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EDITORIAL

Mohd Yusof Ibrahim

Chief Editor

The publication of this journal is made earlier so as to enable all our authors to submit their publication list before the year ended. The usual publication in the months of January, June and December is now rescheduled to January, May and September. We have also made some changes to the cover and layout of our journal with attractive colours.

In this issue we published two review papers, three original articles and three case reports. In the original articles, we have included the topic on Malaysian experience in the usage of some medications among renal-transplanted patients; a study on stroke survivors and KAP study amongst patients towards painkillers.

The topic on renal disease will be of interest by many. This topic was also discussed widely in the Sabah State recently in conjunction of the official opening of our first University Haemodialysis Unit by our first lady Deputy Prime Minister of Malaysia, who happened to be a medical specialist.

It is widely known that the number of patients needing haemodialysis services is increasing by years. However service availability to patients-in-need is limited to major towns and hospitals only. We need more commitments not only from the government but also from various agencies and corporate bodies to provide the services to the people. Public awareness on renal

diseases and its prevention are also vital to be imparted to public.

In few months we will be moving to a new year. This year marked a special event to our country as we celebrate our 61 years of independence with smooth transition to a new government. This will be a government to bring us towards a developed nation by the year 2020. We are looking forward for a successful years for our journal too.

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REVIEW ARTICLE

Role of Immunopathology in Clinical Course of Malaria: A Review

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Keywords: malaria, immunopathology, host, parasites

ABSTRACT

Malaria is a major health problem in various parts of the world especially affecting the tropical countries. It affects the vital organs causing severe complicated malaria. Clinical syndromes like severe cerebral anaemia, coagulation abnormalities, respiratory distress and severe anaemia can increase the mortality of malaria infected cases. Variation in individual susceptibility and severity and type of clinical presentations of malaria raises the need for study of both the parasite and host immune reactions as well as the contribution of inflammatory cytokines in malaria pathogenesis. This study explored the immunopathological basis and advances of severe malaria and their importance in pathogenesis of malaria and its complications. Previous and ongoing studies indicate that changes in endothelium during the sequestration of parasites in organs causes disruption of endothelial barrier function leading to serious effects of malaria. Parasite and host factors contribute to disturbance of cytokine regulation and escape of parasites from the immune system of the host. Immunopathological changes and dysregulation of cytokine production play central role in pathogenesis and disease severity in malaria.

INTRODUCTION

Malaria caused by the intracellular parasite *Plasmodium*, affects many people in the world especially those living in tropical countries. It affects the vital organs causing severe complicated malaria. Life-threatening complications such as cerebral malaria,

coagulation abnormalities, respiratory distress and severe anaemia can increase the mortality of malaria infected cases[1]. Variation in individual susceptibility and severity as well as type of clinical presentations of malaria raises the need for study of both the parasite and host immunopathological mechanisms. Cytokines released by the host cells upon induction by parasite surface antigens play important role in tissue damage and red cell sequestration seen in severe malaria. Immunopathological basis of severe malaria and their importance in outcome prediction and success of management should be explored.

Endothelial Activation and Parasite Cytoadherence

Endothelial activation is a major pathogenetic mechanism in malaria pathogenesis. *Plasmodium falciparum* erythrocyte membrane protein-1 from parasites (PfEMP) is a product of diverse *var* gene[2 – 5]. PfEMP forms knobs on the parasitized red cell surface and binds ligands including CD36 and E-elastin on the endothelial cells which are then activated. Increased expression of adhesion molecules on endothelial surfaces occur and result in sequestration of red blood cells leading to ischaemia of the organ affected. Endothelial permeability is augmented by cytokine cascade[3]. The sequestration process results in firm adhesion of IEs to endothelial cells (ECs), monocyte recruitment, microcirculatory changes and induction of cytokine cascade causing local injury and dysfunction. Endothelial surface expression of intercellular adhesion molecule-1 (ICAM-1), endothelial protein C receptor (EPCR) and PECAM-1 are augmented in severe cases of *falciparum* malaria[2]. These augment the inflammation around the minute vessels and lead to tissue and endothelial injury of pulmonary and brain microvasculature causing acute lung injury and disruption of blood brain barrier in cerebral malaria.

ICAM-1 and EPCR are receptors involved in cerebral malaria[6]. Studies showed that some haemoglobinopathies cause limited red cell invasion by the parasites. Haemoglobin S causes sickling of parasitized red cells rendering protection of malaria. Homozygous (HbSS) and heterozygous (HbAS) states have host microRNA (mRNA) profiles which after fusion with parasite mRNA render inhibition of parasite growth intracellularly. Host polymorphism that affects *P. falciparum* erythrocyte membrane protein-1 (PfEMP-1) may protect against malaria by impairing the parasite's ability to cytoadherence to microvessels[7 – 9]. Spleen is a major organ to remove malaria parasites from the circulation. Cytoadherence of malaria parasites is vital to the parasite survival to escape from splenic removal[10]. Virulence of the parasites differs according to the ability of cytoadherence through several parasite receptors such as plasmodium EMP1 (PfMP1). PfEMP1 proteins mediate cytoadhesion of parasitized red cells lining cells of the organ microvasculature. pfEMP1 has dual binding specificity and these structures can be divided into group A (EPCR binders) and group B (CD 36 binders). Cerebral malaria is caused by dual binding of PfEMP to ICAM-1 and endothelial protein C receptor (EPCR) and this fact can be implicated in prevention of cerebral malaria in future[11 – 13].

Host Immunopathogenesis

In endemic areas of malaria, there is development of immunity by forming acquired antibodies against variant surface antigen (VSA) such as PfEMP, MSP3 and GLURP (RO)[11]. Microparticles derived from platelets or parasitized RBC are seen in association with cerebral malaria in the sites of inflammation. Platelet-derived microparticles activate the capillary endothelium and regulate the pro-inflammatory cytokine production leading to increased vascular permeability[14, 15]. Overproduction of TNFα, IL-1β and chemokines induced by *plasmodium* glycophosphoinositol

(GPI) are responsible for disease mortality and deterioration[6, 16]. Antibodies to GPI is closely correlated with parasitaemia and disease severity[15 – 18]. Cytokine cascade is augmented by some chromosomal proteins called high mobility group box chromosomal protein 1 (HMGB1) which is secreted by activated mononuclear cells and passively through damaged cells. Levels of HMGB1 has been shown to parallel with disease severity and to induce permeability in endothelial cells, induce proinflammatory responses in macrophages through activation ofTLR2, TLR4, or receptor for advanced glycation end products (RAGE)[19, 20]. Elevated levels of HMGB1 can be used as a prognostic marker of disease severity in severe malaria[20, 21]. IFNγ plays a crucial role in the clearance of intracellular pathogen by inducing the MHC molecules[22]. It also causes expression of gene encoding IDO (indoleamine 2, 3-dioxygenase), a rate limiting enzyme of tryptophan metabolism that can generate quinolinic acid (QA). Increased central level of QA is implicated in the causation of hyperexcitability, dementia and neurological dysfunctions seen in complicated malaria[23]. CD40/CD40 ligand binding is important for binding of TNF activated platelets to the endothelial cells[24, 25]. IL-1 increases the expression of ICAM1 and the production of cytokines (such as IL-6) by endothelial cells[24]. Microparticles or moieties derived from blebbing of membranes of platelets and other cells during malaria infection. Platelet-derived microparticles can modulate the macrophage pro-inflammatory cytokine production and increase the endothelium permeability [26]. Cell mediated immunity contributed by CD4+ T cells has a major role in immunity against malaria infection, both in pre-erythrocytic and erythrocytic stage[27, 28]. They help to produce IFNγ and help B cells in control of malaria. People living in endemic areas of malaria possess IFNγ and IL-10 secreting CD4+ T cells[28].

Cytokines-Enhanced Haematological Abnormalities

Disseminated intravascular coagulation (DIC) is a life-threatening disorder occurring as a secondary to malaria. Expression of tissue factor (TF) is essential in initiation of blood coagulation. It occurs when the endothelial cells (EC) are exposed to pRBC. Initial stage of coagulation cascade after TF expression is escalated by amplification, propagation, and consolidation contributed by active role of sequestered pRBC and activated platelets at the sequestered sites[29]. Severe anaemia in malaria can be caused by lysis of infected and uninfected RBCs, splenic sequestration of RBCs[30] dyserythropoiesis and bone marrow suppression[31], erythrophagocytosis[32] and chronic transmission of malaria in endemic regions. *P. falciparum*-derived haempozoin pigment (PfHz) and cytokines (TNF and IFN) promotes the host immune response and potentially causes suppression of the erythropoietic response[32].

Role of Microglial Cells and Apoptosis in Malaria

Plasmodium apoptosis-linked pathogenicity factors (PALPF), PALPF-2, PALPF-5 can induce endothelial cell death in lining cells of microcapillaries in brain and lungs in severe malaria which are responsible for the development of acute respiratory distress and neurological abnormalities in severe malaria[33]. CD8+ T cells act by direct cytotoxicity on endothelial cells by apoptosis or granzyme-induced lysis of cells. This can lead to disruption of blood-brain-barrier and development of cerebral malaria. Microglial cells are activated in human cerebral malaria and shown to produce matrix enzyme, metalloproteinase, and induce cytokines which can be applied in destruction of blood brain barrier and spread of infection to the central nervous system and neuron survival[34, 35].

Malaria Pigment: A Potential Prognostic Marker

Accumulation of haemozoin pigment (HZ) in the phagocytic cells of the immune system is used in the diagnosis and prognosis of malaria[36]. *P. falciparum*-derived haempozoin pigment (PfHz) promotes the host immune response by activating NOD-like receptor of macrophages and potentially causes suppression of the erythropoietic response[37, 38]. It can cause monocyte and macrophage dysfunction by impairing phagocytosis and the expression of MHC class II molecules and ICAM1, inhibiting dendritic cell (DC) maturation and proliferative responses by leucocytes[38].

Role of Nuclear Histones

Histones are acid-soluble proteins found in chromatin complexes released on rupture of parasites and host cells. Level of circulating histones in patients with falciparum malaria is correlated positively with disease severity[39]. Histones can cause endothelial permeability and cytotoxicity by causing disruption of junctional proteins leading to cell death. Activation of toll like receptor (TLR2) and other receptors induces the release of IL-8 and other inflammatory mediators. Research is in progress to find out the potential uses of rhAPC that can cleave histones in hope to inhibit the cytokine induction and vascular permeability[40, 41].

Host Susceptibility

Susceptibility and severity of malaria infection is determined by a variety of host factors. Red blood cells carrying haemoglobin S (HbAS), HbAE, G6PD deficiency and alpha and beta thalassemia have reduced risk of developing severe anaemia by various protective effects such as reduced red cell invasion or impaired multiplication of parasites[42]. There are increased susceptibility and risk of severe malaria in individuals with polymorphism of adhesion molecules and cytokine such as ICAM-1, PECAM1, TLR, CXCL10 and tumour necrosis factor (TNF)[43 – 48].

Host and Parasite Macrophage Inhibitory Factors (MIF)

Macrophage migration inhibitory factor (MIF) is a cytokine produced mainly by host macrophages. It regulates the expression of TNF α and inflammatory mediators such as nitric oxide and cyclooxygenase 2 (COX 2)[49]. Plasmodium MIF (pMIF) is secreted when the parasites ruptured in schizont stage and they are exposed to immune cells. Levels of plasmodium MIF (pMIF) are positively correlated with parasitaemia, TNF a and IL-10. pMIF attenuates *Plasmodium* virulence by modulating functions of monocytes in host immune responses[49 – 51].

Vector-Parasite Association Affecting the Parasite Virulence

Studies have shown that vector mortality varies significantly among the different genotypes of parasites and environmental conditions[52]. Mosquitoes not only act as vectors but also modify the virulence of parasites. Transcriptomic studies showed after several blood passages, there is an expression of PIR gene in blood-stage parasites and increased virulence[53]. Mosquito transmission modifies the diversity and magnitude of gene such as rifin and *var*[54] in malaria parasite which progress through each step of the lifecycle in both vector and host[55, 56].

CONCLUSION

Understanding of basic and advances in immunopathological processes that cause endothelial barrier dysfunction, sequestration of parasites, destructive effects of host and parasite factors and cytokine storm in malaria infection explains the need for defining clinical biomarkers of outcome. It also helps to identify possible new targets for management

in severe *falciparum* malaria such as trial of rhAPC to regulate the endothelial dysfunction and monoclonal anti-cytokine antibody or other drugs that block cytokine such as TNF to inhibit the activated macrophages.

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REVIEW ARTICLE

Medication Errors: A Review of Classifications

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ABSTRACT

Medication errors (MEs) are preventable mistakes that occur when there is a failure in the treatment process of any disease that can cause potential harm to patients. Having an effect on patients, health outcomes and costs incurred, it does burden our economically-developing country. Database systems have been created worldwide for the reporting of MEs, but varying countries practise different classifications of MEs hence it poses a challenge to categorize them. This makes it next to impossible to fully curb this continual problem. There are a number of classifications of MEs, based on mistakes and errors based on skills, based on the mistakes itself, based on symptoms and based on the stages of drug delivery system. This review summarizes the pre-existing classifications of MEs.

INTRODUCTION

A medication error (ME) is a preventable occurrence where there is a failure in the treatment process of any ailments that can potentially lead to the harm of the patients while the medication is still handled by healthcare professionals or patients themselves[1]. Many of these errors can shorten one's life expectancy or even accelerate the death process of someone who is critically ill. These unintended acts and implementation errors cause many preventable deaths worldwide. In the United States alone, it is the third leading cause of death making 78% of the total deaths of 575,000 patients between the years of 2000 and 2002 preventable iatrogenic deaths[2].

Looking at a more local scenario, a geriatric outpatient pharmacy in a teaching hospital in Malaysia, reported approximately 20 cases of medical errors occurring daily. This resulted in a daily cost of RM300 which cumulatively has a projected cost of RM111,000 annually[3]. This cumulative amount is a large burden to our economically-developing country. Two thirds of the medication errors reported were prescription errors, where 98% had no harmful effects, which was detected by the pharmacists as the patients go to them as a second-line in the healthcare system[4].

To improve the number of MEs, Ministry of Health, Malaysia launched a Medication Error Reporting System (MERS) in 2009 for both public and private sectors. MERS is aimed to compile a database of medication errors, analyse the reports made, propose solutions and for monitoring. Even though underreported, this system has drastically improved the rate of occurrences of the preventable mistakes[5].

Methods

A systematic search of studies related to medication errors was conducted on PubMed and Google Scholar. Keywords used were 'medication errors', 'adverse reactions', 'outcomes of medications errors', and 'prescription errors'. We included classification of MEs which mainly looked at the types of MEs and at the stage of ME occurrence.

Terminologies of MEs

The terms used for patient safety in relation to drug administration, procedural errors and prescription mistakes are something that is still very heterogeneous. Amongst the terms used in literature includes, most commonly MEs, looking at the process in medication uses, medication-related adverse drug reactions and its clinical based outcomes. These terminologies broadly classifiy the process and its outcomes under drug-related problems[6]. Besides this, some include unintentional procedural errors and prescription errors in this broad heading of MEs[7]. Due to the lack of homogeneity in the terms used, abundant numbers of MEs are still under reported at primary care, district hospitals and tertiary hospital levels worldwide. This could be due to the complexity of the reporting systems, varying from country to country.

Classifications of MEs

Table 1 Summary of classifications

Classifications	References
Knowledge-, memory-, rule-, and action-based errors	Aronson, 2009[8]
Errors of omission, errors of commission	Benjamin, 2013[9]
Mistakes, skill-based errors (slips and lapses)	Ferner and Aronson, 2006[10]
Adverse drug reaction from MEs, MEs that do not cause adverse events, MEs that cause harm that are not adverse drug reactions	Ferner and Aronson, 2006[10]
Categories A to I based on the extent and the outcome of errors	Agency for Healthcare Research and Quality, 2012

MEs can be classified into knowledge-based, memory-based, rule-based and action-based errors[8]. Knowledge-based error is related to general and specific knowledge. Ignorance of staff to improve themselves continuously education wise is also classified under this category. Rule-based error is further subdivided into misapplication or failure to apply established rules or merely the usage of bad rules. The performance of a specific action which was not intended is characterized under action-based error. Memory-based

rules look more at the memory capacity of the medical staff on the patients' current or underlying issues.

Benjamin classified these errors into an error of commission, where someone had acted incorrectly and error of omission, where there's a failure to act correctly[9]. This classification of errors is also correlated to communication barriers and insufficient interactions between patients and healthcare staff. To curb the illegible handwriting issues in prescription writing, it could potentially be converted into a computerized physician order entry. Benjamin also suggests that the prescriptions be maintained in the universal English language, and not in Latin, to iron out any language barriers.

Ferner and Aronson have categorized MEs into a few different types of classifications[10]. The first classification is based on symptoms, adverse drug reactions from MEs, MEs that cause harm that are not adverse drug reactions and MEs that do not cause adverse events.

Aronson also classified it based on errors that are unintended mistakes and mistakes surrounding skills (slips and lapses), where the occurrence of errors happen in planned actions as shown in Table 1[8].

Table 2 Types and subtypes of medication errors with examples correlating with medical-related side effects[10]

Types of medication errors	Sub-classifications		Examples	Medical-related side effects
Mistakes	Knowledge-based		Administering a type of analgaesic (i.e. diclofenac) without asking patient of his allergy history	Anaphylaxis
	Rule-based	Applying a good rule mistakenly	Injecting diclofenac at the deltoid muscle instead of the gluteus muscle	Haematoma
		Applying a bad rule	Continuously giving intramuscular diclofenac 8 hourly to a patient in the out-patient department; continuously giving loading dose of a medication	Haematoma
Skill-based errors	Action-based (slips)		Intending to write carbimazole on prescription slip instead of carbamazepine; writing a prescription beginning with carb, followed by scribbles	Unnecessary risks for patient (side effects of drug which was unintended to be administered)
	Technical errors		Dispensing the wrong strength of medication in the paediatric ward based on weight; improper blood pressure measurement; failing to turn off the intravenous set post-infusion of medication	Under or overtreatment; air embolism
	Memory-based (lapses)		Omitting the duration of warfarin for a patient with atrial fibrillation in the prescription; failure to inform patient regarding drug-food interactions in patients on warfarin	Bleeding tendencies; failure of efficacy of warfarin

Mistakes in planning actions are further divided into knowledge-based errors and rule-based errors (good rules misapplied or bad rules). The latter includes slips, action-based errors, and lapses, memory-based errors.

A retrospective study conducted in a general hospital in Saudi Arabia showed that MEs were divided into a few main categories, improper dose, wrong drug, wrong route of administration, wrong strength, mistakes with durations, dosages and drug omission. The highest occurring MEs were wrong route of administrations, wrong dosage form and strength[11].

Allard and colleagues had rated these medication errors based on stages[12, 13]. This would make an ideal homogenous classification that can be enforced worldwide as it tackles the problem in a systematic method aiming at each stage of treatment process. The types of MEs for each stage of the drug delivery process are shown in Table 3 with its classes of error and examples[14]. An additional stage, general, is added to summarize errors from the aspect of knowledge, attitude and patient to personnel ratios. If the type of MEs can be correlated to the stage of the occurrences, this problem can be easily curbed as each stage involves a variety of healthcare personnel.

Table 3 Types of MEs based on the drug delivery system with its classes of errors and examples

Stages of the drug delivery system	Classes of error	Examples
Prescribing	Wrong drug	A patient with lung cancer was wrongly given vecuronium and midazolam which was meant for a patient that was involved in a motor vehicle accident that was getting prepped for intubation[15].
	Wrong patient	
	Wrong route of administration	Intended intramuscular diclofenac was given intravenously (unpublished data).
	Wrong dosage	In a study involving HIV/AIDS patient, 9.80 errors per 1000 new prescriptions had wrong dosages[16].
	Incomplete prescriptions	Out of 545 outpatient prescriptions, almost 10% lacked the prescriber's name[17].
	Contraindicated drugs	In a study involving HIV/AIDS patient, 9.51 errors per 1000 new prescriptions had drugs contraindicated to the disease[16].
	Omitting essential information	In a study done in the out-patient department in Oman, 23% of the prescriptions omitted dosage information[18].
Transcribing	Dispensing of wrong drugs	A 71-year-old lady was prescribed thiothixene (Navane) instead of amlodipine (Norvasc) for 3 months[19].
Dispensing	Incorrect preparation of drug(s) or infusion(s)	A 6-month-old child was given intravenous azithromycin diluted using adult dosage and child succumbed to cardiac arrest[20].
	Incorrect drug storage	Around 11% of MEs was due to inadequate drug storage based on a study done in a teaching hospital in Brazil from 2012 to 2013[21].
	Medications with similar shape and size	An octogenarian was dispensed Novasone (scalp lotion) for her eyes instead of lubricating eyedrops[22].

Administration	Rarely prescribed drugs	A 60-year-old man was admitted for a total knee arthroplasty. His maintenance medications included a high-risk medication, dofetilide (an antiarrhythmic agent) which was started by the surgical resident. It was ordered to be administered *bis in die*, 6am and 6pm. As the patient was supposed to be transferred to the operation theatre at 6am, the overnight nurse gave the dose early, at 4am. During preoperative rounds by the doctor, the patient was noted to have severe QTc prolongation on his electrocardiogram which increased his risk of getting torsades de pointes, which can be fatal. This resulted in a postponement of his operation[23].
	Wrong timing	
	Wrong drug	Case of unintended epinephrine ampoule swaps with ephedrine (unpublished data)
	Wrong dosage	An 80-year-old patient was administered 0.2 mL of a 100 µl/mL solution instead of 2 units of insulin[24].
	Wrong route of administration	In 2011, 152 cases of wrong patient and route of administration had occurred in the state of Pennsylvania[25].
	Wrong patient	
	No drug administered	Patient was aware during an operation due to an accidental omission of induction agent[26].
	Infusion pump	A study conducted over 7 months in 2007, resulted in 32% of MEs was due to incomplete labelling of IV tubing, 8% of MEs was omission of infusion diluent from the medication chart and around 2% was caused by the discrepancy between what was infused compared to the prescribed[27].
	Not signing off on the medication chart post administration	A patient was ordered to be given an analgaesic for his headache caused by his blast crisis in the haematology ward. The nurse did not sign in the medication chart due to a rush in the change of shift and it was not passed over to the next shift hence no one on duty knew (unpublished data).
General	Causing harm to patient	A patient was given vecuronium instead of cefazolin developed post-traumatic stress disorder as he was conscious but paralyzed[28].
	Exhaustion of healthcare professionals	An increase in the number of prescriptions per shift of staff was associated with increase rate of pharmacist errors during order checking and dispensing[28].
	Patient-nurse ratio	
	Patient-doctor ratio	
	Inadequate training of healthcare professionals	A trainee doctor (house officer) administered intravenous diclofenac instead of intramuscular for a patient with musculoskeletal pain post motor vehicle accident (unpublished data).
	Lack of pharmacology knowledge	
	Lack of communication	75% of patients on five or more drugs experience MEs due to lack of understanding of physician's instructions which resulted in 5% of very severe consequences[29].

Agency for Healthcare Research and Quality under the US Department of Health & Human Services classified MEs into nine categories as shown in Table 4, based on the extent and outcome of the ME[30]. Categories A to D do not require any intervention or medicational therapies. It merely requires monitoring. Whereas, categories E to I necessitate medicational and interventional managements for potential life-saving efforts.

Table 4 Types of MEs based on the extent and the outcome of errors[30]

Categories	Description
A	No ME occurred but had the capacity for one to occur
B	ME but did not reach the receiving end, the patient
C	ME that reached the patient but unlikely to cause any harm, omission errors
D	ME that reached patient which needed extra monitoring
E	ME that cause temporary/reversible harm
F	ME that caused harm which needed hospitalization
G	ME that results in permanent harm
H	ME that required life-saving interventions
I	MEs that results in death

CONCLUSION

Full, partial and no disclosure of MEs to patient should be made into a full disclosure system if a homogenized classification is aided by a flow chart of ways to disclose such MEs to patients and ways to handle the problem. If this system can be established, consensus can be done on which specific aspect that could be improved on. This system can also be a guide whereby it can prompt and suggest ways for them to inform of the ME to the patient. In the long run, this improves overall efficiency of the healthcare personnel. The funds which are freed up due to the reduction of MEs can be channelled into other aspects of the healthcare system.

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30. Northwestern Memorial Hospital, Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. (2012). Catergories of Medication Error Classifications. Table 6.

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ORIGINAL ARTICLE

Effects of 12-Week Rowing Training on Resting Cardiac Output, Stroke Volume, and Heart Rate of Stroke Survivors

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ABSTRACT

Rowing exercise is one of the cardiorespiratory exercises that induce higher aerobic capacity. Cardiorespiratory parameters, cardiac output (CO), stroke volume (SV), and heart rate (HR) are indicators to measure one's cardiorespiratory fitness. The aim was to study the effects of 12-week rowing training on resting cardiac output (RCO), resting stroke volume (RSV), and resting heart rate (RHR) of stroke survivors. Ten stroke survivors (6 males; 4 females), mean age of 43.6 ± 16.15 years, were subjected to a 12-week rowing training (Concept II Rowing Ergometer, Model C, USA). An individualised programme was prescribed based on %HRR for each of stroke individual. Rowing training was conducted twice per week (12 HIIT; 12 MR). Paired t-test and repeated measures ANOVA (RPM ANOVA) were used for statistical analyses using IBM® SPSS® Statistics 20 software. RPM ANOVA analysis showed no significant effect on RCO [F (5, 45) = 1.066, p = 0.392, RSV [F (2.188, 19.693) = 0.677, p = 0.532)], and RHR [F (5, 45) = 0.856, p = 0.518]. Paired t-test showed no significant difference between pre- and post-test despite the improved values of Mean ± Standard Deviation (RCO: 8129.50 ± 3916.31 to 8494.18 ± 6248.86 mL/min; RSV: 99.27 ± 33.98 to 121.84 ± 66.24 mL; RHR: 78.02 ± 17.39 to 77.17 ± 11.98 bpm) for all respective parameters. Twelve weeks rowing training did not improve resting cardiorespiratory parameters of stroke survivors statistically. Future studies are suggested to include gender difference and medication effect variables.

INTRODUCTION

Stroke is the second cause of mortality worldwide and is the third in developed countries following heart attacks and all cancers combined[1]. In Malaysia, stroke remains the third cause of mortality following ischaemic heart diseases as first and pneumonia as second[2, 3]. Individuals after stroke invariably show various types of post-stroke impairments in which one of them is cardiorespiratory fitness. A very low cardiorespiratory fitness is well established among stroke survivors[4, 5]. Over three quarters of stroke survivors have been estimated to have low levels of physical activity[6] and they spend most of their time in sedentary behaviours that contribute to low cardiorespiratory fitness[7]. Such low physical and sedentary behaviours reduce their ability to perform activities of daily living and also may contribute to a heightened risk of recurrent stroke and other cardiometabolic diseases[8].

Cardiorespiratory fitness is defined as the ability of the circulatory and respiratory systems (the heart, the lungs, and the blood vessels) having central capacity to supply oxygen to be utilized by the peripheral skeletal muscles especially the exercising muscles in an amount that is sufficient enough to meet the demands of the workload and prolonged physical activity[9, 10]. Cardiorespiratory fitness is frequently used interchangeably with terms such as aerobic fitness, cardiorespiratory endurance, cardiovascular fitness and maximal oxygen consumption[9, 11] and is associated with the ability to execute and tolerate a physical activity in continuous mode[10].

The best quantitative measure and most valid to measure functional capacity of cardiorespiratory system is maximal oxygen uptake (VO_2max)[12, 13]. VO_2max is the product of cardiac output and arteriovenous oxygen difference (AO_2 – VO_2 diff)[14] VO_2max (derived from V, volume per time; O_2, oxygen; max, maximum) also known as maximal oxygen consumption or aerobic capacity[13] the rate of oxygen uptake during performance of maximal exercise which reflects the circulatory and respiratory systems to deliver oxygen to working muscles that involves a large part of total muscle mass. Arteriovenous oxygen difference is the difference in the oxygen content of blood between arterial and venous blood, which indicates of how much oxygen is removed from blood capillaries as the blood circulates in one circulation through the systemic system[15]. The VO_2max as criterion measure of cardiorespiratory fitness is widely accepted and used[12].

Stroke volume (SV) and heart rate (HR) are the two major determinants in assessing cardiorespiratory fitness in accordance with VO_2max. The two major determinants are referred as cardiac output (CO)[16]. CO is the amount of blood that is pumped into the aorta by the heart per minute basis[17]. The CO (litres/min) is the product of SV (mL/beats) and HR (beats/min)[18]. The SV is the amount of blood that is ejected from a ventricle of the heart with each heartbeat. An increase in SV may increase the CO. The SV is determined by the preload (degree of ventricular filling when the heart is relaxed), afterload (pressure or resistance against which the ventricle must pump to eject blood), and contractility (contractile state of myocardium). The HR refers to the number of times the heart beats per minute and an increase in the HR may also increase the CO. Factors that affect HR are increased sympathetic activity, concentration of extracellular ions, hormone levels, medication, stress, anxiety, fear, and body temperature[17].

Cardiorespiratory exercise (aerobic exercise) is any type of activity which involves a large group of muscles that can be performed in continuous, rhythmic, and prolonged fashion[15] that lasts a minimum of 3 to 5 continuous minutes[9]. It is characterized by employing the large muscle groups of lower extremities in instances of walking, running, and cycling. Sometimes, it combines with the upper extremities like rowing and

swimming[19]. Performing cardiorespiratory exercise can acquire a higher maximal oxygen uptake (VO_2max). An amount of oxygen that is utilized during the cardiorespiratory exercise will increase significantly and thus allows individual to exercise for a longer period and more intensely prior to becoming fatigued[20].

Indoor rowing exercise using rowing machine (indoor rower) challenges both the upper and lower body musculature which places higher demands on cardiorespiratory fitness compared to exercise that relies merely on either upper or lower body musculature[21]. Rowing exercise provides a complete body workout that mobilizes all of the major muscle groups, including those in the legs, arms, hips abdominals, trunk, shoulders, and back[22, 23]. Exercise using indoor rower is smooth and low-impact, which can improve and maintain flexibility of joints especially those with joint pain or limited mobility[22]. Rowing is one of the types of cardiorespiratory or aerobic exercise that has the nature of constant pushing and pulling against resistance activity. Workloads also can be regulated on most rowing machines to accommodate different fitness levels[23].

In this research, stroke survivors were subjected to rowing exercise training to study the effect of such training on cardiorespiratory parameters, which resting cardiac output (RCO), resting stroke volume (RSV), and resting heart rate (RHR). These three parameters were evaluated to determine cardiorespiratory fitness of stroke survivors.

MATERIALS AND METHODS

This study was conducted using quasi-experimental research design with time-series setting. Ethical approval was obtained and granted from Medical Research and Ethics Committee (MREC), NMRR-16-38-28777 (IIR), Ministry of Health Malaysia. All participants in this study were subjected to intervention programme of 12 weeks. Rowing training was performed twice per week that consisted of High-Intensity Interval Training (HIIT) and Moderate Rowing (MR). Total of 12 sessions for each HIIT and MR were successfully carried out by all the participants.

The study population involved 10 stroke survivors (6 males; 4 females), ranging between 16 to 63 years old. Mean age of 43.6 ± 16.15 years. All subjects were recruited from the Rehabilitation Specialist Clinic in Queen Elizabeth Hospital I, Kota Kinabalu, Sabah in which they were volunteered to participate in this study. Ten subjects were selected according to the exclusion and inclusion criteria. After having a clearance from their physician, all subjects underwent a baseline test and the written informed consent was taken soon after. All the patients involved in this study must be able to communicate and understand instructions given, possesses unilateral hemiparesis either left or right, medically stable (released by physician), able to walk with or without assistance, able to sit or stand with or without assistance, and able to transfer from a higher to lower position, chair to rowing seat (or vice versa) with or without assistance. In the other hand, patient with comorbidities, serious medical condition (bronchial asthma, heart failure, severe hypertension), elbow flexor contracture, plantar flexor contracture, and inability to bend knee (hamstring spasticity) and elbow (biceps spasticity) would be excluded.

Experimental Protocol

After baseline test was conducted, each patient was required to perform a one-minute rowing screen test to determine their rowing speed and abilities. According to their rowing's stroke per minute (SPM), the patients were divided into three groups. The three groups were low (< 18 SPM), moderate (18 – 23 SPM), and high (>24 SPM). The patients were subjected to perform rowing training twice a week, which consisted of high intensity interval training (HIIT) and moderate rowing (MR) for 12 weeks consecutively.

This study employed an electrical bioimpedance invasive technique that used Biopac Student Lab system (BIOPAC® System, Inc.) to measure RCO, RSV, and RHR of the stroke patients for one minute. Mean values of the RCO, RSV, and RHR for all patients were chosen within the timeframe of last 10 to 15 seconds of the one minute of their resting data. Measurement of RCO, RSV, and RHR were conducted at pre-test: week 0 (Test 1), post-test$_1$: week 3 (Test 2), post-test$_2$: week 6 (Test 3), post-test$_3$: week 9 (Test 4), post-test$_4$: week 12 (Test 5), and post-test$_5$: week 15 (Test 6).

Static stretching was performed by the patients before rowing training and cooling down after the training. Blood pressure monitor (OMRON, IA2, Japan) and oxygen level pulse oximeter JPD-500A, (Jumper, China), readings were taken before and after training. Patients wore a heart rate monitor (Suunto, M5) during rowing to monitor their HR. Correct breathing techniques were also taught to patients to prevent Valsalva *manoeuvre* during rowing. For patients with spastic lower limbs, custom-made strap was used to align the limbs' movement and bandage was used to secure handgrip during rowing.

Rowing Mode and Intensity

The main purpose of this study was to use rowing as rehabilitation tool for people with disabilities. A rowing screen test performed by all patients in one minute. The objective was to categorise them into three groups of rowing speed and abilities baseline as described in the experimental protocol. The rowing training was carried out by patients afterwards.

Principle of percentage of heart rate reserve (HRR) was applied to prescribe the patients' training intensity. The formula, THR (target heart rate) = HRR (percentage of intensity) (%) × [HR_{max} – RHR] + RHR was used to calculate training intensity of each patient, where HR_{max} was referred to maximal heart rate and RHR was resting heart rate. As stroke survivors suffered with poor cardiovascular endurance as in the elderly, %HRR is more accurate than %HRmax[24].

Patients with low rowing ability (<18 SPM) started at 50% of heart rate reserve (HRR); patients with moderate rowing ability (18 – 23 SPM) at 55%; and high rowing ability group (≥24 SPM) at 60% of HRR. Rowing training was carried out twice per week with HIIT and MR which were performed consecutively. Progressive load increment was applied throughout the 12-week of rowing training in terms of working time (speed on rowing ergometer), distance covered, and damper setting.

For HIIT rowing session, it was started with a ratio of 1:1 (working: recovery) of 15:15 seconds, and progressively increased to 20:20, 25:25, 30:30, and 35:35 consecutively. Percentage of HRR was measured individually, where each patient was instructed to row at maximal effort (to achieve THR). For MR rowing session, it was started with a 500 meters rowing and progressive increment of 50 meters or more (minimum) was performed according to their %HRR. The increment would be based on patients' effort which in regard to their THR and MBDS (Modified Borg Dyspnoea Scale).

However, it would be depending on the patient's ability to achieve THR during each training session. A subjective scale, MBDS was shown to the patient after each repetition to acknowledge their level of tiredness. All patients were ensured that they would be free from symptoms-limited exercise testing as provided in the American Council of Sports Medicine's guidelines.

Statistical Analyses

Data were analysed using IBM® SPSS® Statistics 20 software. Repeated measure ANOVA was used to test the significant difference of RCO, RSV, and RHR value in six different tests. Paired sample *t*-test was used to determine the differences from pre-test to post-test of RCO, RSV, and RHR. The alpha level was set at $p<0.05$.

RESULTS

This study used a repeated measures design in which ten patients with their exercise prescription that was designed specifically for each of them focusing on their cardiorespiratory endurance for twelve consecutive weeks with a rowing ergometer aid. Mauchly's Sphericity principle had been violated and therefore correction was made using Greenhouse-Geisser (except RSV) correction.

RPM ANOVA (Table 1) analysis showed that the rowing training had no significant effect on RCO [F (5, 45) = 1.066, p = 0.392, RSV [F (2.188, 19.693) = 0.677, p = 0.532)], and RHR [F (5, 45) = 0.856, p = 0.518]. Paired t-test also showed that there was no significant difference between pre- and post-test (Table 2).

Table 1 RPM ANOVA OF RCO, RSV, and RHR

Variables	Wk0	Wk3	Wk6	Wk9	Wk12	Wk15	Repeated Measures ANOVA (RPM ANOVA)		
							Main Effect (t)		
	Mean ± SD						df	*F*	*p*
RCO	8129.50± 3916.31	8638.30± 4309.20	10248.90± 6322.37	11667.30± 8706.93	9133.90± 4986.67	8494.18± 6248.86	5.00	1.066	0.392
RSV	99.27± 33.98	117.48± 57.11	125.30± 83.87	140.95± 91.18	113.51± 59.29	121.84± 66.24	2.188	0.677	0.532
RHR	78.02± 13.53	73.62± 13.53	83.40± 21.39	79.69± 12.87	81.24± 18.16	77.17± 11.98	5.00	0.856	0.518

Significant value set at $p<0.05$

Table 2 Paired t-test of variables

Variables	Mean ± Standard Deviation		*r*	*t*-test	*p*-value
	Pre-test	Post-test$_6$			
RCO	8129.50 ± 3916.31	8494.18 ± 6248.86	0.514	-0.213	0.836
RSV	99.27 ± 33.98	121.84 ± 66.24	0.255	-1.077	0.310
RHR	78.02 ± 17.39	77.17 ± 11.98	0.226	0.140	0.892

Significant value set at $p<0.05$

However, Mean ± Standard Deviation value of RCO was increased from pre to post-test$_6$ (Figure 1), which indicated improvement in efficiency of the heart though there was a downhill in the fifth test. RSV value increased steadily (Figure 2), showed that the heart might have ejected more blood in one beat. There was a drop in fifth test however RSV value still recorded an improvement from pre to post test. RHR value was inconsistent throughout the tests. In post test$_6$, RHR was reduced (Figure 3), suggested that the heart was capable of providing a sufficient amount of blood in a lower beat. Mean differences for RCO, RSV, and RHR were –364.68, –22.57, and –0.85 respectively.

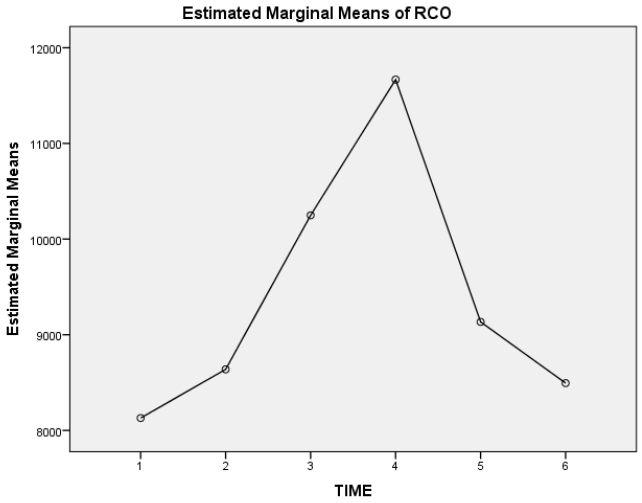

Figure 1 Data of RCO for all six tests throughout 12 weeks of rowing training showed RCO improved from Test 1 to Test 4, it dropped in Test 5 and showed improvement in Test 6.

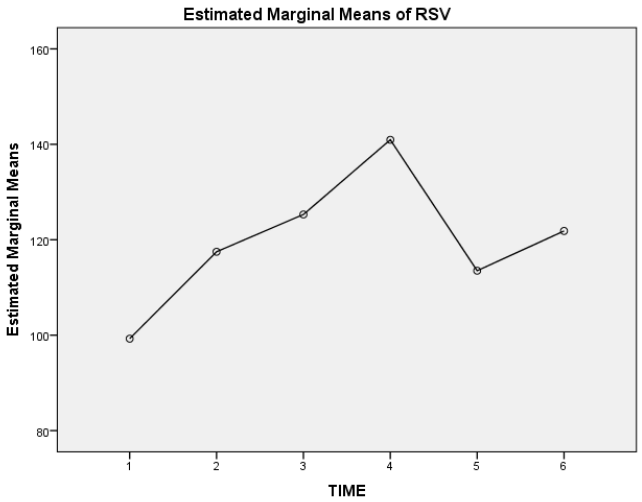

Figure 2 Data of RSV for all six tests throughout 12 weeks of rowing training showed RSV improved steadily from Test 1 to Test 4, declined in Test 5 and showed improvement in Test 6.

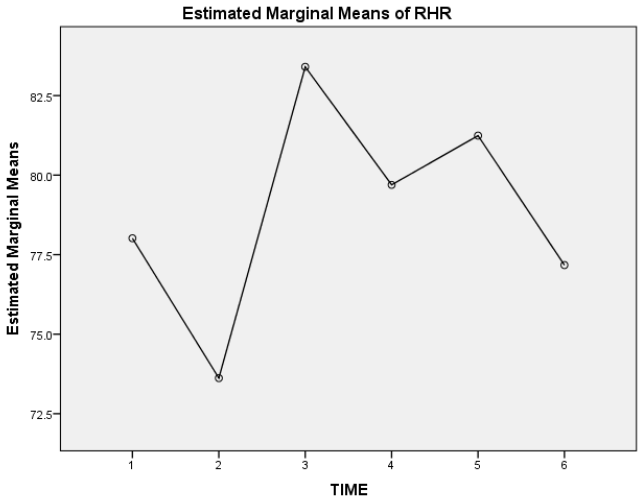

Figure 3 Data of RHR for all six tests throughout 12 weeks of rowing training showed inconsistent reading of RHR, however in Test 6 showed a reduction value from Test 1.

DISCUSSION

The results showed that the 12-week rowing training had no significant effect on cardiorespiratory fitness parameters among the stroke survivors. However, Mean ± Standard Deviation of RCO, RSV, and RHR values showed improvement.

Rowing was found to prevent cardiovascular deconditioning of people with 5-week bed rest condition[25] due to its kinematic pattern exercise and low impact, which their cardiorespiratory parameters were measured during exercise. However, in our study the cardiorespiratory parameters during resting (upright sitting position) state were measured. There was still lack of studies regarding the effect of aerobic exercise on RCO, RSV, and RHR on a resting condition.

During upright exercise, oxygen demands were increased, which required the CO to increase to deliver more blood to the working muscles, therefore HR was increased, and SV was reduced to compensate the HR[26]. Nonetheless in this study, according to Frank-Starling mechanism, increased in plasma volume and venous return contributed to the increased in end-diastolic volume or preload after endurance training programme[27]. To support the result in this study, reduced Mean ± Standard Deviation value of RHR might be due to enhanced vagal tone[27] after 12 weeks of rowing training. Despite, HR would be a less accurate measurement for people who were taking beta-blockers[28], therefore MBDS was used in this study to support the result. In this study, types of beta-blockers taken by the stroke survivors were not discerned as they were not included in research parameters.

A marked increased in CO was proven after isotonic exercises[29]. The increased in maximal CO was largely contributed by increased in SV. There were three factors that contribute in increasing SV, (1) Preload, (2) Afterload, and (3) Inotrophy. RSV measurement was taken in this study under resting condition, SV was mostly dependent on ventricular filling pressure which was the venous return[30, 31]. Higher RSV also indicated greater fitness level[32] thus this showed that increased Mean ± Standard Deviation value of RSV had proven that rowing induced greater aerobic capacity of the stroke survivors. Fick equation proved that there was a positive linear relationship between VO_2max and CO[33, 34]. There was a study proved that resting or exercise CO was improved after 12 weeks of HIIT[34]. The increased Mean ± Standard Deviation value of RCO showed that rowing training improved cardiorespiratory parameters within stroke patients.

LIMITATIONS

Limitation in this study was that the sample was too small to represent a population. More subjects should be recruited in future study to apprehend the significant effects of rowing on cardiorespiratory parameters of this population. In addition, types of medication consumed by the patients were not taken into account. People with stroke who consumed drugs that contained beta-blockers might affect the changes in their HR that would have an effect on RSV and thus influenced RCO. As a consequence, the result of this study was not statistically significant although Mean ± Standard values were improved.

CONCLUSION

Rowing movement engages more gross muscles contractility when compared to other exercises. More motor units are needed to be activated and thus result in higher energy expenditure within the stroke patients. In this study, although there was no statistically significant effect on RCO, RSV, and RHR after 12-week of rowing training based on the results, yet there was improvement in all of the variables of the stroke survivors. Future studies

should consider on types of medication consumed by the stroke patients and its peak effect on HR, SV, and CO. Also there is a need to increase the sample size to withstand the statistic tests.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this paper.

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ORIGINAL ARTICLE

Patients' Knowledge, Attitude and Practice towards Painkillers: Tawau Hospital Experience

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ABSTRACT

Pain management with analgaesics employs a multidisciplinary approach of clinicians towards patients. Nevertheless, preventing drug abuse and misuse in pain management is also an important goal. Understanding patients' behaviour in the usage of painkillers may facilitate more effective communication and to educate them on the appropriate choice of painkillers. This study aimed to assess patients' knowledge, attitude and practice towards painkillers. This was a questionnaire-based cross-sectional study conducted from February to May 2016 among patients in Tawau Hospital. Respondents were selected via convenience sampling and interviewed based on a questionnaire to assess their knowledge, attitude and practice towards painkillers. A total of 193 questionnaires with complete responses were analysed. Most of the respondents (60.1%) obtained their painkillers from public facilities. Generally, they were very satisfied with the painkillers that they had used (36.7%). However, most of them (75.0%) did not know the name of the ingredient of the painkillers that they had taken before. They were also not aware of the side effects (73.1%) and allergic reactions (64.8%) caused by painkillers. Most of the respondents (58.5%) had not been informed regarding the side effects of the painkillers by healthcare professionals. Only 25.0% of the respondents had been asked regarding their past medical history, past medication history and allergic history by healthcare professionals before a painkiller was recommended to them. This study highlights the need of continuous efforts by healthcare professionals to inform patients of the proper use and risks associated with painkillers to improve the quality use of painkillers.

INTRODUCTION

Pain is a complex physiological and psychological phenomenon that is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"[1, 2]. Analgaesics currently represent as mainstay to relieve different types of pain experienced in the body[3]. Adequate pain control is a fundamental right of every patient where effective pain management is an integral and important aspect of quality medical care. Pain management with analgaesics employs a multidisciplinary approach of clinicians towards patients, as well as the development of strategies to ease the suffering of pain[4].

Nevertheless, preventing drug abuse and misuse in pain management is also an important goal. Common complications of inappropriate use of analgaesics include gastrointestinal disturbances, cardiovascular effects, kidney failure and liver failure[3]. Hence, self-prescribing analgaesics even for minor ailments could further lead to serious medical complications. Builders et al. showed prescription pattern of analgaesics involving 12.0% respondents were recommended by doctor, 5.0% by a pharmacist and 3.0% by a nurse while 80.0% were solely on self-medication[4]. A similar study conducted by Li et al. showed significantly high number of subjects (43.4%) answered that they obtained prescriptions from the physician, while 32.8% of the participants purchased an over-the-counter (OTC) analgaesic themselves[5].

Self-medicating in Malaysia has remained more popular and will continue to rise with the rising healthcare costs. A recent Malaysian study reported that 75.0% of the respondents had used OTC drugs at least once[6]. A study conducted by Azhar et al. showed that patients preferred self-prescription because it is more convenient, easier to access and time saving when compared to consulting a doctor[7]. Results from many studies involving Malaysia have pointed out that analgaesics were the most commonly used self-medication, followed by cough remedies and supplements[6, 7]. Based on a study on the knowledge and attitude conducted by Azhar et al., about 82.0% of the respondents stated that their level of knowledge regarding OTC analgaesics was moderate to low[7]. It was also shown that 80.0% of the respondents claimed that they would stop using the OTC analgaesic if it did not work within the proposed time frame, while a small number of them would increase (7.0%) or decrease (5.0%) the dose[7].

In Tawau Hospital, upper gastrointestinal bleeding, kidney failure and acute coronary syndrome due to suspected analgaesic misuse were some of the common causes of admission to medical wards based on previous admission records. Breaking patients' beliefs about the abuse and misuse of analgaesics is a key factor in controlling the unnecessary use of them. Besides, understanding patients' behaviour in the usage of analgaesics may facilitate more effective communication and to educate them on the appropriate choice of analgaesics based on different health conditions. Analgaesics are better known as painkillers among the layman population. Hence, this study aimed to assess patients' knowledge, attitude and practice towards painkillers.

MATERIALS AND METHODS

This was a questionnaire-based cross-sectional study conducted from February to May 2016 among patients from both outpatient and inpatient settings, Tawau Hospital, to investigate their knowledge, attitude and practice towards painkillers. This study was approved by Medical Research and Ethics Committee (MREC) of the Ministry of Health (MOH), Malaysia via the National Medical Research Registry (NMRR) with the registration number NMRR-15-2165-28238. All responses obtained from the interview were kept

confidential, and respondents are allowed to refuse participation in the study.

The minimum sample size required for this study was 255. This figure was arrived by assuming that a 95% chance of our estimate being within ± 5% of the true proportion, assuming that 21.0% of the respondents understand the adverse effects of inappropriate use of painkillers based on literature review[8].

The inclusion criterion in this study was that the respondent must be 18 years of age and above. The exclusion criterion would be those respondents who could not understand Malay, English, Chinese and Tamil.

Recruitment Procedure

A total of five pharmacists were selected as interviewers and data collectors. Prior to the study, all the data collectors and interviewers were given briefing for the purpose of standardization of the methodology used throughout the data collection process so that there would be no misinterpretation or misunderstanding of the study questions that might result in bias.

All eligible patients were approached by researchers. These patients were given an informed consent. If they agreed to participate in the study, they were then interviewed by the researchers on the spot for about 15 minutes based on the questionnaire.

Questionnaire

The questionnaire was developed based on literature review and group discussion and was then validated for its content by experts who had at least five years of experience in the pharmacy practice. The questionnaire was pretested among 30 respondents prior to the actual study. Following pretest, the questionnaire was revised and modified. The questionnaire was divided into three sections: Section A collected patients' demographic information; Section B collected patients' pain experience; Section C collected patients' understanding towards painkillers and local health/community practice about the use of painkillers in Tawau.

Data Analysis

Data entry was done using the Statistical Package for the Social Sciences (SPSS), Version 21. Demographic information of respondents, their pain experience and knowledge, attitude and practice towards painkillers were analysed descriptively either in percentages or median (interquartile range) [IQR].

RESULTS

A total of 214 respondents were interviewed. However, only 193 questionnaires with complete responses (response rate 90.2%) were analysed.

Demographic Characteristics

Of the 193 respondents, 104 (53.9%) of them were from the outpatient facility and 89 (46.1%) of them were from the inpatient setting. A total of 111 (57.5%) respondents were males. The median (IQR) age of the respondents was 40.00 years (IQR 31.00, 51.00 years). Figures 1 to 4 show other demographic and clinical characteristics of the respondents.

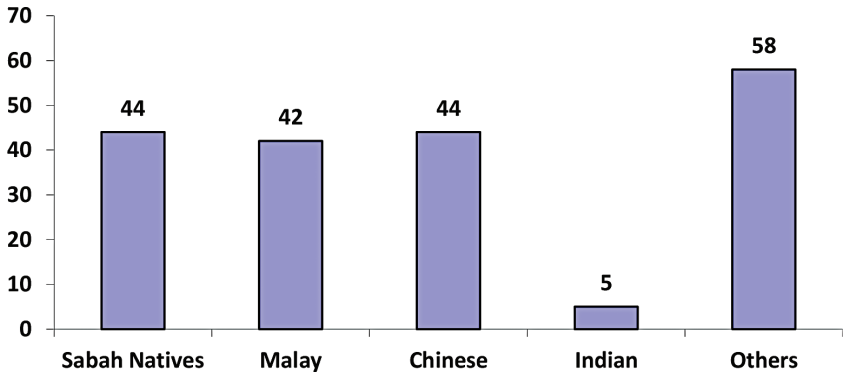

Figure 1 Distribution of race of the respondents

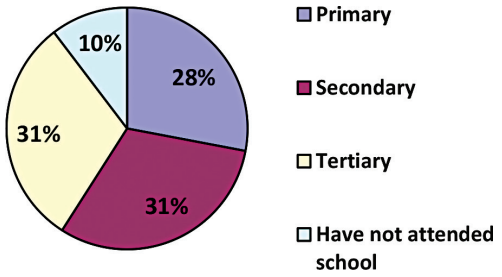

Figure 2 Highest education level of the respondents

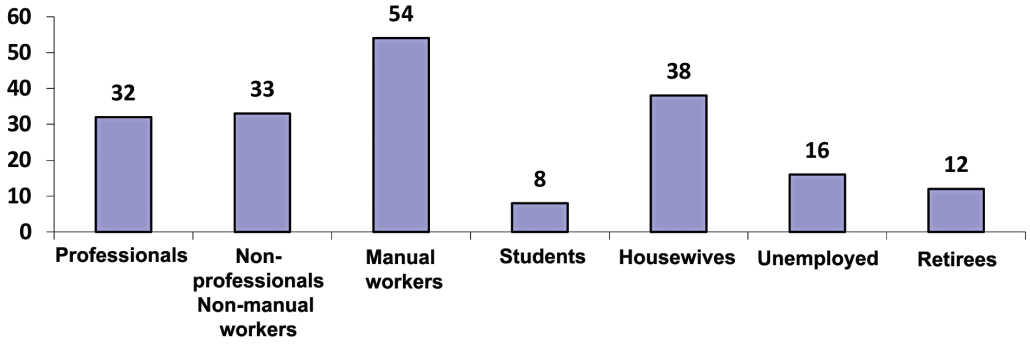

Figure 3 Distribution of occupation of the respondents

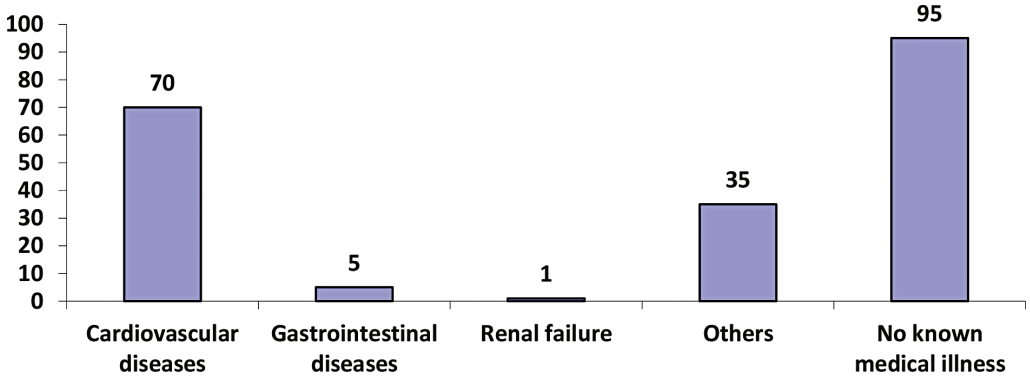

Figure 4 Past medication history of the respondents

Pain Experience and Pain Management

All respondents in this study experienced pain before. Table 1 shows the types of pain experienced by the respondents prior to this study. The three most common types of pain were headache (66.3%), backache (47.2%) and abdominal pain (47.2%). Besides those in the list, 11 (5.7%) of the respondents experienced other types of pain such as heartburn, wound pain, eye pain, chest pain and labour pain.

Table 1 Knowledge about pain

Knowledge about pain (*N* = 193)	Type of pain	No. of patients	Percentage
	Headache	128	66.3
	Backache	91	47.2
	Abdominal pain	91	47.2
	Toothache	81	42.0
	Joint pain	78	40.4
	Muscle pain	68	35.2
	Bone pain	68	35.2
	Period pain	30	15.5
	Others	11	5.7

In terms of pain management, 149 (77.2%) respondents chose to consult their doctors and 54 (28.0%) chose to consult community pharmacists. The study also showed that 54 (28.0%) respondents chose to purchase painkillers without a prescription while 34 (17.6%) consumed herbal or traditional medicines to ease their pain. A total of 4 (2.1%) respondents chose alternative methods such as taking topical applications and watchful waiting.

Respondents' Knowledge towards Painkillers

This study assessed the knowledge of all respondents who participated in this study in terms of the name of the painkillers, side effects of painkillers and whether painkillers would cause allergic reaction or not. In terms of the name of the painkillers, the respondents were given a list of names and they were required to identify the names that they had heard before. In general, most of the respondents (71.5%) had heard of paracetamol before. However, 53 (27.5%) respondents had never heard of any names before (Table 2A).

In terms of side effects caused by painkillers, 141 (73.1%) respondents did not know the side effects of painkillers and 10 (5.2%) of them claimed that painkillers were not associated with any side effects. Only 42 (21.8%) respondents knew the side effects caused by painkillers (Table 2B). The three common side effects claimed by the respondents were kidney problem (40.5%), gastric ulcer (26.2%) and dizziness (14.3%). Most of the respondents (71.4%) obtained the information regarding the side effects of painkillers from their doctors (Table 2C).

Table 2 Knowledge towards painkillers

A. Name of painkillers that the respondents had heard of (*N* = 193)	**Name of painkillers**	**No. of patients**	**Percentage**
	Paracetamol	138	71.5
	Mefenamic acid	58	30.1
	Ibuprofen	36	18.7
	Diclofenac	20	10.4
	Tramadol	22	11.4
	Morphine	16	8.3
	Celecoxib	10	5.2
	Etoricoxib	10	5.2
	I have never heard of any	53	27.5

B. Side effects caused by painkillers (*N* = 42)	**Side effect**	**No. of patients**	**Percentage**
	Kidney problem	17	40.5
	Gastric ulcer	11	26.2
	Dizziness	6	14.3
	Over-secretion of gastric acid	5	11.9
	Cardiovascular effects	5	11.9
	Addiction/Tolerance	3	7.1
	Internal bleeding	1	2.4
	Loss of consciousness	1	2.4
	Gastric disturbance	1	2.4
	Vomiting	1	2.4
	Asthma	1	2.4
	Osteoporosis	1	2.4
	Miscarriage	1	2.4

C. Source of information regarding the side effects of painkillers (*N* = 42)	**Source**	**No. of patients**	**Percentage**
	Doctors	30	71.4
	Pharmacists	18	42.9
	Relatives/friends	15	35.7
	Mass media (television, radio)	12	28.6
	Internet	12	28.6
	Reading materials	11	26.2
	Others	1	2.4

This study also showed that 125 (64.8%) respondents did not know that painkillers could cause allergic reactions. A total of 48 (24.9%) respondents knew that painkillers would cause allergic reactions and 20 (10.4%) of them claimed that painkillers would not cause allergic reactions.

Of the 193 respondents, 188 (97.4%) of them had used painkillers before. A total of 141 (75.0%) respondents in this study did not know the name of the ingredient/drug of the painkillers that they had taken before. Of the 47 of the respondents who did, most of them (87.2%) had taken paracetamol, 11 (23.4%) of them had taken mefenamic acid and 4 (8.5%) of them had taken ibuprofen. Among some of the other painkillers that the respondents had taken before were diclofenac, celecoxib and tramadol.

Respondents' Attitude towards Painkillers

Table 3 shows the level of satisfaction of the respondents towards the painkillers that they had used. Generally, the respondents were very satisfied with the painkillers that they had used.

Table 3 Attitude towards painkillers

Level of satisfaction towards painkillers used (*N* = 188)	Level of satisfaction	No. of patients	Percentage
	Not satisfied	2	1.1
	Somewhat satisfied	16	8.5
	Neutral	36	19.1
	Satisfied	65	34.6
	Very satisfied	69	36.7

Respondents' Practice towards Painkillers

When being asked at what level of pain the respondents would take painkillers to ease the pain, most of them (28.7%) consumed painkillers if the pain score was 8. It was also found that the pain threshold among the 188 respondents was 2 (Table 4A).

Table 4B shows the methods the respondents obtained their painkillers. Most of the respondents (60.1%) obtained their painkillers from pharmacies in public facilities. The next common method was from private general practitioners (46.8%). Community pharmacies were found to be common places also. It was found that 63 (33.5%) respondents obtained their painkillers from community pharmacies via doctors' prescriptions or recommendations by the community pharmacists. However, 86 (45.7%) respondents purchased their painkillers in community pharmacies over the counter. Some of the uncommon methods to obtain painkillers were from sundry shops, battalions and herbal shops.

In terms of frequency of painkiller consumption (Table 4C), most of the respondents (43.1%) consumed painkillers only when necessary.

When being asked whether the respondents read the labels or leaflets before taking their painkillers, 75 (39.9%) patients agreed that they did so, 51 (27.1%) patients claimed that they did not, and the rest of the patients only read the labels occasionally.

Table 4 Practice towards painkillers

A. Pain score and consumption of painkillers (*N* = 188)	Pain score	No. of patients	Percentage
	0	0	0.0
	1	0	0.0
	2	2	1.1
	3	8	4.3
	4	12	6.4
	5	22	11.7
	6	24	12.8
	7	28	14.9
	8	54	28.7
	9	27	14.4
	10	11	5.9

B. Methods to obtain painkillers (*N* = 188)	Method	No. of patients	Percentage
	Pharmacies in public facilities	113	60.1
	Doctors – clinics/dispensary	88	46.8
	Community pharmacies – via community pharmacists/prescriptions	63	33.5
	Community pharmacies – over the counter	86	45.7
	Supermarket	18	9.6
	Family or friends	17	9.0
	Online purchasing	1	0.5
	Others	4	2.1

C. Frequency of painkiller consumption (*N* = 188)	Source	No. of patients	Percentage
	Less than once a month	26	13.8
	About once a month	13	6.9
	Several times a month	66	35.1
	At least one day a week	2	1.1
	When necessary	81	43.1

In terms of meal consideration, it was found that a majority of the respondents (55.9%) consumed their painkillers without regard to meals, 75 (39.9%) respondents consumed them after meals and 8 (4.3%) respondents consumed them before meals.

It was also found that of the 188 respondents who had taken painkillers before, only 9 (4.8%) of them had consumed two or more types of painkillers at the same time. However, the respondents were not able to recall the name of the painkillers that they had taken together, in general. Among some of the combinations that could be identified were paracetamol with mefenamic acid, paracetamol with ibuprofen, paracetamol with tramadol and tramadol with etoricoxib.

Most of the respondents (56.9%) found that the painkillers helped to ease their pain. On the other hand, 79 (42.0%) respondents found that the painkillers only helped to ease their pain occasionally, depending on the nature of the pain. However, two respondents (1.1%) claimed that the painkillers that they had used did not ease their pain.

From this study, it was found that only 27 (14.4%) respondents had been informed regarding the side effects of the painkillers that they had been taking by healthcare professionals. Most of the respondents (58.5%) had not been informed regarding the side effects. On the other hand, 51 (27.1%) respondents claimed that they had been informed regarding the side effects occasionally only. Besides, only 47 (25.0%) respondents had been asked regarding their past medical history, past medication history and allergic history by healthcare professionals before a painkiller was recommended to them. A total of 53 (28.2%) respondents claimed that they had never been asked regarding those information while 88 (46.8%) respondents had been asked regarding those information occasionally only.

DISCUSSION

Adequate pain control is a fundamental right of every patient where effective pain management is an integral and important aspect of quality medical care[4]. A patient who experiences pain will seek treatment by whatever means to relieve the pain. From the results of this study, a majority of the respondents consulted healthcare professionals such as doctors and community pharmacists when they experienced pain. However, there were 17.6% of them who consumed herbal or traditional medicines to ease their pain. A study conducted by Parvin et al. showed that when treatment with *Zingiber officinale* (ginger) for 5 days was given to students who suffered from primary dysmenorrhoea, significant effects were shown in terms of reduction of pain duration and intensity[9]. Despite the effectiveness, consumption of herbal or traditional medicines is associated with safety issues due to the poorly defined active ingredients in the products and the possibility of product adulteration with other substances. In fact, the Food and Drug Administration (FDA) and National Pharmaceutical Regulatory Agency (NPRA) regularly publish reports regarding side effects caused by adulterated or unregistered herbal or traditional products which are unsafe to be consumed[10–12]. Consumption of such products might lead to health problems such as severe liver injury and kidney failure.

The World Health Organisation (WHO) pain ladder is a stepwise approach to the use of analgaesics depending on pain severity[13]. It is stratified into three steps for pain management. Step 1 recommends treatment of mild pain with non-opioid analgaesics such as paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs). Step 2 involves the addition of weak opioids such as hydrocodeine, tramadol or codeine, while Step 3 involves the addition of strong opioids such as morphine, fentanyl, or oxycodone. Adjuvants can be used to decrease anxiety along all the steps. Such analgaesics and adjuvants are used either in regular or as-needed basis depending to the types and severity of pain. However, based on the results of this study, we were not able to correlate the types and severity of pain with the types of analgaesic used and the frequency of consumption because most of our respondents did not know what analgaesics they consumed.

In terms of methods to obtain painkillers, it was noticed that most of the respondents obtained painkillers from reliable sources such as clinics and community pharmacies. In fact, obtaining painkillers from reliable sources is important because of the provision of proper assessment and recommendation by healthcare professionals and to avoid medication errors such as inappropriate choice of analgaesics. It was also noticed that most of the respondents obtained painkillers from public facilities. This phenomenon correlates with the demographic characteristics of the respondents in Tawau where most of them were from lower socioeconomic background and hence most of them sought treatment in public facilities.

The proper administration of painkillers is important. Some painkillers, for example the NSAIDs, are associated with gastrointestinal disturbances[3]. Hence, they should be taken with meals or after meals. In this study, it was noticed that most of the respondents consumed their painkillers without regard to meals. However, conclusions could not be drawn on whether they consumed the painkillers correctly or not because most of the respondents did not know what painkillers they consumed. Besides, only approximately 40.0% of the respondents read labels or leaflets prior to taking their painkillers. Hence, they might miss the direction of administration which had already been printed or written on the labels. This study also assessed whether respondents had consumed two or more types of painkillers at the same time before. This question is relevant because such polypharmacy may not result in better pain control. Conversely, it increases the risk for patients to develop adverse drug reactions (ADRs). For example, consumption of two or more types of NSAIDs at the same time increases patients' risk to develop gastrointestinal ulceration, cardiovascular complications and renal failure[3]. However, no comments could be made on whether the co-administration of two or more types of painkillers by the respondents was appropriate or not because most of them did not know what painkillers they consumed.

The study also showed that the respondents demonstrated poor knowledge in terms of the name of the painkillers, side effects of painkillers and allergic reactions caused by painkillers. Users of painkillers are generally unaware of or unconcerned with the potential harmful effects, as painkillers are perceived to be relatively safe[14]. One study concluded that over 40.0% of people had the misconception that painkillers were weak and not harmful[14]. NSAIDs are a common cause of reported ADRs especially in long term use[15-17]. According to the FDA, NSAIDs may increase the chance of a heart attack or stroke that can lead to death, and this chance increases in patients who consume NSAIDs in long-term basis and in people who have heart disease. In fact, 36.3% of the respondents in this study had underlying cardiovascular diseases. Hence, consumption of painkillers, especially NSAIDs, can actually worsen their underlying cardiovascular problems. NSAIDs also cause

gastrointestinal ulceration and bleeding due to long-term consumption and the risk further increases with smoking, alcohol consumption, elderly, poor health status and taking concurrent medications such as corticosteroids and anticoagulants[17, 18]. Besides, alteration of renal function, effects on blood pressure, hepatic injury, and platelet inhibition due to long-term NSAID consumption may result in increased bleeding[19]. Drug allergy is a serious adverse drug reaction and commonly concerned in healthcare practice[20]. NSAIDs may cause allergic reactions such as skin rash and itchiness[18]. Hence, it is important that patients inform their healthcare providers if such symptoms occur so that prompt management can be provided.

In order to ensure quality use of painkillers, individuals need to understand the risks and benefits of taking painkillers[21]. Inadequate documentation and communication between health providers, and limited health literacy and knowledge in patients could contribute to the re-occurrence of ADRs and allergic reactions[22]. Some studies suggested that healthcare professionals providing counselling to patients about drug allergy and providing basic information about ADRs and their management, together with written information, could result in improved patients' knowledge[20, 22]. Although patients would like to gain more information and be educated about the safety of a medication, some healthcare professionals are reluctant to inform patients about the possible risk of developing unexpected reactions after consuming the medication, particularly medications that have a low risk of adverse events. This was proven from our findings whereby only a small number of respondents had been informed regarding the side effects of the painkillers that they had been taking by healthcare professionals. Besides, only a small number of respondents had been asked regarding their past medical history, past medication history and allergic history by healthcare professionals before a painkiller was recommended to them. In fact, providing education to patients, such as the need of reading labels, the generic name of medications, indications, proper administration methods and unexpected reactions, is important to ensure patients receive the right medication, at the right dose and for the right indication.

This study has a few limitations. First, it was conducted in a small population, namely in Hospital Tawau only, in which the results might not reflect the general perception of the Malaysian population. Second, the knowledge of our respondents towards painkillers was generally low. Most of them did not know what painkillers they consumed. Hence, further details could not be explored. Nevertheless, this study provides an insight of the knowledge, attitude and practice of Tawau population towards painkillers and the need of interventions to improve those aspects. Future studies should focus on specific risk groups of patients and interventions aimed at encouraging quality use of painkillers.

CONCLUSION

This study provides valuable findings regarding patients' knowledge, attitude, and practice towards painkillers within Tawau population. It highlights the need of continuous efforts by healthcare professionals to inform patients of the proper use and risks associated with painkillers to improve the quality use of painkillers.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this paper.

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ORIGINAL ARTICLE

A Comparative Study on the Safety and Efficacy Parameters of Cyclosporine and Tacrolimus on Renal Transplanted Patients: A Malaysia Experience

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ABSTRACT

Calcineurin inhibitors, cyclosporine and tacrolimus are increasingly becoming part of the standard immunosuppresant therapies for renal-transplanted patients in Malaysia. In this study, the clinical safety and efficacy of cyclosporine and tacrolimus in a Malaysian renal-transplanted population is compared. A fourteen-year retrospective review on all renal-transplanted patients (from September 1991 to September 2015) or patients being followed up at University Malaya Medical Centre (UMMC) on cyclosporine or tacrolimus regime was conducted. We collected the clinical and laboratory parameters at 3-month, 6-month, 7-month, 8-month, 9-month, 10-month, 11-month, 12- months, 2-year and 3-year following from transplantation for each drug. The mean cyclosporine and tacrolimus trough levels were within the recommended therapeutic ranges (189.16 ± 69.10 ng/ml and 7.84 ± 2.18 mg/day respectively). The mean low-density lipoprotein (LDL) was significantly higher at eleven months for tacrolimus compared to cyclosporine. Similarly, the mean total bilirubin level was significantly higher with cyclosporine as compared to tacrolimus between 3 – 9 months post transplantation but did not show any significant difference (p = 0.49). The overall monthly means of serum uric acid levels in patients were also similar, 380 ± 87 mg/dL (cyclosporine) and 390.96 ± 95.97 mg/dL (tacrolimus) (p = 0.49). The Kaplan-Meier survival rate is significantly longer (p = 0.03) with cyclosporine-based treatment as compared to tacrolimus. Overall, cyclosporine and tacrolimus did not show any significant difference in terms of safety and efficacy parameters among Malaysian renal-transplanted patients indicating that they may be used interchangeably.

INTRODUCTION

The comprehensive safety and effectiveness of immunosuppressant medications such as calcineurin inhibitors like cyclosporine and tacrolimus are crucial to the overall success of organ transplantations. The discovery of cyclosporine led to tremendous improvements in the outcome following transplantation[1]. This benefit was further improved when tacrolimus began to be widely utilised in liver transplant patients, and subsequently in renal transplantation. At present, tacrolimus is prescribed to more than half of renal-transplanted patients as adjunct immunosuppressants regime[2].

Several studies comparing the use of cyclosporine and tacrolimus conducted in different populations have reported varying outcomes. The studies have indicated the benefits of tacrolimus which includes reduction in steroid use[3], [4], improvement in blood pressures5 and amelioration of lipid profiles in transplanted patients[6]. Furthermore, a study had demonstrated a reduction in the incidence of acute rejections (an average incidence of <20%) as well as improved graft survival (above 90%) in the first year post-transplantation with the use of the newer immunosuppressive regime[7]. Nevertheless, study showed that tacrolimus is associated with an higher risk of new-onset diabetes[8] and has poorer safety profiles in comparison with cyclosporine-based therapy[9]. In addition, the immunosuppressive protocol used may have been unbalanced, particularly with respect to corticosteroid dose tapering.

Besides the conflicting data, most studies are conducted in Caucasian population with paucity of data available for Malaysian renal-transplanted population which may have a different genetic make-up and may respond differently to the therapies. Over the years, there have been an increased number of Malaysian renal-transplanted patients being converted to tacrolimus-based regime. It has been reported that tacrolimus incurs an annual cost of USD23,254.46 as compared to only USD18,206.50 with cyclosporine[10]. Thus, an accurate assessment of the safety and efficacy profiles of the two drugs is timely to justify the increased use of tacrolimus among Malaysian patients. To our knowledge, this is the first report on the safety and efficacy profiles of cyclosporine and tacrolimus in a Malaysian clinical setting.

MATERIALS AND METHODS

This is a retrospective study of more than fifteen years on all renal-transplanted patients on follow up between June 1999 and October 2014 at the University of Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. The patients received either cyclosporine (n = 155) or tacrolimus-based (n = 113) immunosuppressant regimes. The study was approved by the medical ethics committee of the UMMC (reference no 955.11) which complies with the World Medical Association Declaration of Helsinki. Demographic and clinical data were collected at 3, 6, 7, 8, 9, 10, 11 and 12 months as well as subsequently at 2 and 3 years post transplantation for both drugs.

The study subjects were adult, stable renal-transplanted patients with observed high serum creatinine (i.e. not more than 10%) six months prior to the study. Patients with a raised serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) of more than three times the upper limit of normal serum level a month prior to the transplantation, received a solid organ transplantation other than a kidney or had an episode of rejection in the previous six months were excluded. The kidneys were transplanted from living-related donors, non-living related or cadaveric donors.

Laboratory parameters such as trough levels of drugs, serum creatinine, ALT, AST, lipid profiles including total cholesterol,

high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), haemoglobin, haematocrit, total bilirubin, total protein and albumin were retrieved from either the patient's case notes or the laboratory information system of the hospital. Additionally, other concomitant medications received by the patients (if any) were also recorded.

Primary Immunosuppressive Protocol

An interleukin-2 (IL-2) antagonist (Thymoglobulin) was administered as an induction therapy to all patients. For maintenance therapy, the patients received triple immunosuppressive agents which include either cyclosporine or tacrolimus, prednisolone and an antimetabolite or a mechanistic target of rapamycin (an mTOR inhibitor). Following transplantation, cyclosporine was administered at 5.0 mg/kg every 12 hours. Subsequently, the target trough concentration of cyclosporine in whole blood was adjusted to a therapeutic level (150 – 400 ng/ml) in the first 3 months after transplantation and subsequently 100 – 300 ng/ml for the study duration. In case of tacrolimus, it was administered at an initial oral dose of 0.10 mg/kg twice daily. The target trough level was 7 – 10 ng/ml (in the following one year after transplantation) and 3 – 7 ng/ml (thereafter).

Additionally, patients also received either mycophenolate mofetil (Cellcept®) (1 g bid) or mycophenolic acid (Myfortic®) (720 mg bid) in the first three months. The dose of the drugs was gradually tapered to 500 to 750 mg bid (Cellcept®) or to 360 to 540 mg bid (Myfortic®). Prednisone was administered at 10 mg/day and subsequently tapered based on the clinician's decision. As routine practice of the hospital, drug's trough blood levels were conducted a week later to ensure that the level remained within the recommended therapeutic ranges.

Safety Profiles

Other outcomes such as graft and patient survivals were also collected from the patients' case notes. Graft loss was defined as death of patient or graft failures. Specifically, the former includes (1) death of patient, (2) those who needed to undergo nephrectomy, (3) those who died with a functioning graft, or (4) graft failure which had to be retransplanted while the latter is defined as a permanent return to a dialysis (≥30 days). Additionally, renal biopsies were evaluated and scored by a local histopathologist dedicated to the study based on the updated Banff 2007 classification[11]CTA can undergo immune-mediated rejection; therefore standardized criteria are required for characterizing and reporting severity and types of rejection. This article documents the conclusions of a symposium on CTA rejection held at the Ninth Banff Conference on Allograft Pathology in La-Coruna, Spain, on 26 June 2007, and proposes a working classification, the Banff CTA-07, for the categorization of CTA rejection. This classification was derived from a consensus discussion session attended by the first authors of three published classification systems, pathologists and researchers from international centers where clinical CTA has been performed. It was open to all attendees to the Banff conference. To the extent possible, the format followed the established National Institutes of Health (NIH.

Statistical Analyses

Data analyses were performed using SPSS software for Windows (Version 23.0; SPSS, Chicago, IL, USA). Continuous data were expressed as means ± SD, whilst categorical data were presented as percentages (unless otherwise stated). Comparison between cyclosporine and tacrolimus was performed using a chi-square test for categorical variable while paired *t*-test or Wilcoxon Signed Rank were used for continuous variables. A two-sided *p*-value <0.05 was considered as statistically significant. Descriptive summaries

for the time-to-event data for patient and graft survivals were prepared by a using the Kaplan-Meier product limit estimator.

RESULTS

Baseline Characteristics of the Study Population

The study included stable renal transplant patients (*n* = 268) who were predominantly males (64%) and of Chinese ethnicity (74%) as determined by two generations, with a mean age of 40 years (Table 1).

Table 1 Demographic data and patients' baseline characteristics

Patients' characteristics, *n* (%) or mean ±SD	**Cyclosporine (*n* = 155)**	**Tacrolimus (*n* = 112)**
Sex Male Female	 98 (37) 58 (22)	 71 (27) 41 (15)
Race Malay Chinese Indian Others	 20 (8) 116 (45) 19 (7) 1 (0)	 38 (14) 84 (31) 10 (4)
Place of transplantation Overseas Local	 75 (28) 81 (30)	 46 (17) 66 (25)
Number of transplantation Once Twice	 156 (58) –	 – 2 (1)
Donor type Living-related transplant Non-living related transplant Cadaveric	 55 18 82	 39 25 49
Weight (kg)	66.26 ± 15.53	67.65 ± 18.06
Age at transplant (years)	39.67 ± 11.79	40.50 ± 11.56
Dialysis duration (months)	22.2 ± 29.42	31.02 ± 30.58
Primary kidney disease Hypertension Glomerulonephritis Diabetes mellitus Bilateral small kidneys IgA nephropathy Others (polycystic kidney disease, lupus nephritis, reflux nephropathy, etc.)	 40 (15) 22 (8) 23 (9) 30 (11) 16 (6)	 27 (10) 18 (7) 14 (5) 19 (7) 16 (6)
Immunosuppressants (Maintenance period) Prednisolone, azathioprine, cyclosporine Prednisolone, azathioprine, tacrolimus Prednisolone, mycophenolate mofetil (Cellcept®), cyclosporine Prednisolone, mycophenolate mofetil (Cellcept®), tacrolimus Prednisolone, mycophenolic acid (Myfortic®), cyclosporine Prednisolone, mycophenolic acid (Myfortic®), tacrolimus	 27 (10) – 74 (28) – 55 (21) –	 – 7 (3) – 61 (23) – 44 (16)

From the total number, only two patients had to undergo transplantation for the second time. More than half of the grafts originated from deceased donors and the majority (approximately 55%) of transplantation were performed locally. There were no significant difference in terms of age at transplantation ($p = 0.73$), weight at transplantation ($p = 0.20$) and dialysis duration prior to transplantation ($p = 0.25$). The main causative agent for primary end stage renal disease in this study is as similarly seen in other reports i.e. hypertension (25%), bilateral small kidneys (18%), glomerulonephritis (15%), immunoglobulin-A (IgA) nephropathy (12%) and diabetes mellitus (14%). Prednisolone and mycophenolate mofetil are the preferred immunosuppressive agents used as adjuncts.

Cyclosporine and Tacrolimus Trough Level Concentrations

The clinical characteristics are presented on Table 2. The overall means for cyclosporine and tacrolimus trough levels were 189.16 ± 69.10 ng/ml and 7.84 ± 2.18 mg/day respectively which were within the therapeutic range throughout the study period.

Lipid Profiles and Other Important Parameters

Although the mean total cholesterol was higher at three months up to nine months post transplantation for cyclosporine as compared to tacrolimus although this difference was not significant. Nevertheless, starting from 10 months post-transplantation, monthly mean total cholesterol for tacrolimus began to increase and became persistently higher than that for cyclosporine until the end of the three years post transplantation period although again there was no significant difference ($p = 0.31$) seen. Similarly, there was no significant different in the mean HDL and triglyceride levels between the two-treatment groups. However, mean LDL was significantly higher at eleven months for tacrolimus group compared to cyclosporine.

Both drug regimens showed no significant difference in the mean haemoglobin and haematocrit levels for both drugs. There was also no difference in the ALT and AST levels. Interestingly however, the mean total bilirubin level was significantly higher with cyclosporine as compared to tacrolimus between 3 – 9 months post transplantation ($p < 0.05$) although there was no significant difference in the levels after this duration.

In addition, there was no significant difference in terms of overall monthly mean total protein and albumin levels between the two drugs during the 3 years study period which was also similarly seen for serum uric acid levels which progressively increased in both groups, although the difference was not statistically significant ($p = 0.49$).

Renal Allograft Function

At baseline, all patients had stable serum creatinine concentration, but slowly increased during the study period (male: 70 – 120 µmol/L; female: 50 – 90 µmol/L) for both drugs. At 3 months, the levels increased to 134.63 ± 68.87 µmol/L (cyclosporine) and 130.39 ± 50.21 µmol/L (tacrolimus). Finally, at 3 years, the levels were 138.71 ± 75.15 µmol/L (cyclosporin) and 134.35 ± 64.42 µmol/L (tacrolimus). Nevertheless, there was no significant difference in the levels for the two drugs for the study duration.

Table 2 Clinical characteristics

Laboratory results	At 3-month PT			At 6-month PT			At 7-month PT			At 8-month PT			At 9-month PT		
	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*
Trough level (ng/mL or mg/mL))	272.88 ± 103.29	9.03 ± 2.74	NA	215.56 ± 78.27	8.54 ± 3.08	NA	191.09 ± 71.17	7.73 ± 2.86	NA	194.45 ± 83.02	7.78 ± 2.79	NA	179.29 ± 73.51	8.34 ± 3.48	NA
Mean serum creatinine(μmol/L)	134.63 ± 68.87	130.39 ± 50.21	0.61	141.26 ± 85.50	139.34 ± 63.29	0.86	149.07 ± 128.26	139.91 ± 77.11	0.57	140.55 ± 89.7	147.81 ± 74.96	0.58	134.02 ± 82.45	144.90 ± 90.58	0.42
Mean total cholesterol (mmol/L)	6.22 ± 8.20	5.41 ± 1.08	0.43	6.04 ± 8.75	5.06 ± 1.08	0.42	5.23 ± 1.11	5.10 ± 1.32	0.52	5.20 ± 0.99	4.96 ± 0.97	0.22	5.11 ± 0.97	5.05 ± 0.88	0.71
Mean low density lipoprotein (LDL) (mmol/L)	3.15 ± 1.06	2.97 ± 0.91	0.28	2.95 ± 1.14	2.84 ± 0.95	0.57	2.89 ± 0.91	3.15 ± 1.27	0.25	2.96 ± 0.99	2.91 ± 0.83	0.78	2.83 ± 0.90	2.95 ± 0.86	0.54
Mean high density lipoprotein (HDL) (mmol/L)	1.54 ± 0.54	1.55 ± 0.45	0.98	1.46 ± 0.47	1.42 ± 0.44	0.61	1.46 ± 0.46	1.41 ± 0.52	0.63	1.44 ± 0.58	1.37 ± 0.32	0.49	1.46 ± 0.59	1.51 ± 0.66	0.69
Mean triglycerides (TG) (mmol/L)	2.06 ± 0.91	5.95 ± 31.78	0.34	1.84 ± 0.90	1.69 ± 0.98	0.39	1.84 ± 0.99	1.73 ± 0.82	0.55	1.86 ± 0.98	1.73 ± 0.83	0.52	1.79 ± 0.92	1.68 ± 0.83	0.56
Mean haemoglobin (HB) (g/L)	121.30 ± 19.86	121.31 ± 20.33	0.99	122.43 ± 19.88	124.77 ± 19.70	0.40	123.45 ± 19.40	124.53 ± 22.34	0.73	127.26 ± 21.42	123.67 ± 121.24	0.28	128.48 ± 19.15	127.51 ± 21.92	0.76
Mean haematocrit (Hct) (SI)	1.52 ± 13.38	0.37 ± 0.06	0.40	1.62 ± 13.66	0.38 ± 0.06	0.39	0.38 ± 0.06	0.38 ± 0.07	0.52	0.39 ± 0.07	0.38 ± 0.07	0.20	0.39 ± 0.06	0.39 ± 0.07	0.89
Uric acid (mg/dL)	374.51 ± 98.55	369.54 ± 99.09	0.79	392.44 ± 104.30	380.73 ± 82.33	0.54	381.78 ± 72.50	393.06 ± 113.27	0.63	409.12 ± 116.02	419.79 ± 104.51	0.70	378.62 ± 99.05	412.00 ± 107.56	0.18
Mean alanine transferase (ALT) (U/L)	47.49 ± 28.33	45.07 ± 38.87	0.59	45.01 ± 30.94	40.73 ± 22.14	0.27	44.00 ± 43.22	41.83 ± 46.04	0.76	44.07 ± 39.66	33.81 ± 18.05	0.06	45.00 ± 43.12	36.81 ± 22.38	0.16
Mean aspartate transferase (AST) (U/L)	23.82 ± 17.48	23.75 ± 18.21	0.98	24.25 ± 19.85	24.27 ± 13.01	0.99	24.67 *±22.17*	25.15 ± 19.95	0.89	22.95 ± 17.51	20.80 *±9.17*	0.39	26.67 ± 35.73	22.82 ± 11.83	0.41
Total bilirubin (μmol/L)	12.78 ± 6.88	9.02 ± 4.06	**0.000**	12.73 ± 8.42	10.48 ± 5.80	**0.03**	12.35 ± 6.31	10.42 ± 4.39	**0.02**	13.18 ± 6.56	9.84 ± 4.25	**0.00**	13.36 ± 6.06	10.84 ± 4.93	0.01
Total protein (g/L)	67.52 ± 9.48	68.75 ± 6.84	0.29	70.56 ± 8.59	70.55 ± 6.84	0.99	71.97 ± 5.38	71.31 ± 7.07	0.50	72.26 ± 5.29	71.19 ± 5.88	0.25	72.88 ± 5.56	71.99 ± 6.34	0.36
Albumin (g/L)	37.04 ± 6.80	38.14 ± 5.51	0.20	40.05 ± 5.64	40.24 ± 4.67	0.80	38.80 ± 4.47	40.12 ± 5.25	0.08	39.80 ± 4.62	40.03 ± 5.51	0.78	39.79 ± 4.53	39.88 ± 5.91	0.91

Table 2 Clinical characteristics cont.

Laboratory results	At 10-month PT			At 11-month PT			At 12-month PT			At 2-year PT			At 3-year PT			Overall mean		
	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*	CSA	TAC	*p*
Trough level (ng/ml)	173.04 ± 89.31	7.65 ± 3.04	NA	159.04 ± 79.39	7.23 ± 2.70	NA	139.24 ± 56.56	7.21 ± 2.69	NA	92.07 ± 71.56	6.87 ± 2.15	NA	81.53 ± 42.90	6.35 ± 2.41	NA	189.16 ± 69.10	7.84 ± 2.18	NA
Mean serum creatinine (µmol/L)	139.25 ± 94.63	142.86 ± 82.22	0.80	135.16 ± 73.72	137.80 ± 79.97	0.84	136.47 ± 85.98	143.97 ± 79.21	0.56	142.85 ± 137.43	134.69 ± 73.94	0.66	148.26 ± 146.13	131.68 ± 77.77	0.45	138.71 ± 75.15	134.35 ± 64.42	0.48
Mean total Cholesterol (mmol/L)	5.06 ± 0.89	5.09 ± 0.94	0.84	4.96 ± 0.99	5.23 ± 1.14	0.18	5.11 ± 0.92	5.17 ± 1.15	0.79	5.05 ± 0.88	5.16 ± 0.88	0.48	4.91 ± 0.97	5.07 ± 1.16	0.48	5.47 ± 3.78	5.21 ± 0.87	0.31
Mean low density lipoprotein (LDL) (mmol/L)	2.80 ± 0.90	3.02 ± 0.83	0.24	2.70 ± 0.95	3.14 ± 0.96	0.03	2.83 ± 0.89	3.12 ± 0.93	0.16	2.79 ± 0.82	3.01 ± 0.87	0.18	2.71 ± 0.80	2.97 ± 1.00	0.17	2.91 ± 0.92	3.00 ± 0.77	0.47
Mean high density lipoprotein (HDL) (mmol/L)	1.45 ± 0.42	1.53 ± 0.53	0.41	1.43 ± 0.47	1.42 ± 0.33	0.87	1.46 ± 0.50	1.41 ± 0.41	0.63	1.39 ± 0.46	1.46 ± 0.56	0.49	1.37 ± 0.48	1.40 ± 0.39	0.74	1.45 ± 0.43	1.48 ± 0.41	0.46
Mean triglycerides (TG) (mmol/L)	1.83 ± 0.82	2.08 ± 2.55	0.51	1.73 ± 0.81	1.72 ± 0.82	0.97	1.70 ± 1.07	1.57 ± 0.64	0.53	1.92 ± 0.94	1.83 ± 1.06	0.65	1.80 ± 0.93	1.67 ± 0.77	0.47	1.89 ± 0.76	4.15 ± 24.32	0.66
Mean haemoglobin (HB) (g/L)	130.00 ± 21.17	132.41 ± 20.16	0.48	128.44 ± 22.76	130.19 ± 20.32	0.64	128.61 ± 23.49	129.57 ± 21.18	0.80	127.44 ± 21.03	131.15 ± 21.11	0.28	125.91 ± 17.95	130.59 ± 20.50	0.19	125.95 ± 18.11	127.41 ± 18.69	0.64
Mean haematocrit (Hct) (SI)	0.40 ± 0.07	0.41 ± 0.06	0.45	2.28 ± 17.07	0.40 ± 0.06	0.39	0.40 ± 0.07	0.40 ± 0.07	0.98	0.39 ± 0.06	0.40 ± 0.06	0.21	0.38 ± 0.05	0.40 ± 0.06	0.15	1.13 ± 6.91	0.39 ± 0.05	0.24
Uric acid (mg/dL)	367.46 ± 100.75	390.09 ± 134.86	0.45	366.02 ± 105.64	418.5 ± 115.78	0.08	383.83 ± 97.46	409.48 ± 132.6	0.41	370.71 ± 115.92	433.08 ± 137.05	0.14	378.42 ± 87.24	394.00 ± 101.31	0.65	380.87 ± 92.23	390.96 ± 95.97	0.49
Mean alanine transferase (ALT) (U/L)	40.72 ± 23.59	44.22 ± 40.33	0.53	39.36 ± 18.78	41.20 ± 33.75	0.18	40.65 ± 32.79	47.25 ± 55.54	0.66	37.42 ± 18.91	37.65 ± 35.91	0.29	40.10 ± 21.44	41.63 ± 36.63	0.31	42.44 ± 21.95	43.23 ± 33.65	0.59
Mean aspartate transferase (AST) (U/L)	22.72 ± 13.77	26.79 ± 19.92	0.16	23.47 ± 14.24	26.30 ± 21.34	0.53	23.24 ± 18.45	28.43 ± 29.14	0.08	22.72 ± 14.98	23.51 ± 19.10	0.92	24.18 ± 14.14	26.73 ± 17.76	0.72	23.36 ± 12.61	25.22 ± 16.31	0.49
Total bilirubin (µmol/L)	12.13 ± 5.91	12.26 ± 6.46	0.90	13.26 ± 6.51	11.51 ± 6.45	0.13	14.13 ± 8.78	12.43 ± 9.34	0.27	13.42 ± 8.30	12.12 ± 5.55	0.29	12.55 ± 6.63	11.50 ± 5.44	0.38	13.39 ± 6.30	10.96 ± 4.60	0.41
Total protein (g/L)	73.00 ± 5.26	74.63 ± 5.41	0.08	72.85 ± 6.81	73.37 ± 4.17	0.62	73.51 ± 5.85	73.59 ± 4.32	0.93	74.25 ± 5.16	72.85 ± 5.56	0.14	72.33 ± 5.48	72.39 ± 6.15	0.11	71.62 ± 6.02	71.57 ± 5.23	0.20
Albumin (g/L)	39.65 ± 4.55	40.75 ± 4.56	0.16	39.63 ± 4.74	40.52 ± 4.09	0.26	39.76 ± 5.15	40.39 ± 4.41	0.44	40.60 ± 5.66	40.44 ± 5.06	0.87	40.34 ± 3.43	41.04 ± 8.91	0.60	39.30 ± 4.52	39.78 ± 4.47	0.57

Acute Rejection

The findings from biopsy-confirmed acute rejection (BPAR) are shown in Table 3. There were 27 cases of BPAR (excluding borderline cases) which was higher with cyclosporine (17 cases) as compared to tacrolimus (10 cases). On the other hand, borderline changes were observed in 11 cases (cyclosporine) and 17 cases (tacrolimus), whilst an acute antibody-mediated rejection was seen only a single case during tacrolimus treatment which resolved after given plasmapheresis and intravenous immunoglobulin (IVIG).

Table 3 Pathologic findings of BPAR based on BANFF classification

BANFF classification	Cyclosporine	Tacrolimus
All acute rejection	17	10
T-cell mediated rejection: Grade IA	9	6
T-cell mediated rejection: Grade IB	7	3
T-cell mediated rejection: Grade 2A	1	0
T-cell mediated rejection: Grade 2B	0	0
Antibody-mediated rejection (AMR): Immediate	0	1
Antibody-mediated rejection (AMR): Delayed	0	0
New-onset of chronic allograft nephropathy (CAN): Mild	0	0
New-onset of chronic allograft nephropathy (CAN): Moderate	0	0
New-onset of chronic allograft nephropathy (CAN): Severe	0	0
#Other changes	0	0
^Borderline changes	11	17

#Other changes are observed changes which might not be considered as a direct effect on rejection, however, may coincide with acute rejection categories (e.g. mild tubulitis, hypertensive changes, focal segmental glomerulosclerosis).

^Borderline changes is also known as 'suspicious' of acute rejection, the presence of a mild tubulitis with no intimal arteritis[12]Banff 97, developed by investigators using the Banff Schema and the Collaborative Clinical Trials in Transplantation (CCTT.

Patient and Graft Survivals

Six months post transplantation, two patients (all during cyclosporine-based treatment) died while four patients experienced loss of graft [a single case during cyclosporine treatment and three during tacrolimus treatment]. Kaplan-Meier curve indicated that the mean survival time is significantly longer (p = 0.03) with cyclosporine-based treatment (105.48 ± 4.71 months) as compared to tacrolimus-based treatment (81.70 ± 5.71 months) as indicated by Figure 1.

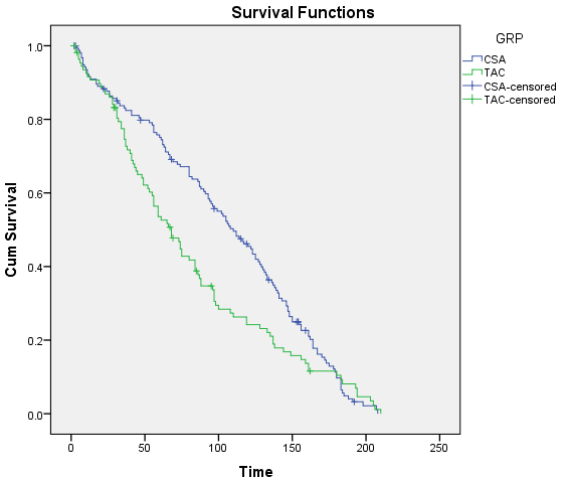

Figure 1 Comparison of mean survival time between cyclosporine-based treatment and tacrolimus-based treatment

DISCUSSION

According to our knowledge, our current study is the first local report to demonstrate that

cyclosporine and tacrolimus have a comparable safety and efficacy profiles among Malaysian renal-transplanted patients. Most importantly, the study shows that the rates of graft and patient survival as well as freedom from BPAR were high in all patients throughout the period of both drugs indicating that that these drugs can be used interchangeably. Additionally, these findings in our unique population are useful, since many factors may affect the pharmacokinetics properties of cyclosporine and tacrolimus, leading to differences in the outcomes of different populations.

Overall, there are no inferior clinical consequence as exemplified by excellent high patient, graft survival rates and a minimal incidence of acute rejection, although the drug's trough level were on the lower side of the targeted range. There are cases of BPAR reported in both drugs (a higher incidence with cyclosporine-based treatment), however, no patients experienced a Banff grade of ≥2A rejection or needed an anti-rejection therapy. This study showed similar results with another study[9] which reported a higher risk of BPAR with cyclosporine. We speculated that the higher occurrence of borderline rejections may indicate that the true difference in BPAR burden between the two drugs may even be smaller than those reported. There are other important factors that could affect the absorption and exposure of drugs that may lead to acute rejection such as CYP3A polymorphisms, dietary intake[13] and rate of gastrointestinal peristalsis[14]. Still others have documented the efficacy of combining tacrolimus with MMF with a lower incidence of acute rejection episodes as compared with combination of cyclosporine and MMF (4% vs 11%)[9]. Interestingly, more than half of the studied populations were on combination with MMF during the maintenance period.

In our current study, two patients died at 6 months post transplantation (during cyclosporine treatment and unrelated to the treatment regime) and four patients experience loss of graft (one during cyclosporine treatment and three during tacrolimus treatment) at 6 months post transplantation. Interestingly, an analysis by Kaplan-Meier showed significantly higher survival time with cyclosporine-based treatment compared with tacrolimus-based treatment. Our results are similar to the data that were recently reported for a large, phase III U.S. multicentre trial, comparing tacrolimus and cyclosporine in adult renal-transplanted patient[15]. The differences in the incidence and severity of acute rejection in renal-transplanted patients amongst cyclosporine and tacrolimus raise an important issue with regards to long-term patient and graft survival. It has been shown in several studies that acute rejection is a major risk factor for graft loss, due to a subsequent development of chronic rejection.

Although we did not observe any significant difference in mean monthly level in terms of lipid profiles between cyclosporine and tacrolimus group of treatment, an interesting trend was seen. Both treatment group shows a decrease in the serum total cholesterol and serum LDL (22% vs 6.3%, 14% vs 0% at 3-month and 3-year post transplantation). It is proposed that cyclosporine blocks the 25-hydroxylase step in bile acid synthesis. This enzyme inhibition results in increased levels of LDL cholesterol[16]. It is plausible that the mean LDL and total cholesterol are higher on overall with tacrolimus-based treatment in this study. A study by Joung et al.[17] had also demonstrated no significant changes of lipid profiles after conversion from cyclosporine to tacrolimus. This is in contrast with the reported positive effect on hyperlipidaemia with tacrolimus caused by removing the adverse effect cyclosporine on lipid metabolism[6]. Moreover, serum HDL levels rose higher in cyclosporine-based treatment by 11% (only 9.7% increase in tacrolimus group). Interestingly, a higher decrease in the mean monthly triglyceride level with tacrolimus-based treatment by 72% as compared with cyclosporine group of only 13% at 3-month and at the end of 3-year post transplantation was observed in this study. This

is in agreement with a similar clinical studies which reported a beneficial effect of tacrolimus in decreasing cardiovascular complication in renal-transplanted patient[18]. This finding is crucial as update guidance to clinicians on the increasingly crucial role of triglycerides in the evaluation and management of cardiovascular disease (CVD) risk. Cyclosporine has also been associated with elevated triglyceride levels through inhibition of lipoprotein lipase. However, the difference in response may be a result of the lack of diabetic patients in the previous study[18], and in this study we were not able to collect data on diabetic profiles due to incomplete collection of data.

In addition, our study indicates that liver function test remained stable in both periods of cyclosporine and tacrolimus. Studies have shown that renal-transplanted patients exhibit a higher rate of tacrolimus clearance[7], partly due to low haematocrit and albumin levels. Although a decrease in the mean level of albumin and ALT was observed, these values were still within the normal range. This explains the incidence of BPAR with a trough level within a therapeutic range and excellent patient and graft survival as observed in both periods of drug treatment. However, to confirm these findings, a bioequivalence study of cyclosporine and tacrolimus should ideally be undertaken in the future among the Malaysian populations.

In this study, we found that both cyclosporine and tacrolimus administration increases the serum uric acid level in renal-transplanted patients, in contrast to previous study[19]. There are several factors[20] which may contribute to the development of hyperuricaemia, including poor graft function (decreased glomerular filtration rate), hypertension, immunosuppression (especially cyclosporine), and diuretic therapy. The drug's effects are important because hyperuricaemia and gout may adversely affect renal function, and also may complicate the rehabilitation of renal-transplanted patients. Moreover, a more recent finding suggests that uric acid levels are independently associated with cardiovascular events and related to mortality and long-term transplant survival. The result of this study showed that hyperuricaemia is not an indication to convert from cyclosporine to tacrolimus in our renal-transplanted patients since both drugs produced a comparable outcome.

With regards to renal function, we did not find any significant difference in terms of serum creatinine level between cyclosporine and tacrolimus. This is despite the facts shown by other investigators the effects of calcineurin inhibitors on renal haemodynamics, especially with cyclosporine[21]. In contrast, tacrolimus has been reported to have protective effect on the renal function[22]. However, a more sensitive test for renal function formula such as Modification of Diet in Renal Disease (MDRD)[23] may be useful to demonstrate if this benefit really exists.

The strength of our study includes a long period of three years follow-up which enables a better comparison between cyclosporine and tacrolimus, thus allowing both laboratory and clinical findings to be more likely to occur in stable conditions, lending a higher degree of validity of the findings. Nevertheless, there were some drawbacks. There is the possibility of food and drug interactions which may affect the laboratory findings since patient's diet could not be controlled especially in a retrospective study. Therefore, future prospective studies with a larger number of patients will strengthen the data further.

CONCLUSION

In conclusion, tacrolimus is a convenient and safe drug to be used among renal-transplanted patients in Malaysia as well as another useful alternative to the standard cyclosporine.

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CASE REPORT

Breast Cancer with Isolated Metastatic Temporomandibular Joint: A Surgeon's Challenge

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ABSTRACT

Breast cancer is the number one malignancy in women worldwide. It tends to metastasize distantly via lymphatic and haematogenous route. Skeletal metastases are frequent with more than three quarter of cases in all malignant bone tumours. Breast cancer can infiltrate the axial bone especially spine, but rarely affect the temporomandibular joint. In view of its rarity and the significance of early detection, the diagnosis is always challenging and shall be considered in the differential diagnosis. We endeavour to highlight this unfortunate 37-year-old lady who had just undergone left mastectomy and axillary dissection but was complicated with left temporomandibular joint metastasis.

INTRODUCTION

Secondary metastasis of the jaw and mouth is uncommon. This is attributed by the fact that of all oral malignancies, only 1% of them are secondary metastases[1]. The most commonly involved primary malignancies include lung, kidney, liver, prostate, female genital organ, and colorectum. Predilected as the number one aetiologies of malignancy among women, the breast also has the inclination to metastasize to the jaw and mouth. In view of this rare occurrence, the diagnosis is always dubious.

Most patients with temporomandibular metastasis complain of swelling, pain, and paraesthesia. Occasionally, they can present with trismus, temporomandibular joint dysfunction and malocclusion, and even

present with pathological fracture. Clinical examination mostly is unremarkable in occult metastasis. Simple radiograph is helpful to diagnose fracture but little for oblivious metastasis. Herein we describe a 37-year-old premenopausal lady who was diagnosed as left temporomandibular joint metastasis with previous left mastectomy and axillary dissection for locally advanced breast cancer and discuss its literature review.

CASE PRESENTATION

A 37-year-old lady presented with 2-month history of left breast lump which rapidly increased in size. It was associated with intermittent dull aching pain. Otherwise, there were no other swellings, no skin changes and no nipple discharge. She is a mother of 4 with no unremarkable gynaecological history. She denied consuming any hormonal or oral contraceptive pills. There is no family history of breast or ovarian carcinoma. She is a non-smoker and non-alcohol consumer.

Ultrasonography was consistent with suspicious lesion suspecting of malignancy. Core biopsy of the lump yielded an invasive carcinoma with malignant cells arranging in nests and islands. The cells had mild to moderate nuclei pleomorphism with abundant cytoplasm. Immunohistochemistry study revealed positive oestrogen receptor (ER), positive progesterone receptor (PR), and equivocal HER2. D-DISH for HER2 however was not amplified. Computed tomography (CT) scan of the thorax, abdomen and pelvis upon diagnosis showed calcified solitary subpleural nodule seen at the anterior segment of right upper lobe, measuring 0.3 cm in diameter with multiple hypodense liver lesions in segment VIII suggestive of simple cyst.

She then underwent left mastectomy and level II of axillary dissection. Final histopathologic result was consistent with invasive carcinoma of no special type. The modified Bloom and Richardson score revealed grade 3 with no lympho-vascular invasion. There was no positive lymph node out of 21 harvested nodes. The resection margins were free of malignancy. Unfortunately, she did not receive any chemoradiation, hormonal or targeted therapy due to financial constraints as she is a non-local residence.

Two months after the surgery, she started to experience left preauricular and jaw tingling sensation with pain of the left mandibular region, especially during chewing. She felt difficulty opening her mouth due to locking sensation. She otherwise denied any hearing loss or halithosis. Clinical examination was unremarkable except for some mild tenderness over the left preauricular region. The surrounding skin had similar temperature compared to the surrounding tissue. She was admitted for pain management and physiotherapy.

A CT of brain and neck was performed after showing normal skull radiograph. There was destructive bony lesion of left mandibular condyle. There was also widening of the left temporo-mandibular space, filled with enhancing soft tissue component which extends to postero-lateral left lateral pterygoid muscle (Figure 1). However, there was no enhancing brain intraparenchymal lesion. She was subsequently referred to the oncology team. Unfortunately, in view of her non-local resident status, she was not able to receive proper adjuvant treatment. She was under palliative treatment with oral analgaesia. She lost to follow up after discharge.

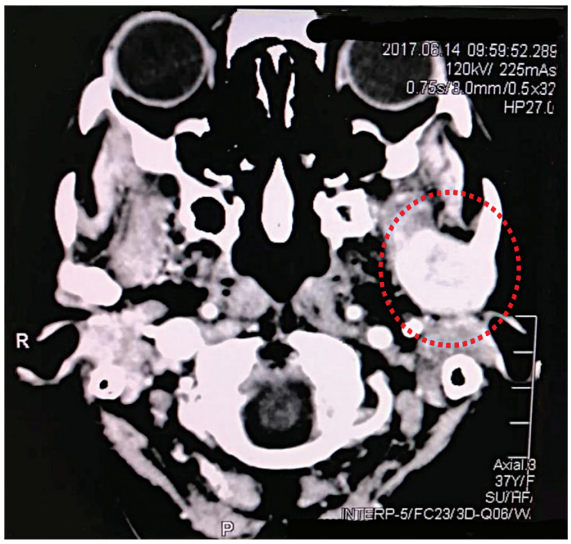

Figure 1 CT scan shows destructive bony lesion of left mandibular condyle with widening of the left temporo-mandibular space, filled with enhancing soft tissue component which extends to postero-lateral left lateral pterygoid muscle (inside red dotted circle)

DISCUSSION

The mandible is more frequently involved compared to the maxilla[1]. Despite the fact, Hashimoto et al. has proven the incidences of jaw metastases are probably higher when the autopsies showed 16% of positive micrometastatic foci were identified in the jaws even in the absence of imaging detection[2]. Many literatures have expressed that breast carcinoma as the commonest primary site, followed by thyroid; however, it is notable that the incidences vary with geographical distribution, genetic mutations, age and gender[3, 4, 5]. The Japanese literature has proclaimed that in females, metastases to the jawbones are most commonly from choriocarcinoma instead of the breast or thyroid cancers[6, 7]. The Korean literature meanwhile stated that lung is the commonest primary site for jawbone metastases, followed by the liver[7]. A study on 114 patients with metastatic jaw lesions, they were most commonly found in women aged between 31 – 40 and men aged between 71 – 80 years old, attributing to breast and thyroid malignancies in females and prostate malignancies in males at later age[3].

The most frequently involved sites in the mandible, from the commonest, are the molar, premolar and the ramus. Factors that favour metastatic deposits in these areas are blood stasis, presence of haematopoietic bone marrow well connected with sinusoidal spaces, predisposing to haematogenous route of metastasis, and tortuous course of inferior alveolar nerve[8, 9]. Therefore, metastasis to the mandibular condyle is extremely rare, with only about 5% of all secondary oral malignancies, due to relatively lack of marrow as compared to the body and ramus[10, 11]. In this patient, osteolytic lesion was seen at the left mandibular condyle, sparing the mandibular body and ramus.

The common symptoms involving the TMJ are localised pain, swelling, trismus, TMJ dysfunction and malocclusion. Patient rarely presents with pathological fracture[12]. In this patient, given the history of breast malignancy diagnosed just 4 months ago prior to the jawbone symptoms, high suspicion of metastatic jawbone disease was considered. However, it is not a routine workup to detect jaw metastasis in patients with breast malignancies unless symptomatic.

The conventional radiograph such as orthopantomogram is useful but it may not be able to visualize obvious metastatic lesions in the jaws[13]. Further imaging modalities can be ordered in symptomatic patients namely CT scan of the temporomandibular region, skeletal scintigraphy and fluoro-deoxy-glucose positron emission tomography (FDG-PET) scan. FDG-PET/CT has higher specificity than skeletal scintigraphy and is a better modality in identifying bone metastases, however, it is important to note that these imaging modalities cannot detect micrometastatsis[14]. Metastasis of breast adenocarcinoma can progress without any signs or symptoms and radiological evidence. Therefore, it is

very important to obtain the past history of malignancy and to perform a biopsy for definitive diagnosis.

Patients with jaw metastases have poor prognosis with 70% of them succumbed within one year of diagnosis. A 4-year survival rate is estimated to be 10%[15]. Most of the patients, at the time of diagnosis, are either with widespread metastases or terminally ill[8]. Thus, they are managed conservatively with chemoradiation and pain control, with the goal of preserving oral functions and quality of life. However, in patients who are treated of the primary tumour previously and are medically fit, the metastatic lesion should be aggressively treated with surgical resection. Treatment with segmental mandibulectomy with subsequent adjuvant chemoradiation, enucleation of metastatic lesion or osteotomy can be offered based on individual's condition[15].

CONCLUSION

Temporomandibular joint metastasis from breast warrants the usual adjuvant treatments after local surgical treatment of the primary and secondary pathologies. The delivery of adjuvant chemoradiation, hormonal and targeted therapy help to improve the prognosis of the patient. Even bearing a poorer prognosis, temporomandibular joint metastases need pain control with the goal of preserving oral functions, nutrition, cosmesis as well as quality of life.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written informed consent was obtained from the patient to publish the case. A copy of written consent is available for review by the Chief Editor.

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CASE REPORT

A Fascinating Case of the 'Purple Urine Bag Syndrome'

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Keywords: purple urine bag syndrome (PUBS), urinary tract infections (UTIs), catheter-related urinary tract infection.

ABSTRACT

Purple urine bag syndrome (PUBS) is a rare presentation of urinary tract infections (UTIs). It is commonly seen in constipated patients. There is a deep purple discoloration of contents of urine bag due to presence of indigo and indirubin pigments which are metabolites of tryptophan. We would like to describe an interesting case of purple urine bag syndrome of 88-year-old woman who presented with catheter-related urinary tract infection. She had low-grade fever and suprapubic discomfort for three days duration. She had increased white cell count and C-reactive peptide (CRP). Urinalysis showed protein 2+, nitrite and leucocyte esterase positive. Urine culture grew *Escherichia coli* and *Klebsiella pneumoniae*. She was treated with oral cefuroxime and recovered. This case report may be the first case of PUBS reported in this region.

INTRODUCTION

Purple urine bag syndrome is uncommonly seen where there is purple discolouration of the urine, collecting bag, and tubing[1]. This is first described by Barlow and Dickson in 1978, due to the indigo and indirubin producing bacteria in urine tract infections (UTIs)[2]. Since the first report in 1978, PUBS remains a fascinating condition affiliated with chronic constipation, alkaline urinary pH, a bed-ridden state, advanced age, tryptophan rich foods, cognitive disorders, renal dysfunction and chronic urethral catheterization[3]. We would like

to describe a case of purple urine bag syndrome who presented with catheter-related urinary tract infection.

CASE PRESENTATION

An 88-year-old lady who was on long-term continuous bladder drainage (CBD) for diabetes cystopathy was presented with low-grade fever and suprapubic discomfort for three days duration. She also noticed a change in her urine colour from yellow to purple recently (Figure 1). The last change of her bladder catheter was one week ago at the local health clinic. Clinically, she was not septic, her blood pressure was 115/70 mmHg and heart rate of 92 beats per minute. She had a low-grade fever of 37.8 degree Celsius. Her suprapubic region was tender on palpation. Laboratory results showed an elevated total white cell count of 18×10^9/L and raised C-reactive peptide (CRP) of 200 mg/dl. Urinalysis showed the following: pH7, specific gravity of 1.02, leucocytes of 500 µL, nitrite positive, protein 2+, ketone negative and leucocyte esterase positive. Urine culture grew *Escherichia coli* and *Klebsiella pneumoniae*. She had a negative blood culture result. She was treated with oral cefuroxime 500 mg twice daily for five days per local antibiotic protocol. She made a smooth recovery and was discharged. During her subsequent follow-up, her urine colour has returned to normal and repeated urinalysis was normal.

Figure 1 Purple discolouration of the urine in the urine collection bag

DISCUSSION

Purple urine bag syndrome is an uncommon case. It is more common among urinary catheterized elderly patients[4]. Bacterial enzymes in the urine trigger biochemical reactions that release metabolic products that make the urine purple in colour[5]. Amino acid tryptophan is broken down into indole by the gastrointestinal tract flora organism which is later converted into indoxyl sulfate in the intestines[5]. In the urine, the indoxyl sulfate is further broken down into indoxyl in the alkaline environment with the presence of bacterial enzymes (indoxyl sulfatase and indoxyl phosphatase). Indigo and indirubin are the breakdown products which makes the urine blue and red. Frequently, bacteria with these enzymes seen are *Providencia*, *Klebsiella* and *Proteus species*[6].

In general, urinary catheters are placed for a number of reasons. Urine tract infection risks are increased with the presence of urine catheters[7]. The reported incidence of bacteriuria related to indwelling catheters

occurs at a rate of five per cent per day of urinary catheterization[8]. In patients with bacteriuria, around twenty per cent reported evidence of urinary tract infection symptoms[7, 8]. There is a lack of overall consensus about the optimal approach to catheter-associated urinary tract infections (UTIs), apart from removing the catheters when it is no longer necessary. This leads to increase in healthcare burden of catheter-associated UTIs in hospitalized patients[4].

In a systemic review done on purple urine bag syndrome (PUBS) by Llenas-Garcia, there were 169 PUBS cases reported: 63.5% woman, median age 78 years old, 59.4% asymptomatic. Outcome: 7.7% death and 21.4% recurrence. The only factor associated with recurrence was dementia (OR: 5.44; P = 0.046). *Escherichia coli* and *proteus mirabilis* were the organisms most often isolated[2].

Risk factors for catheter-related urinary tract infection include female gender, older age, diabetes mellitus, bacterial colonization of the drainage bag and errors in catheter care[9].

The common complaints include flank or suprapubic pain, costovertebral angle tenderness, and catheter blockage. Elderly patients may present with new-onset delirium due to urinary tract infection[10].

The best approach to urinary catheter management during urinary tract infection (UTI) is to minimize the usage of indwelling catheters. Strict aseptic technique when placing the catheter should always be adhered to. Practically, patients who do not require catheterization should have the catheter removed and receive appropriate antimicrobial therapy[9, 10].

CONCLUSION

Catheter-related urinary tract infection is a common healthcare-associated infection. Purple urine bag syndrome is an uncommon presentation of catheter-associated urinary tract infections.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written informed consent was obtained from the patient to publish the case. A copy of written consent is available for review by the Chief Editor.

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CASE REPORT

Abdominal Flap: A Reconstructive Option for Hand Defect in Rural Setting

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Keywords: degloving injury, hand, reconstruction, abdominal flap

ABSTRACT

Reconstruction of hand injury is the challenge for the surgeon especially in rural settings. This case report is about a 10-year-old boy, who sustained large degloving wound of dorsum of right hand with extensor tendon injury following a road traffic accident. We performed a staged abdominal flap with tensor fascia lata graft for tendon reconstruction as microsurgery facilities was not available. Post-operatively he was subjected to physiotherapy and he has a functional right hand. This case report aimed to highlight abdominal flap as reconstructive option as compared to skin grafting which is reproducible with limited resources. Besides that, overall exposure to all surgical options is of paramount importance in the training of trainees to equip them with skills to serve in rural setting.

INTRODUCTION

Hand is an intricate part of the body that plays an essential role in social functioning, expression, productivity and interactions with our environment[1]. Various degree of soft tissue defects are encountered in our daily practice. The principle of basic soft tissue coverage includes adequate surgical debridement, early and appropriate antibiotics, immobilization, obliteration of dead space, drainage when indicated and coverage of the wound with well vascularized tissue[2].

Full thickness soft tissue hand injury is a challenge for surgeons in rural area without

easy access to microsurgical expertise[3], Microvascular free tissue transfer has been a major advancement in the treatment of soft tissue defects of the hand[4]. Logistic and socioeconomic constrains leave surgeons in dilemma and previously resulted in amputation of the hand or skin grafting which had inferior outcomes[5]. Application of an easily reproducible local flap technique is surely an added armamentarium for surgeon in rural setting to salvage the limb[6]. Herein, we would like to report a case of severe degloving injury of right hand reconstructed with an axial based abdominal flap to salvage his hand[7].

CASE PRESENTATION

A 10-year-old Bajau ethnic boy involved in motor vehicle accident and sustained degloving injury to dorsum of right hand with full thickness skin loss, subtotal extensor tendon loss of index and little finger (Figure 1). First stage (at hospital) involved surgical wound debridement followed by tagging of tendon with nylon sutures. Subsequently he was on daily dressing followed by negative pressure wound therapy as part of wound bed preparation (Figure 2). Following counselling on the functional benefits of a flap, parents agreed for flap reconstruction using abdominal flap and tendon reconstruction using tensor fascia lata (Figure 3).

Upon achieving a favourable bed, we proceeded with the soft tissue reconstruction of dorsal aspect of right hand with abdomen flap and tendon reconstruction with tensor fascia lata (Figures 3 and 4). Flap planning was done with outlining the left superficial circumflex iliac vessel using a handheld Doppler (Echo Sounder, Hadeco). Tubed flap design was made on the left groin and flap was raised at the sub-fascial plane (Figure 5). Flap was inserted to the defect followed by partial closure of the donor defect done in layers. Right upper limb attached to the flap was immobilized with a custom-made splint and kept in position for three weeks, care was taken not to kink the pedicle. Flap division and refashioning was done three weeks later (Figures 6 and 7). Skin grafting was applied at a few raw areas. Post debridement with extensor tendon reconstruction (tensor fascia latae) was done (Figure 8). He was advised for active and supervised physiotherapy and was discharged well. The cosmetics appearance of the right hand was good (Figure 9). The donor's scar site looked healthy (Figure 10).

During the last review, the patient could achieve acceptable range of motions of the wrist and fingers. Above all, he could use his hand for basic daily usage, whereby he is able to hold a cup and able to do legible handwriting.

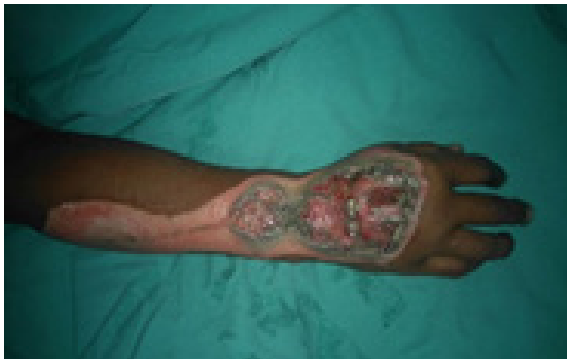

Figure 1 Initial wound (degloving injury of the dorsum of the right hand

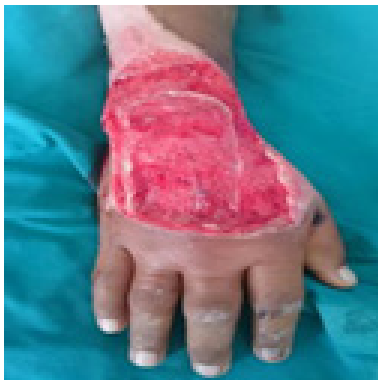

Figure 2 Wound bed post vacuum-assisted closure dressing for a week duration

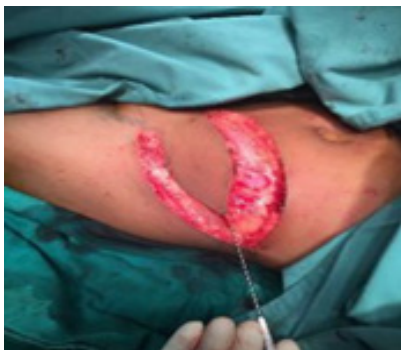

Figure 3 Flap preparation done by outlining the left superficial circumflex iliac vessels using a handheld Doppler

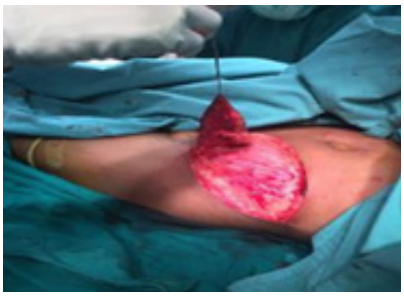

Figure 4 Abdominal flap with pedicle harvested

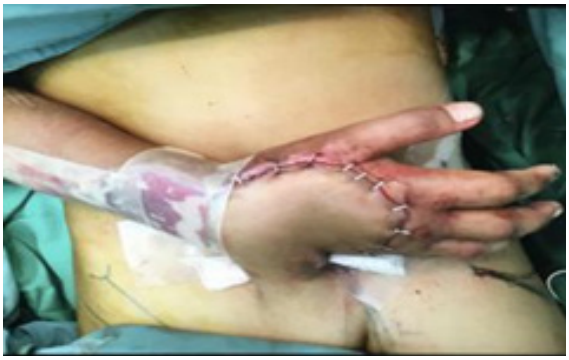

Figure 5 Flap inset to the defect followed by partial closure of the donor defect done in layers

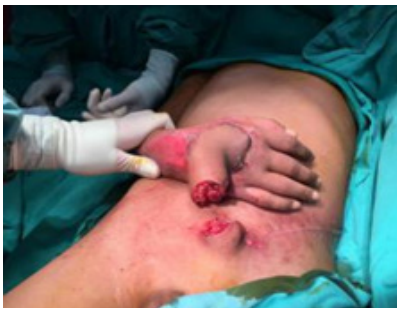

Figure 6 Detachment of matured flap

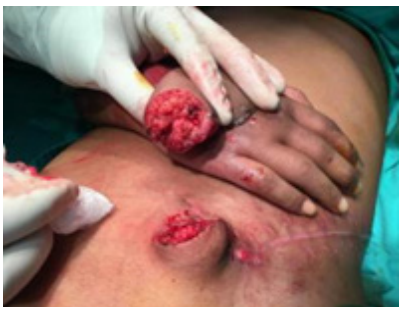

Figure 7 Detachment of matured flap

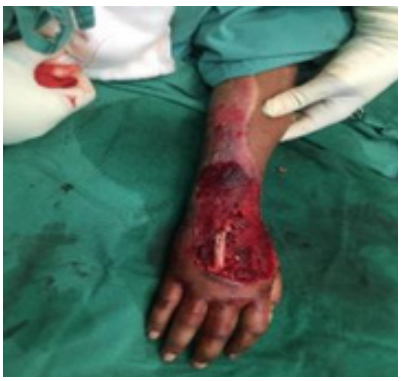

Figure 8 Post-debridement with extensor tendon reconstruction (tensor fascia latae)

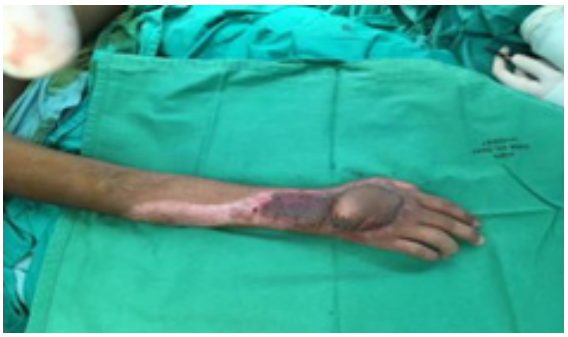

Figure 9 Final product of the flap

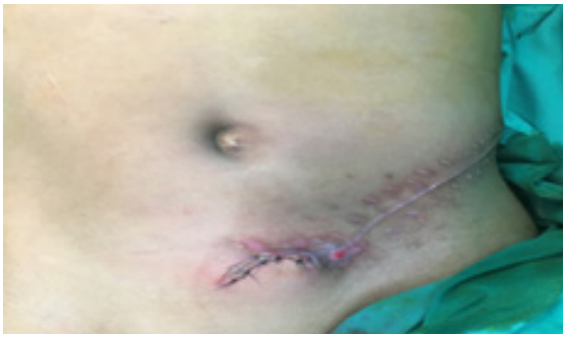

Figure 10 Donor's site scar

DISCUSSION

Dorsum of the hand has complex anatomy and is covered by thin pliable skin envelope. Any form of trauma risks the exposure of these structures which is responsible for the fine motor movement of the hand. Skin grafting produces inferior outcome and has higher risk of tethering of tendon which prevents its free gliding movement[7]. Reconstruction of full thickness defect using a distant pedicled flap is an option when free tissue transfer facilities are not available.

The constant anatomy of the abdominal flap and the ease of raising the flap will surely become handy when dealing with full thickness defect of the hand. Besides that, this flap provides adequate bulk of tissue and contours very well to the skin of the dorsum of hand. Despite the disadvantage of two-staged surgery and need for immobilizing the upper limb for three weeks, we performed abdominal flap which is surely far superior to skin grafting which will cause problem to the tendon gliding that leads to significant functional deficit[8].

Covering soft tissue defects remain challenging for orthopaedic surgeons, especially those in resource-challenged facilities[2]. Staged abdominal flap is an armamentarium in the reconstruction for full thickness dorsum of hand defect especially in remote area when microsurgical facilities are not easily available.

Many of such hand defects cases could be resolved simply and with good outcomes on a more local level if the surgeons at the smaller facilities were trained in the use of flaps and the principles of basic soft tissue coverage[2]. Furthermore, medical officers in rural settings would be able to perform staged abdominal flaps, provided they are given training and exposure.

CONCLUSION

Hand defects could also be resolved successfully by using abdominal flap in remote area with limited microsurgical facilities.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this case.

CONSENTS

Written informed consent was obtained from the patient to publish the case with its related pictures. A copy of the written consent is available for review by the Chief Editor.

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AUTHORS' GUIDELINES
Instructions for authors

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The length of the original articles, excluding References, should not normally exceed 2700 words. Brief and case reports are inevitably shorter. Manuscript should contain the following sections in the order listed.

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The title of the article. Concise titles than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying randomized controlled trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.

Authors names and institutional affiliations.

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Abstract

Abstract should be one paragraph, without sections and provide information on: **Background/ objective** of the study, **Materials and Methods** used (selection of study subjects or laboratory animals, observational and analytical methods etc.), **Results** (main findings giving specific effect sizes and their statistical significance, if possible), and **Conclusion** (it should emphasize new and important aspects of the study or observations). Altogether, abstract should not exceed 250 words. Do not usereference citation in Abstract.

Keywords

The authors should provide 3 to 5 keywords for indexing purpose. These words have to be selected from the terms recommended in the last version of the Medical Subject Headings (MeSH) (http://www.nlm.nih.gov/mesh/meshhome.html).

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It should provide the background of the study (i.e., the nature of the problem and its significance). State the specific purpose or research objective, or hypothesis tested, the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be made clear, and any pre-specified subgroup analyses should be described. Only exact pertinent references should be provided and do not include data or conclusions from the work being reported.

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- Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of p values, which fails to convey important information about effect size. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

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Describe your results in words, with reference to tables or graphs or figures when necessary. Present your results in logical sequence, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations. When data are summarized in the Result section, give numeric results not only as derivatives (e.g. percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain the argument of the paper and to assess its support. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables.

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Emphasize the new and important aspects of the study and the conclusions that follow from them. Do not repeat in detail data or any material given in the Introduction or the Results section. For experimental studies it is useful to begin the discussion by summarizing briefly the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.

ACKNOWLEDGEMENTS

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Matos V, Drukker A, Guignard JP. (1999). Spot urine samples for evaluating solute excretion in the first week of life. Arch Dis Fetal Neonatal Ed 80: F240 – 2.

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