative feedback obtained were analyzed retrospectively in this 12 months study. A total of 246 negative inpatient feedbacks were collected from July till December 2010 whereas a total of 81 negative inpatient feedback were collected from January till June 2011.

This study aims to investigate the nature and resolutions of patient complaints and further explore the use of complaints to drive quality improvement in a selected hospital i.e. KPJ Tawakkal Specialist Hospital. The R&D team analyzed and described these complaints as a collective group. The hospital used these complaints to identify systemic problems and deficiencies to drive business process reengineering and healthcare improvement where remedial action can be undertaken towards enhancing the standard of care and clinical outcomes.

METHOD

A retrospective cross sectional review of 327 inpatient patient’s negative feedback over 12 months from July till December 2010 and January till June 2011.

Setting

A well garnered leading private healthcare provider with KPJ Healthcare branding in Malaysia. Population of patients in KPJ Tawakkal from July till December 2010 and Jan till June 2011 is 170,067 (40,142 inpatients; 128,739 outpatients and 1186 ambulatory care) during which the hospital received total of 8206 (19.8%) inpatient negative feedbacks.

Demographic information and inpatient’s written negative feedback were recorded. 327 cases (3.98%) of negative feedback were received from July till December 2010 and January till June 2011.

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Complaint frequencies were compared between services on its categories of complaints (physical and psychosocial) and the spectrum of causes of the complaints. Researchers had identified complaints regarding medical bills, waiting time, food, environment (cleanliness, noisiness) and facilities categorized into physical factor and psychosocial factor (i.e. courtesy, friendliness and adequacy of communication/explanations).

Definition of Terms

Physical: This term refers to material things. The American Heritage® Dictionary of the English Language, Fourth Edition (2009). In this study physical refer to medical bills, waiting time, food, environment (cleanliness & noisiness) and facilities.

Psychosocial: This term refers to a state of psychological and social behavior. American Heritage® Dictionary of the English Language, Fourth Edition (2009) which in this study psychosocial refers to courtesy, friendliness and adequacy of communication.

RESULTS

Complaints were significantly mainly physical in nature, 287 out of 327 negative feedback (87.8%: physical); 40 cases (12.2%: psychosocial factors.) Table 1 illustrated the finding.

This study revealed that the tendency of hospital to respond to patient complaints in a reactive manner. When comparing the spectrum of inpatient complaints, this study does suggest that some of the types of complaints can be used as indicators to improve quality. The data also suggests to develop a more versatile approach in handling negative feedback as it was noted that most complaints was repetitive and not case-by-case basis hence the negative inpatient feedback can be used to develop a more agile work processes. The study also revealed that complaint handlers were not sufficiently empowered; information sharing was limited within the organization; communication among healthcare provider and with management was inadequate. Moreover, it also became apparent that from this case study the hospital generally responded to patient complaints in a reactive and defensive manner.

DISCUSSION

This study confirmed that patient complaints in healthcare services and facilities are a complex phenomenon resulting from multiple causes. Therefore an in depth study in the future is essential for more effective handling of patient complaints.

Concurrent to this retrospective study, the researchers had also adopted lean improvement methodology i.e. value stream analysis, to ensure more efficient operational flow and clinical improvement. The lean principle of adding value and eliminating waste in KPJTH’s work processes had assisted the researchers to implement solutions by using lean improvement hypothesis, to minimize patient complaints hence increase customer satisfaction. Among the few rapid improvement events that had significantly reduced patient complaints include:

1. “Guarantee Letter (GL) Status Stamp’ on admission forms. This reduces nurses work time to call the admission counter to confirm GL status and admission counter staff time to again check on GL status upon receiving ward enquiries on patient GL status, this resulting in a shorter waiting time in processing medical bills.

2. Fax Core Machine – reduced GL processing time for Finance Department staff to call and re-fax final bills to company and thus shortened waiting time.

<table>
<thead>
<tr>
<th>Table 1 — Types of complaints - Inpatient negative feedback on physical factors</th>
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<td>Medical bills</td>
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<tr>
<td>July-Dec 2010 (n=246)</td>
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<tr>
<td>Jan-June 2011 (n=81)</td>
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<td>Total</td>
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Inpatient negative feedback on physical factors (87.8%) (n= 327)

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<th>Table 2 — Inpatient negative feedback on psychosocial factors</th>
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<tr>
<td>Courtesy</td>
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<td>July-Dec 2010 (n=246)</td>
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<td>Jan-June 2011 (n=81)</td>
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<td>Total</td>
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Inpatient negative feedback on psychosocial factors (12.2%) (n= 327)
3. Patient progress visual board was used to improve standard work, process visibility and effective communication on patient care; to reduce redundancy of work; to reduce time wasted in preparing patients for procedures; to reduce re-work and increase ward process efficiency and increase customer satisfaction thus reducing complaints.

RECOMMENDATION

Complaints are a valuable source of organization learning, useful quality assurance tools and can identify remediable system flaws. A more collective effort from the various services to be involved in reducing or eliminating repetitive complaints is recommended. The researchers propose a structured algorithm of handling complaints by a crisis management team to pre-empt escalating complaints or negative feedback.

The result of the study was utilized when planning interventions for advanced supervision, prevention of adverse events and patient safety. From the patient’s perspective, it is important to create a culture where most problem situations are handled where and when the treatment was provided, thus avoiding a complex complaints process. Hence human capital has identify training modules on handling customer complaints and crisis management to be incorporated in hospital training programs to prepare all staff directly in handling complaints i.e. “Take Charge Program” and Workshop on Handling Hospital Customer Complain.

RESEARCH LIMITATION

The study only took place in one of the KPJ Group of hospitals thus the findings cannot be generalized to the Group. Conclusions drawn are, therefore, intended not necessarily to be extrapolated but rather to provoke reflection about similar complain handling process in other KPJ hospitals.

REFERENCES

Mandibular Actinomycosis: An Unusual Infection

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ABSTRACT
Human actinomycosis is caused primarily by Actinomyces israelii, an anaerobic gram-positive, branched, filamentous bacterium residing as commensal in periodontal pockets and gingival crevices, in carious teeth, dental plaques, tonsillar crypts or in periodontium. In general, Actinomyces species are agents of low pathogenicity and require disruption of the mucosal barrier to cause disease. It is sometimes difficult to diagnose and should be kept in mind in the differential diagnosis of numerous infectious and non-infectious diseases of the oral cavity. Difficulties arise from the fact that it can mimic numerous common conditions in human pathology.

We report a case of cervicofacial actinomycosis of the right mandible in 67-year-old Chinese lady.

Key words: Actinomycosis, mandible, cervicofacial actinomycosis.

INTRODUCTION
Actinomycosis is an infectious disease with a worldwide distribution. It is mostly seen in tropical regions such as Asia, Africa, Central and South America. Human actinomycosis is caused primarily by Actinomyces israelii, an anaerobic gram-positive, branched, filamentous bacterium residing as commensal in periodontal pockets and gingival crevices, in carious teeth, dental plaques, tonsillar crypts or in periodontium. Oral and cervicofacial diseases are commonly associated with dental procedures, trauma, oral surgery, or dental sepsis.¹ Actinomycosis is mostly found in young adults and women are less frequently affected than men.

The diagnosis is established on the basis of the clinical examination confirmed by bacteriological and/or histopathological tests. The condition is considered an important clinical entity, on account not only of the difficulties involved in the diagnosis but also the long-term treatment necessary to eradicate the disease.²

CASE HISTORY
A 67-year old Chinese lady presented with history of pain in the right jaw for 1 month. It was not associated with facial swelling. She denied any history of trauma or dental procedures. Oral cavity examination showed an edentulous jaw with an area of fibrosis with small fistula on the right side. Minimal pus discharge was also noted. There were no neck nodes palpable. Routine blood investigations were normal.

Computed tomography of the mandible showed expansion of the body of the right mandible with a lytic lesion within and a break in the cortex anteriorly (Fig. 1). The lesion was surrounded by soft tissue thickening. She underwent biopsy of the lesion under general anaesthesia. Intra-operatively, there was a widened cavity and bony sequestrum in the right mandible. There was no pus noted. Post-operative recovery was uneventful. Histopathology examination showed colonies of actinomycoses surrounded by dense colonies of actinomycoses.

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Mandibular Actinomycosis: An Unusual Infection

Today because of the widespread use of antibacterial antibiotics for treating minor, unrelated infections.

Actinomyces species that cause human disease do not exist freely in nature but are normal flora of the oropharynx, gastrointestinal tract and female genital tract. They frequently colonize the surface and spaces around teeth and the tonsillar crypts. In general, Actinomyces species, are agents of low pathogenicity and require disruption of the mucosal barrier to cause disease.

Cervicofacial actinomycosis is the most common form of the disease. It is considered to be a specific infection in the orofacial area in which the mandible is more frequently affected than the maxilla. Actinomycotic infection of the bone is usually a result of an adjacent soft tissue infection, but may be associated with trauma (e.g., fracture of the mandible), or it may be hematogenous. The lack of integrity of the oral mucosa resulting from trauma or operative treatment measures may serve as a portal of entry for potential pathogens. After having settled in the tissues, the germ population begins to grow; this may lead to recurring neck abscesses of a rough, stiff, livid-blue consistency or abscesses in the mandible in the form of osteomyelitis. Subsequently, this fibrosis and infection may produce tumor-like masses, which clinically have been mistaken for malignancy. The destructive process can also be severe and disfiguring.

In this present case, the patient denied any clinical history of oromaxillofacial trauma and showed no sign of immunodeficiency. The lack of these risk factors did not help us to make diagnosis.

Computed tomography (CT) and magnetic resonance imaging (MRI) usually yield non-specific findings. They are important to delineate the exact location, extent of the infection and to track spread of the infection. In this case, CT scan of the mandible showed expansion of the body of the right mandible with a lytic lesion within and a break in the cortex which resembled a tumour.

Definitive diagnosis can be established by biopsy and positive culture. Biopsy can be a great help in the diagnosis of actinomycosis because microbiological identification of this organism is often impossible. The biopsy specimen of an actinomycetic infection shows a typical finding of an outer zone of granulation and a central zone of necrosis which contains multiple basophilic granules, that represent lobulated micro-colonies of Actinomyces. Actinomycetic sulfur granules appear in haematoxylin and eosin stained sections as basophilic structures with elongated eosinophilic clubs that radiate from the periphery. Actinomycosis can be differentiated from nocardiosis in which granules consist of acid fast branched bacilli, and botryomycosis containing non-filamentous cocci (bacilli) respectively.

Penicillin in high doses is the treatment of choice. The length of antibiotic administration should not be less than 6 weeks when treating Actinomyces, to guarantee a sufficiently high and long concentration of the medication at the site of the inflammation.
present time, penicillin, clindamycin, and erythromycin are prescribed as effective antimicrobial substances. Surgical intervention is a valuable treatment modality, especially in cases of thoracic and abdominal involvement. Complete recovery is expected in 90% of patients with cervicofacial actinomycosis.11

REFERENCES
Recurrent Sinonasal Inverted Papilloma Presenting with Metachronous Malignancy and Intracranial Extension

Mazita A, MBBCh, MSurg ORL-HNS,1 Primuharsa Putra SHA, MD, MSurg ORL-HNS,2 Zurin AAR, MD, MSurg,3 and Kenali MS, MSurg ORL-HNS4

ABSTRACT
Inverted papilloma is a benign tumor that usually arises from the lateral wall of the nasal cavity. It has the propensity to be locally aggressive and carries a risk of post-removal recurrence. We report an interesting case of a 42-year-old Chinese male with recurrent inverted papilloma with intracranial and orbital extension, and metachronous malignant change who presented 19 years after initial treatment. The tumor was successfully excised via a craniofacial approach. Treatment was completed with adjuvant radiotherapy. He is currently disease-free after 56 months of follow up. KPJ Medical Journal 2013; 5:65–67

Key words : Inverted papilloma, sinonasal papilloma, squamous cell carcinoma.

INTRODUCTION
Inverted papilloma (IP) is a benign sinonasal lesion with a known propensity for recurrence, local aggressiveness, and potential for transformation to squamous cell carcinoma (SCC). Inverted papillomas of the nasal cavity and paranasal sinuses uncommonly invade the orbit (2.7%) or extend intracranially (2%).1 The incidence of malignant change has ranged anywhere between 2 and 27%. In a series of 51 patients, Lesperance and Esclamado2 noted that metachronous carcinoma occurred in 16% and synchronous carcinomas in 11%. The mean interval between the diagnosis of IP and development of SCC was 63 months (range, 6 months to 13 years). In this case, malignant change occurred 19 years after the initial diagnosis. Disease free survival in patients with IP was better in cases limited to the nasal cavity and paranasal sinuses compared to those extending beyond these regions.

CASE HISTORY
A 42-year-old Chinese male presented with a history of right nasal blockage for many years. He had undergone intranasal endoscopic excision of a benign inverted papilloma of the right nasal cavity in 1985. He had been well for almost 19 years following the primary surgery before his symptoms recurred. He underwent a Caldwell-Luc biopsy, which confirmed recurrent inverted papilloma and was referred to our hospital. At the time of presentation, he complained of right nasal blockage associated with blood-stained rhinorrhea, sudden right eye proptosis, diplopia, paresthesia around the right supraorbital and frontal area, and occasional headaches. He denied any vision blurring, nausea, or vomiting. On clinical examination, there was marked right eye proptosis and ophthalmoplegia on extreme gaze in all directions. There was also mild right cheek swelling in the infraorbital region. Rigid nasal endoscopy revealed a fleshy mass arising from the roof and occupying the entire right nasal cavity. Imaging showed opacification of the right ethmoid, frontal, and maxillary sinuses. The mass extended into the superomedial aspect of the orbit and anterior cranial fossa. There was evidence of bony destruction of the medial wall of the maxillary sinus, ethmoid septum, and the anterior wall

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of the frontal sinus (Fig. 1). The tumor was resected via a bicoronal incision with bifrontal craniotomy and extended lateral rhinotomy with medial maxillectomy. Intra-operatively, the tumor involved the ethmoid sinuses and superior turbinate, and extended into the anterior cranial fossa with erosion of the roof of the right orbit and lamina papyracea. However, the periorbita was intact.

The intracranial extension was extradural and the frontal sinus was filled with inspissated mucus. The skull base defect was repaired using a pericranium graft. Histopathology confirmed the diagnosis of inverted papilloma with focal areas of malignant transformation and the presence of mitotic figures. Postoperative recovery was uneventful and the patient underwent adjuvant radiotherapy. He still has diplopia on right lateral gaze and hyposmia. He is currently disease-free after 56 months of follow-up.

DISCUSSION

The principal determinant in tumor recurrence is the method of removal, which is directly related to the completeness of tumor excision, with many recurrent cases actually representing residual disease. In their series, Lawson et al also noted that recurrence often results from failure to obtain a biopsy sample before surgery. Biopsy of accompanying polypoid disease sections and not the tumor proper, or incorrect diagnosis of the biopsy specimen as inflammatory disease, leads to limited and subtotal removal. In cases with a correct diagnosis of neoplasm, inadequate clinical radiographic assessment of tumor extent, or limited intraoperative visualization and access, result in incomplete excision.

Since most recurrences are at the site of previous resection, a more likely explanation for the high rate of relapses is inadequate resection. Carcinomas complicating IP can vary from poorly to well-differentiated tumors. Carcinoma can be associated with IP either at the time the initial lesion is diagnosed (a synchronous lesion) or could appear in an area where an IP was removed earlier (metachronous). Neither the etiology of IP nor the factors responsible for malignant transformation are fully known to date. One theory of malignant transformation is simply the intermingling of two separate primary tumors arising within a bed of metaplastic epithelium. The risk of developing carcinoma in recurrent IP is estimated up to 11%. Intracranial extension of IP is mostly associated with recurrent disease as seen in this case. Extradural disease can be effectively controlled with craniofacial resection and patients had a survival of 86% at 4.4 years average follow-up.

Computed tomography (CT) is the imaging modality of choice to evaluate the degree of involvement by tumor and to determine the extent of surgery. Images will frequently show a unilateral mass in the nasal cavity with extension in the ethmoid or maxillary sinuses. Bony erosion and tumour extension into the orbit or intracranial cavity may indicate a higher chance of associated carcinoma as was described here.

Treatment of IP can range from endoscopic excision to more extensive open approaches depending on the location and extent of disease. In a retrospective study of 160 patients, Lawson et al concluded that IPs that recur after treatment might represent lesions with inherent aggressiveness, the optimal treatment of which is still undetermined. Because of the aggressive nature of IP, the high rate of recurrence, and potential for malignant transformation, total resection with adequate margins has been the standard of care. Recurrence rates after treatment vary among the types of surgical intervention with quotes of 12.8% for endoscopic procedures, 17.0% for lateral rhinotomy with medial maxillectomy, and 34.2% for limited resections such as nasal polypectomy and Caldwell-Luc approaches. However with advanced endoscopic techniques and the use of navigational instruments, recurrence after endoscopic excision accompanying an external approach for extensive disease has comparable low recurrence rate.

In our case, the patient had preoperative features including bony erosions with intracranial and orbital extension that would suggest carcinomatous changes of the IP. Therefore, a multidisciplinary team of an otorhinolaryngology surgeon and neurosurgeon decided on an open approach for optimal surgical access and complete tumor removal especially in cases of extensive recurrent inverted papilloma. This case illustrated that successful surgical treatment was achieved with acceptable postoperative morbidity of olfactory hypofunction. Some authors have shown that, in appropriately selected patients and in expert surgical hands, endoscopic surgical removal of malignant tumors...
Recurrent Sinonasal Inverted Papilloma Presenting with Metachronous Malignancy

has comparable outcomes to standard open surgical procedures.\(^\text{10}\) Postoperative radiotherapy is indicated when papillomas are associated with squamous cell carcinoma. Other considerations for radiotherapy include advanced T stage, high-grade tumors, bony or perineural invasion, intracranial extension, dural or brain involvement and positive surgical margins. Adjuvant chemotherapy is recommended if histopathology results show undifferentiated carcinoma or high-grade sarcomas, which are very unlikely to be associated with inverted papillomas.\(^\text{10}\)

**CONCLUSION**

Craniofacial resection of intracranial extradural recurrent inverted papilloma with malignant features has good outcomes, whereas intracranial intradural involvement has a poor prognosis regardless of treatment. Therefore, preoperative staging of disease is paramount in deciding the surgical approach. Thorough postoperative histopathological diagnosis is important to determine the presence of associated malignant changes and indication for adjuvant radiotherapy. As most recurrences are due to incomplete resection, it is mandatory to schedule close follow-up, with biopsies when indicated. Life-long follow-up is recommended.

**REFERENCES**

Fetus in Fetu

Amran A Rahman,1 Azlin Azizan,1 Sharifah Aishah Al-Edrus,2 and Wan Usamah3

ABSTRACT
A 2-day-old baby had a follow up ultrasound abdomen after being diagnosed as having left hydronephrosis during antenatal scan. The ultrasound abdomen and subsequent imaging with plain radiograph and CT scan confirmed this typical presentation of a rare and benign disease, fetus in fetu. KPJ Medical Journal 2012; 5:68–71

Key word : Fetus in fetu

INTRODUCTION
Meckel first described the rare pathologic entity fetus in fetu in 1800 and only about 90 cases have been reported in the literature.1,2 It is an unusual congenital abnormality in which one vertebrate fetus is enclosed within the body of another normally developing fetus.

CASE REPORT
A two day old baby girl had an ultrasound abdomen after being diagnosed as having a left hydronephrosis during antenatal scan. The baby was born at 38 weeks by elective caesarian section. The birth weight was 3.2kg. She had a full Apgar score during the delivery. She was the second child. There was no history of twins in the family.

On examination, the abdomen was soft and non tender. No obvious mass was felt. Normal bowel sounds were heard. The liver, spleen and both kidneys were not enlarged. Examination of the other systems was unremarkable.

An ultrasound examination showed a large hyperechoic mass in the left lumbar area displacing the ipsilateral kidney. There is a mild left hydronephrosis. The mass had tubular hyperechoic structures and calcifications at its superior aspect (Fig.1). An abdominal radiograph showed large mass with faint calcification at the left lumbar area with displacement of the bowel gas (Fig.2). CT scan of the abdomen and pelvis was subsequently arranged for the patient. This showed a large mass at the left side of abdomen, which was predominantly cystic and well encapsulated. There was presence of vertebra and neurocranium and with the cystic mass resembled a malformed fetus (Fig. 3).

These radiological findings suggested a left retroperitoneal teratoma or a fetus in fetu.

The patient had laparotomy and excision of the mass a few days later (Fig.4). Intra-operatively, the mass was retroperitoneal to the left side of abdomen. It was adherent to the small and large bowels. The mass was well encapsulated. No major blood supply to the mass was noted. The mass weighed about 228 grams.

Fig. 1. Ultrasound examination showed a heterogenous mass at the left lumbar area with echogenic linear structure within the mass.

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Fig. 2. An abdominal radiograph showed a large mass at the left lumbar and umbilical areas with faint calcification within the mass causing peripheral displacement of the loops of bowel.

Fig. 3. MCT scan images in axial plane (A), reconstructed coronal planes (B and C) and MIP (D) showed presence of large mass at the left lumbar area compressing the left kidney posteriorly. Vertebral column and neurocranium can be seen in the mass.

Fig. 4. Gross specimen of the mass taken during the surgery.
The following is a summary of the histo-pathological examination findings:

**Macroscopic:** The specimen consisted of a rounded fetal tissue measuring 8.0 x 7.5 x 6.5cm. Rudimentary digits and limbs were identified. Presence of an eye was noted.

**Histology:** Presence of organoid tissue with epidermis on the surface was noted. The deeper structure contained cartilage, bone tissue and intestinal segment. Most tissues were in immature form. No cellular atypia or evidence of malignancy was seen.

**Conclusion:** Fetus in fetu.

The patient was discharged well one week after surgery. The patient was also healthy at the follow-up clinic a month later.

### DISCUSSION

Fetus in fetu (FIF) is a rare abnormality, which is estimated to occur in 1 in 500,000 deliveries.\(^1\) The exact embryogenesis of FIF is controversial, some investigators believe it occurs from the anomalous embryogenesis in a diamniotic monochorionic twin pregnancy in which a malformed monozygotic twin lies within the body of its fellow twin\(^2\) and others consider it to represent a highly organized teratoma. A teratoma is defined as a neoplasm with slight potential (about 10% for retroperitoneal teratoma) for malignancy that is composed of multiple tissues foreign to the part in which they are located.\(^3\)

All the reported FIF cases were benign except one, which had a recurrence.\(^1,4\) Traditionally the main distinguishing feature has been the 'unequivocal radiographic or dissectional demonstration of part or whole of a vertebral axial skeleton. Diagnosis is reinforced if other appropriately situated bones or organs are shown to be present.\(^5\)

In a literature review, the author listed down the characteristic findings both in the host and the FIF.\(^6\)

The diagnosis of FIF can be made either with plain radiographs, ultrasound and/or CT. MRI has also been used recently in four cases.\(^1\) The CT findings are those of a mass that consist of a round or tubular collection of fat that surround a central bony structure.\(^2\) CT is also helpful in determining the relationship of the mass to the other abdominal structures.

The treatment of FIF is surgery to relieve obstruction, prevent further compression and possible haemorrhage, and aid diagnosis.\(^3\)

In view of the possible malignant transformation highlighted in a case report, the author recommended that AFP and HCG levels are monitored in patients who have had FIF with immaturity at monthly intervals for the first year and at two monthly intervals for the second year.\(^4\) Cross-sectional imaging should also be performed at 3, 6, 12 and 24 months after therapy.

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**Table 1 — Synopsis of Findings in Literature Reports\(^6\)**

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<td>Age at presentation: Usually presents at infancy (3/4), Sometimes older (1/4)</td>
<td>Number: Usually one, rarely multiple, i.e. up to five</td>
</tr>
<tr>
<td>Sex: Equally distributed between boys and girls</td>
<td>Weight: Varies from 13g to 1.8kg</td>
</tr>
<tr>
<td>Presentation and site: Painless mass</td>
<td>Sex: Similar to host</td>
</tr>
<tr>
<td>Abdominal mass</td>
<td>Skeleton: Vertebral column in all (radiological / dissectional)</td>
</tr>
<tr>
<td>• Common - upper retroperitoneum in the right side</td>
<td>Limbs in all cases in various stages of development</td>
</tr>
<tr>
<td>• Rare - upper retroperitoneum left side pelvis, mesentery, mesocolon, liver, adrenal, undescended testis</td>
<td>Other bones such as ribs, pelvis, teeth, mandible and skull</td>
</tr>
<tr>
<td>Extra-abdominal mass</td>
<td>Organs: Heart is absent in all</td>
</tr>
<tr>
<td>• Very rare - intracranial, oral cavity, scrotum</td>
<td>Common organs - brain, intestine</td>
</tr>
<tr>
<td>Skeleton:</td>
<td>Uncommon organs - thyroid, parathyroid, pancreas, spleen, kidney, testis, ovaries, urinary bladder, tongue, salivary glands, lymph nodes, trachea and teeth</td>
</tr>
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INTRODUCTION

Intestinal obstruction accounts for up to 20% of acute surgical hospital admissions. About 80% of intestinal obstruction affects the small bowel. Computed tomography (CT) is now widely used in the initial assessment of acute abdomen, with a high degree of accuracy in the diagnosis of small intestine obstruction (SBO). However, despite its limitations, abdominal x-ray (AXR) remains an important primary modality in the assessment of patients with suspected SBO, especially in the emergency department, because of their widespread availability, fast and low cost. The AXR examination would confirm obstruction, determine and estimate the site of obstruction, and in a smaller number of cases demonstrate the cause of obstruction.

It has been estimated that plain radiographic findings are diagnostic in about 50-60% of cases; equivocal in about 20-30% of cases; and normal, nonspecific, or misleading in 10-20% of cases. This review revisits the typical and atypical AXR features of SBO; and illustrates specific causes of SBO diagnosable on AXR.

FACTORS INFLUENCING THE AXR APPEARANCES IN SBO

The features of SBO on AXR depend on the relative amounts intraluminal air and fluid in the small bowel, which in turn are determined by the onset of obstruction, the site of obstruction, and the grade of obstruction. The typical AXR features of SBO are generally seen with grade or complete obstruction, and when the dilated small bowel loops are predominantly filled with air.

TYPICAL FEATURES OF SBO ON AXR

In supine AXR, the hallmark of SBO include dilated gas-filled loops of small bowel, with outer to outer wall diameter of more than 3cm with thickening of the small bowel mucosal folds or valvulae conniventes. The thickening of the mucosal fold is due to hypertonic contraction of the muscularis mucosa within the valvulae conniventes. The small bowel distal to the obstruction and the large bowel are collapsed. The dilated small bowel loops are more than 3cm in calibre, appear tense and demonstrates thickened valvulae conniventes greater than 3mm and may assume a ‘bent-finger’ configuration (Fig. 1). Multiple dilated small bowel loops may be arranged in a ‘step-ladder’ fashion (Fig. 2).

Differential air-fluid levels referred to as two distinct air fluid interfaces on a horizontal beam AXR that are at different heights but within the same loop. Differential air-fluid levels on erect AXR, have been considered to be a strong evidence SBO. Air-fluid levels are also seen in ileus. However, air-fluid levels, greater than 2.5 cm in width and differing in heights more than 20 mm are suggestive of SBO. Such differential air-fluid levels are seen in approximately 50-65% of SBO, mostly high grade or complete obstruction. The term ‘hair-pin’ loops describes the ‘inverted-U’ configurations of the small bowel loops (Fig. 3).

The small bowel faeces sign is a finding described on CT. It refers to presence of particulate (colonlike) feculent material mingled with gas bubbles in the lumen of dilated loops of small bowel. This abnormality can also be seen in AXR (Fig. 4). The small bowel faeces sign is most often present in the distal small bowel and usually occur in subacute obstruction. The distal end of the small bowel feces indicates the site of obstruction. The reported prevalence is about 8%.

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Fig. 1. Typical of SBO: The supine AXR showed tense dilated loops of jejunum more than 3cm in calibre with thickening of valvulae conniventes, assuming a ‘bent finger’ configuration.

Fig. 2. The ‘step-ladder’ arrangement dilated small bowel loops (arrows).

Fig. 3. Erect AXR showing differential air-fluid levels. Within the loop, the fluid level on left is higher than on the right (arrows). The small bowel loop is referred to as ‘hair pin loop’.

Fig. 4. The small bowel faeces sign. Faecal-like material within dilated small bowel.
FALSE NEGATIVE DIAGNOSIS OF SBO ON AXR

Atypical features may be seen in early, low grade and very proximal SBO, or when the distended small bowel loops are predominantly or completely filled with fluid. The paucity of air may also be due to nasogastric aspiration or vomiting. In these instances, the AXRs may be interpreted as equivocal, normal, nonspecific, or misleading, which may occur in up to 50% of SBOs. Thus the diagnosis of SBO may not be made in these cases.

Definitive AXR abnormalities are usually shown 12 hours after the onset of abdominal symptoms and particularly in high grade obstructions. If the initial AXR is normal, a follow up AXR the following day may show bowel dilatation (Fig. 5). However, further assessment by CT may be employed to facilitate early diagnosis clinical presentation is suggestive.

The number of distended small bowel loops varies according to the site of obstruction, less in proximal than in distal obstructions. In an extreme case, the only abnormality may be an air-fluid level in the fundus (Fig. 6).

With longer duration of obstruction, the distended proximal small bowel may be totally or predominantly filled with fluid. This may be seen in about 6% of SBO. When bowel is completely filled with fluid; the abdomen would appear ‘gasless’ and the fluid-filled bowel loops may demonstrate soft tissue densities mimicking intraabdominal masses; thus the description of ‘gasless abdomen’ and ‘pseudotumour’ signs respectively in the AXR. In a patient with typical clinical presentation of SBO, such appearances necessitate further assessment with ultrasonography (US) or computed tomography (CT) (Fig. 7), to confirm fluid-filled distended small bowel. US is fast and cheap, and presence of fluid-filled dilated small bowel can quickly establish the diagnosis of SBO. CT examination takes time, besides being costly. However, it has the added advantage of detecting the site of obstruction and the specific cause of obstruction in some cases.

When the distended bowel is not completely fluid-filled, the small amounts of air may be trapped in between the valvulae conniventes, shown as ‘string-of-beads’ or ‘string-of-pearls’ sign in the supine or erect positions (Fig. 8) and the ‘stretch’ sign, ‘slit’ sign or ‘coiled-spring’ sign in the supine position. The string of beads describes air fluid levels less than 10mm consecutively arranged. This abnormality is seen about 10-40% of SBO. In the ‘stretch sign’ the intraluminal air assumes a ‘striped’ appearance oriented perpendicular to the long axis of the small bowel (Fig. 9). The coiled-spring sign refers to an array of striped intraluminal air in a longer bowel segment (Fig. 10).

Fig. 5. Early SBO. A) Initial AXR showed normal appearance, B) follow up AXR the following day showed a loop of small bowel distension in the left abdomen (arrow).

Fig. 6. Very proximal SBO. The AXR may be described as normal. Air fluid level is seen in the fundus, (arrow), suggesting gastric distension with fluid.
Fig. 7. SBO with ‘gasless abdomen’ A) AXR showed air-less bowel with suggestion of ‘soft tissue masses’ (arrows). B) US showing small bowel distended with fluid and thickening of the valvulae conniventes. C) Coronal CT confirmed fluid distension of the small bowel.

Fig. 8. The ‘string-of-beads’ sign. A) Erect AXR showing an array of small air pockets in the left abdomen, B) CT of the abdomen demonstrates the air pockets trapped in between the mucosal folds of the fluid distended small bowel.

Fig. 9. A) ‘Stretch’ sign or ‘slit’ sign showing trapped air (arrow) in between the opaque valvulae conniventes, assuming a striped appearance

Fig. 10. The ‘coiled-spring’ sign shown as a longer array of linear air pockets (arrows) in between the valvulae conniventes.
LARGE BOWEL OBSTRUCTION (LBO) MIMICKING SBO

The AXR appearances of LBO depend on the competency of the ileocecal valve, and categorised into Type 1 and 2. In type 1 the ileocecal valve is competent. In type 1A, only the large bowel proximal to the obstruction is air distended, and type 1B, both the large and small bowels proximal to large bowel obstruction are air distended. In Type 2, the ileocecal valve is incompetent; there is retrograde filling of air into the small bowel, resulting in collapse of the large bowel. Consequently, the only abnormality is small bowel air distension, mimicking SBO (Fig. 11).

If in the case of Type 1B LBO, the distended large bowel is completely filled with fluid and not be shown on AXR, the only abnormality would be the air distended small bowel; thus mimicking Type 2 LBO. The colonic fluid would be demonstrable by US or CT, thus correctly categorising it as Type 1B LBO (Fig. 12).

SPECIFIC CAUSES OF SBO

Most SBOs are caused by adhesions, which are not visible on radiologic imaging. In about 20% of SBOs, specific cause can be inferred from the AXR abnormalities. These include external hernia, intussusception, gallstone ileus, and intraluminal foreign bodies (FB).

Fig. 11. Type 2. LBO due to carcinoma of the rectum mimicking signs of SBO. A) supine AXR showing dilated small bowel loops, B) erect AXR demonstrating air fluid levels in the distended small bowel loops. These changes are due to ileocecal valve incompetence.

Fig. 12. Type 1B LBO. A) AXR showed air filed distended small bowel left upper and lower abdomen, suggesting distal SBO, B) CT showed fluid filled distended ascending and transverse colons (C), C) CT showed a tumour in the splenic flexure (arrow).
In assessing AXR with signs of SBO, the inguinal region is routinely surveyed as this may show an obstructed inguinal hernia (Fig. 13).

Small bowel intussusception is commonly seen in children. AXR may be normal in 33%, showing soft tissue mass in 57%, and signs of SBO in 20% of cases. In patients suspected of intussusception, US is now frequently employed primary modality for diagnosis. Typically, US demonstrates concentric ring of soft tissue, described as ‘dough-nut’ sign (Fig. 14).

Gallstone ileus is rare and accounts for about 1% to 3% of SBO. The SBO is due to impaction of one of more gallstones usually larger than 2.5 cm in diameter, with the most site impaction at the ileocecal junction Rigler’s triad of gallstone ileus consists of pneumobilia, SBO and an ectopic gallstone is seen in a minority of cases, approximately 25% (Fig. 15). Two out of 3 signs are considered sufficient to establish the diagnosis of gallstone ileus.13 Uncommonly ingested foreign bodies may be a cause of SBO (Fig. 16).
CLOSED LOOP OBSTRUCTION

In closed loop obstruction, small bowel loop is occluded at two points along its course by a single constrictive lesion. This results in occlusion of both small bowel and mesentery. Most are caused by adhesions, with remaining causes including volvulus and internal or external hernia. A closed-loop caused by adhesion may also be complicated by volvulus. Radiological appearances of closed loop obstruction vary according to the length of small bowel involved, whether or not the affected bowel loop is predominantly air or fluid filled and orientation of the closed loop within the abdomen. A short segment involvement with air filled distension may demonstrate ‘coffee-bean’ appearance (Fig. 17).14 Longer segment involvement may demonstrate multiple loops with ring-like arrangement referred to as the ‘coiled-spring or ‘cochlear’ sign (Fig. 18). When the closed loop is predominantly fluid filled, this may be seen as a soft tissue density or pseudo-mass. In closed loop obstruction, the affected small bowel loops do not show position change in the supine and erect positions of the position; referred to as fixity of bowel loops (Fig. 19).

NON-OBSTRUCTIVE INTRO-ABDOMINAL CONDITION WHICH MAY SHOW ‘ABNORMAL’ INTRALUMINAL AIR COLLECTION AND OR AIR-FLUID LEVELS

Aerophobia is due to excessive and rapid ingestion of air. The small demonstrates round or polyhedral lucencies, are not distended and no mucosal thickening

Fig. 17. Closed loop obstruction. A short bowel loop is involved and is predominantly air-filled, exhibiting the ‘coffee bean’ appearance.

Fig. 18. Closed loop obstruction. Longer segment of small bowel involved, causing multiple loops demonstrating the ‘coiled-spring’ or ‘cochlear’ configuration.

Fig. 19. Fixity of SB loops in the right lower abdomen in closed-loop obstruction. A) Supine AXR showing a cluster of distended small bowel loops in the right lower abdomen, and B) erect AXR demonstrates air-fluid levels in the same location.
(Fig. 20). There is rapid change of bowel air pattern on serial AXRs taken within a short interval.

In ileus the AXR appearances vary. Typically there are multiple uniformly distended segments of bowel including the stomach, small and large bowel. The air filled small bowel loops are less than 3.0cm, do not appear tense, and lacked differential air-fluid level (Fig. 21).

The AXR is normal in most cases of ischemic enteritis. Nonspecific abnormalities include small bowel distension and air fluid levels which may simulate SBO. In ischemic enteritis, the mucosal folds tend to be thicker with associated wall thickening, due to intramural oedema and haemorrhage (Fig. 19). In the appropriate clinical setting, the presence of intramural air would be diagnostic of small bowel infarction (Fig. 22).

Fig. 21. Ileus. A) Supine AXR showing ‘flaccid-looking’, non-distended air filled small bowel loops, B) erect AXR showing lack of differential air fluid levels.

Fig. 22. Ischemic enteritis. A) Supine AXR showing dilated small bowel loops, with thickened folds and walls, B) Supine AXR showing thickened folds in addition to intramural air in the jejunal loop in the left abdomen (arrows).
SUMMARY

AXR remains a cost effective modality in the diagnosis of SBO. About half of patients with clinical symptoms and signs of SBO demonstrate diagnostic AXR abnormalities which include small bowel distension of more than 3cm, thickening of valvulae conniventes of more than 3mm and differential fluid levels, particularly in high grade obstruction. In a patient with typical clinical presentation of SBO and equivocal AXR findings require further assessment by US and CT would help to confirm fluid-filled distended small bowel loops, thus confirming the diagnosis SBO. In a minority of cases, specific causes for SBO by AXR are possible. The Type 1B with fluid distension of the colon and Type 2 LBO mimics AXR findings of SBO. Non-obstructive intra-abdominal conditions which may show 'abnormal' intraluminal air collection and or air-fluid levels which be mistaken for SBO.

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A Review on Novel Approaches in Ocular Drug Delivery

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ABSTRACT
Ocular drug delivery has been a major challenge for scientists due to its unique anatomy and physiology. Ocular drug delivery is hindered by the barriers protecting the eye. The bioavailability of the active drug substance is often the major hurdle to overcome. Conventional ocular dosage forms, including eye drops, are no longer sufficient to combat ocular diseases. This review will discuss the constraints with conventional ocular therapy, various approaches like viscosity enhancers, prodrug, penetration enhancers, ocular inserts, implants, nanoparticles, nanosuspension, microemulsion and gene delivery to improve the ocular bioavailability of drug and provide continuous and controlled release of the drug to the anterior and posterior chamber of the eye. KPJ Medical Journal 2012; 5:81–85

Key words: ocular drug delivery, enhancers, prodrug, inserts, implants, bioavailability

INTRODUCTION
Ocular drug delivery has remained as one of the most challenging tasks for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required site of action. Drug delivery to the eye can be broadly classified into anterior and posterior segments. Conventional systems like eye drops, suspensions and ointments cannot be considered optimal in the treatment of vision threatening ocular diseases. However; more than 90% of the marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the anterior segment eye diseases. Most of the topically applied drugs are washed off from the eye by various mechanisms (lacrimation, tear dilution and tear turnover) resulting in low ocular bioavailability of drugs. Recently many drug efflux pumps have been identified and significant enhancement in ocular drug absorption was achieved following their inhibition or evasion. But prolonged use of such inhibitors may result in undesirable effects. Treatment of posterior segment diseases still remains a herculean task for the drug formulation scientists. The tight junctions of blood retinal barrier (BRB) restrict the entry of systemically administered drugs into the retina. High vitreal drug concentrations are required in the treatment of posterior segment diseases. This can be made possible only with the local administration (intravitreal injections/implants and periocular injections). Periocular injections are associated with fairly high patient compliance as compared to intravitreal injections. Dramatic changes have been observed in the field of ocular drug delivery over a decade. Insight into various membrane transporters/receptors present on the eye opened a new window of opportunities. Especially polar drug molecules, which fail to permeate ocular barriers, can be conveniently delivered via transporter/receptor targeted drug delivery systems.

The main problem in ocular drug delivery system is rapid and extensive elimination of conventional eye drops from the eye, thus resulting in extensive loss of drug. Only a small amount of drug can penetrate the corneal layer and reach to the internal tissue of the eye. The main reasons of drug loss includes lacrymal drainage and drug dilution by tears. This superfluity reduces the bioavailability and lead to unwanted toxicity and side effects.

The following characteristics are required to optimize ocular drug delivery systems; Good corneal penetration; prolonged contact time of drug with corneal tissue; simplicity of instillation and removal; ‘a non-irritative and at ease form’ (the viscous solution should not irritate lacrimation and reflex flashing); and appropriate rheological properties.

Over the last two decades particular attention has been given to the development of sustained and controlled release drug delivery systems. The focus of such systems is on drug localization on site of action so as to minimise the dose frequency while improving the drug effectiveness.

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DELIVERY ROUTES

Conventionally, many ocular diseases are treated with either topical or systemic medications. Topical application of drugs has remained the most preferred method due to ease of administration and low cost. Topical application is useful in the treatment of disorders affecting the anterior segment of the eye.9 Anatomical and physiological barriers hinder drugs from reaching posterior segment of eye mainly at choroid and retina. A major fraction of drug following topical administration is lost by lacrimation, tear dilution, nasolacrimal drainage and tear turnover. Such precorneal losses result in very low ocular bioavailability. Typically, less than 5% of the total administered dose reaches aqueous humor.

So, in order to maintain minimum inhibitory concentrations, the agents need to be frequently dosed resulting in poor patient compliance.10 Upon topical instillation drugs are absorbed either by corneal route (cornea → aqueous humor → intraocular tissues) or non-corneal route (conjunctiva → sclera → choroid/retinal pigment epithelium). The preferred route depends mainly on the corneal permeability of drug molecules.11 Unlike topical administration, systemic dosing helps in the treatment of diseases affecting posterior segment of the eye. A major drawback associated with systemic administration is only 1–2% of administered drug reaches to vitreous cavity. Blood retinal barrier which is selectively permeable to more lipophilic molecules mainly governs the entry of drug molecules into posterior segment of the eye. This result in frequent administration of high amounts of drugs leading to systemic side effects.12 Though topical and systemic routes are convenient, lack of adequate bioavailability and failure to deliver therapeutic amounts of drugs to the retina prompted the vision scientists to search for alternative routes of administration.

APPROACHES TO IMPROVE OCULAR BIOAVAILABILITY VISCOSITY ENHANCERS

Viscosity-increasing polymers are added to ophthalmic drug solutions based on the assumption that an increased vehicle viscosity should result in slower elimination of the dosage form from the precorneal area, and increase precorneal residence time and hence a facilitate greater transcorneal penetration of the drug into the anterior chamber. To achieve higher viscosity various polymers including methylcellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, etc are employed. However studies suggest that this approach has minimal effect in human in terms of increase in bioavailability of ophthalmic dosage form and also excess increase in viscosity will result in patient discomfort.13

PRODRUG

The aim of using prodrug is to enhance corneal drug permeability through modification of the hydrophilicity (or lipophilicity) of the drug. A prodrug is either chemically or enzymatically metabolized to an active compound after corneal penetration. An ideal prodrug should not only have increased lipophilicity and a high partition coefficient, but it must also have high enzyme susceptibility.14 Enzyme systems present in ocular tissues include esterases, ketone reductase, and steroid 6-hydroxylase.15 Prodrug is considered as a new drug entity; so, extensive pharmacokinetic and pharmacologic information is required for proper design. Some examples of suitable prodrug include the antiviral medications ganciclovir and acyclovir. An acyl ester prodrug formulation of ganciclovir, a drug with a relatively low partition coefficient, substantially increased the amount of drug that can penetrate the cornea. This increased permeability is linearly correlated with increased susceptibility of the ganciclovir esters to undergo hydrolysis by esterases in the cornea.14

PENETRATION ENHANCERS

An increase in permeability of the corneal epithelial membrane will maximize the transport characteristics of the drug across the cornea.15,16 The stratified corneal epithelial cell layer is a ‘tight’ ion-transporting tissue, being exhibited by the paracellular pathway. So, one of the approaches used to improve ophthalmic drug bioavailability is to transiently increase the permeability characteristics of the cornea with suitable substances known as penetration enhancers or absorption promoters.

The rate limiting step in corneal absorption of drugs is the transport process from the corneal to the receptor site. Use of penetration enhancers such as cetylpyridinium chloride, ionophore such as lasalocid, benzalkonium chloride, Parabens, Tween 20, saponinsethas been found to increase corneal penetration. These penetration enhancers act by modifying the integrity of the corneal epithelium which results in increased corneal absorption of drugs.17

EFFLUX TRANSPORTERS

ABC (ATP binding cassette) transporters are mainly responsible for efflux of various substrates across plasma membrane and cytoplasm into extracellular fluid. These ABC transporters are broadly classified into two types (a) complete transporter, that contains four units (two nucleotide-binding domains and two membrane bound domains) and (b) half transporter, which possesses only two units (one nucleotide-binding domain and one membrane-bound domain). To attain this action half transporter must attach with another half transporter.
These ABC proteins regulate the transport of various sterols, lipids, endogenous metabolic products and xenobiotics and hence are actively involved in detoxification process. The two multidrug efflux pumps responsible for the development of chemoresistance regulating the transport of various sterols, lipids, endogenous metabolic products and xenobiotics are (a) P-glycoprotein (ABCB1) and (b) multidrug resistant protein (MRP) (ABCC1). P-gp is a 170 kDa membrane bound efflux protein generally expressed on the apical surface of polarized cells. P-glycoprotein is actively involved in the efflux of drug molecules and reduces accumulation of drug inside the cells. It is evident that P-gp is present in conjunctival epithelial cells, ciliary non-pigmented epithelium, human and rabbit cornea, retinal capillary endothelial cells, iris and ciliary muscle cells. Designing drugs that can efficiently evade MRP1 efflux may play an important role in improvement of ocular penetration. Efflux pumps constitute significant barriers to the entry of drug molecules. It is therefore necessary to develop alternative strategies which can improve penetration of the drug through the barriers constituting enhanced drug absorption.

NOVEL OCULAR DRUG DELIVERY SYSTEMS

Colloidal carriers have been widely exploited in the field of drug delivery science. It provides a more selective targeting along with sustained release of molecules at the desired site. Applications of nanotechnology can be very exciting in the treatment of a gamut of diseases affecting the anterior as well as the posterior segment of the eye. An ideal therapy requires selectively targeting of active agent to various diseases like copy number variation (CNV) such as Parkinson’s disease and Alzheimer’s disease, diabetic retinopathy and solid tumors in the eye. The retina does not possess lymphatic system moreover angiogenesis in this part of the eye has similar features to the solid tumor with enhanced permeability and retention (EPR) effects. Delivery of a drug via nanotechnology based product fulfills mainly three objectives viz., (1) enhances drug permeation (2) controls the release of drug (3) targets drug. Focus was given to colloidal systems consisting of micro/nanoparticles, micro/nanoemulsions, nanosuspensions and liposomes. In the last decade, dendrimers, niosomes, and cyclodextrins have also been exploited to achieve optimal drug delivery. Ocular implants have emerged as an alternative to the conventional delivery systems. The role of iontophoresis and ultrasound has also gained momentum in ocular delivery. Encapsulation of drugs in these colloidal carriers can also significantly enhance permeation across the membrane and prevent degradation from the ocular enzymes. Such biodegradable carriers can be developed as an alternative to the implant prepared from nonbiodegradable polymers, which has to be removed surgically after a certain period.

MICROEMULSIONS

Microemulsions are dispersions of water and oil facilitated by a combination of surfactant and co-surfactant in a manner to reduce interfacial tension. These systems are usually characterized by higher thermodynamic stability, small droplet size (~100 nm) and clear appearance. Selection of aqueous phase, organic phase and surfactant/co-surfactant systems are critical parameters which can affect stability of the system. Optimization of these components results in significant improvement in solubility of the drug molecule e.g. indomethacin, chloramphenicol. Apart from solubility, microemulsion systems have also been exploited to improve permeation across the cornea. An oil-in-water system consisting of pilocarpine using lecithin, propylene glycol, PEG 200 as surfactant/co-surfactants, and isopropyl myristate as the oil phase has been designed, which is nonirritating to the rabbit animal model. Such formulations often provide sustained drug release thereby reducing frequency of the drug administration. In case of pilocarpine, microemulsion based system lowers the frequency of administration to two times as compared to four times with conventional eye drops in a day. This was due to enhancement of the permeation by surfactant-co-surfactant combination. Another microemulsion system consisting of pilocarpine hydrochloride was shown to convert in different forms like (liquid crystalline and coarse emulsion) with a change in rheological parameters which changed depending upon change in water content. This results in higher viscosity which will retain the formulation on the cornea resulting in its enhanced effect. Timolol in microemulsion system was laden in a 2-hydroxyethyl methacrylate (HEMA) gels which was studied to modulate its transport across the gel. Though microemulsions have excellent advantages limitations in selection of surfactant/co-surfactant system and potential toxicity associated with higher concentrations of surfactant/co-surfactant often restricts its use.

NANOSUSPENSIONS

This can be defined as sub-micron colloidal system which consists of poorly water-soluble drug, suspended in an appropriate dispersion medium stabilized by surfactants. Nanosuspensions usually consist of colloidal carriers like polymeric resins which are inert in nature. They help in enhancement of drug solubility and thus bioavailability. Unlike microemulsions, they are also popular because of their non irritant nature. Flurbiprofen encapsulated in eudragit RS 100® and RL 100® polymer resins prevents myosis, which might be induced during extracapsular cataract surgery. Charge on the surface of nanoparticles facilitates its adhesion to the cornea. Methylprednisolone acetate (MPA) was encapsulated in a copolymer of ethylacrylate, methyl-methacrylate and chlorotrimethyl-ammonioethyl methacrylate) and
examined for its effect on the anti-inflammatory symptoms in rabbits with endotoxin-induced uveitis (EIU).\(^{30}\) Nanosuspensions also impart stability to the drug in the formulation. Cloricromene (AD6) was formulated in nanosuspensions by using eudragit RS100 and RL100. AD6-loaded eudragit retarded nanoparticle suspension offered a significant edge in enhancing the shelf life and bioavailability of the drug following ophthalmic application.

**NANOPARTICLES**

These are polymeric colloidal particles, ranging from 10 nm to 1 mm, in which the drug is dissolved, entrapped, encapsulated, or adsorbed. Encapsulation of the drug leads to stabilization of the drug. They represent promising drug carriers for ophthalmic application. They are further classified into nanospheres (small capsules with a central cavity surrounded by a polymeric membrane) or nanocapsules (solid matricial spheres). It is reported that the nanocapsules show a better effect than the nanospheres, probably because the drug (betaxolol, carteolol) is in a unionized form in the oily core and can diffuse at a greater rate into the cornea.\(^{31}\) Several authors suggest that the better efficiency of nanocapsules is due to their bioadhesive properties, resulting in an increase in the residence time and biological response.\(^{32}\) Hence, it improved the ocular bioavailability of the drug and reduced dosing frequency.

**INTRAOCULAR IMPLANTS**

Implants have been widely employed to extend the release in ocular fluids and tissues particularly in the posterior segment. Implants can be broadly classified into two categories based on their degradation property (1) biodegradable and (2) non-biodegradable. With implants, the delivery rate could be modulated by varying polymer composition. Implants can be in the form of solid, semi-solid or particulate based delivery systems.\(^{33}\) These implants have been applied in the treatment of diseases affecting both anterior and posterior segments of the eye. The diseases include anterior segment disorders like glaucoma filtering surgery and posterior segment disorders like proliferative vitreoretinopathy, CMV retinitis, endophthalmitis, and posterior capsule opacification.

**GENE DELIVERY**

Recently, various strategies have been adopted to deliver nucleic acids to a specific site within the eye. Designing delivery system for antisense oligodeoxynucleotides (ODN), aptamers or siRNA (small interfering RNA) is a challenging task for researchers in ocular delivery field because of high molecular weight, size, surface charge, solubility of the active drug and intrinsic complexities associated with the structure of ocular tissues like retina and cornea. Recently, FDA has approved Vitravene\(^{\text{®}}\), an ODNs for the treatment of CMV in AIDS patients and Macugen\(^{\text{®}}\) (pegaptanib sodium injection) which is an aptamer for the treatment of “wet” AMD.\(^{34}\) Non viral vectors have gained wide acceptance in gene delivery because of their ability to overcome disadvantages of viral vectors such as immunogenicity, safety and potential persistence in the brain.\(^{35}\) A major challenge associated with current system is its inability to achieve higher transfection efficiency. “Naked” DNA, physical vectorisation of the genetic material and chemical methods are three main modes of delivery among nonviral gene therapy.

**CONCLUSION**

Effective treatment of ocular diseases is a formidable challenge for scientists in the field especially because of the nature of diseases and presence of the ocular barriers especially in posterior ocular segments. An ideal therapy should maintain effective levels of drug for the longer duration following a single application. Drug delivery by topical and intravitreal routes cannot be considered safe, effective and patient friendly. Transporter targeted delivery can be a promising strategy for many drug molecules. Colloidal carriers can substantially improve the current therapy and may emerge as an alternative following their periocular administration. A clear understanding of the complexities associated with tissues in normal and pathological conditions, physiological barriers and multicompartmental pharmacokinetics would greatly hasten further development in the field.

**FUTURE CONSIDERATIONS**

In future, much of the emphasis will be given to achieve noninvasive sustained drug release for eye disorders in both segments. A clear understanding of the complexities associated with tissues in normal and pathological conditions, physiological barriers, and multicompartmental pharmacokinetics would greatly hasten further development in the field.

An ideal system should be able to achieve an effective drug concentration at the target tissue for an extended period of time, while minimizing systemic exposure. In addition, the system should be both comfortable and easy to use. Patient acceptance will continue to be emphasized in the design of future ophthalmic drug delivery systems. A reasonable strategy to circumvent the drawbacks of individual technologies is to combine technologies.
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Pharmacogenetics of Phase II Metabolizing Enzyme - UDP-glucuronosyltransferase (UGT) 1A6 in the Treatment of Epilepsy with Sodium Valproate: A Brief Review

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ABSTRACT
Epilepsy is a common serious and treatable neurological disorder, yet current treatment is limited by high rates of adverse drug reactions and lack of complete seizure control in a significant proportion of patients. Among anti epileptic drugs (AEDs), sodium valproate is considered to be a broad spectrum AED, effective against all type of seizures and an adverse event profile that differs from other AEDs. Major pathways of valproate metabolism include glucuronidation by UGTs, mitochondrial ß-oxidation and a minor cytochrome P450-dependent oxidation pathway. UGT1A6 (R184S, T181S) missense polymorphism in exon 1 exhibits remarkable interindividual differences in the glucuronidation pathway of valproate altering the metabolite, responsible for the efficacy and adverse drug events. The clinical relevance of these polymorphisms is not yet fully explored, though they are expected to be key in fulfilling the ultimate goal of individualized dosing of sodium valporate in epileptic patients showing toxicity. KPJ Medical Journal 2012; 5:86–88

Key words : Pharmacogenetics, UDP-glucuronosyltransferase, sodium valproate, epilepsy

INTRODUCTION
Pharmacogenetics encompasses the principle of testing for how genetic variation among individuals affects variation in response to medicine, both in terms of efficacy and adverse drug reactions. It provides the ability to identify potential adverse drug reactions or lack of effectiveness of a drug before administration. Differences in treatment outcomes for epilepsy disorders are seen in patients with apparently identical diagnosis and treatment. These differences have been examined biochemically from drug concentrations in serum to assess the distribution of metabolites from individual drugs, which can guide some treatment. The treatment of epilepsy offers a model opportunity for the application of pharmacogenetics into clinical practice in view of the high prevalence of this disorder, the wide variety of individual responses to antiepileptic drugs, the readily quantified outcomes of seizure control, and the availability of validated scales to classify both seizures and adverse effects.1 The effect of genetic polymorphisms on the metabolism of drugs is significant. Many of the drug-metabolizing enzymes have well-characterized functional variants. This variable rate of metabolism alters serum drug and metabolite concentrations, and the clinical effect of this is dependent on the activity and toxic effects of the drug and its metabolites, and in particular the size of the difference between a therapeutic and a toxic dose.

Sodium valproate in epilepsy treatment
Valproic acid (VPA) is a broad-spectrum AED that has been used for more than 30 years and is effective in the treatment of many different types of partial and generalized epileptic seizure. VPA has fewer common side effects than do other AEDs, especially on behavior and cognitive functions. Moreover, its adverse effects can often be minimized by initiating the drug slowly. However, rare serious complications may occur in some patients receiving VPA chronically, including fatal haemorrhagic pancreatitis, bone marrow suppression, VPA-induced hepatotoxicity (VHT) and VPA-induced hyperammonaemic encephalopathy (VHE).2 Therapeutic daily doses range from 1 to 2 g in adults, and from 15 to 60 mg/kg in children. Peak plasma concentrations occur only 4–5 hours hours after ingestion of therapeutic doses of enteric-coated tablets. Peak plasma concentrations may be markedly delayed following acute overdose. Therapeutic serum concentrations range from 50 to 125 μg/ml. The relationship between dose and plasma concentration is nonlinear. Most of the iso-forms involved in valproic acid metabolism are polymorphic, so far, no studies have correlated relevant cytochrome
polymorphs (CYP), genotypes in patients receiving valproic acid with drug blood levels or clinical response; however, given that CYP-mediated oxidation is a relatively minor metabolic pathway for valproic acid, it is not likely that CYP polymorphisms exert major effects on individual differences in responsiveness. With respect to conjugation, the other major metabolic pathway for valproic acid, in vitro data support the possibility that polymorphism of UDP-glucuronyltransferase (UGT) 1A6 influences the kinetics of VPA metabolism. Further study of UGT variation is required to confirm these effects.

Genetic influences in epilepsy: relationship to pharmacogenetics

A large body of evidence now supports the concept that epilepsy may be caused by gene defects and that even the most common forms of epilepsy can be influenced by common allelic variants of specific genes. Thus, numerous genes have been implicated in human epilepsy and they have been the subject of several recent reviews. Examination of the list of known epilepsy-causing genes reveals that many of them encode sodium channel, calcium channel, and gamma-aminobutyric acid (GABA) receptor subunits. Given that these proteins are also targets of antiepileptic drugs, it is possible that disease susceptibility mutations themselves may impact drug binding and therapeutic activity. Therefore, in prioritizing candidate genes for pharmacogenetic studies of antiepileptic drugs, consideration must be given to the potential impact of gene variation that is associated with disease per se. It is possible that the same variation could simultaneously predispose patients to seizures and render them refractory to drug treatment. Teasing apart such differences is one of the challenges of pharmacogenetic research.

Candidate gene approach

In pharmacogenetics, a particularly strong case can be made for candidate gene approaches because the likely modes drug action are usually known or suspected, at least partially. Therefore drug targets make obvious candidate genes and clearly deserve careful evaluation. More over 80 % of genetic variants identified by pharmacogenetics reside in the three major categories for pharmacogenetic candidates: drug targets, drug metabolizing enzymes, and drug transporters. For epilepsy pharmacogenetics, a set of high – priority candidate genes are readily identified on basis of pharmacokinetics and mode of action.

UGT genetic variation

UDP-glucuronosyltransferase (UGT), the microsomal enzyme responsible for glucuronidation reactions, exists as a superfamily of enzymes. Genetic polymorphism has been described for 6 of the 16 functional human UGT genes characterized to date, namely UGT 1A1, 1A6, 1A7, 2B4, 2B7 and 2B15. Given the substrate profile of UGT, genetic polymorphisms of UGT isoforms are potentially of toxicological, pharmacological and physiological significance. However, while genetic polymorphism of numerous UGT isoforms has been reported, in most instances functional significance is unclear for a number of reasons; isoform substrate specificity remains poorly defined, isoforms may exhibit overlapping substrate specificity, and the domains of UGT proteins responsible for substrate binding have not been identified.

UGT1A6

UDP glucuronosyltransferase (UGT) 1A6 is a major UGT isoform in human liver that catalyzes glucuronidation of a diverse range of drugs, carcinogens and endogenous substrates. UGT1A6 gene is highly polymorphic and contains at least three common coding single nucleotide polymorphisms (cSNPs) including S7A, T181A, and R184S. Two missense mutations in exon 1 of UGT1A6 result in Thr181Ala and Arg184Ser substitutions exhibiting remarkable interindividual differences in the glucuronidation pathway of valproate altering the metabolite, responsible for the efficacy and adverse drug events.

The mutations are normally linked on one allele (UGT1A6*2), although the single mutation Arg184Ser allele has been identified. Reported frequency of UGT1A6*2 and the single mutation allele (i.e. Arg184Ser) range from 17-29% and 0.5-2% respectively. Linkage disequilibrium has been proposed for UGT1A6*2 and the mutations in the UGT1A1 promoter region based on over expression of individuals in the same population homozygous for both mutant alleles. Two missense mutations leading to T181A (541A>G) and R184S (552A>C) have been identified in the UGT1A6 gene. The mutations have been detected on a single allele (UGT1A6*2) at a frequency of 30% in a Caucasian population and a second variant allele containing only the R184S change was reported to occur at a frequency of 2% in the same population.

CONCLUSION

Pharmacogenetics of UGTs and their impact on pharmacological or toxicological drug effects is a particularly active area of research and could be useful for risk prediction. Currently numerous variant forms of various UGTs have been reported and new polymorphisms are steadily identified. It can be assumed that a combination of genotyping and phenotyping may be an appropriate tool in the future to optimize the therapy with drugs which are subject to glucuronidation.
Despite the complex pharmacological behavior of sodium valporate pre-therapeutic screening helps us to identify patients with a higher chance of therapy-induced toxicities. Besides identifying patients with higher risk on therapy-induced adverse effects, the implementation of pharmacogenetic-based dosing should also result in the intensification of dosing regimens for fast metabolizers, enlarging their chance of a favorable therapeutic effect. The prospect of predicting drug response, and therefore directing treatment, on the basis of individual genotype, promises significant health and quality-of-life benefits to patients. Additionally, it has potential to advance the science of epilepsy with improved understanding of the complex pathophysiology of this group of disorders. The development of the pharmacogenetic approach to epilepsy treatment may also provide substantial advantages in time and cost savings for both patients and communities by reducing patient–doctor contact time, seizure-related morbidity, drug side effects, medication alterations, and polypharmacy. The choice of appropriate medication for an individual could be influenced by use of a single, simple DNA test. Although the cost-effectiveness of introducing pharmacogenetics into clinical practice has been debated, the diminishing costs of DNA typing suggest that a pharmacogenetic approach is affordable. The potential advantages of pharmacogenetics offer a revolutionary approach to clinical practice and the treatment of epilepsy. The realisation of these potentials will need close liaison between clinicians and scientists to coordinate sound research design and implementation.

REFERENCES

Promoting the Health of Senior Citizens

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ABSTRACT
Promoting the health of ‘senior citizens’ is the responsibility and duty of every single human on earth as every single one of us have ‘senior citizens’ among our family members and relations. Moreover almost every one of us will be a ‘senior citizen’ in our lifetime and improving the health of elderly people is in the best interest of every living individual. People are more aware of health issues now compared to the ‘older days’ and know that they need to go for regular check-ups. They also try to maintain a positive outlook on life and are more open to change which is constantly taking place around them as they know that ‘change is the law of life’.

Nurses need to change their attitudes towards older patients whereby they need to understand that attention should not only be given to the physical care of older people but also to their feelings as what many people fail to understand is that the hurt or dejected feelings of these people can result in deteriorating health issues and health conditions that do not seem to be improving.

One needs to take time to understand what is it that ails them and try to rectify the matter or at least listen to them so that they can pour out their woes and by emptying their hearts and filling them with more positive and inspiring issues, they will naturally be more healthy as we all know that the mind is the root of all illness.

Nurses with the correct knowledge, skills and understanding about healthcare can help to improve and promote health among the senior citizens who are also our mentors and role models and have helped to pave the way for us to follow so that we have a smoother journey and a better future. KPJ Medical Journal 2012; 5:89–92

Older people are known as the ‘senior citizens’ of a country. As they have lived longer, they naturally would have more experience than the younger generation. Thus, it would only be wise to sustain, maintain and if possible promote their health so that this source of experience can continue to inspire the youth and the future generation with their knowledge and wisdom and, with some luck, also warn them against any impending dangers or undertaking any unnecessary risks which could bring harm or injury to oneself, others, the country or the world at large.

HEALTH PROMOTION AND MAINTENANCE
Promoting a healthy lifestyle and maintaining the good health of older people is easier now than before as older people in the present time, in towns and cities, are more concerned about their health and well-being. They have more knowledge about the risks of smoking and drinking heavily as they are quite literate now and read more, and many of them are also aware that they need to constantly maintain a positive outlook on life if they are to be healthy, wealthy and wise. Quite a number of them have access to the internet and most of them, in Malaysia, have televisions in their homes, whereby they are given information about the signs and symptoms of a large number of diseases, common or rare. Many of the older people in the present times get annual health screenings done and also get themselves examined as soon as they feel unhealthy or feel that they have contracted some form of illness.

Older people in the rural areas however, are financially poorer, and may not have access to all the information on health and even if they were informed by the local health clinics, it would usually be in an abrupt manner and in a language that they would most probably not have understood, mostly using medical terminologies. Medical camps are, sometimes, conducted in these areas, usually through private funding, whereby, a few doctors and some medical personnel take time off and give medical services and
free drugs to these people since these senior citizens can not afford to take time off from their work in farms, paddy fields, etc, as they would be living on meagre, daily earnings.

Older people from the rural areas do not think it is necessary to take care of themselves or live a healthy lifestyle and only think of feeding and clothing their large family. They have just enough time and money to raise their children and that would be their sole duty and purpose in life. When they fall sick, and usually, by that time, their children would have grown up, they tend to think that their ‘time is up’ and only think of going back to the ‘Creator’ and not about getting themselves cured.

“For many people growing old has come to represent a period of increasing illness and dependency, as they lose physical strength, stamina and suppleness and are burdened by the symptoms and effects of chronic degenerative disease.”¹

These older people, especially in more remote areas, need to be informed of the importance of taking care of their health, physically, mentally and socially, and that by doing so they can lead a more fruitful and satisfying life. Healthcare providers should be aware of the needs of older people and how to communicate with them so as to effectively provide information and services to them. As McMurray states, “since older people use healthcare services more then people of any other age groups, knowing the implications of ageing would greatly help in giving them the right type of services.”²

Effective health promotion activities will result in older people having better knowledge about their physical body, they are then able to detect at least some physical or mental abnormalities in themselves, have knowledge about the safe use of medications, know where and how to get to the nearest health care centre, and have access to information on health matters which may help them lead somewhat healthy lives.

Resources need to be set aside for these health promotion activities. Certain policies or health practices may greatly affect the type or degree of health promotion that can be conducted in a particular country or state. Meeting with some of the older people and knowing what their fears and needs are may help in providing the necessary and right types of aid or assistance. Most importantly, we need to make sure that most, if not all, the older people in the country, especially the needy, are involved in the activities and receive the benefits of the health promotion activities conducted, and not just a chosen few or some scattered groups in the country.

ATTITUDES TO AGEING

The general attitude towards ageing and the aged is negative and society prefers not to spend ‘unnecessary’ time and resources on them. They would rather spend it on more ‘useful or productive people’ such as the youth or younger people, as they are the generation who supposedly would be contributing, and the older generation are seen as more of a ‘burden’ to the country and will not be contributing anything for the future of the country. People with this type of attitude have forgotten that the older generation has hoards of experience and wisdom which can help mankind not make the same disastrous mistakes they have made before and maybe save themselves and the world from further catastrophes. Quite a number of older people have also contributed tremendously to the success of most of the countries and the world at large.

Nurses too, on the whole, feel less inclined to work with older people. According to Courtney, gerontology nursing is not very much favored by nurses and most of them are not interested to continue their studies in this field.³ Most healthcare providers, including nurses, feel that taking care of older people means ‘getting stuck’ at their bedside and caring for their physical needs, for instance, cleaning and feeding them. They usually find this kind of work to be very routine, boring and not at all challenging. Lack of staff, in the hospital and residential care setting, makes health education and teaching older people to be more independent, almost impossible, and in due course, the older people will grow to depend a great deal on the available health personnel. Conducting health promotion activities for the aged, especially in the rural areas, does not usually draw a big crowd of health personnel and the aged in the rural areas are the least provided for and are usually quite a neglected group of people.

People need help and support as they age and especially when they are ill. Usually, nurses are the main healthcare providers called upon to be of assistance to them and to nurse them during their illness. To be able to nurse older people well and effectively, one has to talk to them and understand their feelings and their needs and not just fulfill their physical needs, such as cleaning and feeding them. Nurses need to be given the necessary education so as to be able to give the right type of care for these special people. Nurses with positive attitudes towards the aged would also greatly help in increasing the quality of care given to older people.

“Knowledge about ageing and attitudes towards older patients may be related to and significantly influence the quality of care.”³

AGED RELATED CHANGES AND ADAPTATION

Older people go through a lot of changes, mostly physical changes and some social changes. These social changes are mostly related to feelings of sadness or loss and could not be avoided such as death of close ones, for instance husbands; changes such as retirement; changes due to loss of income; changes caused by the death of close friends of almost the same age and also changes
due to chronic illnesses or diseases such as hypertension, diabetes and cardiac problems. Unexpected or negative events within a short period of time, can also take a toll on the mental health of an older person. Moreover older people find it harder to handle events or issues which occur when it is least expected. Day to day events prove to be a bigger problem for the older people to handle then actual major events. Financial instability can also be very stressful for people as they age because they do not receive a fixed or steady income, especially if they have retired or lost their husbands.

It has been noted that people adapt better to changes when their self-esteem is raised because they are generally happier, healthier and more self-confident and able to handle problems or stress better then those with low self-esteem. Nurses’ attitudes can increase or decrease the self-esteem of older people in their care. The self-esteem of these people can be raised by communicating positively with them, both verbally and non-verbally.

“Thus, to enhance self-esteem in older adults, nursing interventions must address the many threats to self-esteem that are within the scope of nursing care.”

When one gets old, one goes through changes physically, and one's senses deteriorate. One also goes through some psychological changes, for example becoming more sensitive, easily hurt, often depressed, fear for one's health as well as fear of falling ill. One also becomes more forgetful and is not able to learn or new information quickly. Nurses who look after older people need to promote their well-being by first being patient with them and understanding them and their physical, mental and emotional changes. Nurses need to look out for these patients as these changes can make them more vulnerable to injuries. Eliopoulos feels that nurses who want to effectively care for older people should first have a clear understanding of the changes they go through when they age.

Older people need to be involved in physical exercises and also be praised for all their past and present achievements. They need to be encouraged to participate in positive, social interactions and group discussions to discuss their health issues as well as their fears and, they should also be allowed to make decisions about themselves and their health on their own.

HEALTH TEACHING AND EDUCATION

Promoting health for older people does not mean just looking after patients or older people who are ill. It means promoting well-being by giving health education to these people. It is the duty of the nurses in the aged care facilities, hospitals or medical camps to motivate or promote health care to the older people there by passing knowledge and information to them but, then again, it is also their right to decide if they want to use the information or not. Usually the older people do not understand the health education given to them as it is not explained to them in a manner or way that they would be able to understand.

Health education is given to older people so as to prevent illness, to maintain as well as promote their health. It can also be given so as to cure illness at the early stages and also to reduce the effects of illnesses. Sometimes old people can not hear or see well and that is why they can not look after themselves and sometimes are also unable to understand the health education given to them. The best results of these health education interventions can be achieved by talking and discussing care needs with the older people, knowing their needs as well as their goals and letting them know that they can also participate in deciding on the form of healthcare that they want.

“There is a need to focus on health education that meets the needs of older people in order to promote their health, independence and quality of life.”

Talks on healthy lifestyles; the complications of buying medication over the counter; incontinence of urine, which is a major problem for older people and can lead to skin tears, bedsores and lowered self-esteem; talks on other health issues and counseling carried out at hospitals, health care centers and medical camps can generally help to enlighten older people on the physical changes their bodies will undergo and the problems or issues they are facing at the present moment and would be facing as they continue to age and the ways and means to overcome it.

Education in personal health is very important if older people are to be able to take care of themselves and maintain their health. Sometimes healthcare has to be brought to these people, to their areas of stay and at times these people need to be taken to the healthcare centers. A safe environment, healthy lifestyle, healthy food and keeping physically fit by exercising can promote and maintain the good health of older people.

Older people need information on how and when to take medications, when to see the doctor, what to ask the doctors and what information they need to give the doctors. In this way, they would be taking active steps to improve the condition of their health and would be more interested to live a life of quality and not get depressed with the changes that come with age.

Health education can be given to the older people on nutrition; on safety, such as preventing falls, etc; on access to health services, be it for ordinary medical check-ups or during emergency situation, and, in short, about healthy ageing. Nurses and other healthcare providers need to provide the right and necessary information to the older people and let them know why they need to use this information. Older people should be made to feel comfortable about listening and asking
any questions they may have. Having access to the correct information, they than have the option and right to decide on how and if they want to use the information they have. As Ballantyne states, “older people should be given health education just like other people so that they can take care of themselves.”

Older people should get together and discuss their health and social problems with each other as well as participate in their own healthcare and in this way they can also motivate some of the other older people who are not so motivated so that they too can upgrade their health and their life as well.

THE ROLE OF THE NURSE

An increase in the older client group has made it necessary for nurses to have more knowledge and professional training in caring for older people holistically and not just their physical needs. Nurses, who care for the aged need to manage their place of residence, assess their needs, plan and deliver care and reassess care outcomes to see if changes are necessary to the type of care given.

Nurses need to understand that some of these older people can already function quite well on their own and usually just need some assistance in leading a more healthy and satisfying life. They need a listening ear, some tender loving care and minimal help so that they can have some form of control over their lives. Quality of life could be achieved if older people could maintain somewhat normal bodily. By improving the quality of life and functional independence of older people, most of the chronic diseases can be avoided or at least delayed. Armed with a lot of correct health information, older people can then take charge of their lives with confidence.

Nurses can also contribute to the rehabilitation of older people by restoring the maximum level of function possible of a certain limb or the whole body, so that they are able to live as independently as possible with the handicap or the condition. Rehabilitation is, “trying to restore and maintain the maximum level of normal condition and health as possible.”

Nurses, in a loving way, in ways only nurses are capable of, need to also take care of older people who receive palliative care. He/She needs to attend to them carefully as they are in the last stage of their fragile, precious lives, and try to make the last days of their life as clean and peaceful, and if possible, meaningful as possible so that they can spend their time remembering and recollecting all the good, sweet times they have had throughout their lives and also, so that they can spend the remaining time they have in prayer and thoughts of the Almighty.

“What residents of aged care facilities need when they are declining towards the end of life is holistic care that is competent, coordinated and compassionate.”

REFERENCES

HISTORY

A 43 year old ethnic Chinese female presented with cough and progressive breathlessness of several years’ duration. Chest x-ray showed changes suggestive of chronic obstructive pulmonary disease (COPD).

DISCUSSION

Bronchiolectasis is dilatation of bronchioles and can occur due to obstructive airway diseases, or as a consequence of lung fibrosis. In chronic airway disease, bronchiolectasis is often seen in association with bronchiectasis. Bronchiolectasis is particularly frequent in patients with cystic fibrosis, an inherited disorder common among Caucasians, mostly affecting infants, children and young adults; and in diffuse panbronchiolitis, an acquired progressive obstructive lung disease mostly seen in ethnic East Asians.

On chest radiograph, the characteristic findings include overinflation associated with small nodular opacities. Ring-shaped and tramline-shaped opacities may also be seen representing dilated distal bronchi and bronchioles.

HRCT would showcentrilobular nodules, tree-in-bud opacities, bronchiolectasis and bronchiectasis. There may also be areas of decreased lung attenuation with air trapping, due to narrowing of the bronchiolar lumen.

FURTHER READING

Images in Diagnosis: Lymphangiomyomatosis

Mandalam KR, MD

HISTORY

A 22 year old female subject presented with a history of progressive dyspnoea. A plain chest x-ray showed a right pneumothorax with reticulonodular shadows in both lungs. HRCT of lungs was done.

Two frames from the coronal reconstruction series are shown below.

HRCT Scan of chest shows bilateral pneumothorax, more severe on right side. Multiple thin-walled air-containing cysts were seen in both lungs interspersed with areas of normal lung tissue. Pulmonary vessels were normal.

DISCUSSION

Pulmonary Lymphangiomyomatosis (LAM), is a rare disease that occurs mostly in women of child-bearing age. Patients present with progressive dyspnoea and a majority develop pleural effusions, and pneumothorax. Mortality is inevitable, with most patients dying within 10 years of the onset of symptoms. Improved prognosis has been reported following treatment with progesterone or oophorectomy.

LAM is characterized by progressive proliferation of spindle cells, resembling immature smooth muscle, in the lung parenchyma along the bronchioles that leads to air trapping and the development of thin-walled cysts. Cyst rupture causes pneumothorax. The spindle cell proliferation can also involve the hilar, mediastinal and extrathoracic lymph nodes, sometimes resulting in dilatation of intrapulmonary lymphatics. Rupture of the lymphatics can cause chyloous pleural effusion.

On plain x-rays LAM may show reticulonodular and honeycomb patterns as well as emphysematous changes. On HRCT, both lungs will show numerous thin-walled lung cysts, surrounded by relatively normal lung parenchyma. Cysts are usually 5 to 10 mm in diameter, but can be larger. The cysts are distributed in all zones and all lobes without sparing of any part of the lungs. Interlobular septal thickening and patchy areas of ground glass opacity may also be seen. Other features of LAM include hilar and mediastinal lymphadenopathy and pleural effusion.

Differential diagnosis of cystic diseases of the lung parenchyma include Langerhans histiocytosis and lymphocytic interstitial pneumonia.

FURTHER READING


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Images in Diagnosis: Caroli Disease

Mandalam KR, MD

HISTORY

A 27 year old male patient presented with fever, abdominal pain and jaundice. A sonogram revealed dilated intra-hepatic ducts containing multiple calculi.

Axial and coronal MRI scan images are presented:

DISCUSSION

Caroli Disease is a rare inherited disorder characterized by cystic dilatation of intrahepatic bile ducts. The disease is seen in two forms, the simple form where the bile ducts are widened by ectasia and the more complex form also known as Caroli Syndrome that is associated with portal hypertension and congenital hepatic fibrosis. Caroli disease may also be associated with polycystic kidney disease.

Radiological diagnosis is made on basis of ultrasound CT scan and now more frequently by MRI scan and MRCP. The characteristic appearance of saccular dilatations communicating with the biliary ducts and containing calculi and demonstration of the central dot or streak sign –portal vein branches surrounded by the dilated biliary ducts confirms the diagnosis.

The clinical course of the disease is progressive, characterized by recurrent attacks of cholangitis leading to cirrhosis and hepatic failure. Cholangiocarcinoma is another dreaded complication. The disease may be localized to one lobe, commonly the left lobe, making it amenable to surgical resection. In the more diffuse form liver transplantation may be considered as a long-term therapeutic option.

FURTHER READING


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