

PAIN SYMPTOMS IN DEPRESSED OUTPATIENTS

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Introduction: Major depressive disorder is an important health problem and a major cause of disability worldwide. There is a strong association between depression and pain, which is influenced by various biological and psychosocial mechanisms. The combination of chronic pain and depression is associated with high rate of disability, socio-economic disadvantage, greater utilization of health care resources, as well as a considerable mortality rate.

Objectives: The study was conducted with the objectives of determining the proportion of adult depressed patients who attended the psychiatric clinic with pain symptoms and assessed the characteristics and personality traits of the patients. In addition, the study aimed to determine the association between specific personality traits, depression, and pain symptoms in the respondents.

Patients and Methods: A survey was carried out on patients aged 18 years and above with a diagnosis of major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), who attended the psychiatric clinic in Hospital Universiti Sains Malaysia. Convenience sampling was carried out between February 2008 and June 2009. A questionnaire containing the socio-demographic data form, Hamilton Rating Scale for Depression (HAM-D), the Malay-translation of the Brief Pain Inventory (BPI), and Malay-translation of the Crown Crisp Experiential Index (CCEI) was filled after each patient had given to inform consent to participate in the study. Patients who did not consent, those with a co-morbid psychiatric diagnosis, and those with medical or surgical conditions associated with pain symptoms were excluded from the study.

Results: The study consisted of 51 respondents with mild depression; about half had neurotic traits. Although 80.4% of respondents experienced pain, the overall severity of the pain was mild. When compared with the presence of pain, there was no difference in the socio-demographic characteristic of respondents. However, Fisher's exact test revealed the statistically differences in the status of depression (depressed versus remitted) and anxious depression characteristic, whereby those who were still depressed and those with anxious depression were more likely to experience pain ($P < 0.05$ in both cases). Logistic regression analysis of socio-demographic

and clinical variables did not show any significant finding with regard to their pain status (presence or absence). There were positive correlations observed between the pain severity and the free-floating anxiety, FFA ($r = 0.363$, $P = 0.009$), somatic concomitants of anxiety, SOM ($r = 0.394$, $P = 0.004$), depression subscale of CCEI ($r = 0.478$, $P < 0.001$), as well as the CCEI total score ($r = 0.415$, $P = 0.002$). The CCEI total score accounted for 17.2% of the variance of BPI total score. Positive correlations were also observed between the pain severity and 12 items from the HAM-D pertained to depressed mood and various types of anxiety (including depressed mood, work and interests, psychic anxiety, somatic anxiety, general somatic, and genital symptoms), as well as HAM-D totalscore ($r = 0.608$, $P < 0.001$) which was accounted for 33.2% of the variance of BPI total score.

Conclusion: The proportion of adults with major depressive disorder having pain was 80.4%. The study showed that there are correlation between anxiety, personality traits, and the severity of depression with the severity of pain experienced by depressed patients.

Supervisor :
Professor Dr Haji Mohd Razali Bin Salleh

THE ROLE OF SOCIO-CULTURAL AND DIETARY FACTORS IN EXPLAINING LOW PREVALENCE OF HELICOBACTER PYLORI AMONG KELANTANESE MALAYS

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Introduction: The prevalence of *Helicobacter pylori* is low in North-Eastern Peninsular Malaysia. A sero-epidemiological survey showed a prevalence of only 4.2% among 496 blood donors and 4.8% among 921 subjects who attended health-screening clinic in Hospital Universiti Sains Malaysia. The infection rate among the Malays is lower than among the non-Malays. Few studies have shown that socio-cultural and dietary factors play an important role in explaining the unexpectedly low prevalence of *H. pylori*. However, no study has been conducted locally to investigate the association between socio-cultural, dietary factors, and *H. pylori* infection in the Malay population.

Objectives: The study aimed at comparing the socio-demographic, socio-cultural, and dietary differences between

H. pylori infected and non-infected individuals, as well as identifying the differences in clinical presentation of both groups.

Patients and Methods: A total of 161 subjects were recruited in this case control study. The index cases were identified from the patients who underwent oesophago-gastric-duodenoscopy (OGDS) at Hospital Universiti Sains Malaysia and tested positive for *H. pylori* through histology. The control group comprised patients who underwent OGDS but were negative for *H. pylori*. Stratified random sampling was applied and consented respondents were interviewed using a validated questionnaire. The questionnaire consisted of data on demography, socio-cultural practices, diet, and clinical presentation of disease..

Results: *H. pylori* infection was associated with 8 variables in multiple regression analysis: body mass index, BMI ($P = 0.018$, adjusted odds ratio of 1.17, 95% CI 1.08–1.34), type of toilet used at home ($P = 0.01$, adjusted odds ratio of 4.63, 95% CI 1.89–11.27), symptom of regurgitation ($P = 0.001$, adjusted odds ratio of 0.19, 95% CI 0.07–0.52), frequent use of traditional complementary medicine, TCM ($P = 0.009$, adjusted odds ratio of 0.29, 95% CI 0.11–0.74), frequent intake of “pegaga” or pennywort ($P = 0.024$, adjusted odds ratio of 0.32, 95% CI 0.12–0.86), frequent intake of “budu”, a type of fermented seafood product ($P = 0.010$, adjusted odds ratio of 0.26, 95% CI 0.09–0.73), frequent consumption of tea ($P < 0.001$, adjusted odds ratio of 0.03, 95% CI 0.11–1.00), and frequent consumption of coffee ($P = 0.021$, adjusted odds ratio of 3.45, 95% CI 1.20–9.86).

Conclusion: This study has shown that patients with higher BMI and use pit latrine at home had higher risk of *H. pylori* infection. Patients who had regurgitation were less likely to be infected with *H. pylori*. The intake of “pegaga”, “budu”, and tea also lowered the risk of infection, whereas frequent coffee intake increased the risk. There was no significant association observed between socio-cultural practices and *H. pylori* infection.

Supervisor :
Dr Lee Yong Yeh
Co-supervisor:
Dr Nazri Bin Mustaffa

AN EXPERIMENTAL STUDY ON THE USE OF FIBRIN GLUE IN CORNEAL WOUND REPAIR IN RABBITS

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Objectives: This study was conducted to evaluate the clinical outcomes and histopathological changes after the use

of fibrin glue in repairing different types of corneal wound in rabbits.

Patients and Methods: 10 rabbits were divided into 2 groups, A and B, with each group consisting of five rabbits. Full thickness central corneal wound of 6 mm in length was created in a group A, and peripheral wound of 6 mm was created in a group B. The wounds then were closed using the fibrin glue. Serial clinical examination was conducted using portable slit-lamp at day 1, 3, 7, 14, 21 post-procedure to evaluate wound apposition, corneal clarity, and anterior chamber depth. Enucleation was done on day 21 of study. Histopathology evaluation was performed to assess stromal inflammation, avascularization, granuloma formation, and microscopic wound gapping.

Results: Good wound apposition was achieved in 80% of a group A by day 1 and 100% by a day 3 post-procedure. No wound leakage was reported in group B throughout the study. Clear cornea with a deep anterior chamber was obtained from all rabbits at the end of study. Histopathology examination revealed scanty stromal avascularization in a group B. Majority of the rabbits had a mild inflammatory reaction; however, no granuloma formation or microscopic wound gapping was observed in the two groups of study.

Conclusion: Fibrin glue has shown satisfactory clinical outcomes with a good wound apposition, clear cornea, and deep anterior chamber. These clinical findings correspond with the histopathological results, which revealed acceptable inflammatory reaction without any granuloma formation or microscopic gapping.

Supervisor:
Dr Raja Azmi Mohd Noor
Co-supervisors:
Associate Professor Dr Hasnan Jaafar
Associate Professor Dr Wan Hazabbah Wan Hitam

PREVALENCE OF IRRITABLE BOWEL SYNDROME (IBS) AMONG HEALTHY SUBJECTS USING VALIDATED BAHASA MALAYSIA VERSION OF ROME III IBS QUESTIONNAIRE

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Introduction: Irritable bowel syndrome (IBS) is a very common chronic gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel habit without major organic disease. ROME diagnostic criteria, which are based on subjective gastrointestinal (GI) complaints, are the most widely used criteria for diagnosing IBS. We have developed the Malay-translation of ROME III IBS

questionnaire for the study of IBS in Malaysia. This validated questionnaire was used to study the prevalence of IBS among healthy subjects.

Objectives: The aims of this study were to validate the Malay-translation of ROME III IBS and ROME III psychosocial alarm questionnaires, and investigate the prevalence of IBS among normal healthy subjects in Universiti Sains Malaysia (USM) Health Campus, Kelantan, using the validated Malay-translation of ROME III IBS and ROME III psychosocial questionnaires.

Patients and Methods: This study was divided into 2 phases: 1) the validation process of the proposed translated questionnaire, and 2) a cross-sectional prospective study to examine the prevalence of IBS among healthy subjects in a university campus.

Results: The validated Malay-translation of ROME III IBS questionnaire was shown to have good colonometric properties. The prevalence of IBS among healthy subjects in USM Health Campus was 11.8%. Prevalence of IBS was significantly associated with age, ethnicity, and level of formal education. Red flag and psychosocial alarm symptoms were higher in subjects with IBS compared to non-IBS subjects.

Conclusion: This validated Malay-translation of ROME III IBS questionnaire have a good colonometric properties suitable as a tool for research. Prevalence and characteristics of IBS among healthy subjects in USM Health Campus were almost similar to those reported in another Asian population.

Supervisor:

Dr Lee Yeong Yeh

Co-supervisors:

Dr Amry Abdul Rahim

Dr Sarimah Abdullah

A COMPARATIVE STUDY BETWEEN A TARGET CONTROLLED INFUSION (TCI) AND MANUAL CONTROLLED INFUSION (MCI) OF PROPOFOL FOR SEDATION DURING CEREBRAL PROTECTION IN SEVERE TRAUMATIC BRAIN INJURED PATIENTS

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Introduction: Propofol is the most common sedative agent administered to traumatic brain injured (TBI) patient using manually controlled infusion (MCI) technique. The development of target controlled infusion (TCI) technique has given rise to a new alternative method in propofol administration, and this technique has never been tested in TBI patients.

Objective: The aim of this study was to compare the effectiveness of different methods of propofol infusion (TCI versus MCI) for sedation during cerebral protection in TBI patient in Neurosurgical Intensive Care Unit (NICU).

Patients and Methods: In this prospective, double-blinded, randomized controlled trial, 50 patients (age 16-50 years old) who had TBI with a Glasgow Coma Scale (GCS) between 3 and 8 with no severe medical illness and undergoing craniotomy were randomized into two groups (MCI and TCI) of 25 patients in each using block randomization. However, 1 patient in MCI group had to be excluded due to very agitated state to the extent of requiring muscle relaxant in spite of adequate sedation. During surgery, both groups received anaesthesia according to the standard protocol, and observation began once patients were admitted to NICU for cerebral protection. Sedation level was monitored using Bispectral Index (BIS) monitor and Sedation Agitation Scale (SAS). BIS index of 60-70 and SAS score of 2-3 was considered as adequate sedation. The same infusion pumps that can operate either TCI or MCI was used during drug administration, which was done via a dedicated central venous line lumen. *Hemodynamic* parameters (blood pressure, mean arterial pressure, MAP, and heart rate) and neurological parameters (intracranial pressure, ICP, and cerebral perfusion pressure, CPP) were recorded. Time and volume of propofol used to achieve BIS 70, total volume of propofol used for 24 hours, and time taken to achieve BIS 90 after stopping infusion at the end of cerebral protection were measured. Fentanyl infusion at 1 mcg/kg was given for pain relief and was stopped four hours before the end of the 24-hour study.

Results: There were some significant differences between 2 modes of infusion. TCI mode achieved BIS 60-70 significantly faster than MCI, with mean of 6.32 minutes (SD 2.88) and 19.71 minutes (SD 7.00), respectively. Time taken to recover from sedation to achieving BIS 90 was also significantly faster in TCI, 22.44 minutes (SD 11.50), compared with MCI, 57.29 minutes (SD 19.89). In view of ICP, there was a differentiation between 2 modes; however, no significant difference was observed in MAP and CPP.

Conclusion: TCI mode of propofol is shown to be more effective in sedating neurotrauma patients as it gave adequate sedation faster with lesser volume, as well as faster recovery. It also lowered the ICP to 20 mmHg lower than MCI.

Supervisor:

Professor Dr Nik Abdullah Nik Mohamad

Co-supervisor:

Dr Wan Mohd Nazaruddin Wan Hassan

THE EFFECTIVENESS OF PRETREATMENT WITH LOW DOSE ETOMIDATE OR PROPOFOL IN REDUCING ETOMIDATE-INDUCED MYOCLONUS IN PAEDIATRIC PATIENTS

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Introduction: A good choice of intravenous anaesthetic agent is very important, especially in an extreme age group either pediatric or elderly patient. Etomidate is one of the anaesthetic agent of choice for general anaesthesia and as alternative to propofol and barbiturates for rapid intravenous induction of anaesthesia because of etomidate properties in maintaining hemodynamic stability. Nevertheless, there is a high incidence of myoclonic movement following induction of anaesthesia with etomidate. The myoclonic movement will affect patients' intraoperative monitoring such as blood pressure monitoring, pulse oxymetry reading, and electrocardiogram monitoring.

Objectives: The goal of this study was to compare the effectiveness of pre-treatment with low-dose etomidate or low-dose propofol in reducing etomidate induced myoclonus in pediatric age group. In addition, the study was conducted to observe any significant changes in hemodynamic parameters and incidence of pain following intravenous etomidate injection.

Patients and Methods: Pediatric patients of ASA physical status I or II ($n = 88$) were randomized to two groups. The patients received pre-treatment of either intravenous etomidate (0.03 mg/kg) or intravenous propofol (0.2 mg/kg), followed by induction dose of intravenous etomidate (0.3 mg/kg). Presence of myoclonus and/or pain following etomidate induction was observed and charted in observational data collection.

Results: Pre-treatment with etomidate caused fewer myoclonus compared with propofol (occurring in 31 or 45.6% of patients and 37 or 54.4% of patients, respectively); however, this observation was not statistically significant ($P = 0.132$). Among the patients who had experience myoclonus, it was found that the condition was significantly correlated with age ($P = 0.002$) and body weight ($P = 0.001$). Mean age group for the patients experiencing myoclonus was 10.7 years old (SD 3.21), whereas the mean body weight was 33.4 kg (SD 12.48). Pre-treatment with etomidate caused less pain during subsequent etomidate injection compared with propofol (occurring in 10 or 22.7% of patients and 13 or 29.5% of patients, respectively); however, results were not relevant. There were also no significant changes in the baseline, pre-treatment, and post-induction blood pressure and heart rate in both groups.

Conclusion: Incidence and severity of myoclonus after etomidate injection were related to the patients' age and body weight. There was no significant difference in myoclonus and pain reduction between pre-treatment with low-dose etomidate and low-dose propofol in the pediatric patients, and no significant changes were observed in the hemodynamic parameters following etomidate induction.

*Supervisor:
Dr Mohd Nikman Ahmad*

EFFECTIVENESS OF PAP SMEAR SCREENING PROGRAMME IN DETECTING CERVICAL SQUAMOUS CELL CARCINOMA AND HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESIONS IN KELANTAN: 2002-2006

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Introduction: Cervical cancer is a preventable cause of death in women. Cervical cytology had been proven to be effective as a screening test. This is demonstrated by decreased incidence and mortality rates in many countries worldwide. The specificity of the Papanicolaou smear frequently has been reported to be higher than 90%. However, the sensitivity as well as false negative and false positive rates have been inconsistent and dependent on the study design.

Objective: This study was conducted to determine the effectiveness of cervical cytology screening in detecting high grade squamous intraepithelial lesion and squamous cell carcinoma using histopathology as the gold standard.

Patients and Methods: This is a retrospective study of all patients diagnosed with carcinoma intraepithelial neoplasia (CIN 2 and CIN 3) and squamous cell carcinoma by histopathology in Hospital Universiti Sains Malaysia and Hospital Raja Perempuan Zainab II from 2002 to 2006. The cervical cytology results were reviewed and divided into 3 categories: concordant, minor, and major discordant. The concordance rate between cytological diagnoses and histopathological diagnoses were determined. The smears from the minor and major discordant categories were traced and subjected to re-screening. The 2001 Bethesda system was used to classify the revised diagnoses of re-screening.

Results: There were 182 cases of CIN 2, CIN 3, and invasive squamous cell carcinoma diagnosed by histopathological examination. We found that only 54.5% of the cases had a previous Pap smear. Of the patients who received Pap smears, 65.7% were histopathologically diagnosed as concordant, 15.1% as major discordant category, and 19.2% as minor discordant. The concordance rate between the histopathology and Pap smears was statistically significant ($P < 0.05$). 23 (23.2%) smears from the major and minor discordant categories were subjected to re-screening. The revised diagnoses of the re-screening were similar to the initial screening diagnoses in only 5 (21.7%) smears. In 18 (78.3%) smears, the revised diagnoses were changed. The false negative rate was 15.2% and the sensitivity of Pap smear was 84.8%. This study showed that Pap smear was found to be underutilized in 24.2% of cases, where it was used for diagnosis rather than for screening. It was also noted that there is a higher diagnostic error in the laboratory with the higher workload.

Conclusion: Pap smear is effective in detecting high grade squamous intraepithelial lesions and squamous cell carcinoma with a high sensitivity. The false negative rate is within an acceptable range.

Supervisor:

Dr Mukarramah Che Ayub

Co-supervisor:

Professor Dr Nor Hayati Othman

A LOCAL STUDY ON THE INCIDENCE AND RISK FACTORS OF POST-TRAUMATIC SEIZURES AMONG PATIENTS WITH TRAUMATIC BRAIN INJURY

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Introduction: Post-traumatic seizure is a well-known and serious complication of traumatic brain injury (TBI). The incidence and risk factors vary among study populations. Very little data has been published concerning post-traumatic seizures in the Malaysian population.

Objective: The aim of this study was to investigate the incidence and risk factors for the development of post-traumatic seizures among patients with TBI in Hospital Universiti Sains Malaysia, Kelantan, Malaysia.

Patients and Methods: A total of 157 patients who were diagnosed with TBI from June to December 2007 were included in this prospective observational study. Patients were divided into high-risk and low-risk groups and randomized to receive phenytoin for either 1 week or 1 year (for the high-risk group) and either phenytoin for 1 year or no phenytoin (for the low-risk group). The patients were then followed up for 12 months, until their death or first post-traumatic seizure. Survival analyses were conducted using Kaplan-Meier curves and Cox proportional hazard regression.

Results: Out of 157 patients, 26 patients (16.6%) developed post-traumatic seizures. From these 26 patients, 11 patients (42.3%) developed seizures early, within 7-day post-trauma of the trauma, whereas the remaining 15 patients (57.7%) developed seizures later, between 8-days and 12 months after trauma. The mean duration for development of late post-traumatic seizures was 9.4 months (SD 3.2). The risk factors for developing early and late post-traumatic seizures were different. For early post-traumatic seizures, the risk factors were young age ($P = 0.021$, 95% CI 0.806-0.982) and intubated patients ($P = 0.029$, 95% CI 1.194-25.913). For late post-traumatic seizures, the significant risk factor was a severe head injury with a Glasgow Coma Scale of 3-8 ($P = 0.036$, 95% CI 1.065-6.464). Log-rank tests for phenytoin treatment in both high-risk and low-risk groups were insignificant (log-rank statistic of 0.31 with $P = 0.5784$ for the high-risk group;

a log-rank statistics of 0.23 with $P = 0.6283$ for the low-risk group).

Conclusion: Incidence of post-seizures in the local population was 16.6%. Risk factors for early post-seizures were young age and intubated patients, whereas only severity of head injury was found to be significantly correlated with late post-seizures. Phenytoin was not beneficial as a prophylaxis against post-seizures.

Supervisor:

Associate Professor Hillol Kanti Pal

DETERMINATION OF THE OVER-PENETRATION LENGTH DURING DRILLING PROCEDURE WITH K-WIRE AND DRILL BIT AMONG ORTHOPAEDICS MASTER STUDENT IN UNIVERSITI SAINS MALAYSIA

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MMed (Orthopaedics)

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Introduction: Drilling procedure is the most fundamental surgical skill required by orthopaedic surgeons as many fractures, nowadays, are treated operatively. Neurovascular injuries are known to be one of the complications of over-penetration during drilling procedures.

Objective: The purpose of this study was to determine the length of over-penetration in drilling technique among orthopaedics master students in Universiti Sains Malaysia.

Patients and Methods: A total of 14 junior postgraduate students (Year 1 and 2) and 14 senior postgraduate students (Year 3 and 4) were recruited in this study. Each student performed drilling procedure on a bovine bone block using the battery-powered drill with 3.2 mm drill bit and 2.0 mm K-wire. Drilling was stopped immediately when penetration of the far cortex was felt. The distance from the tip of the instrument to the far cortex was measured. The procedure was repeated three times for each instrument. The mean values were calculated and compared using parametric paired t test. The length of over-penetration in Experience Level group and Exposure to an AO course group for each drilling instrument were compared using non-parametric Mann-Whitney U test.

Results: The mean length of over-penetration for the drill bit and K-wire were 21.50 mm (range 10.33-35.66 mm) and 10.18 mm (range 3.00-18.66 mm), respectively. Using the drill bit, the median lengths of over-penetration for junior students and senior students were 25.55 mm and 16.66 mm, respectively, while the use of K-wire resulted in shorter over-penetration, 16.50 mm and 5.50 mm for junior students

and senior students, respectively. For the group of students exposed to AO course, the median lengths of over-penetration were 13.33 mm with drill bit and 5.00 mm with K-wire, while for those students without AO course exposure, the lengths were 21.66 mm with drill bit and 10.66 mm with K-wire. The differences were statistically significant with regard to the type of instrument and experience level ($P < 0.001$ in all comparison) and exposure to AO course ($P = 0.02$ for drill bit and $P = 0.05$ for K-wire). There was a significant correlation between postgraduate training years in with personal experience in Orthopaedics ($r = 0.55$, $P = 0.003$).

Conclusion: The study provides the overall results regarding the depth of over-penetration in drilling procedure among orthopaedics master students in Universiti Sains Malaysia. It may benefit as the reference for related studies in the future.

Supervisor:

Dr Amran Ahmed Shokri

Co-supervisor:

Dr Ahmad Tajuddin Abdullah

A CROSS SECTIONAL STUDY OF THE PROXIMAL FEMUR MORPHOLOGY OF THE NORMAL MALAY POPULATION USING COMPUTED TOMOGRAPHY IMAGES (SCANOGRAM) AT HOSPITAL UNIVERSITI SAINS MALAYSIA

Dr Dzuraimy Bin Ismail
MMed (Orthopaedics)

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Introduction: Previous studies have shown significantly smaller proximal femur parameters in the Asian population in comparison with the Caucasian population. Currently used proximal femur implant size was based on Caucasian studies. However, due to the smaller size of the proximal femur in the Asian population, improvement in the design of implant is required to optimize component fixation and restore the normal biomechanics of the hip joint.

Objectives: This study was conducted to quantify the proximal femur dimensions in Malay patients, compare the parameters of the proximal femoral bones between male and female patients, and determine the correlation between these parameters.

Patients and Methods: This cross-sectional study involved 140 Malay patients (70 males and 70 females), aged between 18 and 80 years, who were treated in Hospital Universiti Sains Malaysia. Each patient was confirmed as having normal proximal femur morphology by analysing the computerized tomographic scan, which was conducted for various pelvic pathologies. The following parameters of the proximal femoral bones were studied: 1) femoral neck shaft

angle, 2) femoral head diameter, 3) femoral neck isthmus diameter, 4) vertical offset of femur, and 5) horizontal offset of the femur. The data obtained were statistically analysed using independent t test to determine the difference between male and female patients. The mean of all the parameters was compared with published Western and Asian studies using one sample t test. Significant level was set at $P < 0.05$.

Results: There were significant differences between male and female patients in the femoral head diameter, femoral neck isthmus diameter, vertical offset, and horizontal offset of the femur. However, there was no significant difference in the neck shaft angle. Female patients have significantly smaller dimensions in all parameters measured except for the neck shaft angle, which was larger than the male patients'. When observation in the current study was compared to radiographic study by Sugano et al. and Noble et al., significant differences were found in the head diameter, neck isthmus diameter, vertical offset of femur, and neck shaft angle. The head diameter, neck isthmus diameter, and vertical offset of the femur observed in this current study were significantly smaller compared with their reports; however, the neck shaft angle in this study was significantly larger.

Conclusion: The current study has shown that the proximal femur morphometry of the Malay population was smaller compared to the Caucasian and Thailand population.

Supervisor:

Dr Amran Bin Ahmed Shokri

A STUDY ON GLYCEMIC CONTROL AMONG INSULIN-TREATED TYPE 2 DIABETES PATIENTS ATTENDING DIABETES CENTRE, HOSPITAL UNIVERSITI SAINS MALAYSIA, KELANTAN

Dr Haryati Hamzah
MMed (Family Medicine)

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Health Campus, 16150 Kelantan, Malaysia*

Introduction: The goal in management of type 2 diabetes mellitus is to achieve a good control of HbA_{1c}. Unfortunately, many diabetic patients were unable to this target. Combination of insulin and oral anti-diabetic (OAD) agent, or full dose insulin, is an alternative treatment to improve the glycaemic control. Recent studies indicate that insulin is able to improve HbA_{1c} level and reduce the risk of microvascular and macrovascular complications, thus reducing the economic burden of diabetes mellitus.

Objectives: The study was conducted to examine the percentage of insulin-treated diabetes patients with good glycaemic control and determine the factors that contribute to glycaemic control.

Patients and Methods: This cross-sectional study was conducted by collecting case report form (CRF) or proforma from 236 insulin-treated type 2 diabetes mellitus patients who attended the Klinik Diabetik and Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia (HUSM), from January until November 2008. The CRF was divided into 2 sections: Section 1 consisted of socio-demographic data while Section 2 consisted of background history of diabetes and clinical characteristics that was filled up by the researcher by reviewing the patients case notes.

Results: The result showed that the percentage of insulin-treated diabetes patients with good glycaemic control was 21.2%. The factors that contribute to good glycaemic control were female, high education level, combination of insulin and OAD regime, basal bolus insulin, and fasting blood sugar. Factors that were found to be protective of glycaemic control include financial status, high low-density lipoprotein (LDL), high total cholesterol, and normal weight (non-obese).

Conclusion: Glycaemic control among insulin-treated type 2 diabetes mellitus attending the Diabetes Centre, HUSM, was still unsatisfactory. Assessment of glycaemic control should be a routine during follow-up. By recognizing the factors that contribute to good glycaemic control, healthcare providers can plan an intervention program to improve glycaemic control and subsequently reduce the cost of treating the diabetes mellitus and its complications.

Supervisor:

Dr Adibah Hanim Ismail

Co-supervisor:

Dr Nor Azwany Yaacob

PREVALENCE OF FALLS AND ITS ASSOCIATED FACTORS AMONG ELDERLY DIABETES ATTENDING KLINIK PAKAR PERUBATAN AND KLINIK RAWATAN KELUARGA HOSPITAL UNIVERSITI SAINS MALAYSIA

Dr Hasniza Hasim
MMed (Family Medicine)

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Objectives: The study aimed to assess the prevalence of fall and its associated factors among elderly type 2 diabetes mellitus patients attending outpatient clinics (Klinik Pakar Perubatan & Klinik Rawatan Keluarga), Hospital Universiti Sains Malaysia (HUSM).

Patients and Methods: This cross-sectional study was conducted among 288 elderly type two diabetes mellitus in HUSM, from April 2007 until March 2008. The patients were selected using systematic random sampling method. Baseline data on socio-demographic, diabetes history, co-morbid

diseases, drug use, and activity of daily living (Barthel's index) were collected. The patients were examined physically, and gait assessment was carried out. Information on laboratory investigation results, medication, and concomitant illness were obtained from reviewing the patients medical records. Prevalence of fall was determined, where fall was defined having at least one history of fall in the past one year from the interview date.

Results: Prevalence of fall among elderly diabetes was 18.8%; 72.2% out of these patients had experienced more than one falls. Female gender (OR 2.54, $P < 0.05$), age of more than 75 (OR 2.97, $P < 0.05$), retinopathy (OR 2.19, $P < 0.05$), and orthostatic hypotension (OR 2.87, $P < 0.05$) were associated with higher risk for falls in elderly diabetes; in contrast, high balance and gait scores was associated with reduced risk of fall (OR 0.89, $P < 0.05$).

Conclusion: In this cross-sectional study among elderly diabetes type 2, the prevalence of falls was found to be lower compared with previous studies in the Western countries. The factors associated with higher risk for fall were gender (female), age of more than 75, retinopathy, and orthostatic hypotension. Those who had higher balance and gait scores were found to be less likely to experience fall compared with those with lower scores.

Supervisor:

Dr Azidah Abdul Kadir

Co-supervisor:

Dr Zunaina Embong

SOFT TISSUE CHARACTERISTICS OF REPAIRED CLEFT LIP AND PALATE OF MALAY CHILDREN IN KELANTAN

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MMed (Plastic Surgery)

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Introduction: Facial growth and soft tissue are essential parameters in the assessment of a cleft surgery outcome. Many studies have been focusing on the effects of the cleft surgery on the facial development, mainly on the skeletal development. Only a few studies have investigated the influence of surgical intervention on the soft tissue morphology.

Objectives: This study aimed to examine the facial morphology of Malay cleft lip and palate (CLP) patients who had been treated surgically without any osteoplasty and received a complete lip repair at 3-6 months, and palate closure at 9-12 months.

Patients and Methods: A total of 26 CLP patients of Malay ethnic origin with age range of 4-10 years old were recruited in this cross-sectional comparative study. Serial

analyses of the soft tissue morphology using 2-D photographs pre-operatively and 3-D computer generated images post-operatively were conducted, and the data were compared with non-CLP subjects of same ethnic origin, which acted as the control group. The observations were then compared with other studies on CLP patients.

Results: The results revealed statistically significant changes in intercanthal distance, mouth width, and nose width between pre-operative and post-operative measurements. Compared with the control group, CLP patients had wider intercanthal distance and nose width. However, CLP patients showed restriction of facial growth at the prolabial and anteroposterior dimension of the midface. Results of this study suggested that all recorded changes occurred in the horizontal plane, and that the dento-facial growth disturbance can extend up to the orbital region.

Conclusion: The facial profile changes in CLP patients following cleft surgeries were statistically significant when compared to the non-CLP subjects. Most of these changes that occurred in the orbital and nasal regions were due to intrinsic factors. The effect of cleft surgeries played a major role in the changes at the prolabial region. Highest degree of dento-facial differences between CLP patients and control subjects was in the horizontal dimensions of the nose. There were no significant differences in vertical dimensions between these groups. These soft tissue characteristics of repaired CLP would be useful in the development of a more ideal treatment protocol, which can enhance the quality of life in CLP patients.

Supervisor:

Dr Wan Azman Wan Sulaiman

Co-supervisor:

Professor Dr Ahmad Sukari Halim

CORRELATION OF SIGNIFICANT LEFT MAIN CORONARY ARTERY STENOSIS WITH 12-LEAD ECG

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MMed (Internal Medicine)

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Objectives: The purpose of this study is to determine the correlation of significant left main coronary artery stenosis with 12-lead ECG. We also determine the sensitivity and specificity of ECG in predicting left main coronary artery disease.

Patients and Methods: A total of 220 patients who had left main coronary involvement were included in this study. Their ECGs were reviewed blindly by the investigator under 11 different ECG criteria which previous studies have formulated. The patients were then subdivided into 2 groups depending on whether there was significant LMCA stenosis or not.

Results: After establishing the frequency of ST elevation in leads aVR < V1 (criteria 5) occurred in 79.5% cases. The ST elevation in aVR and V1 (criteria 7) occurred in 0.5% of cases. This showed that a combination of ECG criteria only occurred in very few cases. After using the McNemar test as a non-parametric test for the data, it was found that ECG criteria 5 had the highest sensitivity (75%) but with a low specificity (12.5%). Other ECG criteria having high specificity however did not have high sensitivity. Therefore, new ECG criteria or a new combination of criteria needed to be devised that have both high sensitivity and good specificity. After several attempts at defining new ECG criteria, we came across new criteria (aVR = V1) which had a sensitivity of 92.9% but still having low specificity of 13.3%. We suggest using ST depression, I, II, V4-V6 (criteria 10) which has high specificity of 97.3% to exclude cases of significant LMCA stenosis.

Conclusion: We can conclude that aVR = V1 (new criteria) can be used to identify patients with significant LMCA disease and ST depression, I, II, V4-V6 (criteria 10) to exclude significant LMCA disease.

Supervisor:

Dr Mohd Sapawi Mohamed

Co-supervisor:

Assoc. Associate Professor Dr Zurkurnai Yusof

ACCURACY AND RELIABILITY ANALYSIS OF LOWER LIMB LENGTH DISCREPANCY MEASUREMENT USING TAPE MEASURING METHOD AND CT SCANOGRAPHY

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MMed (Orthopaedic)

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Introduction: Clinical measurement using the tape measurement method (TMM) is easily performed and required no special instrument. However, it was reported to be less accurate compared with radiological measurement. Currently, there is no available data on the accuracy of TMM in the clinical measurement of the lower limb length.

Objectives: The study was design to assess the reliability and accuracy of TMM in comparison with computed tomography (CT) scan in measuring the length of lower limb.

Patients and Methods: This was a cross-sectional study involving 50 patients who had been treated in Hospital Universiti Sains Malaysia: 37 patients with limb-length discrepancy (LLD) and 13 patients without LLD. All of them had limb-length measurement done using TMM by 2 blinded observers. From 37 patients with LLD, only 25 of them had undergone CT scan, and their CT scanogram were used for radiological measurement done by 2 blinded radiologists. Intra class correlation coefficient (ICC) and mean difference were

calculated to assess interobserver reliability for TMM and CT scanogram measurement. Accuracy of the TMM was assessed by comparison with CT scanogram as the gold standard.

Results: The interobserver reliability for TMM was high, with Intraclass correlation coefficients (ICC) of 0.912 (0.851 to 0.949) and mean difference of -0.7 (-3.3 to 1.9) mm. The interobserver reliability for CT scanogram is also high, with ICC of 0.964 (0.921 to 0.984) and mean difference of -1.14 (-3.4 to 1.1) mm. When compared to CT scanogram, the accuracy of one measurement by TMM was fair, with ICC of 0.672 and mean difference of 3.1 (-3.6 to 9.8) mm. A mean of two measurements by TMM was good, with ICC of 0.781 and mean difference of -3.4 (-9.0 to 2.1) mm.

Conclusion: Both measurements of LLD using TMM and CT scan to have been high interobserver reliability. In comparison with CT scanogram, the accuracy of the TMM was improved from fair to good if the mean of two measurements by TMM was taken instead of a single measurement. The TMM can either over- or underestimate the LLD up to 10 mm.

Supervisor:

Associate Professor Dr Abdul Razak Sulaiman

Co-supervisor:

Associate Prof Dr Mohd Ezane Aziz

Dr Juhara Haron

OUTCOME OF IMMEDIATE PARTIAL WEIGHT BEARING FEMORAL SHAFT FRACTURES, TREATED BY SINGLE PROXIMAL LOCKED INTRAMEDULLARY NAILING, IN HOSPITAL IPOH

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Introduction: Femoral shaft fracture is a common fracture encountered in daily orthopaedic practice. Literature review showed that this type of fracture had been treated with different modalities since many years ago, and the treatment method has advanced rapidly over the past few decades. Single proximal locked femoral nail fixation has not been widely practiced. This method of fixation was only used for proximal third and mid-shaft fractures of the femur. Femur fractures with simple transverse configuration and up to 50% contact of the cortices were suitable for this method of fixation. Dynamic intramedullary femoral stabilization had been previously studied by Brumback et al. using interlocking screws at only one end of the nail, and the authors concluded that dynamic intramedullary femoral stabilization should be performed for transverse or short oblique fractures of the femoral isthmus with Winkquist-Hansen type-I and type-II comminution.

Objectives: The objective of this study was to review

the results and clinical outcomes of immediate partial weight bearing in the treatment of femoral shaft fractures using single proximal locked intramedullary nailing for type-o, type-I, and type-II comminution according to Winkquist-Hansen classification.

Patients and Methods: This is a case-review, retrospective study using secondary data. Study subjects were 31 patients who were admitted to the ward after sustaining a single femoral fracture, with no other associated injuries, from June 2005 until May 2007. Patients with femur fractures that were beyond the mid-shaft were not included in this study due to rotational instability with single proximal locking screw fixation. Patients in this study were categorised according to the types of fracture using the Winkquist-Hansen classification: type-o, type I, and type II. All patients underwent single proximal locked intramedullary nail fixation. Patients were advised for partial weight bearing on the fractured limb using crutches starting on the second day post-operation in order to achieve primary dynamization to enhance fracture healing process. They were followed up every 6 weeks for a period of 18 weeks. Throughout the follow-up period, fracture union and clinical outcome were assessed by a senior orthopaedic surgeon. The union of the fracture was considered delayed if the fracture had failed to unite by 18 weeks.

Results: Out of the 31 patients, 25 patients were males (81%) and the remaining 6 patients were females (19%). Patients' age ranged 20-40 years with a mean of 27 years. There were 5 patients with type-o fractures (16%), 20 patients with type-I fractures (65%), and 6 patients with type-II fractures (19%). The cause of fractures was motor vehicle mishaps; 71% involved motorcycle accidents. The common site of fracture was midshaft (54.8%) compared with proximal third (45.2%). All patients were operated within a week post-injury. The operation time ranged 30-86 minutes with average of 46 minutes. Independent *t* test analysis showed statistically significant reduction in the operation time for the fixation of femur using single proximal locking method compared with proximal and distal locking method. In this study, all fractures achieved union. The average time to union for Winkquist-Hansen type-o fractures (14 weeks) was significantly shorter compared to Winkquist-Hansen type-I (18 weeks) and type-II (25 weeks). There was 3.2% incidence of post-operative superficial wound infection; all were superficial and successfully treated with intravenous antibiotic given for 2 weeks. In 2 Winkquist-Hansen type-II fracture cases, there was shortening of 1 cm each. None of them had post-operative complication such as nerve injury, mal-union, non-union, and implant failure.

Conclusion: There was a significant reduction in the operation time for the fixation of femur using single proximal locking method compared with proximal and distal locking method. The average time to union for Winkquist-Hansen type-o fractures were significantly shorter compared with Winkquist-Hansen type-I and type-II. Based on the result, we conclude that single locked intramedullary nail is safe and beneficial to patients who sustained Winkquist-Hansen type-o

and type-I femur fracture.

Supervisor:

Dr Bal Kishan

Co-supervisor:

Dr Liau Kai Ming

Dr K Manoharan

RESPIRATORY SYMPTOMS AND LUNG FUNCTIONS AMONG DOMESTIC WASTE COLLECTORS IN KOTA BHARU, KELANTAN

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Introduction: A variety of common injuries and diseases involving eye, skin, musculoskeletal systems, respiratory, and systemic diseases exist as a result of exposure, via inhalation or skin absorption, to a large variety of chemical compounds, bioaerosols, dusts, gases, and pathogens encountered by domestic waste collectors during the handling of solid waste.

Objectives: This study was aimed to determine the respiratory status, level of knowledge, attitude, and practice (KAP), and associated factors that could potentially impair the respiratory function among male domestic waste collectors in Kota Bharu.

Patients and Methods: A comparative cross-sectional study was conducted in September–October 2008 among 95 male domestic waste collectors (exposed group) and 96 male office workers (non-exposed group) in Kota Bharu. Subjects were individually interviewed using 2 sets of questionnaire to obtain information pertaining socio-demography, personal, occupation, respiratory symptoms as well as knowledge, attitude, and practice (KAP) towards health and respiratory risks from workplace exposure to biohazards. Physical examination and lung function test were conducted to each study subjects at their workplace.

Results: All 191 participants were Malay males with mean (SD) age of 39.9 (9.14) years among the domestic waste collectors compared with 41.4 (9.06) years among office workers. The mean (SD) working duration among domestic waste collectors was 11.2 (8.76) years compared with 10.3 (9.36) years among office workers. The most frequently reported respiratory symptom was shortness of breath (42% waste collectors, 31% office workers), followed by chest tightness (37% waste collectors, 27% office workers), morning phlegm (33% waste collectors, 17% office workers), and morning cough (20% waste collectors, 3% office workers). Physical examination revealed normal findings and there were no significant differences in all respiratory function parameters among exposed and non-exposed groups.

Exposed group had significantly lower mean percent score for knowledge and attitude, but higher mean percent score for practice; there was no significant difference of mean percent score for total KAP between exposed and non-exposed group. Height, duration of smoking, duration of working, and age were factors significantly related to FEV1 and FVC, and age was a factor significantly related to FEV1/FVC.

Conclusion: The study showed that chronic exposure to domestic waste could lead to higher prevalence of respiratory symptoms and mild effect on respiratory health among domestic waste collectors compared with office workers. Height, duration of smoking, duration of work, and age were factors associated with at least 1 of the lung function parameters among the exposed group. The level of knowledge, and attitude towards health and respiratory risks from biohazard exposure at workplace in the exposed group was unsatisfactory compared with non-exposed group.

Supervisor:

Dr Mohd Nazri Shafie

Co-supervisor:

Associate Professor Dr Mohamed Rusli Abdullah

A STUDY OF FEMAL SEXUAL DYSFUNCTION BY USING FEMALE SEXUAL FUNCTIONAL INDEX (FSFI) AMONG WOMEN AT THE AGE OF 40–55 YEARS OLD IN UNIVERSITI SAINS MALAYSIA, KUBANG KERIAN, KELANTAN

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MMed (O & G)

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Introduction: Sexual life is considered as one of the important aspect in a woman's quality of life; it reflects on physical, psychological, and mental well-being of the individual. Middle age women are additionally influenced by the hormonal changes that occur during menopause that affects their sexual functions, especially libido and orgasm.

Objectives: The study aimed to determine the prevalence of sexual dysfunction among 40–55 years old women, socio-demographic and sexual factors that influence libido (sexual desire) and orgasm domain, and the impact on HRT on sexual domain.

Methods: This cross-sectional descriptive study involved 434 local women, age of 40–55 years old, attending the Hospital Universiti Sains Malaysia. Sexual function was measured by using a self-administered, validated, Malay-version of the Female Sexual Function Index questionnaire. The questionnaire consists of socio-demographic data and a 19-item, multidimensional, self-report measure of female sexual functioning, which covers 6 basic domains of female

sexual functions: desire, arousal, lubrication, orgasm, satisfaction, and pain. Statistical analyses were performed using chi-square test and multivariate regression analysis.

Results: The mean age of the women was 47.5 (SD 4.3) years old. The overall prevalence of sexual dysfunction was 8.0%. The prevalence of sexual dysfunction for each domain was 18.4% for desire, 5.1% for arousal, 4.4% for lubrication, 2.1% for orgasm, 7.4% for satisfaction, and 6.9% for pain. The most significant predictors for desire were age of 40–45 years old (P value = 0.047) and more than 50 years old (P value = 0.017), Malay ethnicity (P value = 0.024), Chinese ethnicity (P value = 0.013), sexual arousal ($P < 0.001$), lubrication ($P < 0.001$), and satisfaction ($P < 0.001$). Lubrication and illness (renal disease) had significant association with the lack of orgasm ($P < 0.05$). Ageing, parity (2–5 and more than 5 children), and lack of lubrication were significantly associated with sexual pain disorders ($P < 0.05$). Hormone replacement therapy (HRT) did not significantly improve any sexual domain. Other socio-demographic variables, such as level of education, type of occupation, duration of marriage, and medical conditions, were less likely to result in significant disturbances on sexual function.

Conclusion: The prevalence of sexual dysfunction among the middle age, local women was not high. There is a negative association between age and sexual response in these women; the most affected sexual function domain was sexual desire. From this study, it was concluded that HRT did not have any positive impact on the sexual domain.

Supervisor:

Associate Professor Dr Shah Reza Johan Noor

REVIEW OF COMPLICATIONS OF ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY (ERCP) IN HOSPITAL UNIVERSITI SAINS MALAYSIA FROM 2000 TO 2006

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MMed (General Surgery)

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Introduction: Endoscopic retrograde cholangiopancreatography (ERCP) is an important procedure for the investigation and management of pancreaticobiliary diseases; endoscopists perform ERCP on a regular basis. However, the procedure has many risks. There is a recognized potential for significant morbidity, and a number of studies have identified patient and operator risk factors for the development of complications, such as small case volume. ERCP practice may vary between different institutions, endoscopic settings and health care environments, as well as physician's expertise and skill; all these variables may affect the outcome of the ERCP. The ERCP service in Hospital

Universiti Sains Malaysia (HUSM) has been in existence since the last two decades. However, until now, no formal study has been done to audit the ERCP service, and no information on the outcomes and complications of this procedure is available.

Objectives: This study was performed to review ERCP complications in HUSM. The information on complications of ERCP was obtained from a tertiary referral centre and compared with published figures.

Patients and Methods: Data were collected retrospectively from medical records of patient who had ERCP from January 2000 to December 2006. Complications were reviewed, and several factors were analyzed as risk factors for post-ERCP complications using univariate and multivariate analyses.

Results: The study involved 195 patients, for which 246 ERCPs were performed during the study period. There were 54 major complications with 7 cases of ERCP-specific mortality. The incidence of ERCP complications and mortality in HUSM were within the reported global range. Post-ERCP pancreatitis was the most frequent complication and occurred in 25 patients: mild in 15 patients, moderate in 5 patients, and severe in 5 patients. Cholangitis occurred in 19 patients: mild in 3 patients, moderate in 6 patients, and severe in 10 patients. Bleeding occurred in 4 patients, while only 2 patients had perforation during the procedure. ERCP was performed for 2 pregnant patients; 1 had abortion 10 days after the procedure. However, this patient also had post-ERCP pancreatitis preceding her abortion. The other patient continued her pregnancy and delivered with no complications. Other major complications were acute pulmonary embolism in 1 patient, cardiorespiratory arrest after sedation in 1 patient, and atrial fibrillation in 1 patient. Based on univariate analysis, several factors were identified as significant risk factors for post-ERCP overall complications: history of pancreatitis, performance of pancreatogram, use of pre-cut cannulation, normal cholangiogram, absence of stones, and failure of complete stone clearance. Only 2 factors were independently associated with high risk of overall complications by multivariate analysis, i.e., pancreatic duct injection and absence of stones. For post-ERCP pancreatitis, several conditions have been identified to be significant risk factors using univariate analysis: young age, history of pancreatitis, pancreatic duct injection, normal serum bilirubin, normal cholangiogram, absence of biliary stones, and pre-cut cannulation. Young age, history of pancreatitis, and pancreatic duct injection were also identified as independent risk factors using multivariate analysis. Several conditions were also identified as significant risk factors for cholangitis. Based on univariate analysis, significant factors were malignant jaundice, normal serum bilirubin, co-morbidity with high American Society of Anaesthesiologists (ASA) score, and presence of stricture or stenosis. Successful removal of bile ducts stones was found to contribute to lower risk of cholangitis compared with other therapeutic procedures. Multivariate analysis showed that, out of the tested factors, only the presence of stricture or stenosis was independently increasing the risk of post-ERCP

cholangitis.

Conclusion: The study verified the ERCP complication rate in HUSM, the nature of these complications, and their associated factors. Furthermore, the study highlighted the need for actions to limit or reduce the incidence and severity of the ERCP complications. Hopefully, this will result in better ERCP practice, providing a clearer picture of the risk–benefit ratios in different clinical scenarios and a greater ability in advising patients about their options.

Supervisor:

Dr Mohd Nor Gohar Rahman

Co-supervisor:

Dr Syed Hassan Syed Abd Aziz

NEOANGIOGENESIS AND CYCLIN D1 EXPRESSION IN COLORECTAL CARCINOMA

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MPath (Anatomic Pathology)

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Introduction: In Malaysia, colorectal carcinoma is the most common type of cancer among men. Clinical behaviour of colorectal cancer is currently determined by prognostic parameters, which include tumour size, site, stage, and histological grade. Many patients are having recurrences despite the tumour being diagnosed as a local disease.

Objectives: The aim of this study was to determine Cyclin D1 expression and its relationship with clinicopathological variables, especially the Modified Dukes stage.

Patients and Methods: In this cross-sectional study, 61 colorectal carcinoma patients were selected after applying inclusion and exclusion criteria. The patients' archived, paraffin-embedded tissue blocks were obtained from the Department of Pathology, Hospital Universiti Sains Malaysia. Cyclin D1 expression was evaluated based on the intensity and percentage of positive nuclei. In addition, microvessel density, especially at the peritumoural and intratumoural area, was assessed using CD34 endothelial marker. The relationships between Cyclin D1 expression, microvessel density, and clinicopathological variables (particularly with the Modified Dukes stage, which was assessed using immunohistochemical EnVision technique) were analysed.

Results: For the expression of Cyclin D1, samples were divided into low expresser and high expresser groups. 93.5% of cases expressed Cyclin D1 as nuclear brownish precipitate with 55.7% of cases showing low staining intensity. Univariate analysis showed no significant correlation between staining intensity and clinicopathological variables, i.e., sex, race, size of tumour, site of tumour, histological grade, lymph node

metastasis, and tumour stage. 54.1% of colorectal carcinoma cases were in the distribution of less than 10% positive nuclei. Univariate analysis resulted in significant correlations between percentage of positive nuclei and sex, race, lymph node metastasis, and stage of tumour. Other parameters, i.e., size, site of tumour, and histological grade, were not significantly correlated with the percentage of positive nuclei. Multivariate analysis showed that the percentage of positive nuclei was significantly correlated with only lymph node metastasis and tumour stage with ($P < 0.05$). The mean (SD) of peritumoural and intratumoural microvessel densities were 66.8 (17.9) vessel per mm² and 76.7 (28.7) vessel per mm², respectively, indicating the presence of more vessels in the intratumoural areas. The microvessel densities were later grouped into low vascularity and high vascularity; both peritumoural and intratumoural areas had low vascularity. Peritumoural area did show some correlations with clinicopathological parameters, i.e., size, histological grade, stage, and lymph node metastasis; however, the results were not statistically significant. In contrast, intratumoural area did not show any correlation with the clinicopathological parameters.

Conclusion: Percentage of positive nuclei is the most important and useful way to evaluate Cyclin D1 expression. It was significantly correlated with sex, race, tumour stage, and lymph node metastasis. In addition to this, the percentage of positive nuclei was found to be an independent parameter in predicting lymph node metastasis and tumour stage. Microvessel density does not play any role as a prognostic factor in colorectal carcinoma.

Supervisor:

Dr Venkatesh R Nair

EFFECT OF THE SEA CUCUMBER EXTRACT AND TRICHLOROACETIC ACID (TCA) IN THE HEALING PROCESS OF THE TYMPANIC MEMBRANE PERFORATION—PILOT STUDY

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MMed (ORL–Head and Neck Surgery)

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Introduction: Gamat is a marine invertebrate that has high therapeutic value, such as its capability to rejuvenate tissues and hasten wound healing. Its effectiveness is species-specific and dose-dependant. Trichloroacetic acid (TCA) has been utilized to promote tissue generation; the acid cauterization breaks up the fibrosis on the perforation's rim and promotes the formation of granulation and proliferation of new tissues. It has been proposed to be used in treating tympanic membrane perforation. Tympanic membrane perforation is a common problem in otorhinolaryngology.

Many materials and procedures have been used to promote the healing process of the tympanic membrane perforation; these include the use of amniotic membrane, cigarettes paper, and fat plug.

Objective: The objective of this study was to evaluate the healing effect of co-treatment of gamat with TCA versus TCA alone in tympanic membrane perforation.

Patients and Methods: This was a prospective single-blind randomized control trial involving patients with perforated tympanic membrane at the ORL-HNS department, Hospital Universiti Sains Malaysia. The patients were divided into 2 treatment groups: gamat with TCA, and TCA alone. Treatments were performed following the Derlacki method, with some modifications. Both groups were serially examined every 2 weeks. Their tympanic membrane were visualized using rigid otoscope (otoscope size = 2.7 mm), and a photo was taken in every procedure and during follow-up. The perforation area was measured using Material Word Station-Image Analyzer.

Results: There were significant healing improvements of perforated tympanic membrane by using TCA cauterization alone. There were also significant healing improvements of perforated tympanic membrane by using gamat extract with TCA cauterization in perforated tympanic membrane. There was no significant difference of mean healing pattern between the co-treatment of gamat with TCA and single treatment of TCA.

Supervisor:

Professor Dr Dinsuhaimi Sidek

Co-supervisor:

Professor Dr Syed Mohsin Syed Sahil Jamalullail

AN EVALUATION OF QUALITY OF LIFE AMONG PATIENTS UNDERGOING ANGIOGRAM / PERCUTANEOUS CORONARY INTERVENTION IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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MMed (Internal Medicine)

Department of Medicine

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Introduction: Percutaneous coronary intervention (PCI) has emerged as an important mode of treatment in coronary artery disease (CAD). Despite extensive and complexity of PCI, there is no local data to support the benefits of PCI, including the improvement of the quality of life (QOL).

Objective: The goal of this study was to evaluate the impact of PCI on self-perceived QOL among patients after PCI by using Medical Outcome Survey Short Form-36 (MOS SF-36) questionnaires.

Patients and Methods: This is a single centre cross-

sectional study in Hospital Universiti Sains Malaysia (HUSM) conducted among patients electively planned for PCI. We administered the MOS SF-36 questionnaire which has eight domains of QOL such as a physical function, social function, physical role, vitality, general health, mental health, bodily pain, and emotional role. Total scores of improvement were calculated at Day 1 (pre-PCI) and Day 30 (post-PCI).

Results: 75 patients were enrolled in this study. The results showed significant improvement of QOL, with increments in all domains: total score (from 426.1 to 671.1), physical role (from 32.3 to 86.7), emotional role (from 40.0 to 92.9), general health (from 52.4 to 84.8), bodily pain from (54.6 to 83.9), physical function from (56.7 to 84.3), vitality from (56.2 to 77.0), social functioning from (69.5 to 84.0), and mental health from (64.4 to 77.6). All improvements in domains were statistically significant with $P < 0.001$.

Conclusion: Post PCI / angiogram showed significant improvement of QOL assessed by MOS SF-36 questionnaires at Day 30 post-procedure. SF-36 questionnaires provide a simple, reliable, and better predictor in overall QOL assessment by summarizing all eight domains of QOL. Early time return to normal activity with minimum hospital stay along with significant improvement of QOL perceived at Day 30 post-intervention are favourable factors to be considered in choosing PCI as a mode of treatment in CAD.

Supervisor:

Associate Professor Dr Zurkurnai Yusof

Co-supervisor:

Dr Suhairi Ibrahim

RELATIONSHIP BETWEEN INTERVERTEBRAL DISC HEIGHT, LATERAL FORAMEN SIZE, AND NERVE ROOT IMPINGEMENT OF LUMBAR VERTEBRA

Dr Mohammad Nazir Bin Md Hassan
MMed (Orthopaedic)

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Introduction: Degenerative disc disease is a common condition in elderly patients, and its incidence increases with ageing. Patients usually present with back pain and, sometimes, with symptoms of nerve root compression. The degenerative disc disease usually worsens with time. It can be recognized radiographically as a decrease in the intervertebral disc height. Reduction of disc height results in the reduction of lateral foramen size, where the nerve roots exit from the spinal canal.

Objectives: The main objective of this study was to establish the relationship between the lateral foramen size and nerve root impingement in degenerated disc disease. In addition, the study aimed to determine the correlation

between intervertebral disc height and lateral foramen size in degenerative disc disease and radiographically normal disc.

Patients and Methods: This cross-sectional study analysed data taken from the magnetic resonance imaging (MRI) of 62 subjects randomly selected from the radiology archives. The data consisted of measurements of the intervertebral disc height, lateral foramen size, and nerve root size, bilaterally. Reports on symptoms of nerve root compression (such as numbness and weakness) were attained from the patient medical record dated around the day MRI was performed. The findings were analysed using SPSS bivariate correlation test and independent sample t test.

Results: The mean intervertebral disc height was 6.7 ± 1.4 mm at L1L2 level and showed increasing trend at subsequent levels: L2L3 (7.8 ± 1.4 mm), L3L4 (8.7 ± 1.6 mm), and L4L5 (9.0 ± 1.8 mm). At L5S1 level, the mean intervertebral disc height was 8.7 ± 2.0 mm. The lateral foramen height measurements (L1L2–L4L5) were between 17.75 ± 2.30 mm and 19.65 ± 2.25 mm. The mean L5S1 foramen height was 16.40 ± 2.71 mm. The nerve root compression symptoms most commonly occur at L5S1. Statistic analysis showed strong correlation between the intervertebral disc height and lateral foramen height at all levels of the lumbar spine in both degenerated disc and normal disc; however, no correlation was observed between intervertebral disc height and lateral foramen width. There was also no significant correlation between lateral foramen size and nerve root compression at lumbar vertebral.

Supervisor:
Associate Professor Dr Mohd Imran Yusoff
Co-supervisor:
Dr Mohd Shafie Abdullah

NON-ATTENDANCE TO THE PAEDIATRIC CLINIC IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

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MMed (Paediatrics)

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Introduction: Non-attendance is suspected to be a major problem in the paediatric clinic. Non-attendance could lead to severe consequences to the patients, and this could contribute a major burden to the health care system. Several studies have reported more than 30% of non-attendance cases. In Malaysia, no such report was available.

Objectives: The study aimed to determine the rate of non-attendance in the Paediatric Clinic, Hospital Universiti Sains Malaysia (HUSM), and to verify the efficacy of a phone call, given to fix a new appointment for every contactable non-attending patient, in improving clinic attendance.

Patients and Methods: This cross-sectional study

involved all non-attending patients who had an appointment in the Paediatric Clinic during the study period, from 1 January 2009 to 28 February 2009. Non-attendees who were contactable by phone were included for the interventional segment of the study. A prepared proforma was completed for every non-attender. Primary outcome measures included attendance rate and efficacy of a phone call to improve attendance.

Results: During the 1-month study period, 1563 patients had appointment in Paediatric Clinic. A total of 497 patients (31.8%) failed to attend their appointment. There were significant differences of attendance depending on clinic sessions, weather condition, and types of clinic. From 160 patients who were successfully contacted, 95 patients were interested in having a new appointment. There were 55 patients who already had a new appointment at the time they were contacted, 3 non-attendees had died at home, 3 had been admitted, and 2 had moved to another state and were followed-up there. The other 2 patients were not interested in getting a new appointment. 23.3% from the intervention group did not attend the clinic after the given new appointment.

Conclusion: Non-attendance rate is high in the Paediatric Clinic, HUSM. A phone call to fix a new appointment is effective in reducing the non-attendance rate.

Supervisor:
Professor Dr Hans Amin Rostenberghe
Co-supervisor:
Associate Professor Dr Nik Zainal Abidin Nik Ismail

ASSESSMENT OF KNOWLEDGE, ATTITUDE, AND PRACTICES AMONG OPERATING ROOM STAFF NURSES TOWARDS THE STANDARD AND TRANSMISSION-BASED PRECAUTION IN UNIVERSITY HOSPITAL

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Introduction: The standard and transmission-based precautions are strongly recommended as the guidelines for preventing infections and ensuring occupational safety. This survey discussed the level of knowledge, attitude, and practices in relation to the standard precautions and transmission-based precautions among the staff nurses.

Objective: The objective of this survey was to identify relationship between demographic profiles of participants and the knowledge, attitude, and practices towards standard precautions and transmission-based precautions.

Patients and Methods: This self-reported survey was conducted in April 2009 among operating room staff nurses. The questionnaire comprised 3 major components:

knowledge, attitudes, and practices towards the standard and transmission-based precautions.

Results: Out of 100 staff nurses, 75 of them had returned the completed questionnaires on the same day of distribution. There was a significant difference between male and female staff nurses in terms of the practices of the standard and transmission-based precautions. There was a weak correlation between the level of knowledge and the age of the female staff. However, in overall, the results did not show any clear correlation, and there was no statistical significance observed in the different demographic profiles concerning the knowledge, attitudes, and practices towards the standard and transmission-based precautions.

Conclusion: This study on knowledge, attitudes, and practices of operating room staff may benefit healthcare educators in planning and developing appropriate educational programmes, assist organizations to provide a safe workplace climate, and aid healthcare workers to learn the importance of personal responsibility in preventing the transmission infectious disease.

Supervisor:

Associate Professor Dr Saedah Ali

Co-supervisor:

Associate Professor Dr Wan Aasim Wan Adnan

ASSOCIATED FACTORS AND SALIVARY BIOMARKER OF STRESS AMONG ASSISTANT MEDICAL OFFICERS IN MINISTRY OF HEALTH (MOH) HOSPITALS IN KELANTAN AND TERENGGANU

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MMed (Occupational Health)

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Objectives: The objectives of this study were to determine the prevalence of stress among assistant medical officers and the factors contributing to stress. In addition, the presence of biomarker of stress (cortisol) in the saliva was assessed.

Patients and Methods: Study subjects were assistant medical officers from the government hospitals in Kelantan and Terengganu. A questionnaire consisting of demographic, work-related, and stress-related information were completed and returned by the subjects. Salivary cortisol level was also measured.

Results: The prevalence of stress among assistant medical officers was 13.7% (95% CI 8.61 to 18.79). Simple linear regression showed that age ($P = 0.012$), duration of employment ($P = 0.023$), skill discretion ($P = 0.039$), decision authority ($P = 0.039$), decision latitude ($P = 0.012$), psychological job demand ($P = 0.015$), job insecurity ($P =$

0.000), co-worker support ($P = 0.001$), social support ($P = 0.003$), hazardous conditions ($P = 0.001$), toxic exposures ($P = 0.008$), and total physical hazards ($P = 0.001$) were significant factors associated with stress. However, only decision latitude ($P = 0.025$), psychological job demand ($P = 0.021$), job insecurity ($P = 0.009$), and total physical hazards ($P = 0.008$) were significant by general linear regression. There was no significant ($P = 0.393$) correlation between salivary cortisol and stress score. The observed Spearman correlation was 0.066, which suggested no correlation between these 2 parameters. However, salivary cortisol was found to be significantly higher ($P = 0.033$) among stressed compared to non-stressed assistant medical officers (0.78 $\mu\text{g/dL}$ versus 0.67 $\mu\text{g/dL}$, respectively).

Conclusion: The prevalence of stress was 13.7%. Decision latitude, psychological job demand, job insecurity, and total physical hazards were the significant associated factors of stress. There was no correlation between salivary cortisol and stress score. However, salivary cortisol was significantly higher among stressed assistant medical officers. Hence, improving the working environment, joint workplace initiatives, team-oriented approaches practice, empowering, and giving more autonomy would improve the work climate and alleviate stress among assistant medical officers.

Supervisor:

Dr Aziah Daud

Co-supervisor:

Dr Wan Mohd Zahiruddin Wan Mohammad

THE EFFECT OF SINGLE DOSE GABAPENTIN ON HAEMODYNAMIC CHANGES FOLLOWING LARYNGOSCOPY AND TRACHEAL INTUBATION

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Introduction: Adrenergic responses manifested by tachycardia and hypertension are known to occur following laryngoscopy and intubation. Various drugs have been used in attempts to attenuate this response; however, all have their limitations. A more satisfactory approach for this situation might be to use 800 mg gabapentin, which can provide good control for a short period of laryngeal tracheal intubation for a planned elective case that require general anaesthesia. Gabapentin also have other complimentary actions. Many studies using gabapentin as a single agent peri-operatively showed promising outcomes. In this study, the capability of this drug to attenuate the haemodynamic response to laryngoscopy and tracheal intubation was evaluated.

Objectives: The objectives of this double-blinded,

randomized study were to compare the effect of haemodynamic changes after laryngoscopy and tracheal intubation in patients pre-treated with placebo or a dose of gabapentin (600 mg or 800 mg) and to determine the optimal dose of gabapentin to attenuate the haemodynamic changes.

Patients and Methods: A total of 111 patients of ASA physical status I or II undergoing elective surgery were selected and divided into 3 pre-treatment groups: placebo (control group), 600 mg gabapentin, and 800 mg gabapentin, all as pre-treatments prior to intubation. All patients were then induced using intravenous fentanyl (1.5 µg/kg), propofol (2 mg/kg), and esmeron (1.5 mg/kg). Intubation was performed 3 minutes following esmeron injection. Anaesthesia was maintained with nitrous oxide in oxygen with a ratio of 2:4 and 2.0% sevoflurane. Selected parameters, i.e., heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded prior to injection of study drugs as baseline, at 1 minute after laryngeal tracheal intubation, and every minute after laryngoscopy and tracheal intubation for 5 minutes. Patients were also monitored for complications, such as bucking, moving limbs, bronchospams, hypotension, and arrhythmia.

Results: The results showed that mean HR, SBP, DBP, and MAP were increased in all groups after laryngoscopy and tracheal intubation compared with baseline. However, percentages of increase in the HR, SBP, DBP, and MAP after laryngoscopy and tracheal intubation in the 800 mg gabapentin group were the least compared with the other groups.

Conclusion: This study has shown that the dose of gabapentin at 800 mg was able to give the minimum percentage changes of the mean HR, SBP, DBP, and MAP after laryngoscopy and tracheal intubation within a certain period (5 minutes). It can be concluded that pre-emptive treatment with gabapentin (800 mg) can be used to attenuate the haemodynamic response during laryngeal tracheal intubation.

Supervisor:
Dr Nizar Abd Jalil

EFFECTIVENESS OF OCCUPATIONAL STRESS MANAGEMENT PROGRAM AMONG PETROCHEMICAL INDUSTRY WORKERS IN KERTEH, TERENGGANU

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Introduction: Occupational stress is an increasingly important occupational health problem that can lead to a significant economic lost. Petrochemical industry workers are

one of several occupational groups potentially experiencing high level of stress. They work in high-pressure environment, handling hazardous material, and managing large amount of chemical energy.

Objectives: The aim of this study was to determine the prevalence and associated factors of depression, anxiety, and stress among workers in the petrochemical industry. In addition, an intervention program on occupational stress was introduced and evaluated.

Patients and Methods: This was an intervention study to assess the effect of stress management intervention program based on DASS42 score. The stress management program adopted consisted of lectures on stress and stress management, video sessions, question and answer sessions, pamphlet distribution, and aerobic exercises. Validated Malay-versions of the Depression, Anxiety, and Stress score (DASS42) and Job Content Questionnaire (JCQ) were used. The respondents were asked to complete DASS42 and JCQ at the beginning of the program. This gave the prevalence and associated factors of depression, anxiety, and stress. The respondents were again asked to complete the DASS42 immediately after the intervention program and 1 month post-intervention. Multiple linear regression analysis was done to evaluate the stress-associated factors, and repeated measures of analysis of variance (ANOVA) were done to determine the effect of intervention.

Results: Out of 51 participants, there were 50 Malays and 1 Indian. The mean (SD) age was 33.57 (7.39) years old and duration of work was 7.27 (3.47) years. The prevalence (95% CI) of depression, anxiety, and stress of moderate severity or more were 23.53 (95% CI 11.48 to 35.58), 31.37 (95% CI 18.19 to 44.55), and 21.57 (95% CI 9.89 to 33.25), respectively. Type of work, decision latitude, and psychological job demand were found to be associated with depression. Level of education and exposure to toxic material were associated factors for anxiety. Marital status and psychological job demand were associated factor for stress. In the assessment of effectiveness of stress management program, it was found that there were significant reduction in occupational stress post-intervention (immediate and 1 month after) with estimated marginal mean of depression score, anxiety score, and stress score ($P < 0.001$).

Conclusion: There is an evidence of occupational stress in the petrochemical workplace where prevalence of stress, anxiety, and depression were considerably high. It indicates the needs to improve the work environment, in terms of decision latitude, psychological job demand, and toxic exposure. A regular, short stress management program is effective in reducing some aspect of depression, anxiety, and stress in the petrochemical workers.

Supervisor:
Associate Professor Dr Mohamed Rusli Bin Abdullah
Co-supervisor:
Dr Aziah Binti Daud
Dr Nor Azwany Yaacob

THE PROPORTION OF METABOLIC SYNDROME PATIENTS AND ASSOCIATED FACTORS AMONG SUBJECTS UNDERGOING CORONARY ANGIOGRAM IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM), KOTA BHARU, KELANTAN, USING IDF AND ASIAN MODIFIED NCEP ATP III CRITERIA

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MMed (Family Medicine)

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Introduction: There is an increasing prevalence of metabolic syndrome worldwide, which is closely related to the presence of coronary artery disease. Metabolic syndrome worsens the severity of coronary artery disease. However, information on the percentage of metabolic syndrome among heart disease patients in Malaysia is lacking.

Objectives: The objectives of this study were to determine the proportion of metabolic syndrome using both the Internal Diabetes Federation (IDF) and Asian-modified National Cholesterol Education Program—Third Adult Treatment Panel III (NCEP ATP III) criteria, and to determine the factors associated to metabolic syndrome among patients undergoing coronary angiogram in Hospital Universiti Sains Malaysia.

Patients and Methods: A cross-sectional study was conducted among 236 patients who fulfilled the inclusion criteria and were suspected of having coronary artery disease. These patients came for elective coronary angiograms from September 2006 to April 2008; 228 patients underwent angiogram procedure while 8 patients were unable to do so due to several reasons. Metabolic syndrome was defined using both the IDF and Asian-modified NCEP ATP III criteria. The required information on demographic, physical, and biochemical parameters related to the metabolic comorbidities was recorded in a data collection form. The patients' medical records were then reviewed to assess the degree of coronary artery disease severity.

Results: The proportion of metabolic syndrome based on IDF criteria among patients undergoing coronary angiogram in HUSM was 50.0%, and based on Asian-modified NCEP ATP III criteria, 76.8%. The majority of patients who underwent angiograms were diagnosed with coronary artery disease (73%). There were 20% patients with one-vessel disease while 53% patients had multi-vessel disease; 22% patients with two-vessel disease and 31% patients with three-vessel disease. There was a significant association between metabolic syndrome patients (based on IDF criteria) and smoking (OR = 2.08, 95% CI 1.20 to 3.63). Based on the Asian-modified NCEP ATP III criteria, there were associations between metabolic syndrome and age (OR = 2.20, 95% CI 1.04 to 4.68), female sex (OR = 3.99, 95% CI 1.28 to 12.30), and smoking (OR = 7.00, 95% CI 3.05 to 16.00).

Conclusion: The proportion of metabolic syndrome among patients undergoing coronary angiogram was similar to other studies. The proportion of metabolic syndrome was higher if the Asian-modified NCEP ATP III criteria were used compared with IDF criteria. Age of more than 60 years old, female sex, and smoking were significantly associated with presence of metabolic syndrome.

Supervisor:
Dr Azidah Abdul Kadir

MULTIMODALITY ASSESSMENT OF MILD AND MODERATE HEAD INJURY PATIENTS

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MSurg (Neurosurgery)

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Objectives: The aim of this research was to compare the disability, which may be proven using the analysis of the Barrow Neurological Institute (BNI) Screen for Higher Cerebral Functions, as well as the disturbance in balance control, sensory perception, and the presence of nystagmus in patients with mild and moderate head injury.

Patients and Methods: This was a prospective study conducted from August 2006 until November 2007. The selection criteria were patients who sustained mild and moderate head injury and admitted or referred to the Hospital Universiti Sains Malaysia. Qualified patients were called within 4 to 6 weeks after the occurrence of head injury. Their complaints of headache, memory loss, sensory disturbance, as well as gait and visual abnormalities would be noted. The patients were given a series of tests, starting with the BNI Screen for Higher Cerebral Functions, conducted in the local, Malay language. The Sensory Organization Test (SOT) was conducted using the SMART Balance Master (NeuroCom International, Inc, USA) to test for balance, i.e., how visual, somatosensory, and vestibular inputs affect a patients' ability to maintain functional balance. The presence of nystagmus was tested using the Visual Eyes Nystagmography (Micromedical Technologies, USA) where a stimulus was delivered via a tower, and the movement of the eye was followed, recorded, and analyzed for abnormalities. The cold detection threshold (CDT) was measured with Computerised Assisted Sensory Evaluator (WR Medical Electronics, USA) using the 4, 2, and 1 stepping algorithm with null stimuli. The test was performed on the dorsal aspect of the palm of the left hand; a subject indicated that a stimulus was felt by pressing the iyesí button (and no button, if otherwise), and the just noticeable difference (JND) was calculated from the subjects responses. Data's analyses were done using the SPSS version 12.0.

Results: The study involved 11 male patients (92%) and one female patient (8%). The age of the patients ranged over 18-63 years, with a mean of 33.3 years and a median of 29.0 years. A majority of the patients cases were categorized under moderate head injury (75%), and all (100%) injuries resulted from motor vehicle accidents. Patients with mild head injury have higher BNI score compared with those with moderate head injury, with mean values of 45.00 and 43.11, respectively. A similar pattern was observed in BNI sub-test scores, particularly in speech and language, attention/concentration, visuo-spatial and visual problem solving, and memory. However, none of the results were significant by Mann-Whitney test. There was no evidence to support the hypothesis that moderate head injury causes significant disturbance in balance. Both groups of patients, with mild and moderate head injury, has normal balancing reflex when tested using the computerized post urography. In addition, no significant sensory disturbance or post-traumatic nystagmus was observed.

Conclusion: The disability reported by the patients, such as complaints of forgetfulness and lack of concentration, could not be demonstrated by using the BNI Screen for Higher Cerebral Functions. Other tests carried out failed to prove any significant disturbances. Therefore, the cause and effect of a post-concussive syndrome can only be diagnosed clinically.

Supervisor:
Professor Dr Jafri Malin Abdullah

ANAEMIA AMONG HIV-INFECTED PATIENTS: PREVALENCE, ASSOCIATED RISK FACTORS, AND QUALITY OF LIFE

Dr Nik Norashikin Binti Nik Ab Rahman
MMed (Family Medicine)

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School of Medical Sciences, Universiti Sains Malaysia
Health Campus, 16150 Kelantan, Malaysia

Introduction: Anaemia is a common manifestation of HIV infection, with reported prevalence ranging from 30% in asymptomatic HIV patients to 80% in clinical AIDS patients. It is associated with disease progression, poor quality of life, and increased mortality in HIV-infected individuals.

Objectives: The objectives of the study were to determine the prevalence of anaemia, its associated factors, and impact on quality of life in HIV-infected individuals. Correlation between haemoglobin level and CD4 count was also assessed.

Patients and Methods: A cross-sectional study was conducted among 248 HIV-infected adults attending the Infectious Disease Clinic, Hospital Raja Perempuan Zainab II, Kota Bharu, from 1 January 2008 until 31 December 2008. Patients who were pregnant or on combination antiretroviral therapy were excluded from the study. The socio-demographic

and medical data, including the latest haemoglobin and CD4 results, were taken for analysis. Assessment on the quality of life was done using Medical Outcome Study-HIV (MOS-HIV) questionnaire.

Results: Overall prevalence of anaemia was 46.0% (95% CI 39.77 to 52.10), with a mean (SD) haemoglobin value of 12.3 (2.4) g/dL. In multiple logistic regression analysis, several factors were observed to be significantly associated with anaemia: CD4 count of less than 200 cells/ μ L (OR 5.28, 95% CI 2.53 to 11.01), oral candidiasis (OR 5.02, 95% CI 1.82 to 13.87), history of blood transfusions (OR 4.87, 95% CI 1.53 to 15.49), and income of RM501-RM1000 (OR 0.40, 95% CI 0.17 to 0.94 and more than RM1000 (OR 0.24, 95% CI 0.12 to 0.52). There was a significant correlation between the haemoglobin value and CD4 count ($P < 0.001$, Spearman correlation = 0.443). Anaemic patients had significantly lower MOS-HIV subscale scores in general health perception, pain, physical function, role function, energy, and quality of life ($P < 0.05$).

Conclusion: The high prevalence of anaemia among HIV-infected individuals was comparable with other countries. Anaemia significantly impaired the quality of life of these individuals. Knowing the associated factors for anaemia should prompt a more careful evaluation into the presence of anaemia in any HIV-infected individuals.

Supervisor:
Dr Juwita Shaaban:
Co-supervisors:
Dr Amaluddin Ahmad
Dr Mahiran Mustafa

FAMILY PRESENCE DURING CARDIOPULMONARY RESUSCITATION: ATTITUDES AND EXPERIENCES OF MEDICAL PERSONNEL AND PARENTS

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MMed (Paediatrics)

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Introduction: Presence of family during cardiopulmonary resuscitation (CPR) is not a widespread practice; however, it is becoming more common nowadays. Normally, family members are not allowed to be present during CPR, and this is a true medical practice in most hospitals in Malaysia.

Objectives: The study aimed to determine the attitudes and experiences of medical personnel and parents in Hospital Universiti Sains Malaysia and Hospital Sultanah Nur Zahirah regarding family presence during CPR in children and the associated demographic factors that contribute toward such attitudes.

Patients and Methods: This was a prospective cross-

sectional study. Respondents include medical personnel caring for sick children and convenience sample of parents whose children were admitted in these hospitals. A questionnaire was developed based on previous literature review; the questionnaire incorporated demographic data, questions on CPR experiences, and a series of attitude statement that were rated using 5-point Likert scale. A self-administered questionnaire was given to the medical personnel while the parents were interviewed using a standard questionnaire after giving their verbal consent. A brief video was showing to the parents before the interview to increase the understanding of CPR. The attitude, experiences, and association of demographic factors with the acceptance of family presence during CPR in children were studied.

Results: Only 86 (19.9%) of medical personnel had previously participated in the CPR in children in the presence of family members. Out of 100 parents, 19 (19%) had experienced being present during CPR of their children. A majority of 279 medical personnel (64.5%) did not approve allowing family members to be with their children during CPR; However, a majority of 253 medical personnel (58.6%) would like to be present during CPR of their own children. On the other hand, 74 parents (74%) were of the opinion that family members should be allowed to be present during CPR. Logistic regression analysis demonstrated no significant association between the agreement of family presence during CPR with the demographic factors in both medical personnel and parents.

Conclusion: Medical personnel and parents showed different attitudes toward family presence during CPR in children.

Supervisor:

Professor Dr Quah Ban Seng

Co-supervisor:

Dr Noraida Ramli

THE PREVALENCE OF URINARY INCONTINENCE, ITS ASSOCIATED RISK FACTORS, AND THE IMPACT ON QUALITY OF LIFE AMONG MARRIED WOMEN IN HOSPITAL SULTANAH NUR ZAHIRAH, KUALA TERENGGANU

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MMed (O & G)

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Introduction: Urinary incontinence is defined by the International Continence Society as the complaint of any involuntary leakage of urine. Urinary incontinence is a common condition with significant medical, social, and psychological problems in women. It is very common in women that it is often mistakenly viewed as a natural process

of ageing.

Objectives: The aim of this study was to determine the prevalence of urinary incontinence as well as its risk factors and impact among married women.

Patients and Methods: A cross-sectional descriptive analysis was conducted among 300 married women attending Hospital Sultanah Nur Zahirah. A structured questionnaire, prepared in Malay language, was used to collect the data. The questionnaire consisted of 3 parts. Part 1 was on the demographic data and medical history of the respondent, e.g., age, education, occupation, weight, height, parity, menopause status, surgical, obstetrical, gynaecological history. Part 2 and 3 were the validated Bristol Female Lower Urinary Tract Symptom (BFLUTS) questionnaire consisting of 34 questions that provided the assessment of incontinence, other urinary symptoms, sexual function, and aspect of quality of life. Statistical analyses were performed using chi-square test and multiple logistic regression analysis.

Results: The mean age of the women was 41.0 (SD 9.86) years old. The overall prevalence of urinary incontinence was 37.7%. The prevalence of stress incontinence was 16.7%, urgency incontinence, 9.3%, and mixed incontinence, 11.7%. Factors that influenced overall urinary incontinence were parity, menopause, duration of menopause, and mode of delivery. Among the different modes of delivery, spontaneous vagina deliveries and instrumental deliveries had significant influence on urinary incontinence. Mode of delivery and the increases in parity and duration of menopause were significantly influencing stress incontinence. Mixed incontinence was significantly influenced by menopausal status of the women and the increases in age and duration of menopause. No risk factor that could be significantly associated with urgency incontinence was observed in this study. All types of urinary incontinence (stress, urgency, and mixed) significantly affected the quality of life of the women, especially in physical activities ($P < 0.05$), functional activities ($P < 0.05$), social life ($P < 0.05$), and sexual life ($P < 0.05$). Only 14.3% of the women experiencing incontinence sought treatment.

Conclusion: The prevalence of urinary incontinence was high among the studied population. Stress incontinence had the highest prevalence, followed by mixed incontinence and urgency incontinence. All types of urinary incontinence were significantly affecting the quality of life of the women. The percentage of incontinence women who sought treatment was very low. It was recommended for public education to focus on cognitive and affective learning in order to increase the public knowledge about the causes and treatments of incontinence, and to remove the stigma surrounding incontinence.

Supervisor :

Dr Mohd Pazudin Ismail

Co-supervisors:

Professor Dr Nik Mohamad Zaki Nik Mahmood

Dr Nasir Tak Abdullah

EVALUATION OF 8-HYDROXYDEOXYGUANOSINE ENZYME AND MICROSCOPIC FEATURES IN PRIMARY AND RECURRENT PTERYGIA

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MMed (Ophthalmology)

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Introduction: Pterygium is a common external ocular disease that normally occurred in the tropical regions because of the exposure to sunlight, which is considered as a major factor in the development of pterygium. Sunlight contains ultraviolet B radiation that causes oxidative damage to the DNA of the cells. This leads to the production of 8-OHdG enzyme, which is highly mutagenic, that increase cellular proliferation and development of pterygium.

Objectives: The study objectives were to demonstrate the association between the presence of 8-OHdG enzyme and the type of pterygium, as well as to determine the microscopic features (cell maturation, epithelial cell layers, and stromal vascularity) of primary and recurrent pterygia, and comparing these features between those with positive and negative 8-OHdG enzyme in pterygia.

Patients and Methods: A total of 92 samples were collected from the pterygium patients. The samples were processed for histopathology examination and immunohistochemistry test to detect the presence of 8-OHdG enzyme.

Results: The presence of 8-OHdG enzyme was 63.6% in primary pterygium, 16.6% in recurrent pterygium, and 16.0% in normal conjunctiva (control) group. There was a significant association between the presence of 8-OHdG enzyme and primary pterygium ($P < 0.001$). The highest cell maturation (Grade 3 of 10 or more nucleated cells) was observed in normal conjunctiva (in 5 samples), followed by primary pterygium (in 2 samples) and recurrent pterygium (none). The mean epithelial cell layer in primary pterygium was 6, and in recurrent pterygium, 5; both were higher than the mean of control group, which was 3. The means of stromal vascularity were 9 in primary pterygium and 12 in recurrent pterygium, while in normal conjunctiva it was 3. There was no significant difference in the mean cellular maturation, epithelial cell layers, and stromal vascularity between those with positive and negative 8-OHdG enzyme in all types of pterygium.

Conclusion: There was significant association between the presence of 8-OHdG enzyme and primary pterygium. Histopathology examination revealed increased cellularity and vascularity in recurrent pterygium, which is higher than primary pterygium; both showed higher figures than in normal conjunctiva. There was no significant difference in the mean cellular maturation, epithelial cell layers, and stromal vascularity between those with positive and negative 8-OHdG enzyme in all types of pterygia. There was no significant

difference in the mean cellular maturation and epithelial cell layers associated with 8-OHdG enzyme between the different pterygium groups; however, there was significant difference in the mean stromal vascularity associated with 8-OHdG enzyme between primary pterygium and normal conjunctiva.

Supervisor:
Associate Professor Dr Mohtar Ibrahim
Co-supervisor:
Associate Professor Dr Hasnan Jaafar

A STUDY OF BLOOD GLUCOSE LEVEL DURING ADMISSION AND 24 HOURS POST-OPERATION WITH THE OUTCOME OF TRAUMATIC BRAIN INJURY IN HOSPITAL KUALA LUMPUR: AN OBSERVATIONAL STUDY

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MMed (Neurosurgery)

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Introduction: Traumatic brain injury (TBI) has been associated with acute stress response via sympathoadrenomedullary axis of which, clinically, can be reflected in the increase of blood sugar level.

Objectives: This study aimed to determine whether isolated TBI would cause any increase in blood sugar level on admission and 24 hours after having surgical intervention for the injury.

Patients and Methods: This prospective observational study was conducted among patients treated for TBI in Hospital Kuala Lumpur from January 2007 until December 2007. A total of 294 patients were selected following the inclusion and exclusion criteria; the patients include those with mild, moderate, and severe TBI. A standard performa was used to collect the data.

Results: The patients' age ranged 18–65 years old with mean (SD) of 34.2 (13.0) years old. The median age was 31 years old with a mode of 22 years old (50th centiles at 31 years old and 75th centiles at 43 years old). The majority of the cases were young adult patient. Out of 294 cases, 83.0% ($n = 244$) patients were male and 50 patients 17.0% ($n = 50$) were female, with male to female ratio of 5:1. The subjects comprised mostly Malay ethnicity, 53.4% ($n = 157$), followed by Chinese, 20.8% ($n = 61$), Indians, 14.6% ($n = 43$), and others, 11.2% ($n = 33$). The majority of cases were direct admission from Emergency Department, 57.8% ($n = 170$), followed by referrals from district hospitals, 39.8% ($n = 117$), and others, 2.4% ($n = 7$). Road traffic accident presented as the most common type of injury, 91.5% ($n = 269$), whereas fall presented 6.8% ($n = 20$) and assault cases, 1.7% ($n = 5$). From this study, computed tomography scan of the brain revealed mass lesions in 93.2% of patients ($n = 274$). These lesions include subdural hematoma,

45.6% ($n = 134$), extradural hematoma, 27.9% ($n = 82$), and intraparenchymal/contusion hematoma, 26.5% ($n = 78$). The mean (SD) of Glasgow Coma Scale upon admission was 9.3 (2.5). Most patients suffered severe head injury, 47.6% ($n = 140$), followed by moderately severe head injury, 35.4% ($n = 104$), and mild head injury 17.0% ($n = 50$). Patients subjected for major operation was 82.3% ($n = 242$), minor operation, 6.6% ($n = 19$), and conservative treatment, 11.2% ($n = 33$). The mean (SD) admission blood glucose level was 6.26 (1.30) mmol/L, while for 24 hours post operative, it was 6.64 (1.44) mmol/L. There is only slight increment of mean glucose level to suggest that isolated TBI was the main cause for raise blood sugar level ($P < 0.001$ in analysis of variance). Mild TBI group has a mean (SD) glucose level of 5.04 (0.57) mmol/L, moderate TBI group, 5.78 (0.89) mmol/L, and severe TBI, 7.04 (1.24) mmol/L. There is significant difference of admission glucose level for severe TBI compared with mild and moderate TBI ($P < 0.01$ in independent t test). Mean (SD) admission glucose in isolated TBI patient associated with poor outcome was 6.98 (0.10) mmol/L; however, it was not significant ($P > 0.05$ in independent t test). However, patients with mean (SD) admission glucose of 5.56 (0.88) mmol/L were more likely to have favourable outcome ($P < 0.001$ in independent t test).

Conclusion: This study showed significant differences of blood glucose level in isolated TBI. Mild, moderate, and severe TBI would cause a raise in blood sugar level during admission, and the mean increased according to the severity of isolated TBI. Surgical intervention did not cause any significant changes in the blood glucose level. Isolated TBI with minimal increase of blood sugar level would have favourable outcome.

Supervisor:

Dr Mohammed Saffari Mohammed Haspani

PROSPECTIVE RANDOMIZED CONTROL TRIAL COMPARING METFORMIN AND CLOMIPHENE CITRATE AS OVULATION INDUCTION AGENT IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME AT ALOR STAR HOSPITAL, MALAYSIA

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MMed (O & G)

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Objectives: The study was design to evaluate the effects of metformin on weight reduction, waist-hip ratio (WHR), menstrual cycle, and ovulation rates among women with polycystic ovarian syndrome and infertility.

Patients and Methods: A total of 115 patients diagnosed with polycystic ovarian syndrome (according to the revised Rotterdam ESHRE/ASRM criteria, 2003) attending Infertility Clinic of Alor Star Hospital were recruited and

later randomized into 3 group: Group A, metformin alone ($n = 38$), Group B, clomiphene citrate alone ($n = 39$), and Group C, combination of metformin and clomiphene citrate ($n = 38$). During the first visit, the WHR of each patient was measured. Baseline levels of serum follicular stimulating hormone, luteinising hormone, testosterone, liver function test, renal function test, and serum prolactin, were evaluated. In Group A, metformin (500 mg tds) was given for a period of 6 months. In Group B, clomiphene citrate (100 mg) was given daily, from day 2 to day 6 of menstruation. The dosage was increased by 50 mg for each cycle should anovulation was noted, to a maximum of 200 mg. In Group C, a combination of metformin and clomiphene citrate were given according to the dosage received by Groups A and B. Ovulation was confirmed by performing transvaginal scan. The evaluation of the WHR and levels of serum follicular stimulating hormone, luteinising hormone, and testosterone was repeated every 3 months.

Results: Metformin has no effects on weight reduction or WHR. Only 9 out of 38 patients (23.7%) who took metformin had ovulation compared with 28 out of 39 patients (71.8%) who took clomiphene citrate. This difference was statistically significant ($P < 0.001$). There was no significant difference in the number of patients who had ovulation between those taking clomiphene citrate alone (28 out of 39 patients, 71.8%) and combination of clomiphene citrate and metformin (26 out of 38 patients, 68.4 %).

Conclusion: Metformin has no effect on weight and WHR reduction. It should not be used to regulate menstrual cycle in patients with polycystic ovarian syndrome. Its usage was not superior to the traditionally used clomiphene citrate in inducing ovulation among patients of polycystic ovarian syndrome with fertility problem, and no additional advantage could be gained if it was combined with clomiphene citrate. Therefore, the current protocol of using clomiphene citrate as the first-line drug in the induction of ovulation among patients with polycystic ovarian syndrome and infertility should remain.

Supervisor:

Associate Prof Adibah Ibrahim

Co-supervisors :

Dr Murizah Md Zain

Dr Mohd Rushdan Md Nor

A STUDY OF DEPRESSION AND/OR ANXIETY AMONG ADULT TYPE 2 DIABETES MELLITUS PATIENTS ATTENDING DIABETIC CENTER, HOSPITAL UNIVERSITI SAINS MALAYSIA

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MMed (Family Medicine)

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Objectives: The study objectives were to determine the prevalence of depression and/or anxiety and their associated factors among patients with diabetes mellitus in USM.

Patients and Methods: This was a cross-sectional study involving 260 Type 2 Diabetes Mellitus adult patients attending the Diabetic Centre, Hospital Universiti Sains Malaysia from November 2007 until March 2008. The patients were interviewed using a set of questionnaires on socio-demographic, family dynamic, and medical history. Screening for depression and anxiety was done using self-administered Hospital Anxiety and Depression Scale. Patients who obtained a score of 9 and above were considered positive for anxiety and depression. They were referred to psychiatrist for further assessment to confirm the diagnosis according to the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) criteria.

Results: The prevalence of depression was 20.8%, and anxiety, 10.8%. The factors that significantly increase the risk for depression in these patients were working in private sector, receiving income from other family members, cared by children during acute illness, and the presence of diabetic retinopathy as well as diabetic foot ($P < 0.05$ in each). Those who had received secondary and tertiary level of education, satisfied with their income, and had retired had a significantly lower risk for depression ($P < 0.05$ in each). Patients with diabetic foot were significantly more prone to anxiety ($P < 0.05$); in contrast, result showed that males and those with occasionally dominance in family decision-making process were associated with less anxiety ($P < 0.05$ in each).

Conclusion: Prevalence of depression among Type 2 Diabetes Mellitus patients was similar with most studies; however, the prevalence of anxiety was lower in this group of patients. Depression and anxiety risks increased with presence of one or more problems related to occupation, family matters, and the disease complications.

Supervisor:

Dr Azidah Abdul Kadir

Co-supervisors:

Dr Asrenee Abdul Razak

Dr Azriani Abd Rahman

THE EFFECT OF INTRATHECAL BUPIVACAINE VS ROPIVACAINE ON SEDATION REQUIREMENT OF PROPOFOL

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Introduction: Regional anaesthesia with supplementary sedation is often performed for patient's comfort during surgery. Continuous infusion of propofol is a useful sedation method because of the easy management

by titration and rapid emergence. Spinal anaesthesia is known to have the sedative effect and decreases the sedative or anaesthetic dose requirement of general anaesthetics. Therefore, it is possible that after a spinal anaesthesia, even routine doses of sedatives can lead to some unwarranted effects.

Objectives: The study was designed to evaluate whether 2 different types of local anaesthetic (plain bupivacaine and plain ropivacaine) can affect the quality of sedation of propofol during bispectral index (BIS)-guided sedation in lower limb orthopaedic surgery.

Patients and Methods: A double-blind randomized clinical trial was conducted among 70 ASA Grade I and II patients who underwent orthopaedic surgery of the lower limb, with the duration of operation of less than 3 hours. These patients received an intrathecal injection of either 15 mg ropivacaine (3 ml of 0.5% solution) or 15 mg bupivacaine (3 ml of 0.5% solution). 15 minutes after obtaining the appropriate level of spinal anaesthesia, propofol infusion was started at a rate of 6 mg/kg/hr to achieve a BIS level of less than 75 (onset time), then reduced to 3 mg/kg/hr and titrated to maintain the BIS level between 65 and 75. Propofol infusion was stopped at 50th minutes after spinal anaesthesia to measure the time taken to reach a BIS level of 90 (recovery time).

Results: Median anaesthetic level was T4 in the bupivacaine group and T10 in the ropivacaine group. In both the bupivacaine and the ropivacaine groups, the onset times were 243.1 (SD 48.1) seconds versus 269.1 (SD 50.7) seconds ($P < 0.05$), the recovery times were 278.2 (SD 46.8) seconds versus 251.0 (SD 47.5) seconds ($P < 0.05$), the loading doses of propofol were 0.50 (SD 0.09) mg/kg versus 0.54 (SD 0.10) mg/kg ($P < 0.05$), and the maintenance doses were 2.13 (SD 0.38) mg/kg/hr versus 2.40 (SD 0.33) mg/kg/hr ($P < 0.01$), respectively. Haemodynamic variables during sedation period did not show any significant difference between the 2 groups.

Conclusion: Bupivacaine at 15 mg, 0.5% solution was associated with a faster onset time, delayed recovery time, and lower dose of propofol sedation requirement compared with ropivacaine at the same dosage. The height of spinal anaesthesia and potency of local anaesthetic were factors that influenced the requirement of propofol for sedation. Haemodynamic variables in bupivacaine group and ropivacaine group were comparable and did not show significant difference.

Supervisor:

Professor Dr Nik Abdullah Nik Mohamad

FEATURES AND PATHOGENS IN COMMUNITY-ACQUIRED PNEUMONIA

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MMed (Internal Medicine)

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Introduction: Community-acquired pneumonia (CAP) is associated with significant mortality rate. Despite that, the initial treatment is mainly empirical because the precise aetiology is usually unknown at the time of initiating the antibiotic therapy.

Objectives: The objectives of this study were to determine the prevalence and the local pattern of aetiological pathogens causing CAP among hospitalized patients, and to look at the associated risk factors (old age, co-morbidities, and smoking), the severity of CAP at presentation (based on CURB-65 score), as well as the clinical and radiological features with any specific group of pathogens in order to guide for empirical antibiotic therapy and its subsequent management.

Patients and Methods: The cross-sectional study was performed from June 2008 to March 2009 in Hospital Universiti Sains Malaysia. All adults aged 18 years old and above who were admitted to general medical wards for CAP, willing to participate with informed consent, and fulfilled the inclusion criteria were selected. The largest sample size required was 152 samples. Diagnostic microbial specimens that were collected were tested in blood and sputum cultures, serology, viral studies, and sputum acid-fast bacilli (AFB) or tuberculosis (TB) culture. Demographic data, risk factors, clinical and radiological features, CAP severity at presentation, and laboratory results were recorded. Variables obtained were analysed for the prevalence as well as significant associations using chi-square test and logistic regression analysis.

Results: A total of 143 subjects were enrolled in this study. The prevalence of identified pathogens in CAP was $38 \pm 5\%$ (95% CI 30% to 47%). The most commonly isolated pathogens were the Gram-negative bacteria, namely, *Haemophilus influenza* (6.3%) and *Klebsiella* spp. (6.3%), including *Klebsiella pneumoniae*. *Mycobacterium tuberculosis* was found in 6.3% of samples. Multivariate analysis revealed that antibiotic therapy given prior to the test reduced the ability to correctly identify the pathogens ($P = 0.040$, OR = 0.42). Underlying bronchiectases ($P = 0.026$, OR = 4.19) or presence of alveolar infiltrates ($P = 0.045$, OR = 3.54) were significantly associated with identified pathogens. Presence of purulent sputum ($P = 0.001$, OR = 9.43) or underlying bronchiectases ($P = 0.005$, OR = 6.73) were associated with Gram-negative bacteria. Diabetes mellitus ($P = 0.013$, OR 8.53) and cavitation on chest radiograph ($P = 0.003$, OR = 19.32) were associated with *Mycobacterium tuberculosis*. Univariate analysis on Gram-positive pathogens showed its association with only fever of more than 38.5°C ($P = 0.014$). Blood culture were more likely to be positive in the presence of fever of more than 38.5°C ($P < 0.001$), haemodynamic instability with systolic blood pressure of less than 90 mmHg and diastolic blood pressure of 60 mmHg and less ($P = 0.002$, OR = 15.50), or underlying diabetes mellitus ($P = 0.047$, OR 5.81). Presence of purulent sputum ($P = 0.024$, OR 3.47) or underlying bronchiectases ($P = 0.030$, OR = 4.46) were associated with positive sputum culture. Subjective feeling of breathlessness were less likely to be associated with identified pathogens ($P = 0.012$, OR = 0.35) or Gram-negative

pathogens ($P = 0.030$, OR = 0.321). There was no significant association between old age (more than 60 years old), current cigarette smoking status, or severity of CAP on admission with any specific group of pathogens ($P > 0.05$). Atypical pathogens were not associated with any factors or features.

Conclusion: The prevalence of identified pathogens in our study was within the expected range. Gram-negative bacteria were the most common pathogens identified; this was similar to a previous local study. *Mycobacterium tuberculosis* was not an uncommon cause of CAP. Certain factors and clinical presentation of CAP were associated with specific group of pathogens. Prescription of empirical antibiotic therapy that covers Gram-negative pathogens as well as further investigation to look for tuberculosis in high risk patients are recommended.

Supervisor:

Associate Prof Che Wan Aminud-din Hashim

Co-supervisors:

Dr Shaharudin Abdullah

Dr Siti Suraiya

THE ASSOCIATION STUDY BETWEEN MAGNETIC RESONANCE IMAGING (MRI) AND PERCUTANEOUS TRANSPEDICULAR BIOPSY (HPE) FINDINGS IN VERTEBRAL LESIONS

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MMed (Orthopaedics)

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Introduction: Magnetic resonance imaging (MRI) has become the instrument of choice for disease detection in spine pathology. More recent reports have questioned the specificity of MRI detection and concluded that signal intensity change alone is not diagnostic of a metastatic lesions. The introduction of percutaneous biopsy has substantially benefited the diagnosis of skeletal diseases. It avoids the need for open surgical biopsy in most patients. Percutaneous transpedicular biopsy for vertebral lesions can be performed with minimal morbidity and good diagnostic yield with accuracy of up to 92% in bone metastases.

Objectives: The main objective of this study was to determine the sensitivity and specificity of MRI in the diagnosis of a vertebral spinal lesions, specifically in vertebral tuberculosis and metastases. The association between MRI and transpedicularbiopsy (histopathological) findings was to be studied. The secondary objective was to determine the correlation of transpedicularbiopsy done under C-arm fluoroscopy with respect to major influencing variables such as spinal level, tissue type (lytic and sclerotic), and ultimate histopathological examination (HPE).

Patients and Methods: In this retrospective case-series study, 72 patients admitted to the Department of Orthopaedic in Hospital Kuala Lumpur and Hospital Universiti Sains Malaysia between January 2002 and December 2007 were reviewed. All patients with suspected case of metastases, tuberculosis, and pyogenic disease (based on their clinical sign, symptoms, and X-ray findings involving spinal vertebra) who underwent MRI and percutaneous transpedicular biopsy were included in the study. The data collected were reviewed, including all data pertaining to laboratory investigations to support clinical diagnosis, i.e., full blood count (FBC), erythrocyte sedimentation rate (ESR), tumour marker, sputum acid-fast bacilli (AFB), Mantoux test, and polymerase chain reaction (PCR) analysis. In addition, the MRI findings of each case reported by the radiologist and the HPE results from tissues taken through percutaneous transpedicular biopsies (which were performed later to MRI) were also examined. The data were analyzed for association between the different diagnostic assessments.

Results: The overall HPE diagnoses obtained through a percutaneous transpedicular biopsy were 65.3% positive (47 out of 72 cases). And 34.7% negative (25 out of 72 cases) for both vertebral tuberculosis and metastases, while the overall disease detection by MRI was 97.2% (70 out of 72 cases). There was no significant association between MRI findings and percutaneous transpedicular biopsy (HPE) for disease detection ($P > 0.05$). The disease prevalence was 0.653 for diagnosis via percutaneous transpedicular biopsy (95% CI 0.543-0.763), and 0.972 for MRI (95% CI 0.934-1.011). The sensitivity and specificity of MRI compared with percutaneous transpedicular biopsy, which was taken as the gold standard in this study, which were 0.979 (95% CI 0.937-1.020) and 0.040 (95% CI 0.018-0.062), respectively. There was a significant association observed between the level of vertebral lesion and HPE by percutaneous transpedicular biopsy ($P = 0.021$); however, HPE is not significantly associated with the types of tissue in the vertebral body lesion ($P > 0.05$).

Conclusion: MRI is highly sensitive for disease detection in vertebral lesion. However, MRI has low specificity and is not reliable in detecting true negative cases. There is no significant association between MRI and percutaneous transpedicular biopsy with regards to disease detection. For inconclusive MRI findings or MRI findings with vertebral metastases and tuberculosis, percutaneous transpedicular biopsy clinically useful and reliable for vertebral disease confirmation.

Supervisor :

Associate Prof Mohd Iskandar Mohd Amin

24-HOUR AMBULATORY BLOOD PRESSURE MONITORING AMONG HYPERTENSIVE PATIENTS ATTENDING FAMILY MEDICINE CLINIC, HOSPITAL UNIVERSITI SAINS MALAYSIA, KELANTAN

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MMed (Family Medicine)

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Introduction: Hypertension is a common and an important, modifiable risk factor for cardiovascular, cerebrovascular, and renal diseases. Although the percentage of patients who are being treated for hypertension has increased, the percentage of those who demonstrate control of blood pressure (BP) has declined. Clinicians increasingly rely on ambulatory BP monitoring (ABPM) to improve the diagnosis and treatment of hypertension, as there is a firm evidence of its prognostic value in predicting cardiovascular outcome.

Objectives: The objectives of this study were to illustrate the circadian BP profile of hypertensive patients attending Family Medicine Clinic, Hospital Universiti Sains Malaysia (HUSM), to describe the prevalence of uncontrolled hypertension based on 24-hour ambulatory BP monitoring (ABPM) and office BP, and to identify the associated cardiovascular risk factors among dippers and non-dippers.

Patients and Methods: This cross-sectional study was conducted from 1 January 2008 to 30 June 2008 among hypertensive patients attending Family Medicine Clinic, HUSM. All patients who fulfilled the inclusion criteria were selected via systematic random sampling. Schiller BR-102 plus was put on patients to get 24-hour BP reading. Mean of 2 office BPs were also taken. Non-dippers were defined as systolic or diastolic nocturnal drop of less than 10%. Statistical analyses were done using SPSS version 12.

Results: A total of 105 patients were recruited: 59 (56.2 %) males and 46 (43.8%) females with a mean age of 51.8 (SD 9.34) years old. The patients' mean 24-hour SBP and DBP were 128.4 (SD 12.7) mmHg and 79.7 (SD 8.74) mmHg, respectively. The mean daytime SBP and DBP were 132.1 (SD 11.72) mmHg and 82.4 (SD 9.41) mmHg, while the mean nighttime SBP and DBP were 123.3 (SD 12.78) mmHg and 76.2 (SD 9.01) mmHg, respectively. Percentages of non-dippers were 68.6% for systolic and 61.9% for diastolic BP. Percentages of uncontrolled systolic and diastolic 24-hour ambulatory BP were 26.7% and 23.8%, respectively, and the percentage of uncontrolled diastolic nighttime BP was 56.2%. Percentages of uncontrolled office BP was high, 57.1% systolic and 61.0% diastolic, and the difference between office BP and 24-hour ambulatory BP were statistically significant. However, the simple logistic regression analysis performed to determine the relationship between cardiovascular risk factor and non-dippers were not significant.

Conclusion: The means for 24-hour and daytime ambulatory BP were normal; however, the mean diastolic nighttime was above normal value. The majority of patients were categorised as non-dippers. The percentage of uncontrolled office BP was high compared with 24-hour ambulatory BP. Therefore, rather than using simple clinical measurements, ambulatory BP was clinically and practically important to get a better understanding of BP fluctuations over 24-hour periods.

Supervisor:

Dr Juwita Shaaban

Co-supervisors:

Dr Harmy Mohamad Yusoff

Dr Tengku Alina Tengku Ismail

CLINICAL CHARACTERISTICS AND HOSPITAL COST OF HOSPITALIZED CHILDREN WITH RESPIRATORY SYNCYTIAL VIRUS INFECTION IN HOSPITAL UNIVERSITI SAINS MALAYSIA, KUBANG KERIAN

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MMed (Paediatrics)

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Introduction: Insertion RSV is a major pathogen for respiratory illness in children less than 2 years of age, causing significant morbidity and mortality, especially in those with underlying disease. RSV infection shows a seasonal variation in its yearly distribution, and it imposes a substantial burden to the health care provider. In the East Coast of Malaysia, there has been no study reporting the medical cost incurred by the hospital in managing patients with RSV infection.

Objectives: This study aimed to describe the epidemiological characteristics, clinical profile, and seasonal trends of infection, and to determine the direct medical cost in managing hospitalized children with RSV infection in Hospital Universiti Sains Malaysia (HUSM) from 2006 to 2008.

Patients and Methods: This was a cross-sectional retrospective study conducted at HUSM, Kubang Kerian, Kelantan. Data of children admitted to wards 6S, Neonatal Intensive Care and High Dependency Unit with positive RSV respiratory specimens from the Laboratory of Virology in Department of Microbiology and Parasitology from 1 January 2006 until 31 December 2008 were collected. Medical charts were reviewed retrospectively. The epidemiological and clinical profiles were obtained from the medical records. Seasonal variations were determined by analyzing the monthly RSV-positive isolation rate and comparing with local meteorological parameters. The direct medical cost was calculated by using raw data of various costing derived from the various departments in HUSM.

Results: There were 155 positive cases from 2006 to 2008. However, only 131 cases were included as the medical records for the remaining 24 cases could not be traced. Bronchopneumonia was the predominant diagnosis (60.3%), followed by acute bronchiolitis (26.0%). From 131 patients, 23 patients (17.6%) had underlying diseases, with congenital heart disease being the most common condition, occurring in 13 patients (9.9%). The patients were older (11 vs five months, $P < 0.05$), had a longer length of stay (17 vs 8 days, $P < 0.01$), and 10 times higher risk for ventilation ($P < 0.001$). The mortality rate was 3.8%, all involving those with underlying diseases.

Patients who were younger than six months of age required more intensive care admission (19% vs 1.5%, $P < 0.001$) and oxygen therapy (48.9% vs 31.3%, $P < 0.05$). On the contrary, they required less bronchodilator therapy (64.9% vs 86.0%, $P < 0.01$) and less of them presented with fever (74.3% vs 96.5%, $P < 0.001$). Apnoea was a common atypical presentation in neonates. The significant risk factors for ventilation were previous underlying diseases ($P < 0.001$) and age younger than 6 months ($P < 0.01$). RSV infection distribution patterns had changed from previous trends, but still maintaining its peak during the North–East monsoon from October to December. The mean direct medical cost for all patients was estimated at RM 74 301.66 per annum. The mean cost per patients for those with underlying diseases was higher than those without diseases (RM 2624.30 vs RM 1505.00).

Conclusion: RSV infection is associated with significant morbidity and mortality in children with underlying diseases. The seasonality of RSV infection in Kelantan showed an association with the rainfall distribution, with its peak during the rainy season (October–December). The economic burden of RSV infection to the health care provider was significant, and this was even more so for those with underlying diseases, especially congenital heart disease.

Co-supervisor :

Dr Noraida Binti Ramli

Co-supervisor :

Dr Mohd Ismail Bin Ibrahim

PERCEIVED STIGMA AMONG PATIENTS WITH SCHIZOPHRENIA IN KELANTAN

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MMed (Psychiatry)

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Health Campus, 16150 Kelantan, Malaysia

Introduction: Stigma has been identified and recognized as a major concern in healthcare services. Stigma is manifested by bias, distrust, stereotyping, fear, embarrassment, anger, and avoidance; it leads the society to avoid living, socializing, or working with, renting to, or employing people with mental disorders. Although perceived stigma in schizophrenia is a known fact, it has not been widely studied in Malaysia.

Objectives: The aims of the study were to determine the distribution of perceived stigma toward patients with schizophrenia and its association with self-esteem, clinical factors, and socio-demographic variables.

Patients and Methods: This was a cross sectional study conducted in Hospital Raja Perempuan Zainab II and Hospital Universiti Sains Malaysia from September 2008 to March 2009. The subjects consisted of 227 stable patients with schizophrenia according to the definition of the Diagnostic and

Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), selected through convenience sampling. The perceived stigma and self-esteem were assessed with the Devaluation and Discrimination Scale (DDS) and the Shamsunnisah Self-Esteem Scale (SSES), respectively. The psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS). The main measured outcome in this study was the mean stigma score of the DDS, which is considered as a dependent variable. Descriptive analysis, simple linear regression, and analysis of variance (ANOVA) were applied in data analyses.

Results: The majority of the patients were Malays, 223 (98.2%); male, 151 (66.5%); single, 142 (62.6%); unemployed, 129 (56.8%); and had mild or doubtful symptoms on BPRS psychotic sub scale, 136 (59.9%). The mean duration of illness was 11.6 (SD 8.1) years. The mean stigma score was 2.38 (SD 0.67), with a majority of 132 patients (58.1%) scoring lower than the mid-score, which indicated low level of perceived stigma. A majority of 131 patients (57.7%) had a moderate levels of self-esteem, with a mean score of 91.4 (SD 14.5). There was a significant difference in the mean stigma score between the three levels of self-esteem ($P < 0.001$). Other socio-demographic and clinical factors were not significantly associated with a perceived stigma.

Conclusion: This study found that perceived stigma was low among patients with stable schizophrenia. The perceived stigma was significantly associated with the level of self-esteem, where subjects with a high level of perceived stigma tended to have a low level of self-esteem.

Supervisor:

Professor Dr Haji Mohd Razali Bin Salleh

Co-supervisor:

Dr Mohd Nawan Hamzah

RETROSPECTIVE CROSS-SECTIONAL STUDY FOR COMPLETENESS OF PRE-OPERATIVE SECTION OF ANAESTHETIC RECORD IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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MMed (Anaesthesiology)

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Introduction: The pre-operative section of the anaesthetic form is the main concern in this study. Proper pre-operative assessment is very important, and this is also true for the documentation of pre-operative assessment in the anaesthetic form for patients who will undergo any type of anaesthesia.

Objective: This study was done to assess the difference in the quality of completing the pre-operative section of the anaesthetic form between emergency and elective operations, as well as between anaesthetic records in January 2008 and

May 2007.

Patients and Methods: This retrospective cross-sectional study was conducted from May 2007 to January 2008 in Hospital Universiti Sains Malaysia (HUSM). Patients' names and identification numbers were traced from the operation theatre records, and patients were selected according to the inclusion criteria. Selected patients' medical records were obtained from the record office. Anaesthetic records were assessed. The completeness of 22 variables was evaluated based on their respective criteria, and the global quality index (percentage of completeness) was scored. SPSS version 12 was used for data tabulation and analyses.

Results: There were 325 anaesthetic records traced and evaluated. The mean percentage of completeness of all the anaesthetic records in the pre-operative section was 67.98%. For anaesthetic records in January 2008, the mean percentage of completeness was 73.1%; whereas, in May 2007, it was 62.3%. For anaesthetic records from elective operations, the mean percentage of completeness was 74.55%; in contrast, mean for anaesthetic records from emergency operations was 64.38%.

Conclusion: Although the form-completeness is improving (as seen in the higher percentage of completeness in January 2008 compared with May 2007), important measures are needed to further improve the quality of completing the pre-operative segment of the anaesthetic form in HUSM.

Supervisor :

Associate Professor Dr Wan Hashim Wan Adnan

A DIAGNOSTIC VALUE OF MANTOUX TEST IN TUBERCULOSIS: A CASE CONTROL STUDY IN HOSPITAL UNIVERSITI SAINS MALAYSIA IN 2009

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MMed (Internal Medicine)

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Introduction: The prevalence of tuberculosis (TB) is increasing despite aggressive strategies and control programmes exercised. Although new methods had been introduced to diagnose TB, these tests are expensive and not widely available. Mantoux test remains important in developing countries, especially in extra-pulmonary, pediatric, and smear-negative cases. However, its accuracy in the diagnosis of active TB remains uncertain.

Objectives: This study aimed to determine Mantoux test diagnostic accuracy and the best cut-off points of positive Mantoux, as well as to identify the associated factors that influence Mantoux induration among TB patients.

Patients and Methods: Case-control design was used for diagnostic study, and cross-sectional study using

confirmed active TB was applied to identify the associated factors of Mantoux reading. A total of 140 subjects were involved, including 50 cases of active TB and 90 subjects in the control group. Control was defined as those who had never been exposed to or diagnosed with TB in the past. TB cases were retrieved from Chest Clinic, Hospital Universiti Sains Malaysia (HUSM) from 1 January 2008 until 31 March 2009, and the control subjects were chosen from around Kota Bharu, the capital of Kelantan. The patients' folder and TB wallet were reviewed by the researcher. The required information on demography, Mantoux result, and other related parameters were recorded into the data collection form.

Results: Based on the diagnostic study, three cut-off points showed comparable results. The sensitivity of 8, 10, and 12 mm cut-off points were 72%, 66%, and 50%, respectively. Among these cut off points, 12 mm induration showed greater specificity and positive predictive value rate, 96% and 86%, respectively. In contrast, 10 mm induration was observed to be the best cut-off point based on a receiver operating characteristic (ROC) curve. Multivariable logistic regression analysis showed no association between Mantoux size and factors such as gender, race, Bacille Calmette-Guerin (BCG) vaccination, co-morbidities, degree of TB involvement as reflected by sputum smear positivity, and radiological involvement.

Conclusion: It is concluded that, in population of high TB burden, Mantoux test is fairly sensitive and specific in the diagnosis of TB. The analysis showed that 10 mm induration was the best cut-off points of positive Mantoux test. However, 12 mm induration should be reconsidered as the best cut-off points due to its greater specificity and positive predictive values. There is no association between Mantoux size and confounding factors such as age, BCG vaccination, gender, co-morbidities, and degree of TB involvement.

Supervisor :

Associate Professor Dr Che Wan Aminuddin

Co-supervisor:

Dr Shaharuddin Bin Abdullah

RISK PERCEPTION ON FOOD POISONING AMONG COMMUNITY IN SALOR, KOTA BHARU, KELANTAN

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MMed (Environmental Health)

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Introduction: Food poisoning is the most common infectious disease that has come to the public health attention in Malaysia. In a 2003 survey, typhoid, cholera, and food poisoning were considered as endemic diseases in Kelantan.

Objectives: This study aimed to explore the knowledge, attitude, and practice (KAP), as well as to determine the risk

perception and socio-demographic factors associated with the risk perception on food poisoning in Salor, Kota Bharu, Kelantan.

Patients and Methods: A cross-sectional study was conducted in Salor from June to September 2008. A total of 447 members of the community were selected for the study using enumeration block sampling. Data were collected using a self-administered, validated questionnaire, which consisted of information on socio-demography, KAP, and risk perception on food poisoning.

Results: The majority of the respondents were Malays (99.3%), married (81.4%), and females (57.5%), with the mean (SD) age of 38.1 (12.58) years old. Most of the respondents had good knowledge (71.1%), positive attitude (88.4%), and positive practices (87.2%) towards food poisoning. Majority of the respondents had perceived risk of food poisoning. However, respondents' perceived risk of food poisoning (64.7%) was better than perceived severity of food poisoning (37.1%). The significant factors associated with the risk perception on food poisoning were female (OR = 1.91, 95% CI 1.26 to 2.91, $P = 0.003$) and higher household income (OR = 2.48, 95% CI 1.13 to 5.47, $P = 0.024$). Age, marital status, and education level were not associated with the risk perception on food poisoning.

Conclusion: Data from the study showed that the community in Salor had high percentage of good KAP and risk perception on food poisoning. However, in a detailed assessment of KAP, it was demonstrated that there were deficit areas that should be addressed in the health education program. Better risk perception among females and high-income group indicated showed that these people were more aware and interested in the food safety issues.

Supervisor :

Dr Nor Azwany Yaacob

Co-supervisor:

Dr Zaliha Ismail

Dr Zaharah Sulaiman

FACTORS INFLUENCING QUALITY OF LIFE IN PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

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Introduction: The availability and efficacy of medical treatment have delayed disease progression and prolonged the survival in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS). Consequently, the quality of life (QOL) has emerged a significant medical outcome measure for people living with

HIV/AIDS.

Objectives: The aim of this study was to determine the socio-demographic, clinical, psychological, and spiritual factors influencing quality of life (QOL) in patients with HIV/AIDS.

Patients and Methods: This cross-sectional study was conducted using convenience-sampling method. The study population consisted of 271 patients with HIV/AIDS from April 2008 to March 2009. These patients completed the Malay-version of the Functional Assessment of HIV Infection (FAHI) and the Spiritual Well-being (SpWB) Scale. Statistical analyses were performed using SPSS version 12.0. Multivariable linear regression analyses were performed using socio-demographic, clinical, spiritual, and psychological factors as the independent variables. The total FAHI score and 5 domains or subscales from FAHI, such as the physical well-being, social well-being, and cognitive functioning, were analysed as the dependent variables.

Results: The mean (SD) of FAHI total score was 113.03 (29.08) and it ranged 0–176, with higher score indicating better QOL. The most affected domain was social well-being. Patients who were non-Malays, employed, had CD4⁺ count of more than 200, and not having anxiety or depression had better overall QOL. Lower educational level, longer duration of illness, low CD4⁺ count, anaemia, and possible anxiety and depression seemed to compromise the patients' physical well-being. Those of older age, Muslim, and having possible anxiety and depression had a poorer emotional well-being. Those who were employed, had no anxiety or depression, and had higher spirituality level significantly showed better functional and global well-being. Older patients, those of heterosexual source of infection, possible anxiety and depression, as well as poor spirituality were significantly associated with poorer social well-being. In addition, 65% of male patients did not disclose their HIV status, and non-disclosure was also significantly associated with poorer social well-being. Being unemployed, with possible anxiety and depression, and weaker spirituality showed significant association with lower cognitive functioning.

Conclusion: This study showed differential effects on the different domains of QOL of patients with HIV and AIDS. The worst impaired domain was the patients' social well-being. The high percentage of male patients failing to disclose their HIV status to their significant others and the fact that women were being infected via heterosexual relationship (and seemed to suffer more impairment) should be addressed with a better primary prevention and management approaches. It appears that the HIV/AIDS requires the sufferers to stop being silent, and the caregivers as well as the policy makers to be more vocal in order to curb this epidemic.

Supervisor :

Associate Professor Dr Hasanah Che Ismail

Co-supervisor :

Dr Mahiran Mustafa

ANTI-TUBERCULOSIS DRUG-INDUCED HEPATITIS: OUTCOME OF ANTI-TUBERCULOSIS DRUG RE-CHALLENGE IN HOSPITAL UNIVERSITI SAINS MALAYSIA

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Objective: The study was conducted to determine the outcome of a re-challenge of anti-tuberculosis drugs in patients with anti-tuberculosis drug-induced hepatitis.

Patients and Methods: This was a single-centre, retrospective study conducted in Hospital Universiti Sains Malaysia from January 2006 until December 2008. The medical records of patients with tuberculosis were examined to determine the durations of developing anti-tuberculosis drug-induced hepatitis and its resolution.

Results: Only 22 out of 595 tuberculosis patients were included in the study. The review showed that 31.8% of the patients developed anti-tuberculosis drug-hepatitis in week 2, and another 22.7% in week 3. Resolution of the drug-induced hepatitis occurred during week 1 after the cessation of anti-tuberculosis drugs in 22.7% of patients, and another 31.8% recovered during week 2. All the patients could tolerate the first-line anti-tuberculosis drug regime during the re-challenge period.

Conclusion: Anti-tuberculosis drug-induced hepatitis usually occurred in week 2 or 3 after the initiation of anti-tuberculosis drug treatment and usually resolved within two weeks after cessation of the drugs.

Supervisor :

Associate Professor CheWan Aminud-din Hashim

Co-supervisor:

Associate Professor Dr Zainal Darus

MODULATION OF CELL GROWTH AND PPAR- γ EXPRESSION IN HT-29 AND COLO 205 CELLS BY CIGLITAZONE

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Introduction: Colon cancer is one of the most common malignancies in both men and women in Malaysia. Most therapies for the disease are still unsatisfactory since they cause adverse effects to patients. Current research are now focusing on a better understanding of the tumour response and resistance to treatment, apart from finding drugs that will not cause such adverse effects. The nuclear receptor, peroxisome proliferator-activated receptor (PPAR)- γ , is reported to be expressed in various cancer cells, including breast, prostate, and colorectal cancer. PPAR- γ is a ligand-dependent transcription factor that regulates expression of genes involved in cellular proliferation, differentiation, and apoptosis. Although this receptor has been shown to be highly expressed in colorectal cancer, its exact role in colorectal carcinogenesis is still unclear.

Objectives: This study was carried out to study the possible involvement of PPAR- γ in modulating the growth of 2 human colorectal carcinoma cell lines, HT-29 and COLO 205. A synthetic PPAR- γ ligand, ciglitazone, which is also a member of the antidiabetic drug thiazolidinediones (TZDs), was used in this study to treat the colorectal cancer cell lines.

Materials and Methods: To evaluate whether ciglitazone induced inhibition of cell growth, both cell lines were treated with increasing doses of ciglitazone (2.5–100 μ M) for 6 to 72 hours. Cytotoxicity was determined by measuring the lactate dehydrogenase (LDH) leakage from the cell membrane. In addition, a fluorescein-conjugated monoclonal antibody against cytokeratin 18 (CK18) that recognizes the caspase-cleaved epitope within the CK18 was used to measure apoptosis by flow cytometry. Additionally, the mRNA expression levels of PPAR- γ 1 and PPAR- γ 2 from the cell lines were quantified by real-time quantitative PCR technique using specifically developed homologous internal standards for each of the genes. The level of PPAR- γ protein was determined by Western blotting.

Results: Ciglitazone significantly inhibited the growth of colorectal cancer cell lines in a dose- and time-dependent manner ($P < 0.01$). The EC₅₀ values of ciglitazone obtained after 48 hours of incubation was about 20 μ M for HT-29 cells and about 30 μ M for COLO 205 cells, and these concentrations were then used in subsequent experiments to treat the

corresponding cell lines in a time-dependent manner. Flow cytometry results demonstrated that ciglitazone significantly induced apoptosis in the cell lines ($P < 0.01$). However, real-time PCR results revealed that the levels of PPAR- γ 1 and PPAR- γ 2 mRNA expression were significantly reduced following treatment with ciglitazone compared to controls ($P < 0.05$). Furthermore, ciglitazone also decreased the level of PPAR- γ protein expression as shown by Western blotting.

Conclusion: Treatment with ciglitazone suppressed colon cancer cell growth and cell death. It is postulated that the antitumour effects of this synthetic PPAR- γ ligand may not depend solely on PPAR- γ activation. Since previous reports shown that PPAR- γ was upregulated in cancer cells, including colon cancer cells, compared with their normal counterparts, the downregulation of PPAR- γ expression following ciglitazone treatment suggested the potential of ciglitazone to be used as an adjuvant for the treatment of colon cancer. However, further research is needed to evaluate the anticancer activity of TZDs, which appear to be both dependent and independent PPAR- γ pathway.

Supervisor:
Professor Dr Norazmi Mohd. Nor

HLA POLYMORPHISM IN MALAY SUB-ETHNIC GROUPS IN PENINSULAR MALAYSIA

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Materials and Methods: In this study, the Human Leukocyte Antigen (HLA) class I and II were examined through Sequence Specific Primer (SSP) typing in 176 unrelated individuals from 6 Malay sub-ethnic groups of Peninsular Malaysia: Kelantan ($n = 25$), Minangkabau ($n = 34$), Jawa ($n = 30$), Bugis ($n = 31$), Banjar ($n = 33$), and Rawa ($n = 23$). The common HLA alleles in all the sub-ethnic groups were HLA-A*24 (26%–48%), HLA-B*15 (22%–41%), -Cw*07 (21%–32%), DQB1*03 (25%–55%), and DRB1*12 (15%–40%).

Results: The Malay sub-ethnic groups studied showed close relationship to each other and to Asian populations despite specific differences between them. Banjar, Jawa, and Bugis Malays showed no significant differences to each other, which could be a result of their related origin from the islands around the Java Sea. Besides sharing in the most common haplotype found, phylogenetic and principal coordinate (PCO) analysis showed a genetic similarity between Minangkabau

and Rawa Malays. This could be a consequence of their common origin from Sumatera. The Kelantan Malays, show statistical significant difference with the other groups and revealed differences for the most frequent haplotypes, which could be related to their different origin, and the different populations influence along time. Statistical analysis on the Malay sub-ethnic groups HLA data also revealed credible forensic parameters for forensic applications.

Conclusion: The HLA data obtained from this study can be applied for vaccine development, searching for suitable donor for transplantation, disease association studies, and as a guideline for infectious disease prevention programs

Supervisor :
Dr Zafarina Zainuddin

THE DEVELOPMENT OF A CANDIDATE TUBERCULOSIS DNA VACCINE EXPRESSING Mtb8.4 AND Ag85B OF MYCOBACTERIUM TUBERCULOSIS

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Introduction: Tuberculosis (TB) is still one of the major health problems worldwide. The only TB vaccine currently available is an attenuated strain of *Mycobacterium bovis*, Bacille Calmette–Guerin (BCG). However, the efficacy of BCG vaccine continues to be debated. Therefore, a more effective vaccine against TB is urgently needed. DNA vaccination is a new approach to the control of infectious agents.

Materials and Methods: In this study, a DNA vaccine encoding the candidate TB antigens Mtb8.4 and Ag85B was developed using assembly PCR. Balb/c mice were immunized intramuscularly with 50 µg of the DNA vaccine, pNMNO23, containing the 2 antigens in each hindleg.

Results: Reactivity against the Ag85B peptides, P1, and P3 as well as Mtb8.4 showed a consistent Th1 type of immune response by virtue of the increased expression of IL-2, IFN-γ and IgG2a. Splenocytes from immunized mice were also found to proliferate more aggressively when stimulated with the antigens compared to the vector alone. In order to improve the vaccine efficacy, a preliminary prime-boost approach was used. Priming with pNMNO23 and boosting with recombinant BCG (rBCG) in Balb/c mice was carried out. Flow cytometric intracellular cytokine analyses of splenocytes from mice immunized with the DNA-rBCG prime-boost regime showed that both CD4⁺ and CD8⁺T cells showed an increase in IL-2 and IFN-γ production following stimulation with either antigens at significantly higher levels than those immunized with rBCG-DNA prime-boost.

Conclusion: The data obtained from this study suggested that DNA vaccination in combination with the prime-boost approach provide a potential strategy for

developing a candidate vaccine against TB.

Supervisor:
Professor Dr Norazmi Mohd. Nor

MAGIC POLYMER GEL DOSIMETRY USING X-RAY COMPUTED TOMOGRAPHY: A FEASIBILITY STUDY

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Introduction: The aim of this project was to carry out feasibility study of developing Methacrylic and Ascorbic Acid in Gelatin Initiated by Copper (MAGIC) polymer gel dosimetry system by utilizing helical multislice X-ray computed tomography (CT) available in Hospital Universiti Sains Malaysia to determine dose.

Materials and Methods: The MAGIC gel was prepared based on the formulation proposed in the literature by Fong et al. (2001), with some modifications. The characteristics of the gel were studied for its water-equivalent properties. The mass density (ρ) was determined based on Archimedes' principle. The weight fraction of elemental composition and the effective atomic number (Z_{eff}) were calculated. The electron density was also measured with 90-degree scattering angle at room temperature. The linear attenuation coefficient (μ) of unirradiated gel, irradiated gel, and water were determined using Am-241 based on narrow beam geometry.

Results: The measured linear attenuation coefficient of unirradiated MAGIC gel and water was found to be 0.84 (SD 0.04) cm⁻¹ and 0.85 (SD 0.02) cm⁻¹ respectively. The results showed that the MAGIC gel is water-equivalent. The data obtained using irradiated gel showed a linear relationship between linear attenuation coefficient and absorbed dose in the range 2–40 Gy. The protocol for CT imaging to obtain the best quality image of irradiated MAGIC gel was determined for evaluating dose information. The irradiated gel placed inside the cylindrical water phantom was scanned using various available scan parameters (kV, mA, and reconstruction algorithm) with the field of view 25 x 25 cm and 5 mm slice thickness. The signal to noise ratio (SNR) and standard deviation (SD) were the parameters chosen to determine the image quality after image averaging process was carried out. The image that has the highest SNR and lowest SD was the best quality image, and the corresponding scan parameters were used as the protocol for scanning the irradiated gel. The scan parameters of 140 kV and 400 mA with 5 mm slice thickness, 1000 ms exposure time, standard reconstruction algorithm and 25 x 25 cm field of view were chosen as scanning protocol. Using this scanning protocol, the irradiated MAGIC gels of different doses were imaged to establish relation between average CT numbers and doses. A linear relation was found

between average CT numbers and doses in the range 2–40 Gy with CT number (HU)-dose sensitivity of 0.30 (SD 0.02) HU Gy⁻¹. In order to verify the usefulness of the CT based gel dosimetry to measure dose, the percentage depth dose (PPD) and isodose curve (beam profile) of 8 x 8 cm field size photon beam from 6 MV linear accelerator were measured. The measured PDD and isodose curves were compared with that calculated in water using radiotherapy treatment planning computer system (TPS). The disagreement of irradiated gel PDD compare to TPS at 5 cm and 10 cm depth were found to be + 1.8% and + 2.1%, respectively. The maximum disagreement of gel PDD compare to TPS calculation in the water was + 3%. The maximum disagreement of gel isodose curves compare to TPS calculation in the water at 5 cm and 10 cm measurements were + 10% and + 11.6%, respectively.

Conclusion: The results show that the CT based MAGIC gel dosimetry system using HUSM CT scanner could determine the dose of high energy photon in the range 2–40 Gy.

Supervisor:

Professor Dr Ahmad Bin Zakaria

THE ALLELE AND GENOTYPE VARIATIONS OF FIFTEEN SHORT TANDEM REPEAT (STR) LOCI IN MALAY, CHINESE, INDIAN, AND JAVANESE GROUPS OF THE MALAYSIAN POPULATION

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Materials and Methods: Allele and genotype frequencies for 15 short tandem repeats (STR) loci (D3S1358, TH01, D21S11, D18S51, Penta E, D5S818, D13S317, D7S820, D16S539, CSF1PO, Penta D, vWA, D8S1179, TPOX, and FGA) among 185 Malays, 216 Chinese, 195 Indians, and 109 Javanese were determined.

Results: For these 4 distinct groups investigated, the observed heterozygosity (HO) at these STR loci ranged from 56.0% to 82.1%. The values of the combined power of discrimination of these loci for the Malays, Chinese, Indians, and Javanese were 1 in 4.362 x 10¹⁸, 1 in 6.268 x 10¹⁸, 1 in 2.370 x 10¹⁸, and 1 in 2.543 x 10¹⁷, respectively. The values of the polymorphism information content (PIC) ranged 0.52–0.91. The probability of paternity for the Malays, Chinese, Indians, and Javanese were 0.99999932, 0.99999937, 0.99999971, and 0.99999888 respectively. The distribution patterns of the STR alleles were different in each group, especially the Indian group. The genetic data indicated the Penta E locus to be the most highly polymorphic and the TPOX locus the least polymorphic. Several loci demonstrated deviations from the Hardy–Weinberg Equilibrium (HWE) when tested with chi-square goodness-of-fit and exact test. Comparison of the population databases showed close genetic relationships

between the Malay and Javanese groups and with greater variations when compared with the Chinese and Indian groups. The overall co-ancestry coefficients, θ , were estimated and the value ranged 0.005–0.015, which is consistent with the National Research Council II recommended value of 0.03. The pair-wise comparisons between the various groups of population based on co-ancestry identity were performed and were demonstrated by using phylogenetic tree.

Conclusion: The results showed that the genetic relationship between the Malays and Javanese are very close, and supported the possibility that there were genetic ties between the Malays and Chinese. The result also clearly showed that genetically the Indians were different from the Malays, Chinese, and Javanese.

Supervisor:

Dr S Panneerchelvam

IMMUNOGENICITY STUDY OF DNA VACCINE AND DNA VACCINE CARRIER EXPRESSING VP1 OF ENTEROVIRUS 71 IN THE PRIME BOOST VACCINATION STRATEGY

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Introduction: Enterovirus 71 (EV71) is a highly infectious causative agent of hand, foot, and mouth disease (HFMD) in children and could lead to severe neurological complications. In Malaysia, the first epidemic occurred in 1997 in Sarawak and caused 34 deaths due to severe neurological syndrome. There is currently no vaccine available against EV71. Vaccination is considered the most effective means to control EV71 infection.

Materials and Methods: A candidate vaccine was developed, involving the construction a synthetic VP1 gene of EV71 fused to a ubiquitin (UbGR) gene and cloning into a DNA vaccine vector with a strong eukaryotic promoter known as pVAX1, to create the candidate DNA vaccine pVaxUbVP1. The immunogenicity of the constructed DNA vaccine was evaluated in BALC/c mice involving 2 methods of delivery, as a naked DNA vaccine delivered intramuscularly or delivered orally via the live attenuated bacteria *Salmonella typhi* Ty21a, of which the recombinant strain carrying pVaxUbVP1 was designated as StUbVP1. Both candidate vaccines were used in homologous and heterologous prime boost approaches: Formats A (pVaxUbVP1 alone), B (StUbVP1 alone), C (StUbVP1 as primer vaccine and pVaxUbVP1 as booster), and D (pVaxUbVP1 as primer vaccine and StUbVP1 as booster).

Results: The results indicated that total IgG levels in serum was significant in Formats A and D whereas IgG subclasses assay showed that IgG2a levels were higher than

IgG1 levels in both immunization formats. Production of in vitro IFN- γ was significant in mice vaccinated using Formats A, B, and D, whereas IL-4 production was relatively low in all groups of immunization but shows a significant increase in Format D. The percentage of intracellular cytokine (IFN γ , IL-2, and IL-4) production by CD4⁺ and CD8⁺ population of T cells showed a moderate to high response in Formats A and D. The analyses also showed that the use of pVaxUbVP1 in a homologous prime boost format (Format A) resulted in a Th1 type of immune response whereas using Format D (pVaxUbVP1 as primer vaccine and StUbVP1 as booster) gave a mixed Th1–Th2 types of immune response.

Conclusion: The pVaxUbVP1, used alone in a homologous prime boost approach or as the primer vaccine in a heterologous prime boost immunization format together with StUbVP1, showed potential for further development as a vaccine against EV71.

Supervisor:
Professor Dr Zainul Faziruddin Zainuddin

CONSTRUCTION OF RECOMBINANT BCG EXPRESSING THE VP1 ANTIGEN OF ENTEROVIRUS 71 FOR THE DEVELOPMENT OF A CANDIDATE VACCINE

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Introduction: Enterovirus 71 (EV71), the causative agent of outbreaks of hand, foot, and mouth disease (HFMD) in children require urgent control due to the high number of cases. Vaccination is one of the most effective methods to control disease outbreaks.

Materials and Methods: In this study, a recombinant BCG vaccine candidate was constructed against EV71. The recombinant BCG (rBCGV1) expresses a synthetic gene encoding the VP1 protein of EV71 fused to ubiquitin complex (UbGR), which was constructed using the technique of assembly PCR. The synthetic gene was codon optimized for expression mycobacterium. The AgB5A promoter and signal peptide sequence from *M. tuberculosis* was used to drive the expression and secretion of the synthetic gene.

Results: The expression of the UbGR-VP1 fusion protein was confirmed by Western blotting using rabbit polyclonal antibody specific to the VPI protein and was found in the cell pellet of the recombinant BCG. rBCGV1 showed the ability to induce moderate antibody production BALB/c (H-2d) mice when sera from immunized mice were tested against purified UbGR-VP1 fusion protein. IgG2a subclass antibody was shown to be induced at a significantly higher level than IgG1. Splenocytes obtained from rBCGV1 immunized mice showed significant higher level of lymphocyte proliferation

when stimulated with UbGR-VP1 compared to control. Analyses of intracellular cytokines show that CD4⁺ T cells and CD8⁺ T cells from rBCGV1-immunized mice were stimulated by UbGR-VP1 protein to express significant levels of IL-2, IFN- γ , and IL-4 when compared to the control. Extracellular cytokine analyses also showed significantly higher levels of IFN- γ compared to control.

Conclusion: Overall, the immunogenicity studies results suggested that the rBCGV1 enhanced the stimulation of immune system towards the Th1 pathway. Data from this study also suggested the potential of rBCGV1 to be developed as a vaccine, and further studies must be carried out to evaluate the efficacy of this candidate vaccine.

Supervisor:
Professor Dr Zainul Faziruddin Zainuddin

THE EXPRESSION OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR- (PPAR- γ 1 AND PPAR- γ 2) IN NAIVE AND MEMORY CD4⁺ T LYMPHOCYTES

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Introduction: Peripheral CD4⁺ T cells can be divided into 2 functional groups based on the expression of distinct isoforms of the surface molecule that contains an intracellular 2-domain phosphatase portion, known as CD45. Memory T cells express the lowest molecular weight CD45RB isoform, whereas naive T cells express CD45RA (human) or CD45RB (mouse) isoforms. CD45 is a protein tyrosine phosphatase which plays an important role in TCR-mediated signaling through its activation of Lck by dephosphorylating the regulatory Tyr505. Human naive and memory CD4⁺ T cells differ in the requirements for activation and magnitude of the cellular responses. The nuclear receptor, peroxisome proliferator-activated receptor (PPAR)- γ has been reported to be involved in regulating the activities of immune cells such as macrophages or monocytes and T lymphocytes.

Materials and Methods: Given their roles in immune regulation, the current study was carried out to determine the expression of PPAR- γ in human naive and memory CD4⁺ T cells, since it is possible that PPAR- γ may be differentially expressed in the different isoforms of CD45. In addition, the differential signaling patterns and cytokine secretion of these subsets of T cells may require engagement with PPAR- γ isoforms—a possibility that has not been explored thus far. To further dissect the role of PPAR- γ in the regulation of naive and memory CD4⁺ T cell activation, the PPAR- γ agonist ciglitazone, was used to modulate the activation status of naive and memory CD4⁺ T cells, as well as the expression of PPAR- γ and selected cytokines.

Results: From real-time PCR, it was observed that unstimulated naive and memory CD4⁺ T cells did not express PPAR- γ 1 and PPAR- γ 2, whereas stimulated naive and memory CD4⁺ T cells express high levels of these receptors, with PPAR- γ 2 expression being higher than PPAR- γ 1 in both cell types ($P < 0.01$). In addition, the PPAR- γ 1 expression was higher in stimulated memory compared with stimulated naive CD4⁺ T cells ($P < 0.05$), whereas there was no significant difference between PPAR- γ 2 expression in both types of stimulated cells. The addition of the PPAR- γ agonist, ciglitazone significantly increased the expression of PPAR- γ 1 by about 61-fold and 175-fold in stimulated naive and memory CD4⁺ T cells, respectively ($P < 0.01$ in each). In contrast to PPAR- γ 1, the addition of ciglitazone significantly decreased the expression of PPAR- γ 2 by about 650-fold and 140-fold in stimulated naive and memory CD4⁺ T cells, respectively ($P < 0.01$ in each). In addition, the expression levels of TGF- β and IL-1 β gene were higher in unstimulated naive and memory CD4⁺ T cells, but were decreased in their stimulated state ($P < 0.01$). IL-8 gene was expressed at low levels in unstimulated but elevated in stimulated naive and memory CD4⁺ T cells ($P < 0.01$). However, there were no significant differences in the levels of these cytokines between naive and memory CD4⁺ T cells of both states. IL-2, IFN- γ , IL-5, IL-13, TNF- α , GM-CSF, and IL-6 were only expressed in stimulated naive and memory CD4⁺ T cells, but not in their unstimulated state. The expression levels of IL-2 and IL-13 were significantly higher in stimulated naive compared with stimulated memory CD4⁺ T cells ($P < 0.01$). In contrast, the expression levels of IFN- γ were significantly higher in stimulated memory as compared to stimulated naive CD4⁺ T cells ($P < 0.05$). However, there were no significant differences in the expression of IL-5, IL-6, TNF- α , and GM-CSF between both stimulated cell types. The addition of ciglitazone decreased the expression levels of TGF- β , IL-1 β , IL-8, IL-2, IFN- γ , IL-5, TNF- α , and GM-CSF in stimulated memory and naive CD4⁺ T cells. The induction of PPAR- γ 1 and suppression of PPAR- γ 2 expression in naive and memory CD4⁺ T cells in the presence of ciglitazone suggested that the PPAR- γ isoforms may have different functions in T cell regulation.

Conclusion: The expression of selected cytokine genes in activated naive and memory CD4⁺ T cells is consistent with previous studies. The exact mechanism of how PPAR- γ inhibit cytokine expression in stimulated naive and memory CD4⁺ T cells and which PPAR- γ isoforms is responsible for this effect remain uncertain. It is possible that PPAR- γ inhibit the expression of cytokine genes in these stimulated cell subsets via interacting with NF- κ B, AP-1, and STATs, which are important transcription factors for these cytokines, as shown by previous studies in other cells.

Supervisor:
Professor Dr Norazmi Mohd. Nor

CLONING, EXPRESSION AND IMMUNOGENICITY OF RECOMBINANT BACILLE CALMETTE-GUERIN (BCG) CONTAINING T AND B CELL EPITOPES OF MYCOBACTERIUM TUBERCULOSIS

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Introduction: Tuberculosis (TB) remains as one of the leading causes of morbidity and mortality in humans. The only TB vaccine currently available is an attenuated strain of *Mycobacterium bovis*, Bacille Calmette–Guerin (BCG). However, the efficacy of BCG continues to be debated. The BCG protection against adult pulmonary TB ranged 0%–80 % in randomized control trials. In addition, the rising rates of multi-drug resistant *M. tuberculosis* have worsened the situation. Thus, an improved TB vaccine is urgently needed. Recombinant BCG (rBCG) is one of the most potential approaches in evoking the immune response against TB.

Materials and Methods: In this study, 2 different types of rBCG were constructed: rBCG expressing T cell epitopes from *M. tuberculosis* Ag85B antigens and Mtb8.4 protein (rBCG018) or a combination of the antigens fused to B cell epitopes from ESAT-6, CFP10, and MTP40 proteins (rBCG032). Polyclonal anti-Mtb8.4 was successfully raised in rabbit and subsequently used for rBCG expression. Immunogenicity study of the vaccine constructs were used for immunization of Balb/c mice. Specific IgG response was obtained against the ESAT-6 and CFP10 in the sera of rBCG032-immunized mice.

Results: Splenocytes from these mice showed a high response against the Ag85B antigens and the Mtb8.4 protein, whereas splenocytes from rBCG018-immunized mice elicited a lower response against Ag85B epitopes and a high response against Mtb8.4 protein. Mice immunized with the rBCG strains produced a Th1 pattern of response against the T cell epitopes. Six weeks after the final immunization, the rBCG constructs were recovered from spleen, lung, liver, and peritoneal washout. The presences of both constructs in the colonies grown from the organ were detected by PCR.

Conclusion: The data obtained from this study demonstrated that T and B epitopes expressed in a single rBCG construct induced appropriate humoral and cellular immune responses against immunogenic epitopes from *M. tuberculosis*.

Supervisor:
Professor Dr Norazmi Mohd. Nor

DEVELOPMENT OF RECOMBINANT MYCOBACTERIUM BOVIS BACILLE CALMETTE–GUERIN (rBCG) EXPRESSING THE 22 kDa SERINE REPEAT ANTIGEN (SE22) OF PLASMODIUM FALCIPARUM

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Introduction: The *Plasmodium falciparum* serine repeat antigen (SERA) is one of the promising blood stage malarial vaccine candidates.

Materials and Methods: In this study, we have developed a recombinant *Mycobacterium bovis* Bacille Calmette Guerin (rBCG) expressing a synthetic 22 kDa protein (SE22) from the 47 kDa N-terminal domain of SERA using assembly PCR. This synthetic gene was driven by the 65 kDa heat shock protein (hsp65) of *M. tuberculosis* and the signal peptide from MPT63 *M. tuberculosis*. Immunoblotting analysis using a monoclonal antibody against SE47 revealed that the SE22 protein was detected in the cytoplasm. The rBCG carrying SE22 protein (rBCG/SE22) was administered intraperitoneally into Balb/c mice to determine the humoral and cellular immune responses against the SE22 antigen.

Results: Significant SE22-specific IgG and IgG subclasses were observed after immunization with the rBCG/SE22. In addition, the lymphocytes proliferative response to SE22 antigen was significantly higher in the rBCG/SE22 vaccinated group compared to the control groups. The expression of cytokines (IL-2, IL-4, and IFN- γ) in CD4⁺ and CD8⁺ splenocytes were also detectable following stimulation with SE22. The rBCG expressing SE22 antigen induced a mixed Th1/Th2 response. The IFA results showed that rBCG could induce SE22 specific antibodies in mice and react against SE22 protein expressed on the merozoites.

Conclusion: These results indicate that the rBCG/SE22 could enhance and regulate both humoral and cellular immune responses, therefore it is proposed as a potential vaccine.

Supervisor:
Professor Dr Norazmi Mohd. Nor

THE ANTICANCER MECHANISM OF IBUPROFEN AND INDOMETHACIN IN COLORECTAL CANCER CELLS

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Introduction: Ibuprofen and indomethacin are among the frequently studied non-steroidal anti-inflammatory drugs (NSAIDs) for their anticancer activities. Besides being non-selective cyclooxygenase (COX)-2 inhibitors, both NSAIDs are also direct ligands for peroxisome proliferators-activated receptor (PPAR)- γ . However, the precise mechanism(s) of action whereby both NSAIDs exert their anticancer effect remain unclear.

Objectives: In this study, the effects of both NSAIDs in constitutively COX-2-expressing (HCA-7 and HT29) and non-constitutively COX-2-expressing (HCT116) cell lines were investigated with the initial aim of determining the NSAID growth inhibitory effect, as well as the effective concentration to inhibit 50% of cell growth (EC₅₀) of each NSAID in each cell line, assessed by using lactate dehydrogenase (LDH) release assay.

Materials and Methods: The apoptosis mechanism was then investigated using M30 CytoDEATH assay prior to flow cytometry analysis. The apoptotic-related proteins, such as caspase-8, -9, -3, and -7, were also investigated using Western blot analysis, whereas the modulation of mRNA expression of relevant molecular targets such as COX-2, c-myc, β -catenin, TCF-4, and PPAR subtypes (α , δ , γ 1, and γ 2) mRNA was quantified using real-time PCR analysis.

Results: The results demonstrated that both NSAIDs produced remarkable inhibition on the growth of all 3 cell lines tested. The inhibitory effect occurred in a concentration- and time-dependent manner, with indomethacin (EC₅₀ value > 100 μ M) being more potent compared to ibuprofen (EC₅₀ value > 1000 μ M). Furthermore, the ability of both NSAIDs in inhibiting the growth of cells is likely not to be associated with COX-2 expression. The evidence from M30 CytoDEATH assay suggested that the major mode of cell death caused by both NSAIDs was caspase-dependent apoptosis. This evidence was further supported by Western blot analysis, which indicated that the induction occurred via caspase-9-dependent pathway, whereas the real-time PCR analysis showed that both NSAIDs appear to modulate gene expression via a variety of different molecular targets in COX-2-dependent and/or independent pathway(s) depending on the colorectal cancer (CRC) cell type. However, alteration of TCF-4 and PPAR- γ 1 mRNA expression are likely essential for both NSAIDs to induce apoptosis. Thus, Wnt and PPAR- γ signaling pathways may be involved in mediating the apoptosis induced by both NSAIDs in CRC cells. In addition, PPAR- δ was found to be another essential molecular target for indomethacin-induced CRC cell apoptosis.

Conclusion: This study may provide additional information and evidence of the various mechanisms and actions of NSAIDs in human CRC cells, which may be useful in selecting effective apoptotic drugs against specific CRC types. As shown in this current study, as well as others, both NSAIDs have anti-CRC activities and are potential anti-CRC agents. Further studies on the effect of both NSAIDs on CRC cells are important, as drugs may be developed as chemotherapeutic agents for human CRC.

Supervisor:

Associate Professor Dr Nik Soriani Yaakob

Co-supervisor:

Professor Dr Norazmi Mohd. Nor

THE DEVELOPMENT AND EVALUATION OF A NASBA SYSTEM FOR THE DIAGNOSIS OF CHOLERA USING ELISA AND BIOSENSOR METHODS

Lee Su Yin

PhD Biomedicine (Disease Diagnostic)

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Health Campus, 16150 Kelantan, Malaysia

Introduction: Cholera is a diarrheal disease caused by *Vibrio cholerae*. Cholera is potentially lethal if not diagnosed on time. Hence, early detection is crucial for patient treatment and containment of outbreak. Conventional culture and biochemical tests are laborious, time-consuming, and lacking of sensitivity. Although molecular-based methods are rapid, more sensitive and specific, they require expensive equipments and cold storage of reagents. Furthermore, DNA-based tests, such as PCR, do not distinguish between viable and nonviable cells. Nucleic acid sequence-based amplification (NASBA) is an isothermal RNA amplification technique that specifically detects viable cells. The objective of this study was to develop and evaluate a thermostabilized cholera-NASBA-ELISA assay with biosensor detection for *V. cholerae* based on the *lolB* gene.

Materials and Methods: RNA transcripts as positive control were first constructed and specific primers and probes were designed. NASBA and ELISA conditions were optimized and the analytical specificity was tested with 41 reference strains comprising of *V. cholerae*, *Vibrio* spp., and enteric pathogens. The analytical sensitivity was tested with serial dilutions of RNA transcripts and *V. cholerae* cells. Clinical evaluation of the assay was performed using spiked stool samples ($n = 200$). Subsequently, biosensor detection for the NASBA-ELISA assay was optimized and the results compared to spectrophotometry. The NASBA mix was thermostabilized by freeze-drying, and its stability at different temperatures was determined periodically. In addition, suitability of *lolB* mRNA as a viability indicator was investigated by subjecting cultures to lethal treatments and detecting the NASBA signal. The optimized cholera-NASBA-ELISA assay detected amplicons using fluorescein-labeled probes and TMB/HRP signal.

Results: The analytical specificity of the assay was 100%, while the analytical sensitivity was 102 molecules/ μ l RNA transcripts and 10 CFU/ml cells. Clinical evaluation gave 100% sensitivity, 84.52% specificity, 89.92% PPV, and 100% NPV. Biosensor detection was comparable to spectrophotometry, yielding similar analytical sensitivity level, excellent correlation ($R_2 < 0.964$) and near perfect kappa agreement (95.1%, $\kappa = 0.828$). Thermostabilization of the NASBA mix was able to preserve its stability at 8 °C and -20 °C

for 2 months. In the viability assay, *lolB* mRNA was detected even after 48 hours post-treatment, therefore precluding its use as a viability indicator.

Conclusion: We have, for the first time, developed a sensitive cholera-NASBA-ELISA assay with biosensor detection that can be performed using simple equipments within 4 hours. The dry NASBA mix reduces multiple pipetting steps and facilitates transportation and storage. The test is suitable for use as a rapid diagnostic test or screening test in the field.

Supervisor:

Dr P. Lalitha

DEVELOPMENT OF RECOMBINANT MYCOBACTERIUM BOVIS BACILLE CALMETTE-GUERIN (rBCG) EXPRESSING THE 19 kDa C-TERMINUS OF MEROZOITE SURFACE PROTEIN-1 (MSP-1C) AND THE 22 kDa OF SERINE REPEAT ANTIGEN (SE22) OF PLASMODIUM FALCIPARUM AS A POTENTIAL BLOOD-STAGE MALARIAL VACCINE

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PhD Biomedicine (Vaccinology)

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Introduction: Recombinant *Mycobacterium bovis* Bacille Calmette-Guerin (rBCG) expressing the 19 kDa C-terminus of merozoite surface protein-1 (MSP-1C) and a 22 kDa protein (SE22) from the 47 kDa N-terminal domain of serine repeat antigen (SERA) of *Plasmodium falciparum* is a potential blood-stage malarial vaccine candidate. In the present study, the MSP-1C and SE22 were synthetically generated in favour of mycobacterial codon usage by assembly PCR. More importantly, the synthetic MSP-1C was mutated at various sites to induce the production of inhibitory but not blocking antibodies as previously reported.

Materials and Methods: The MSP-1C and SE22 fragments were cloned into a shuttle plasmid to facilitate expression by BCG. The expression of the blood-stage epitopes were driven by the heat shock protein 65 (*hsp65*) promoter from *M. tuberculosis* and the signal peptide from the MPT63 *M. tuberculosis* antigen. Expression of the recombinant clones were detected by specific monoclonal antibodies using Western blotting: SE47 mAb against the SE22 and 12.10 and 1E1 mAbs against the MSP-1C.

Results: The SE22 successfully reacted with SE47 mAb while the MSP-1C protein reacted with the inhibitory mAb 12.10, but not the blocking of mAb 1E1. The immunization of BALB/c mice with the rBCG elicited specific humoral responses against both blood-stage epitopes with a mixed Th1/Th2 profile. Immunized sera containing high levels of specific IgG2a against both epitopes (as determined by ELISA) were reactive with fixed *P. falciparum* merozoites as demonstrated

by the indirect immunofluorescence assay (IFA). In addition, the antibody titres against the MSP-1C and SE22 epitopes appeared to be correlated with the levels of inhibition of merozoite invasion of erythrocytes in vitro. Furthermore, the lymphocyte proliferative response to MSP-1C and SE22 from rBCG-immunized mice was significantly higher than the control groups. The expression of intracellular cytokines (IL-2, IL-4, and IFN- γ) in CD4⁺ and CD8⁺ cells were also detectable following in vitro stimulation with both epitopes. Preliminary and long-term in vivo stability analyses showed that the rBCG were stable in spite of being a non-integrative plasmid.

Conclusion: This study demonstrated that a single construct expressing a combination of 2 blood-stage epitopes of *P. falciparum* induced appropriate humoral and cellular responses against the parasites, paving the way for the construction of a potential blood-stage malarial vaccine.

Supervisor:
Professor Dr Norazmi Mohd. Nor

Conclusion: These results suggested that VCUSM1 and VCUSM2 are the least toxic, highly immunogenic, promising vaccine candidates against *V. cholerae* O139 Bengal.

Supervisor:
Professor Dr Zainul Faziruddin Zainuddin

DEVELOPMENT AND EVALUATION OF hema MUTANTS OF *VIBRIO CHOLERA* O139 BENGAL AS A POTENTIAL VACCINE

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PhD Biomedicine (Vaccinology)

School of Health Sciences, Universiti Sains Malaysia
Health Campus, 16150 Kelantan, Malaysia

Objectives: The study aimed to describe the development of live attenuated oral vaccine strains VCUSM1 and VCUSM2 against *Vibrio cholerae* O139 Bengal. These strains are metabolic auxotrophs and require exogenous aminolevulinic acid (ALA) for their survival.

Materials and Methods: The auxotrophy was achieved by mutating a house-keeping gene hema that encodes for glutamyl tRNA reductase, an important enzyme of the C5 pathway of ALA biosynthesis. Experiments carried out in infant mice and adult rabbits have shown that these vaccine strains are good colonizers of the small intestine. Subsequent experiments have revealed that these strains shed for a maximum of 4 days in the stool and elicit greater than a 4-fold rise in vibriocidal antibodies in the vaccinated rabbits. Rabbits vaccinated with VCUSM1 and VCUSM2 were fully protected against subsequent challenges with virulent wild type.

Results: Dose optimization studies have shown that as little as 1×10^6 CFU of VCUSM1 and VCUSM2, given orally 2 weeks apart, yielded 100% protection against subsequent challenge. Experiments carried out in ligated ileal loops of rabbits have shown that these strains are not absolutely non-reactogenic; however, they are 2.5-fold less toxic at a dose of 1×10^6 CFU. VCUSM1 and VCUSM2 survived no longer than 6 days in environmental waters as compared with the wild type, which was still detectable on day 20 post-inoculation.

CLINICAL AND RADIOLOGICAL STUDY OF IMMEDIATE PLACEMENT OF CORAL COATED DENTAL IMPLANT

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MSc Dentistry

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Objectives: The study was conducted to determine clinically the efficacy of bone healing of immediate dental implantation with coral augmentation at the bone-implant interphase and to compare radiographic bone density around immediate dental implants with and without coral augmentation

Material and Methods: A comparative vertical prospective study design was employed, comparing 2 groups of patients receiving dental implants in Hospital Universiti Sains Malaysia. A group of patients received implants (Frialit-2 implant system, Germany) coated with natural coral (obtained from the National Tissue Bank, Universiti Sains Malaysia) and the other group received non-coated implants. All the implants were placed immediately into the extracted tooth socket. The inclusion criteria were healthy patients, age 18–40 years old, indicated for single tooth extraction, no endodontic and periodontic lesions at site of extraction, and extraction socket was left with intact 4 walls. The exclusion criteria were patients with systemic disease and if the extraction socket has lost 1 or more wall. Out of 13 patients selected, 8 patients had immediate implant with coral coating (test group) and 5 patients had non-coated implant (control group). However, 2 patients in the test group dropped out of the study. Clinical and densitometric assessments were done after 1, 2, 3, and 12 weeks post-operation.

Results: Clinically, all the 11 patients in both groups showed normal wound healing. Densitometric analysis showed that the bone density was significantly higher in the immediate coral-coated implant group compared with the control group on at least 1 point around the implant ($P < 0.01$). The values for densitometric analysis at 5 different points were higher in coral-coated implant group. However, the difference was significant only at the coronal mesial and midway distal points, with $P < 0.002$ and $P < 0.024$, respectively.

Conclusion: Locally produced coral (obtained from the National Tissue Bank) is a suitable material for coating the surface of implants since it was shown to provide primary stability to the immediate placement of the coated implants in the extraction sockets. This primary stability will ensure new bone growth to provide the more stable secondary stability. The biocompatibility of the coral graft and its role

as an osteoconductor would have encouraged this very useful phenomena in dental implantology.

Supervisor:
Professor Dr Ab Rani Samsudin
Co-supervisor:
Dr Sam'an Malik Masudi

DENTAL CAST AND CEPHALOMETRIC ANALYSIS OF UNILATERAL CLEFT LIP AND PALATE USING FINITE ELEMENT ANALYSIS

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Objective: The purpose of this study was to localize differences of Malay population between non-cleft (NC) and unilateral cleft lip and palate (UCLP) in terms of the size and shape of the maxilla and mandible using Finite Element Analysis (FEA).

Material and Methods: In this cross sectional study, 31 subjects with UCLP and NC (6–12years old) were selected, and their dental casts and lateral cephalometrics were compared. The mean (SD) age was 9.4 (1) years for UCLP compared with 9.5 (1.17) years for NC. No patient had received orthodontic treatment. Dental casts were digitized into 6 elements with 12 homologous landmarks while lateral cephalometrics were digitized into 7 elements with 11 homologous landmarks.

Results: The maxilla was more affected by cleft in all dimensions than mandible. Difference in the size and shape of the mandible between UCLP and NC were limited.

Conclusion: Size and shape differences between UCLP and NC can be identified with finite element analysis.

Supervisor:
Dr Zainul Ahmad Rajion
Co-supervisor:
Dr Rozita Hassan

MICROLEAKAGE OF REPAIRED FISSURE SEALANT USING NANO-FILLED RESIN: IN VITRO STUDY

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MSc Dentistry

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Objectives: The aims of this study were to investigate whether differences in the technique of repair influence a seal of a repaired nano-filled, resin-based fissure sealant and to determine the effect of different curing time on microleakage of a repaired fissure sealant.

Materials and Methods: A total of 108 extracted molars were randomly allocated to 1 of 4 groups of 28 teeth each. A light cured, nano-filled, resin fissure sealant (Filtek Z350) was placed on their occlusal surface following cleaning by prophylaxis and acid etching. Following storage in artificial saliva for a week, duplication of sealant failure was carried out. The teeth were then subjected to 4 different methods of repair: Group 1, a slow-speed prophylaxis brush followed by acid etching and 10 seconds curing time (control); Group 2, prophylaxis brush, acid etching, application of bonding agent, and 10 seconds curing time; Group 3, prophylaxis brush, acid etching, and 5 seconds curing time; and Group 4, prophylaxis brush, acid etching, and 20 seconds curing time. Then, they were stored for 1 week in artificial saliva, painted with 2 layers of impermeable varnish. Their apices were sealed with wax, and the teeth were immersed in 1% methylene blue for 48 hours. The teeth were then sectioned longitudinally in a mesiodistal plane to achieve 3 cuts resulting in a maximum of 4 blocks, i.e., 6 surfaces per tooth. A total of 648 surfaces from 108 teeth were scored for microleakage using scoring system on the intact and the repaired side of the fissure sealant.

Results: Chi-square analysis indicated no significant difference between the tested techniques of repair, except for Group 3 that resulted in the highest number of surfaces exhibited maximum score of microleakage ($P = 0.027$).

Conclusion: The present data did not demonstrate any single method of repair to be superior to the control method, which was the use of prophylaxis brush without any medium, followed by acid etching, applying fissure sealant, and light curing for 10 seconds. The control method seems to be the simplest and the most appropriate method of repair; therefore it is recommended.

Supervisor:

Dr Siti Noor Fazliah Mohd Noor

Co-supervisor:

Dr Dasmawati Mohamed

THE APICAL SEALING ABILITY EVALUATION OF A NEW EXPERIMENTAL NANO HYDROXYAPATITE-FILLED EPOXY RESIN BASED ENDODONTIC SEALER: IN VITRO STUDY

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MSc Dentistry

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Health Campus, 16150 Kelantan, Malaysia*

Objectives: The study was conducted to evaluate the apical sealing ability of experimental nano hydroxyapatite

(HA)-filled epoxy resin-based endodontic sealer and compare it with the commercial AH26 sealer.

Material and Methods: School of Dental Science, Universiti Sains Malaysia (USM) had prepared a new experimental nano HA-filled epoxy resin based endodontic sealer. The HA nano crystal, sizes ranging 40–60 nm, were synthesized at the School of Chemical Sciences, USM by wet chemical method using calcium hydroxide, Ca(OH)_2 , and phosphoric acid, H_3PO_4 , as the Ca and P precursors, respectively. The components of experimental nano HA-filled epoxy resin sealer were nano HA, bismuth (III) oxide, hexamethylene tetramine, and epoxy resin. A total of 76 extracted human anterior teeth were instrumented using nickel–titanium (NiTi) files and randomly divided into 2 test groups of 33 teeth each and 2 control groups of 5 teeth each. The first group was obturated using gutta-percha with AH26 sealer. The second group was obturated with the nano HA-filled epoxy resin based sealer. All teeth were coated with nail polish, except 2 mm from foramen apical, and then suspended in 2% methylene blue for 7 days. All teeth were sectioned longitudinally for the measurement of penetration of the dye using stereo-microscope (36 x magnification). The maximum length of the dye penetration in each root was examined and measured by Imaging System (LEICA, UK). All the measurements were then noted and tabulated. Every measurement was repeated twice by 2 blinded researchers, the mean of the 2 measurements was recorded for each case. Intraclass correlation coefficient (ICC) was nearly 0.983, which suggest that the measurement was almost identical or with negligible errors of measurements.

Results: Statistical analysis of the results was performed using independent sample *t* test. The mean penetration distances of methylene blue across the AH26 silver-free sealer and experimental nano HA sealer was 0.44 (SD 0.63) mm and 0.75 (SD 0.81) mm, respectively. The result showed that there was no statistically significant difference ($P > 0.05$) in apical sealing ability between AH26 silver-free sealer and experimental nano HA sealer.

Conclusions: Experimental nano HA-filled epoxy resin endodontic sealer provided an adequate apical seal against dye penetration in similar level with AH26 silver-free and could be used as an alternative to the commercial available endodontic sealer. Further study should be carried out to determine the setting time, radio-opacity, solubility, and antibacterial properties of nano HA root canal sealer.

Supervisor:

Dr Sam'an Malik Masudi

Co-supervisors:

Dr Dasmawati Mohamad

Dr Norhayati Luddin

VARIATIONS IN TOOTH SIZE, DENTAL ARCH DIMENSIONS, AND SHAPE AMONG MALAY SCHOOL CHILDREN

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MSc Dentistry

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Objectives: The aims of the present study were to measure the mesiodistal tooth size and dental arch dimensions in Malay schoolchildren with Class I, Class II, and Class III, and compare the tooth size and arch dimensions among different classes of malocclusion.

Materials and Method: The current study consisted of dental casts of 150 subjects: 78 males and 72 females aged 12 and 16 years. Every malocclusion group consisted of 50 subjects. An electronic digital caliper was used to measure the individual mesiodistal tooth width of all maxillary and mandibular permanent teeth (except 2nd and 3rd molars). Inter-canine and inter-molar widths were also measured. To measure maxillary and mandibular arch perimeter and length, AutoCAD software was used.

Results: The teeth width and arch dimensions were significantly larger in males than in females except for lower arch perimeter and upper arch length ($P < 0.05$). Moreover, the arch widths were significantly smaller in Class II compared with Class I normal occlusion. Significant difference was observed only in the mandibular inter-canine width ($P < 0.05$). There were no significant differences neither in arch perimeter or arch length in the maxillary and mandibular dental arches.

Conclusion: Knowledge of arch width and tooth size that is associated with malocclusion is helpful in determining orthodontic treatment goals and likely post-treatment sequence for the malocclusion.

Supervisor:

Dr Zainul Ahmad Rajion

Co-supervisor:

Dr Rozita Hassan

Dr Siti Noor Fazlia Mohd Noor

EVALUATION OF APICAL SEALING ABILITY OF A NEWLY DEVELOPED NANO HYDROXYAPATITE SEALER USING COLD LATERAL AND CONTINUOUS WAVE CONDENSATION TECHNIQUES: AN IN VITRO STUDY.

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MSc Dentistry

School of Dental Sciences, Universiti Sains Malaysia
Health Campus, 16150 Kelantan, Malaysia

Objectives: The study was designed to evaluate in vitro apical sealing ability of experimental nano hydroxyapatite (HA)-containing endodontic sealer and compare it with AH 26 sealer using cold lateral and continuous wave condensation techniques.

Materials and Methods: This was a randomized controlled single-blind experimental study involving 232 freshly extracted single rooted human teeth. Crowns of the teeth were amputated at the cemento–enamel junction using Exakt cutting system. The root canals were prepared using a crown-down technique with ProTaper nickel–titanium rotary system and randomly divided into 4 experimental groups to be obturated by the nano HA sealer and cold lateral condensation technique ($n = 53$), the AH 26 sealer and cold lateral condensation technique ($n = 53$), the nano HA sealer and continuous wave condensation technique ($n = 53$), and the AH 26 sealer and continuous wave condensation technique ($n = 53$). The remaining 20 teeth served as positive and negative control groups of 10 teeth each. All teeth were stored in an incubator, at 37 °C for 7 days to allow adequate setting of sealers. Root surfaces were covered with 2 layers of nail polish except for the apical 2 mm and then placed in an aqueous solution of 2% methylene blue dye. After 72 hours, the teeth were rinsed under running tap water and dried, and the nail polish was removed. Each specimen was then embedded in isobornyl methacrylate resin to facilitate their mounting in a hard tissue cutter. Six transverse sections of 1 mm thickness were taken starting at the apical limit of the preparation and ascending apico–coronally to a total of 6 mm of each tooth. The coronal surface of each consecutive section was assessed for dye penetration using stereomicroscope supported by image analyzer software. Overall dye penetration for each tooth was then calculated as the ratio between the total methylene blue infiltrated surface areas and the total dentinal surface areas of the 6 levels. Data was entered into SPSS software and analyzed using two-way ANOVA where $P < 0.05$ was considered as statistically significant.

Results: The positive controls demonstrated maximum dye penetration at all levels in all teeth. In contrast, the negative controls showed no evidence of leakage at any level in any of the samples. Means of overall apical dye penetration were 9.33% for nano HA sealer and 8.94% for AH 26 sealer with no significant difference ($P = 0.087$) between the 2 tested sealers. The means of overall apical dye penetration were 12.15% and 6.11% for cold lateral condensation and continuous wave condensation techniques, respectively. Cold lateral condensation leaked significantly more ($P < 0.001$) than continuous wave condensation technique.

Conclusion: Experimental nano hydroxyapatite sealer provided a comparable apical seal to that obtained by AH 26 sealer and could be used as an alternative to the commercial available endodontic sealer. In addition, continuous wave condensation technique using system B created a better apical seal than conventional cold lateral condensation technique.

Supervisor:

Dr Sam'an Malik Masudi

Co-supervisor:

Dr Wan Zaripah Wan Bakar

GENOTOXIC EVALUATION OF LOCALLY PRODUCED DENTAL PORCELAIN USING THE AMES SALMONELLA AND COMET ASSAYS

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MSc Dentistry (Prosthodontics)

School of Dental Sciences, Universiti Sains Malaysia
Health Campus, 16150 Kelantan, Malaysia

Objectives: The study was conducted to determine the genotoxicity of locally produced dental porcelain (Universiti Sains Malaysia, MY) using the Salmonella/mammalian-microsome mutagenicity assay (Ames assay) and the single cell gel electrophoresis assay (Comet assay).

Materials and Methods: In the Ames assay, 4 genotypic variants of the Salmonella strains (TA98, TA100, TA1535, and TA1537) carrying mutations in several genes were used. The dental porcelain was incubated with these 4 strains at 5 different concentrations (0.3125, 0.625, 1.25, 2.5, and 5 mg/plate) along with concurrent appropriate positive and negative controls, both in the absence and presence of metabolic activation (S9). The results were assessed based on the number of revertant colonies per plate in comparison with that of the negative control. In the Comet assay, L929 (CCL-1 ATCC, USA) mouse fibroblast cells were treated with the locally produced dental porcelain at 3 different concentrations (50, 100, and 200 mg/mL) along with concurrent negative and positive controls. Fifty cells were captured randomly from each slide and scored under a fluorescence microscope. The mean value of tail moment was used as a measurement of DNA damage.

Results: For a substance to be considered mutagenic in the Ames assay, the number of revertant colonies per plate containing the test material must be at least more than double the number of colonies per plate containing the negative control. The test material do not show more than double the number of colonies than the negative control or any dose-dependent increase in the number of revertant colonies both in the absence and presence of metabolic activation. The results of the Comet assay showed that the mean tail moment with the test material was similar to that of the negative control; there was also no dose-dependent relationship on the tail moment.

Conclusion: Locally produced dental porcelain is non-genotoxic by both Ames and Comet assays under the present test conditions.

Supervisor:

Dr Adam Husein

Co-supervisor:

Dr TP Kannan

PREVALENCE OF ORAL MUCOSAL LESIONS AND THE ASSOCIATION BETWEEN DIABETES MELLITUS AND ORAL PRECANCEROUS LESIONS AMONG MALAY PATIENTS ATTENDING HOSPITAL UNIVERSITI SAINS MALAYSIA

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MSc Dentistry

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Health Campus, 16150 Kelantan, Malaysia

Objectives: The study aimed to determine the prevalence of oral mucosal lesions among Malay diabetic patients, and the association between oral mucosal lesions and diabetes factors, as well as diabetes and oral precancerous lesions.

Materials and Methods: This cross-sectional study involved 420 diabetic patients and 420 non-diabetic subjects in Hospital Universiti Sains Malaysia, Kota Bharu, Kelantan, from January until August 2009. Demographic information, duration and type of diabetes, glycosylated hemoglobin values (HbA_{1c}), and previous and current uses of medication were obtained from medical records. Detailed oral examination of the oral cavity was done based on international criteria and World Health Organization codes. The number of remaining teeth and presence of dentures were also noted.

Results: The frequency of oral mucosa lesions was significantly higher in diabetes patients, 45%, in comparison with 38.3% in controls ($P < 0.05$). There were 12 types of oral mucosal lesions identified. Specific oral lesions that were found to be of significantly greater frequency in diabetes patients than controls include geographic tongue ($P < 0.01$), denture stomatitis ($P < 0.05$), and angular cheilitis ($P < 0.05$). The prevalence of traumatic ulcers was higher in diabetics; however, this was not significant ($P > 0.5$). About one-third of subjects in both groups used dentures and diabetic patients have a lower mean number of remaining teeth compared to non-diabetics ($P < 0.001$). There was an association between the prevalence of oral mucosal lesions and metabolic control ($P < 0.05$). However, no association between diabetes mellitus and oral precancerous lesions was found.

Conclusions: Diabetic patients showed higher prevalence of oral mucosal lesions than control subjects did. There was an association between oral mucosal lesions and metabolic control of diabetes; however, no association was observed between diabetes and oral precancerous lesions.

Supervisor:

Associate Professor Dr Hj Abdul Rashid Hj Ismail

Co-supervisors:

Dr Rajan Saini

Associate Professor Dr Hjh Noorliza Mastura Hj Ismail

DENTAL AGE IN KELANTANESE MALAY POPULATION BASED ON DEMIRJIAN'S METHOD

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Objectives: The purposes of this study were as follows: (1) Examining the applicability of Demirjian's methods for estimating the chronological age of male and female Kelantanese Malay children aged 5 to 16 years; (2) Establishing a new dental age standard, if Demirjian's methods were not applicable on the Kelantanese Malay population; (3) Comparing the dental age curves between Malay children and French-Canadian children; (4) Determining the sexual dimorphism in the dental age assessment of Kelantanese Malay children; (5) Detecting the differences in "dental ages" and "maturity scores" between the lower left permanent teeth and the lower right; and (6) Detecting the median ages of attainment of each stage of dental development according to Demirjian's stages for the lower left 7 teeth.

Materials and methods: A total number of 905 panoramic radiographs (OPG) for healthy Kelantanese Malay children aged 5 to 16 years old were collected from the Radiographic Unit, Hospital Universiti Sains Malaysia (HUSM), and the Orthodontic Clinic, Hospital Kota Bharu. The dental age was assessed cross-sectionally by using Demirjian's methods (1973 and 1976). Children who had any disease that was known to affect the dental development or have agenesis in the lower arch were excluded, as well as those poor quality OPG images.

Results: Demirjian's method (1973) overestimated the chronological age by 1.2 years for boys and 1.3 years for girls. The 4 teeth: M_2 , M_1 , PM_2 , PM_1 method overestimated the age by 1.2 years for both sexes, while the 4 teeth: M_2 , PM_2 , PM_1 , I_1 method overestimated the age by 0.6 year for boys and 0.7 year for girls. As the methods of Demirjian's were not applicable on Kelantanese Malay children, new modified specific standards curves and tables were produced for Demirjian's method (1973). An external sample of 47 Kelantanese Malay children (28 boys and 29 girls) randomly selected from HUSM was used to test the accuracy of the modified Demirjian's method on Kelantanese Malay population. The results showed a mean difference between the chronological age and dental age of about 2 months for both sexes. The median ages of attainment of each developmental stage according to Demirjian's stages for the lower permanent left 7 teeth for both sexes were produced. Moreover, girls showed more advancement in dental age compared with boys. In comparison between the dental development between the Kelantanese Malay and French-Canadian children, the results showed that the "dental age" for younger age groups of boys (7.00–9.99 years) and age groups of girls (7.00–8.99 years) was not significantly different from the French-Canadian children. After the age 10 years, the difference increased in boys, whereas in girls, the

increase started earlier, i.e., after the age 9 years. The greatest difference between Kelantanese and French-Canadian girls was at age 12 years with mean difference of about 2 years, while for boys was 1 year earlier than the girls with a difference reach about 2 years and 3 months. In the older age groups (14.0–15.99 years) the maturation scores were similar with the French-Canadian children. No significant difference was found in the dental development of the lower left teeth when compared with the right lower teeth.

Conclusion: Demirjian's methods (1973 and 1976) were shown to be less accurate to estimate the chronological age in Kelantanese Malay children samples. Variations in the dental development should be considered especially for the genetic factor and less for non-genetic factors. The modification of the system had resulted in a new dental age system that is more precise and more applicable for the Kelantanese Malay children.

Supervisor:

Dr Siti Noor Fazliah Mohd Noor

Co-supervisor:

Dr Mohd Fadhli Khamis

THE CORONAL SEALING ABILITY OF A NOVEL NANO HYDROXYAPATITE-FILLED ENDODONTIC SEALER

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MSc Dentistry

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Objectives: The study aimed to evaluate the sealing ability of a novel nano hydroxyapatite (HA)-containing endodontic sealer in preventing coronal leakage before and after post preparation and to compare it with the commercial AH26 sealant.

Material and Methods: A total of 152 extracted human single-rooted teeth were instrumented using nickel-titanium (NiTi) files and the crowns were then amputated. After cleaning and shaping procedure were completed using step back technique, samples were randomly divided into 2 groups. The 2 groups were obturated with either gutta percha and AH 26 sealer, or gutta percha with the nano HA-containing sealer. All teeth were then stored at 37 °C for 7 days to allow the sealer to set. Each group was then further subdivided into 2 groups: a group was prepared for post using para-post drill and the other group was left intact. All 4 study groups consisted of 38 samples per group. The teeth were then thermal-cycled at 5°C and 55°C in water baths at dwell time of 30 seconds for a total of 500 cycles. External surfaces of the roots were coated with 2 layers of nail varnish that did not cover the coronal opening. Specimens were then submerged in 2% methylene blue dye for 24 hours. Each root was sectioned vertically into 2 halves, and microleakage was measured under microscope (36 x magnifications) by taking

the maximum linear dye penetration coronal-apically. Micro leakage readings were analyzed by the independent *t* test ($\alpha = 0.05$).

Results: The result showed that there was no statistically significant difference in the coronal sealing ability between the 2 sealers, before and after preparation for post. The experimental nano HA-containing and AH26 sealers with post space preparation showed significantly more leakage compared with sealers with no post space preparation.

Conclusion: Preparation for post caused a significant decrease in the coronal sealing ability of both sealers; however, it did not result in any difference between the performances of the 2 sealers. The novel nano HA-containing sealer tested had a comparable coronal sealing ability with the commercial AH26 sealer.

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ASSESSING AND MANAGING RISK OF OCCUPATIONAL STRESS IN MALE AUTOMOTIVE ASSEMBLY WORKERS IN MALAYSIA

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Introduction: Occupational stress is a major occupational health problem in many industries. Automotive assembly industry workers are among the occupational groups reportedly experiencing disproportionately high levels of occupational stress.

Objectives: The main purpose of this study was to assess and manage the risk of occupational stress in male automotive assembly workers in Malaysia. Other objectives include validating the Malay version of the Job Content Questionnaire (JCQ) and Depression Anxiety Stress Scales (DASS) 21- and 42-item; determining the prevalence and associated factors of self-perceived depression, anxiety, stress, and quality of life (QOL); modeling the relationship between job demand, job control, and social support in relation to the self-perceived depression, anxiety and stress, and QOL; and evaluating the immediate effects of a 4-hour stress management training on the self-perceived depression, anxiety, and stress in male automotive assembly workers.

Material and Methods: As parts of the longitudinal research design, a cross-sectional study and quasi-experimental intervention were carried out between November 2004 and October 2007. A total 728 workers from 2 automotive assembly plants in Selangor and Pahang were enrolled in this study.

Results: The Malay version of the JCQ and DASS (21-item and 42-item) were reliable and valid for assessing job content, self-perceived depression, anxiety, and stress. The prevalences of self-perceived depression, anxiety, and stress were 35.4%, 47.2%, and 31.1%, respectively. Multiple linear regression (MLR) analyses revealed that psychological job demand, job insecurity, and hazardous conditions were positively associated with the DASS-Depression, DASS-Anxiety, and DASS-Stress; supervisor support was inversely associated with DASS-Depression and DASS-Stress. The prevalence of reported good or very good overall self-perceived QOL and general health status was 64.9% and 53.7%, respectively. MLR analyses indicated that created skill was positively associated with physical health and psychological domains of QOL while skill discretion was positively associated with the social relationship and environment domains of QOL. Social support was positively associated with the physical health and environment domains of QOL while co-worker support was positively associated with the psychological and social relationship domains of QOL. Job insecurity and hazardous condition were negatively associated with all domains of QOL while psychological job demand was negatively associated with the environment domain of QOL. In the structural equation modeling analysis, the final model showed that social support in the workplace was directly related to all 4 domains of QOL (physical health, psychological wellbeing, social relationships, and environmental conditions) and inversely related to self-perceived depression and stress. Job demand was directly related to self-perceived stress and inversely related to the environment domain of QOL. Job control was directly related to the social relationships domain of QOL. Surprisingly, self-perceived stress, anxiety, and depression were also found to be important mediating factors in the relationships between job demand and social support and the 4 domains of QOL. Meanwhile, in the quasi-experimental study, we found that the stress management training significantly improves self-perceived depression and anxiety in the experimental group as compared with the control group.

Conclusion: Reducing psychological job demand, job insecurity, and hazardous condition factors and promoting good support from co-workers and supervisors may improve the worker's self-perceived depression, anxiety, stress, and QOL in the automotive assembly plant. At the individual level, the findings suggest that the stress management training is effective in reducing the self-perceived depression and anxiety.

Supervisor:
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DEMONSTRATION OF ANTIGENIC AND SPECIFIC OUTER MEMBRANE PROTEIN(S) OF *ACINETOBACTER BAUMANNII*

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Introduction: *Acinetobacter baumannii* has been recognized as an emerging nosocomial pathogen and is often multi-resistant to antibiotics. Current identification of *A. baumannii* is by conventional culture method and biochemical tests, which take about 2 to 7 days to produce results. Hence, there is a need for a new rapid, sensitive, and specific test that would allow better management of nosocomial infections. The aim of this study was to detect the presence of a specific and antigenic biomarker for *A. baumannii* from the outer membrane protein (OMPs) that can be used for the development of a rapid and specific diagnostic test.

Material and Methods: Protein profiles of OMP lysates from the ATCC strain and clinical isolates of *A. baumannii* were obtained by SDS-PAGE and compared. The protein profiles of the clinical isolates were 95% identical to that of the ATCC strain. Following this, the protein electrophoretograms were subjected to Western blot using sera from patients infected with *A. baumannii*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and sera from normal healthy subject using labeled anti-IgM, IgA, and IgG to check for cross reactivity.

Results: There was 1 band of molecular weight 34.4 kDa that was found only in clinical isolates of *A. baumannii* and it does not cross react with other tested sera. The observations suggested that the protein was specific for *A. baumannii* and can be used as a biomarker for development of a diagnostic test.

Conclusion: The results are encouraging in that the 34.4 kDa protein identified is specific for *A. baumannii* and can be used as a biomarker for development of a diagnostic test that would be faster and more specific than the current techniques of diagnosis. However, further studies need to be done to measure the antibody level against this specific protein, the sensitivity and specificity of the protein, and the retention time of the antibody detectable in the serum of the infected patients.

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CLONING, EXPRESSION, AND PURIFICATION OF *TOXOCARA CANIS* RECOMBINANT ANTIGENS (rTES-32, rTES-120) AND DEVELOPMENT OF SERODIAGNOSTIC TEST FOR TOXOCARIASIS

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Introduction: Routine serodiagnosis of human toxocariasis is based on indirect IgG-ELISA kits which employ native *Toxocara canis* excretory-secretory (TES) antigen. However, these assays lacked specificity especially when used in tropical countries where multi-parasitism are prevalent. In an effort to improve the diagnostic test for infection, we have developed an IgG4-ELISA assay that uses 3 recombinant antigens.

Material and Methods: Recombinant *T. canis* DNA that encodes for rTES-26, rTES-32, and rTES-120 were produced by cloning of open-reading frames (ORF) of the respective genes via reverse-transcriptase-PCR (RT-PCR) using mRNA extracted from a culture of *T. canis* second stage larvae into PCR2.1 TOPO vector. Sequence analysis revealed that TOPO/TES-32 and TOPO/TES-120 were 100% similar to the reported sequences in the GenBank; however, TOPO/TES-26 gene fragment had 4 mutations. After all mutations in TOPO/TES-26 gene fragment had been corrected, TES-26 and TES-32 were subsequently subcloned into a GST-tagged prokaryotic expression vector, while TES-120 was subcloned into a HIS-tagged vector. All constructs were expressed in *E. coli* BL21(DE3) expression host.

The recombinant proteins were subsequently purified under native condition by affinity chromatography using GST and His-Trap resins, since these recombinant proteins are abundantly expressed in soluble form. The site-specific protease, Factor Xa, was used to remove GST tag in the TES-26 and TES-32 fusion proteins. Western blot analysis revealed that these recombinant antigens were immunologically reactive and specific.

Results: Sera from patients infected with toxocariasis had IgG4 antibodies that recognized these recombinant antigens, while sera from individuals with other infections and healthy controls did not. When the 3 recombinant antigens

were tested in ELISAs specific for immunoglobulin IgM and IgE classes, as well as IgG subclasses (IgG1-IgG4), the results clearly showed that only IgG4 assay displayed good specificity. The diagnostic utility of each purified recombinant antigen and rTES-30USM (previously produced in our laboratory) was further evaluated by IgG4-ELISA assay using 242 serum samples, which included 30 sera from patients with clinical, haematological, and serological evidence of toxocariasis. Both rTES-26 and rTES-32 IgG4-ELISAs demonstrated sensitivity of 80.0%, while rTES-120 IgG4-ELISA showed sensitivity of 93.3%, which is similar to that previously reported for rTES-30USM IgG4-ELISA. The sensitivity of rTES-120/rTES-30USM IgG4-ELISA was found to be significantly higher than rTES-26/rTES-32 IgG4-ELISA ($P < 0.001$). However, the mean ODs of the 30 toxocariasis samples among the IgG4 assays using the 4 recombinant antigens were shown not to be significantly different. There was marginally no significant difference between the specificities of rTES-26 and rTES-120, rTES-26 and rTES-30USM, or rTES-30USM and rTES-120.

In the final assay, rTES-32 was excluded since it did not show better sensitivity or specificity than rTES-26. Instead, rTES-30USM was included due to its high sensitivity and the fact that a 100% detection of toxocariasis cases was achieved with the combined use of rTES-30USM and rTES-120 in IgG4-ELISA.

Conclusion: A final assay which is sensitive (80.0%–93.3%) and specific (92.0%–96.2%) for detection of toxocariasis was successfully developed using 3 adjacent wells, each separately coated with rTES-26, rTES-30USM, and rTES-120. This study is novel in several ways: it is the first report on the use of multiple recombinant antigens for serodiagnosis of toxocariasis, the use of rTES-26 (and rTES-32) in *Toxocara* serodiagnosis, the use of IgG4 assay for rTES-120 and rTES-26, and the use of GST tag in the expression and purification of *Toxocara* recombinant proteins. The test may provide a significant improvement over commercially available tests for diagnosis of toxocariasis and may be used especially in countries co-endemic with other soil-transmitted helminthes.

Supervisor:
Professor Dr Rahmah Noordin

CYTOCHROME P450 2C8: AN INVESTIGATION OF TYPES AND FREQUENCIES OF CYP2C8 POLYMORPHISM IN MALAYSIA AND IN VITRO ANALYSIS OF CATALYTIC ACTIVITY

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Introduction: CYP2C8 is a polymorphic gene. Polymorphisms and drug interactions may imply susceptibility to adverse effects with drugs of CYP2C8 substrate. The objective

of this study is to investigate the types and frequencies of CYP2C8 polymorphism in Malaysia and to analyze the in vitro catalytic activity of CYP2C8.

Materials and Methods: Subjects were healthy adult Malays ($n = 313$), Chinese ($n = 335$), and Indians ($n = 200$), as well as male Malay patients with hypertension ($n = 154$). DNA extracted from the blood was subjected to PCR method developed for CYP2C8 genotyping. HPLC method was developed using Amodiaquine for the in vitro catalytic activity and inhibitory study of CYP2C8 utilizing recombinant CYP2C8 protein expressed in *E. coli*. The in vitro inhibitory study with natural products consisted of herbs extracts of *Eurycoma longifolia* Jack (ELJ) or locally known as Tongkat Ali, *Labisia pumila* (LP) or Kacip Fatimah, *Andrographis paniculata* (AP) or Hempedu Bumi, *Echinacea purpurea* (EP) or Purple Coneflower, and *Ginkgo biloba* (GB), as well as Tualang Honey (TH) and Policosanol, a cholesterol lowering tablet produced from sugarcane wax.

Results: The allele frequencies of CYP2C8*2 and *3 were 0.2% and 0.3% in Malays and 1.5% and 2.3% Indians. In Malay patients with hypertension, CYP2C8*2 and *4 were detected with allele frequencies of 0.3% each. The kinetic parameters, V_{max} and K_m for CYP2C8 were 2.41 (SD 0.014) pmol/min/pmol CYP2C8 and 1.28 (SD 0.047) μ M respectively. Extracts of LP, AP, TH, and Policosanol inhibited Amodiaquine metabolism via the CYP2C8 pathway in an uncompetitive (LP and AP), competitive (TH), and noncompetitive (Policosanol) inhibition mechanism.

Conclusion: We have successfully developed a specific, sensitive, and less tedious allele-specific multiplex PCR method for genotyping CYP2C8 polymorphism in Malaysia. We also have successfully expressed recombinant CYP2C8 protein and developed a specific and sensitive HPLC method for the in vitro analysis of CYP2C8 catalytic activity and the herb and food inhibition effect on CYP2C8 activity. Future studies are required to investigate the inhibitory effects of natural products on CYP2C8 activity to improve the understanding between genotypes and drug-herb or drug-food interactions in relation to susceptible diseases.

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