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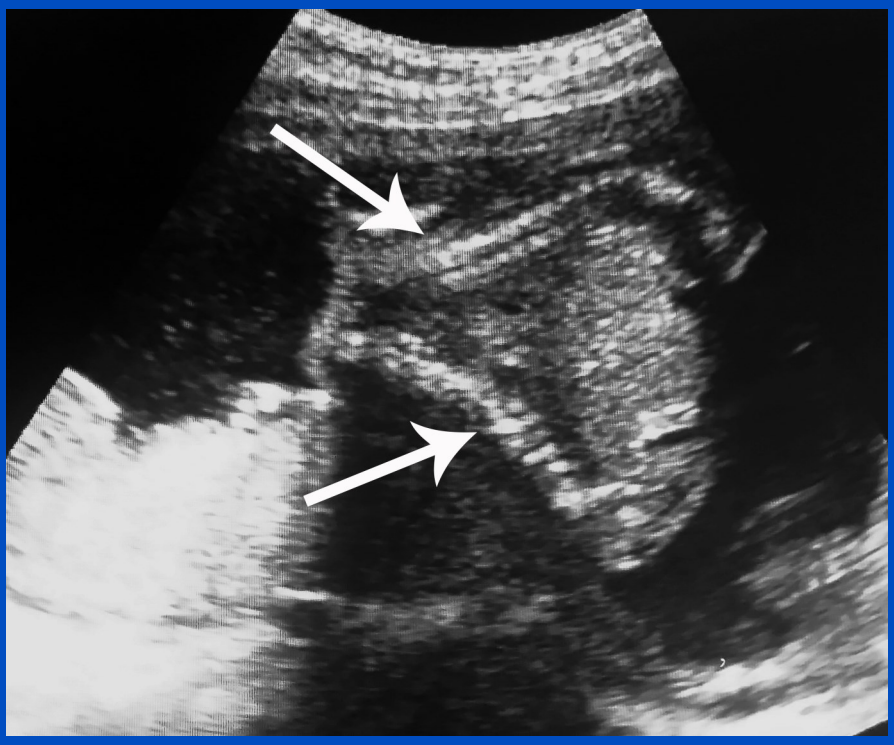

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The Brunei International Medical Journal (BIMJ) is a six monthly peer reviewed official publication of the Ministry of Health under the auspices of the Clinical Research Unit, Ministry of Health, Brunei Darussalam.

The BIMJ publishes articles ranging from original research papers, review articles, medical practice papers, special reports, audits, case reports, images of interest, education and technical/innovation papers, editorials, commentaries and letters to the Editor. Topics of interest include all subjects that relate to clinical practice and research in all branches of medicine, basic and clinical including topics related to allied health care fields. The BIMJ welcomes manuscripts from contributors, but usually solicits reviews articles and special reports. Proposals for review papers can be sent to the Managing Editor directly. Please refer to the contact information of the Editorial Office.

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Acknowledgements
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RIPASA Treatment Without Operation (TWO) – A Non-Inferiority Prospective Randomised Clinical Controlled Trial of Antibiotic Non-Operative Management Strategy versus Surgery Management Strategy for Early Uncomplicated Acute Appendicitis.

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ABSTRACT

Introduction: The role of an antibiotic non-operative management strategy (AMS) in managing early-uncomplicated acute appendicitis (EUAA) is still debatable and most meta-analysis have not shown significant benefit of AMS over SMS, partly due to variable treatment efficacy, high recurrence rate within a year and a lack of agreement of whom would constitute a group of EUAA. This research proposal provides the framework to investigate the role of AMS versus Surgical Management Strategy (SMS) in patients with clinical diagnosis of EUAA. The primary aim of the study is to compare treatment efficacy of both treatment arms.

Design: A single centre, prospective non-inferiority Randomised Controlled Clinical Trial comparing AMS with SMS in the main tertiary referring hospital in Brunei Darussalam.

Participants and Interventions: Patients aged 13 and above with a clinical diagnosis of EUAA with RIPASA score from 7.5 to 11.5, will be invited to participate in the trial. Once consented, participants will be randomised to either AMS or SMS using a computer-based randomisation allocation programme. Recruitment is planned to start in October 2017 and will recruit 228 patients over a 2 year period. Patients randomised to the AMS arm will receive amikacin IV 1.5mg/kg/day given in 2 doses for 48 hours followed by oral ciprofloxacin 500mg twice daily for 5 days. Patients randomised to SMS will receive standard antibiotics combination of IV cefuroxime 1.5g and metronidazole 500mg three times a day and surgery.

Outcomes: Primary outcome is treatment efficacy within 30 days in each arm and compliance with RIPASA guidelines. Secondary outcomes include length of stay, 30-days treatment related complications, recurrence rate from 1 month up to 1 year, treatment cost, defining effective RIPASA score range for AMS and medical sick leave days taken.

Analysis: Data analysis will be carried out based on intention-to-treat principle combine with per protocol analysis for non-inferiority of AMS arm. Non-inferiority margin is set based on FDA approved 50% reduction of treatment efficacy for AMS arm

Novelty and Significance: The novelty of this research study is that it is the only non-inferiority RCT comparing AMS with SMS that uses a clinical prediction rule (CPR) such as RIPASA Score for clinical diagnosis of EUAA.

The significance of this research study is that it will complete the final and third part of the creation and validation of the RIPASA score as a CPR by assessing its impact on change behavior in managing patients with EUAA with AMS rather than SMS and hence improves patient outcomes by reducing unnecessary negative appendicectomy rate, complications related to undergoing emergency appendicectomy and ultimately reducing cost of managing acute appendicitis surgically.

Keywords: Appendicectomy, Antibiotic Management strategy, Clinical Prediction Rule, Early Uncomplicated Acute Appendicitis, RIPASA Score.

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INTRODUCTION

Acute appendicitis (AA) is a very common surgical emergencies. The life time prevalence of AA is approximately 1 in 7 with a reported incidence of 1.5-1.9 per 1000 in male and female population and is approximately 1.4 times greater in men than in women. [1,2]

Diagnosis of AA can be difficult to establish, particularly in the young, elderly and female of reproductive age where a host of other genitourinary and gynaecological inflammatory conditions can also present with signs and symptoms similar to AA.[3] Improving diagnostic accuracy through radiological investigations may lead to delay in appendicectomy and risks appendicular perforation and sepsis, which increases morbidity and mortality.[4] Similarly early appendicectomy in favour of diagnostic accuracy may lead to an increase in unnecessary surgery and reported negative appendicectomy rate is 20-40%.[5]

Several clinical prediction rules (CPR) such as the Alvarado, modified Alvarado or RIPASA scores have been developed to aid in the rapid and accurate diagnosis of AA.[5-10] The RIPASA score has been well validated across the world with sensitivity, specificity and diagnostic accuracy of 98%, 82% and 92% respectively and is significantly better at diagnosing AA than Alvarado score and with significantly reduced negative appendicectomy rate.[9–33]

The standard management of AA has remained unchallenged since it was first introduced in the late 19th century, largely because of the belief that if left untreated surgically, acute uncomplicated appendicitis will progress to perforation and peritonitis with increased morbidity and mortality.[34] However since 1990s, antibiotic non-operative therapy has been increasingly proposed as an alternative management strategy for early uncomplicated acute appendicitis (EUAA), driven by evidence from the routine conservative management of diverticulitis (with or without perforations) with antibiotics. [35]

However, despite multiple randomised controlled trials (RCT) and meta-analysis, the role of antibiotics in the management of EUAA remains controversial. [36–48] Earlier RCT have reported treatment efficacy for antibiotic non-operative management strategy (AMS) of EUAA as high as 88-91% with recurrence rate of acute appendicitis at 13-14% at 1 year follow up, which supported the AMS.[37,38] However in one RCT, the high treatment efficacy of 91% was based on per protocol analysis which is generally not recommended but based on intention-to-treat analysis, the efficacy for AMS dropped to 48%.[38] More recent RCTs comparing AMS versus early surgery management strategy (SMS) have not confirmed the non-inferiority status of the former strategy.[39-41] These later findings have also been supported by multiple recent meta-analysis.[42–48]

Thus this study is designed with the primary objectives of investigating the efficacy of AMS compare to SMS in patients with a clinical diagnosis of EUAA and effectiveness of RIPASA score in guiding clinical management decisions.

METHODOLOGY

Trial Design

This study is designed as a single centre, non-inferiority, prospective randomised clinical controlled trial to compare 2 management strategies for suspected EUAA, AMS versus SMS, using RIPASA score to identify the group of patients with EUAA and to monitor progression of disease and guiding surgical decision based on the participants' RIPASA score.

Population and Study Setting

The study setting is based at the tertiary referral centre of the Department of General Surgery at Raja Isteri Pengiran Anak Saleha (RIPAS) Hospital. All staffs of the Department

of General Surgery and Accident & Emergency Department at RIPAS Hospital will be brief of the trial design and purpose.

Eligibility Criteria

All patients presenting to Accident & Emergency Department at RIPAS Hospital, with right iliac fossa pain suspected of acute appendicitis,

Inclusion criteria

1. More than 12 years of age,
2. Clinical diagnosis of EUAA with confirmed RIPASA score of 7.5 to 11.5, by oncall surgical doctor

Exclusion criteria

1. 12 years of age or less,
2. RIPASA score 7 or less, or greater than 12,
3. Confirmed diagnosis of acute complicated appendicitis with perforation (based on ultrasound or CT investigation) or signs of generalized peritonitis.
4. Refusal to consent for study

Recruitment and Retention

Patients with right iliac fossa pain will be triaged and seen by the Casualty Officer on duty. RIPASA score will be derived. Patients with RIPASA score between 7.5 to 11.5 will be referred onto the on-call surgeon on duty for recruitment to the study. Antibiotics will be withheld until patients have been seen by the on-call surgeon and the RIPASA score has been confirmed to be between 7.5-11.5. The on-call surgeon will inform and explain to the patient and family of the study and a study information sheet will be provided to the patient and family. Upon written signed consent, patients will be randomised to either arms – AMS or SMS.

Allocation concealment

A variable block randomisation sequence stratified to two RIPASA score range, 7.5-9.5 and 10.0-11.5, will be used to randomly allocate participants to either AMS or SMS. Randomisation codes will be generated using computer generated variable random sequence. The block randomisation sequence will be contained within a programme specifically designed for randomisation allocation. Access to the programme is via secured Log-in, which can only be accessed by doctors from the Department of General Surgery, using individually provided username and password. The programme will screen all potential patients to ensure they satisfy the inclusion and exclusion criteria before accessing their randomisation allocation arm and code. Once the randomisation code and arm have been obtained, the on-call surgeon will inform the participants of their allocation.

Study Protocol

Upon allocation, the patient will then be admitted to surgical wards. Patients randomised to AMS arm will receive the allocated antibiotic treatment. (Figure 1 – Consort flow chart). Those randomised to SMS arm will receive the usual Departmental antibiotic policy of preoperative antibiotics prior to appendicectomy.

Patients randomised to AMS arm

For patients in the AMS arm, the RIPASA score will be repeated to monitor progression of the patient's condition after 24 hours. If RIPASA score remain stable or decreasing, the patient will continue on the allocated intravenous (iv) antibiotic treatment. If RIPASA score is increasing but remain below 11.5, the team looking after the patient can consider ordering further investigations such as ultrasound or CT scan to confirm the diagnosis based on the RIPASA score guidelines, but patient will continue at this point on the antibiotic. If the RIPASA score increases to above 12, the surgeon can consider appendicectomy as suggested by RIPASA score. Alternatively the surgeon can consider surgery for RIPASA score between 7.5 and 11.5 if there are clinical signs of perforation or generalised peritonism.

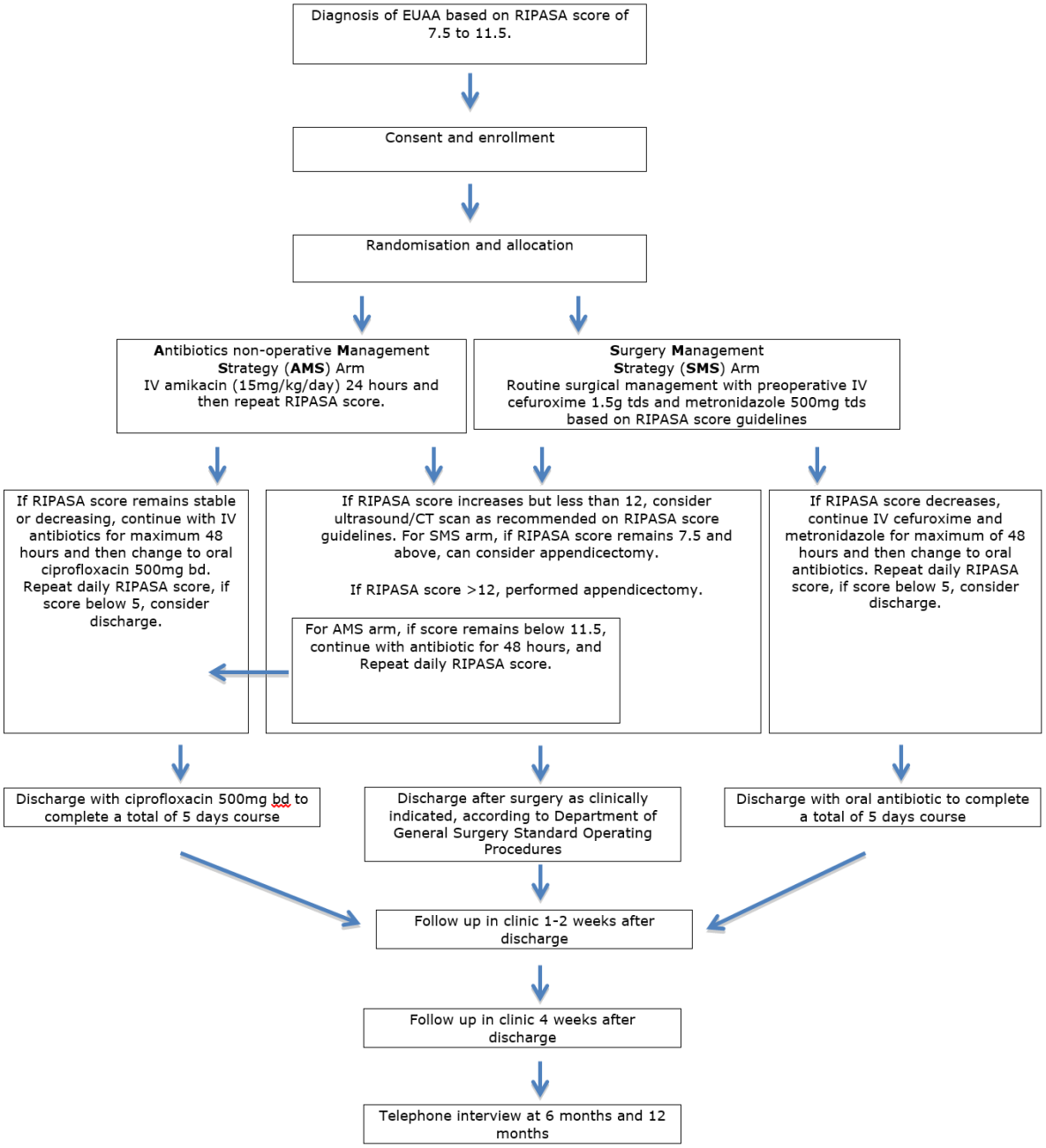

Figure 1: RIPASA TWO Non-Inferiority Prospective Randomised Clinical Controlled Trial study protocol consort diagram.

For patients in the AMS arm who have not cross over to surgery, they will continue with iv antibiotics for 48 hours and if symptoms improved with decreasing RIPASA score to below 7.5, the antibiotic will be changed to oral route and patient monitor. If RIPASA score goes below 5, patient can be considered for discharge and follow up in 1 week in clinic with oral antibiotic for 5 days.

Patients randomised to SMS arm

For patients randomised to SMS arm, the patients will receive the usual Departmental antibiotic policy as preoperative antibiotics prior to surgery. If patients are admitted during office hours or before 12 midnight, appendicectomy can be considered immediately. For admission after 12 midnight, the patients will remain on preoperative antibiotics and get review the

next morning with repeat RIPASA score. If RIPASA score is increasing but remain below 11.5, the team looking after the patient can consider ordering further investigations such as ultrasound or CT scan to confirm the diagnosis based on the RIPASA score guidelines, but patients will continue at this point on the antibiotic. Alternatively the surgeon can consider surgery if there are clinical signs of perforation or generalised peritonism. If the RIPASA score increases to above 12, the surgeon can consider appendicectomy as suggested by RIPASA score guidelines.

For patients in the SMS arm whose symptoms improved with decreasing RIPASA score to below 7.5, their antibiotic will be changed to oral route and patient monitor. If RIPASA score goes below 5, patient can be considered for discharge and follow up in 1 week in clinic with oral antibiotic for 5 days.

Antibiotic

Selection of the antibiotic of choice for the AMS arm is based on the microbial antibiotic sensitivity from pus swab taken for all appendicectomy specimens from previous year (2016: Figure 2). Microbiological data showed that the 3 commonest microbes were E. Coli, Pseudomonas aeruginosa and Klebsiella pneumonia. Based on recommendation from the clinical microbiologist, IV Amikacin 15mg/Kg/day given in two divided doses per day for the first 48 hours and then converted to oral ciprofloxacin 500mg twice daily for 5 days will be the antibiotic regime for AMS arm.

A prospective registry for microbial antibiotic sensitivity of all appendicectomy specimens from the trial will be kept to monitor changes in antibiotic sensitivity. Based on data from this registry, the AMS antibiotic proposed can be changed as the trial progresses. Any changes propose will be submitted to MHREC for approval.

				S %	I %	R %
Escherichia coli	39	Amikacin	37	94.872	2.5641	2.564
		Amoxy/Clavu Acic	28	71.795	15.385	10.26
		Ceftazidime	34	87.179	5.1282	7.692
		Cefepime	19	48.718	0	2.564
		Cefoperazone	31	79.487	5.1282	15.38
		Ciprofloxacin	30	76.923	0	23.08
		Ceftriaxone	33	84.615	2.5641	10.26
		Cefuroxime oral	20	51.282	28.205	10.26
		Cefuroxime parer	31	79.487	0	10.26
		Ertapenem	19	48.718	0	0
		Gentamicin	31	79.487	0	20.51
		Imipenem	39	100	0	0
		Meropenem	39	100	0	0
		Netilmicin	34	87.179	2.5641	0
		Piperacillin	11	28.205	2.5641	38.46
		Co-trimoxazole	18	46.154	0	46.15
		Piperacillin/Tazob	12	30.769	0	0
		Ampicilin/Sulbact	12	30.769	28.205	15.38
Pseudomonas aerugi	9	Amikacin	8	88	0	0
		Ceftazidime	9	100	0	0
		Ciprofloxacin	9	100	0	0
		Gentamicin	9	100	0	0
		Imipenem	9	100	0	0
		Meropenem	9	100	0	0
		Netilmicin	7	77	0	0
		Piperacillin/Tazob	3	100	0	0
Klebsiella pneumonia	4	Amikacin	4	100	0	0
		Amoxy/Clavu Acic	4	100	0	0
		Ceftazidime	4	100	0	0
		Cefoperazone	4	100	0	0
		Ciprofloxacin	4	100	0	0
		Ceftriaxone	4	100	0	0
		Cefuroxime oral	3	75	25	0
		Cefuroxime parer	4	100	0	0
		Gentamicin	4	100	0	0
		Imipenem	4	100	0	0
		Meropenem	4	100	0	0
		Netilmicin	3	75	0	0
		Piperacillin	3	75	0	25

Figure 2: Antibiotic sensitivity for common microbials isolated from pus swab taken at time of appendicectomy for year 2016.

Outcomes

The primary outcomes are treatment efficacy (Rate of treatment success) between the two management strategies, AMS versus SMS within 30 days of randomisation and effectiveness of RIPASA score in guiding clinical management decisions.

Treatment efficacy in the AMS group is defined as successful treatment of EUAA with antibiotics from time of randomisation till discharge and follow-up to 30 days without incurring surgery and cases of negative appendicectomy if surgery is performed. Treatment failure for AMS is defined as cases where surgery is carried out despite antibiotic therapy from time of admission or surgery performed at anytime up to 30 days follow up after discharge with histology confirmation of acute, suppurative or gangrenous or perforated appendicitis.

Treatment efficacy for SMS group is defined as all cases of confirmed acute, suppurative or gangrenous or perforated appendicitis on histology specimen. Treatment failure for SMS group is defined as cases of neg-

ative appendicectomy and cases successfully treated with antibiotics and discharged and follow-up to 30 days without incurring surgery. Negative appendicectomy is defined as an unnecessary operation performed where the outcome is one of normal appendix or periappendicitis on histological examination.

Effectiveness of RIPASA score in guiding clinical management decisions will be based on compliance and adherence to RIPASA score guidelines. Non-compliance or non-adherence is defined as action performed outside the RIPASA score guidelines, for example, not performing appendicectomy for cases with RIPASA score >12 or performing surgery when RIPASA score is less than 7.5 and this will be considered as loss of effectiveness.

Secondary outcome measures are length of hospital stay, 30 days treatment related complications (For AMS group: appendiceal perforation, peritonitis, abscess or phlegmon formation and for SMS group: surgical site infection, bowel obstruction secondary to adhesions or sepsis), recurrence rate* at any time of follow up > 1 month, and up to 12 months, number of medical sick leave days taken related to condition of study, defining a group with RIPASA score range where AMS is most beneficial and treatment cost in US dollar, calculated at completion of study and follow up at 1-year post randomisation, which will include all radiological examinations carried out during the study period related to the condition of study.

Data collection and management

All clinical details, RIPASA score, daily entry, surgery details, discharge details, complications and outcomes will be entered into Bru-HIMS patient electronic management system and can be retrieved later for analysis. Data entry into Bru-HIMS will be carried out daily by the attending surgeon and his/her team and checked for completion and accuracy by one of the investigators (or research assistant if this is available). Data will be entered into an Access database/Excel for analysis at the end of the study.

Bru-HIMs patient electronic management system can only be accessed onsite via intranet and is protected by firewall. All computers are protected by antivirus software. The Access database/Excel file will be kept in a laptop and locked in a secure office at the end of everyday by the principal investigator.

Statistical methods

Sample size calculation

Based on our previous study, the expected negative appendicectomy rate based on the RIPASA score was 14.7%, giving surgical treatment efficacy of 85.3%.[10] Hence using the FDA approved non-inferiority margin of 50% reduction in efficacy, we would accept an approximate 7.3% reduction of treatment efficacy for the AMS, thus the non-inferiority margin will be set at 22% and a treatment failure between 14.7-22% will be considered as confirmation of non-inferiority. [49] A treatment failure of less than 14% will be considered as superiority. Thus based on a difference in treatment efficacy rate of 7.3% (22% vs 14.7%), with a sample size powered at 80% at 5% significance, the sample size needed to show non-inferiority is 91 patients in each group.[50] Assuming a dropout rate of 25%, we plan to recruit a total of 228 patients, based on a 1:1 recruitment; each arm will have 114 patients.

On completion of the study, the main analysis will be carried out based on intention-to-treat principle but per-protocol analysis will also be carried out to ensure robustness of the results and that substandard treatment has not been provided to the SMS arm. The intention-to-treat analysis will include all ran-

*(Recurrence is defined as readmission for suspected AA or proven AA on histological specimen following surgery for AMS group after discharge. Recurrence will not be categorise as treatment failure in the AMS group since the appendix has not been surgically removed and patients in this group although at a higher rate of recurrence of about 13-14% at 1-year follow up, does not represent failure of treatment for the initial episode of acute appendicitis. [47,48])

domised patients with outcome results, excluding those lost to follow-up and those who have withdrew from the study and have prespecified that they do not wish for their data to be used.

All statistical analysis will be performed using SPSS statistical program. Categorical data will be presented using frequencies and percentages. Continuous data will be presented as mean ± SD. Statistical analysis for categorical data will be carried out using Chi Square exact test. Differences between groups with normally distributed variables will be tested using independent sample t-test. Variables with no normal distribution will be tested using Mann-Whitney test. Non-inferiority for AMS will be tested using one-sided Wald tests with an α level of 0.05.

Duration of Study

Based on our previous study, we recruited 200 consecutive patients over 8 months.[10] But only 192 were included in the study final analysis. Out of these 192 patients, 96 had RIPASA score from 7.5 to 11.5, which accounted for over 50% of the study sample size of 192. Thus for a sample size of 228, we expect to recruit the required sample size over a period of 19 months. Hence the study will be expected to complete within 2 years.

Funding

This study will be carried out by the Department of General Surgery and in collaboration with Accident and Emergency Department. Deputy Head of Department of Accident and Emergency Department as Co-Investigator for this trial, will oversee the recruitment process in Accident and Emergency Department. The Head of Department of General Surgery as Co -Investigator, will oversee the recruitment and allocation of treatment group when patients are admitted to General Surgical Wards.

Care and subsequent follow up provided to participants will be part of the clinical care package provided by the Department of General Surgery which should not be any different from the general care provided to other patients. The Department of General Surgery has been given permission to conduct this trial by the RIPAS Hospital Administrative Head. Hence cost of antibiotics and any investigations will be covered by the hospital as routine cost of managing patients admitted with AA in general.

No other sources of funding from any external parties or organisations will be sought for, to conduct this study.

RIPASA Score Registry

Participants who have not consented to be recruited for the trial or those who withdraw from the trial after randomisation and are not analyse in the trial, as well as those who are excluded from the trial (see exclusion criteria) will be entered into the RIPASA Score Registry. Data from this registry can be analysed at a later date to obtained real world experience of RIPASA score practice as well as comparison of the two arms.

Interim Analysis

Interim analysis will be conducted at 2 time points. For changes to antimicrobial sensitivity, the interim analysis will be conducted at every 6 monthly and any changes will be discussed with the DSMB for proposed changes to the antibiotic regime. Proposed changes and all interim reports will be submitted to MHREC for approval. The main study interim analysis will be conducted at 1-year post recruitment to assess safety efficacy of the trial. This is to ensure that we are not getting more cases of acute complicated appendicitis (ACA) in the AMS arm, which is set at a cutoff of 30%. This 30% cutoff is chosen as it would mean a treatment efficacy difference of 15% from current surgical management based on the RIPASA score of 14.7% failure rate, suggesting that the AMS arm is no better than placebo.

Ethical Consideration

Participants' Rights, Consent and Confidentially

This study will be conducted in accordance with the principles of Good Clinical Practice Guidelines according to the Declaration of Helsinki, to ensure that all clinical research participants are not exposed to undue risk, and the data generated from the research are valid and accurate.[51]

The participant's free and voluntary involvement in the trial will be stressed at the time of recruitment. The patients will be reassured that their decision whether or not to take part or continue in the study will not affect the standard or availability of their care in anyway. The participants and their family will also be informed that they can withdraw from the study at anytime if they feel the need to do so and that they can contact the MHREC via address and email given on the participants information sheet, should they have any concerns during working hours. Participants who withdrew from the trial will not be included in the final analysis if they have specified instruction not to be included but their data will be entered into the RIPASA Score Registry.

Patients' confidentiality will be maintained by using their randomised allocation code as their unique identifier, linked to their Bru-HIMs number. Patient's name will not be recorded down in the Access database/Excel file to ensure confidentiality. Bru-HIMs number is secure as access is via intranet and only accessible via allocated staff's username and password.

Ethics approval for the study was approved by MHREC based in RIPAS Hospital (MHREC/2017/3/4) and the study is registered with the ClinicalTrial.gov registry for RCT (NCT03169114).

Reimbursement

There will be no proposed payment or reimbursement for the participants. All care and follow up will be carried out as part of the Department of General Surgery standard clinical care provision upon recruitment and admission. Private patients who consented to be recruited will have to cover the usual cost of their care and surgery during their hospital stay and subsequent follow up.

Monitoring (Interim data, auditing, Harm and adverse event reporting)

Monitoring for safety will be carried out throughout the duration of the study as part of the participants' clinical care during their admission and follow up. Current standard of care for patients seen in Accident & Emergency Department at RIPAS Hospital who are suspected to have acute appendicitis generally will have a RIPASA score taken at time of consultation and based on the RIPASA score, the appropriate action taken based on the RIPASA guidelines.[10] For RIPASA score 7.5 or greater, patients are given iv antibiotics prophylactically and referred onto the on-call surgeon who will review the patient and reassess their RIPASA score. Once confirmed to be 7.5 or greater, the patients will be admitted to the surgical ward and a decision for appendicectomy will be made by the on-call surgeon or upon discussion with the consultant on-call. If there is any uncertainty, an ultrasound or CT abdomen may be requested to confirm the diagnosis of acute appendicitis. If the on-call surgeon feels that the patient has ACA, the decision will be to consent the patient for appendicectomy.

The same standard of care pathway above will be applied to all patients recruited to the trial. Thus there should not be any major concerns in general with regards to care provided to patients involved in the trial. The only major concern is for the AMS arm, which is the possibility of progression of disease to ACA with perforation and generalized peritonitis. The study protocol includes daily assess-

ment of RIPASA score to monitor progression of participants condition and guided by RIPASA score guidelines to cross over to the SMS arm for appendicectomy or not. If the RIPASA score progressed to above 12, then based on the RIPASA guidelines, the indication is for performing surgery and patients will cross over to SMS arm. For scores up to 11.5, if the trend for the RIPASA score is increasing, management options include radiological investigations such as ultrasound or CT scanning and if confirmed presence of acute appendicitis and patients' clinical picture is not improving, then based on the RIPASA score guidelines, the attending surgeon has the option of performing surgery. If radiological investigations are negative, options is either continue with antibiotics or if clinical indications is there, to proceed with surgery.

Harm and adverse events monitoring will be carried out by 3 senior clinicians (Gastroenterologist Physician, Orthopaedic Surgeon and Clinical Microbiologist), as part of the DSMB and are not involved with recruitment or as investigators. The principal investigators will provide the DSMB with interim data at the mid point of the study period (1-year interim analysis) or every 6 months and whenever requested by DSMB, on: recruitment and retention rates, any protocol violations and any harm or adverse events and other unintended events, which will be reported as soon as it is ascertain to have occurred.

The main function of the DSMB is to alert both the principal investigator and MHREC via interim reports (6 monthly and at 1 year) on issues of participant recruitment, trial conduct and safety of participants. Any serious adverse events reported by participants or observed by the staffs or investigators will be clearly documented on pre-specify adverse events clinical trial forms and reported to the principal investigator who will notify the DSMB immediately (during working hours) or within 24 hours. Any adverse events deemed severe by the DSMB will be discussed with the principal investigator and reported directly to the MHREC. The board may recommend trial termination or suspension pending an MHREC review.

Protocol amendments

Any protocol amendments will be made by applications through MHREC and these changes will be communicated to the DSMB. Protocol amendments which affect participants in terms of what is required of them or what is consented to will be communicated to the participants with renewed consent sought where appropriate. Trial registries will be updated and materials amendments noted in any subsequent publications.

Ancillary and post-trial care

Any post-trial care required by participants will be provided by the admitting surgeon as part of RIPAS Hospital patient care policy, which will not be any different from other patients not taking part in the trial.

Dissemination Policy

The protocol for this study has been registered on ClinicalTrials.gov under the ClinicalTrial.gov identifier number of NCT03169114. The findings of this study will also be presented at local, regional and international conferences. The protocol and outcomes of the study will be published in local and international journals.

Expected Outcomes, Novelty and Significance

Based on our previous publications, the negative appendicectomy rate based on RIPASA score is 14.7%, giving surgery a treatment efficacy rate of 85.3%.[10] Accepting an increase of 50% more failure rate for AMS arm would give a treatment failure rate of about 22% and a treatment efficacy rate of 78% for AMS arm. From our previous publications, for RIPASA score range from 7.5 to 11.5, the rate of perforated and gangrenous appendicitis, a

group, which is unlikely to benefit from antibiotic therapy alone, is 21%. The remaining 79% consisted of EUAA, which is the group that will most likely to benefit from AMS and hence giving a probable treatment efficacy rate of 79%, which is just 1% more than the predicted non-inferiority treatment efficacy rate. Thus we are confident our trial will achieve non-inferiority of AMS to SMS.

Since the trial will be conducted based on RIPASA score guidelines, all doctors, surgeons and staffs will be fully brief and instructed to achieve compliance to the RIPASA score guidelines. Any deviation or non-compliance will be considered as failure of RIPASA score to influence change on physician behavior. To ensure compliance, weekly support and reinforcement of compliance sessions will be carried out in the Department of General Surgery weekly meeting.

The novelty of this research study is that it is the only non-inferiority RCT comparing AMS with SMS, that uses a CPR such as RIPASA Score to define a group with EUAA. Previous and pending non-inferiority RCTs on the same theme of comparing AMS with SMS have always used clinical judgement to define the group of patients with EUAA. As most cases of AA are seen first by the most junior member of the surgical team, there is always a margin of error in defining this group. Using a CPR such as RIPASA score with a define range of score that predicts high probability of AA, will objectively eliminate this margin of error.

The significance of this research study is that it will complete the final and third part of the creation and validation of the RIPASA score as a CPR by assessing its impact on changing physician behavior in terms of an AMS for treatment of EUAA and hence improves patient outcomes by reducing unnecessary negative appendicectomy rate, complications related to undergoing emergency appendicectomy and ultimately reducing cost of managing AA surgically. Thus results of this study will go as far as to consolidate RIPASA score as a good validated and effective CPR for the diagnosis of AA, not just locally but worldwide and also determine the role of AMS in a specific group of patients with RIPASA score that defines them as EUAA.

RIPASA TWO Non-Inferiority Randomised Controlled Trial Study Group and Roles (RIPAS Hospital)

Mr CHONG Chee Fui, **Principal Investigator:** Role is to oversee the whole project and ensure data collection are kept and maintain for the duration of the trial, to liaise with DSMB members and provide interim reports to them and to MHREC via DSMB.

Mr TAN Lian Tat, HoD, Department of General Surgery, **Co-Investigator:** Role to oversee recruitment in General Surgery Department and coordination with Accident & Emergency Department.

Dr Linawati JUMAT, HoD, Accident and Emergency Department, **Co-Investigator:** Role to oversee recruitment in Accident & Emergency Department and coordination with General Surgery Department.

Recruiting, admitting and Follow up Consultant Surgeons and team

Unit 1: Samuel YAPP Kai Seng, CHONG Chean Leong and Amy THIEN.

Senior Medical Officer/Medical Officer: Role to recruit, inform and consent patients, allocate randomization, ensure minimally required trial data entry

AUNG Kyaw Phyo, KOH Kai Shing, Anis AHMED, Nurul Ayu Elmi MOHD YUNUS.

Unit 2: TAN KK, TAN Lian Tat and Mohd Ady Adillah AHMAD.

Senior Medical Officer/Medical Officer: Role to recruit, inform and consent patients, allocate randomization, ensure minimally required trial data entry

Sonal TRIPATHI, Ahamed Jiffri AHAMED MACKIE, Shahriman HUSAIN, CHUA Hong Sang.

Data Safety Monitoring Board Members

CHONG Vui Heng (Gastroenterologist)

Ketan PANDE (Orthopaedic Surgeon)

Terence Rohan CHINNIAH (Microbiologist)

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Prempreet Kaur Manjit SINGH, TEOH Jian Woei, Zakinah YAHAYA, FONG Voon Hoong, Mohd Razif MOHAMAD YUNUS

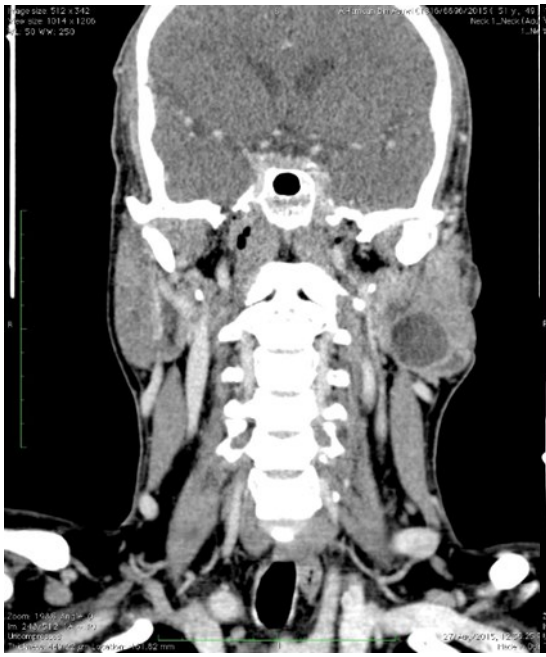

Figure 1a

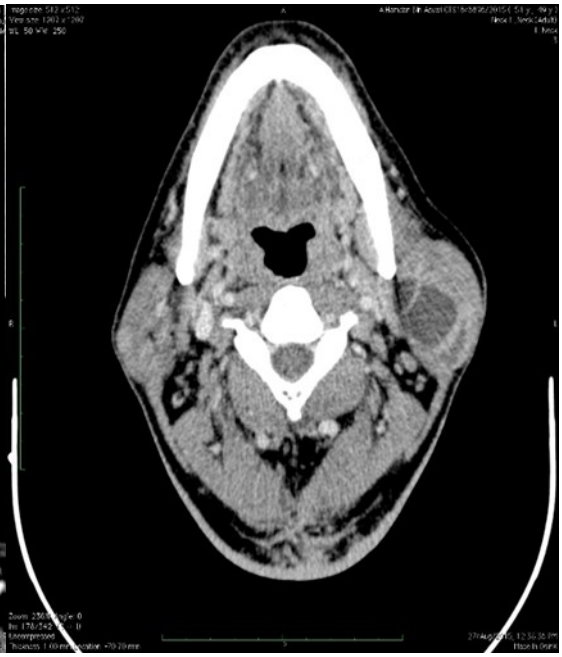

Figure 1b

A 49 years old Malay gentleman presented with left painless parotid mass of three years duration with no other significant symptoms. Patient gave a history of visiting a brothel 10 years ago. Clinical examination noted a firm and fixed left parotid mass measuring 4x4cm. CT scan of the neck confirmed a single left parotid cyst with thick enhancing wall (Figure 1a&b). FNAC of the mass showed mainly inflammatory cystic content with no malignant cells.

What is the diagnosis?

***Answer**: refer to page 144*

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Wardati Sahimin YAKOB and Mohin MOMIN

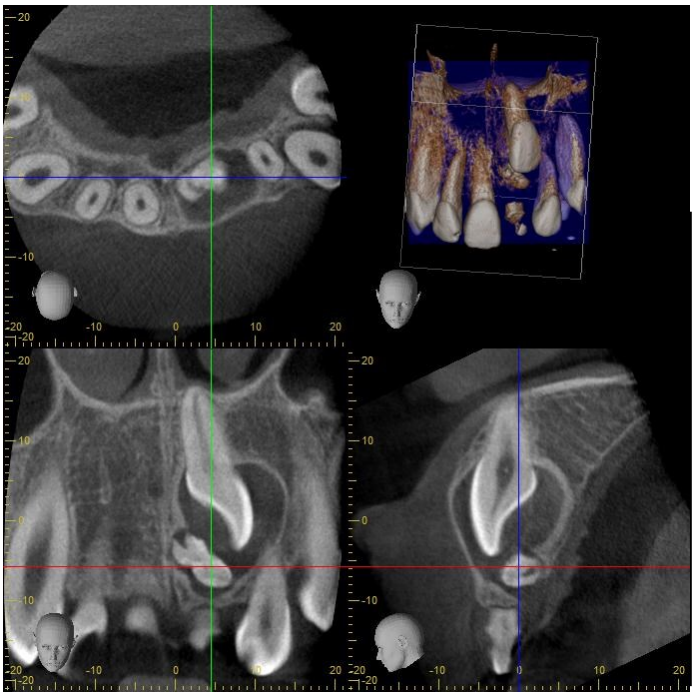

Figure 1

A 12 year old boy presented with an over-retained maxillary left primary central incisor. Clinical examination revealed the presence of all his permanent incisors except the maxillary left permanent central incisor. The crown of the maxillary left permanent central incisor was palpable on the buccal mucosa, apical to the over-retained tooth. Special investigation including cone-beam CT scan of the area of interest was requested. One of the snapshot images of the cone-beam CT is shown here.

What is the diagnosis?

Answer*: refer to page 145*

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Systemic Calciphylaxis: Diffuse Cutaneous Involvement and Ischemic Optic Neuropathy – a case report.

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ABSTRACT

Calciphylaxis, or calcific uraemic arteriolopathy, is a rare disease that is difficult and challenging to treat and has a high mortality rate. Its pathogenesis remains to be fully elucidated. Cutaneous manifestations usually predominate although systemic calciphylaxis has been reported, whereby calcifications occur in other organs, including brain, eyes, lungs, intestines and the mesentery. Treatment option is limited. The most common disease-modifying treatment used is intravenous sodium thiosulphate. We report a case of systemic calciphylaxis in a dialysis-dependent patient who presented with cutaneous lesions and later developed bilateral ischemic optic atrophy. Our case had a poor clinical outcome despite optimal supportive care with multi-disciplinary approach and four weeks of intravenous sodium thiosulphate treatment.

Keywords: calciphylaxis, systemic calciphylaxis, diffuse calciphylaxis, calcific uraemic arteriolopathy, ischaemic optic neuropathy, sodium thiosulphate

INTRODUCTION

Calciphylaxis, or calcific uraemic arteriolopathy, is a rare disease that is difficult and challenging to treat. Its pathogenesis remains to be fully elucidated, despite its well-characterized features clinically and histologically. The disease was first described by Selye et al. in 1961 in a condition observed in rodents, defining it as 'a hypersensitivity in which, after sensitization by a systemic calcifying factor, exposure to certain challengers causes an acute, local calcification followed by inflammation and sclerosis'.[1] Calciphylaxis was then reported in uraemic patients presenting with cutaneous ulcerations.[2, 3] These investigators hypothesized that secondary hyperparathyroidism could be a 'sensitizing' agent, and iron therapy or local trauma could be the 'challengers' precipitating the formation of calciphylactic lesions. Cutaneous manifestations of calciphylaxis consist of excessively tender, firm cutaneous lesions that can ulcerate and produce a black eschar.[4] It usually has a proximal or distal distribution, less likely to be diffusely spread. Although cutaneous manifestations predominate, systemic calciphylaxis has been reported, whereby vascular calcifications occur in other organs, including brain, eyes, lungs, intestines and the mesentery.[4-7] Treatment option for calciphylaxis is limited. The most common off-label treatment is intravenous sodium thiosulphate.[1,4] We report a case of systemic calciphylaxis with biopsy-proven cutaneous skin

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lesions and an extra-cutaneous manifestation presented as bilateral optic nerve atrophy. This case illustrates systemic calciphylaxis with a poor clinical outcome despite optimal supportive care with multi-disciplinary approach and four weeks of intravenous sodium thiosulphate treatment.

CASE REPORT

A 42-year-old Malay woman presented to accident and emergency with a two-week history of severely painful lesions on her thighs. She suffered from end-stage renal disease secondary to chronic glomerulonephritis. She has been on regular haemodialysis through a left radiocephalic arteriovenous fistula for nine years. Her other co-morbid conditions included hypertension, morbid obesity (body mass index 43 kg/m^2) and atrial fibrillation. She was started on warfarin for atrial fibrillation eight months prior to presentation. She also had poorly controlled secondary hyperparathyroidism, for which she had declined parathyroidectomy. She was on calcium-based phosphate binders (calcium carbonate), calcitriol and cinacalcet.

On admission, she had a low blood pressure of 99/56mmHg. Physical examination revealed several tender subcutaneous, violaceous nodular lesions in both lower extremities predominantly on the thighs. Her pedal pulses were normal. Laboratory findings on admission included a corrected calcium of 2.43 mmol/L phosphate 2.41 mmol/L, blood urea nitrogen 22 mmol/L, creatinine 1061 µmol/L, intact parathyroid hormone level of 45.3 ng/L and albumin 34 g/L. Her inflammatory markers were also elevated and continued to increase in the initial days of hospitalization, with C-reactive protein peaking at 35.2 nmol/L, white cell count $19.5x10^3$/uL and a neutrophilia of $16.1x10^9$/L. Her previous parathyroid hormone levels were between the range of 31 and 42 ng/L. Clinical suspicion was high for calciphylaxis.

Skin biopsy was performed and pathology findings were suggestive of calciphylaxis with granular calcium deposits in the arteriolar wall, thrombosed thick-walled mid-dermis arterioles, septal inflammatory infiltrates with septal panniculitis (Figures 1a, 1b, 1c).

Calcium carbonate was stopped and sevelamer was started. Warfarin and calcitriol were discontinued. Cinacalcet was increased to its maximum dose of 180mg daily. The extensive cutaneous ulcerations could have a neuropathic component from injury to cutaneous nerves. Thus, her pain was managed with multimodal analgesia with intravenous fentanyl infusion, oral gabapentin and breakthrough fentanyl boluses as required. Despite these, she reported poor control of her pain.

Twenty-five grams of intravenous sodium thiosulphate was administered thirty minutes before the end of every haemodialysis session. A low dialysate calcium concentration of 1.25 mmol/L was used. Dialysis frequency was increased to four times a week. She did not experience any side effects from sodium thiosulphate, such as hypotension, nausea, emesis, fluid overload and metabolic acidosis.[1,4]

Two weeks into her admission, she developed an acute onset of bilateral blurry vision. There was no associated retro-orbital pain or headache. An ophthalmologist consult was made. Fundoscopy examination revealed bilateral optic nerve atrophy, consistent with bilateral optic nerve ischaemia. Computed tomography scans of the brain and orbits were unremarkable. Transthoracic echocardiography revealed no evidence of thrombus.

She was started on broad spectrum antibiotics for empirical treatment of sepsis as she developed febrile episodes, leukocytosis and high C-reactive protein levels. Blood cultures did not reveal any bacteraemia. Her skin

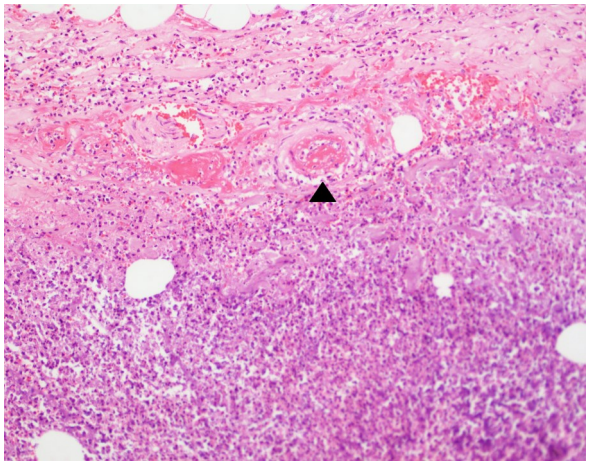

Figure 1a: Thrombosed arteriole in the dermis (shown by arrow head)

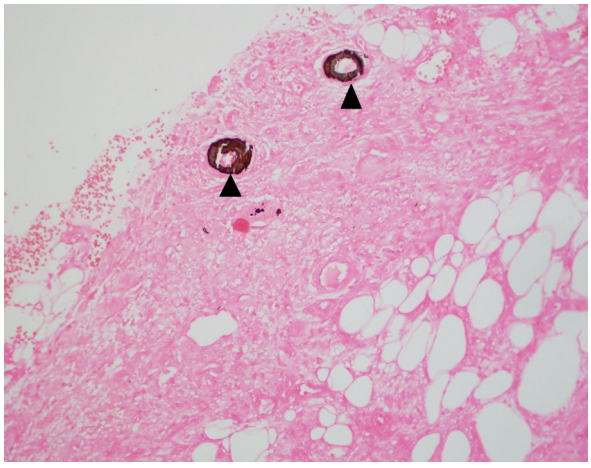

Figure 1b: Von-kossa stained slide showing calcified blood vessels (shown by arrow heads)

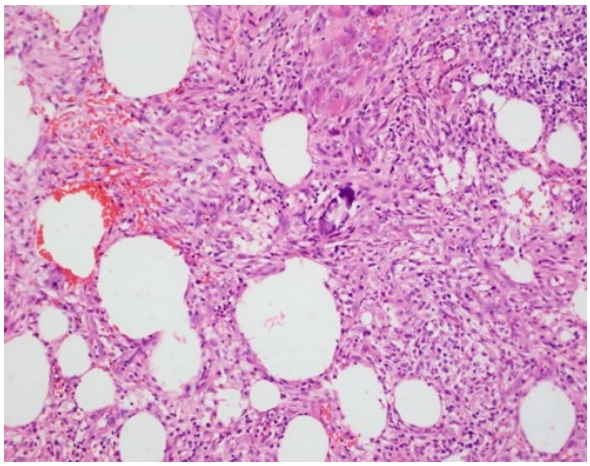

Figure 1c: Inflammatory infiltrates between adipocytes in septal panniculitis
(Histology slides courtesy of Histology Department, RIPAS Hospital, Brunei)

lesions were treated with regular dressings and wound care. These lesions unfortunately extended to her buttocks and lower back, forming ischaemic plaques and ulcerations (Figure 2a&b). Multidiscipline health care teams were involved in her care including nephrology, dermatology, ophthalmology, palliative medicine team, physiotherapy, and dietetics. She unfortunately continued to deteriorate and succumbed to her illness.

DISCUSSION

Our case illustrated systemic calciphylaxis in a morbidly obese patient on long term haemodialysis. This patient had a poor clinical outcome. Calciphylaxis is associated with a high mortality rate, ranging from 45% to as high as 80%.[1, 8-9] Similar to previously reported, the predisposing factors for our patient to develop calciphylaxis include female gender, obesity, poorly controlled secondary hyperparathyroidism and warfarin therapy.[1, 8] Warfarin is known to antagonize Vitamin K2, which is involved in the inhibition of calcium deposition in the vasculature. This is hypothesized to be the mechanism behind warfarin creating an unbalanced environment favouring vascular calcification in calciphylaxis.[10]

Our patient presented initially with proximal calciphylaxis with violaceous lesions on her thighs. Proximal calciphylaxis, which occurs predominantly on the thighs and abdomen, has been described in the literature, which suggested that morbid obesity (body mass index greater than 35 kg/m^2), white race and low serum albumin (decrement of at least 10 g/L) were associated with proximal calciphylaxis in dialysis-dependent patients.[4, 11] Our case was morbidly obese, one of the reported risk factors for the disease.[8, 11, 12]

She then developed bilateral optic nerve atrophy, with acute onset of painless bilateral blurry vision a few weeks after she presented with cutaneous calciphylaxis lesions. She also experienced intermittent hypotensive episodes during haemodialysis treatments. Hypotension together with calci-

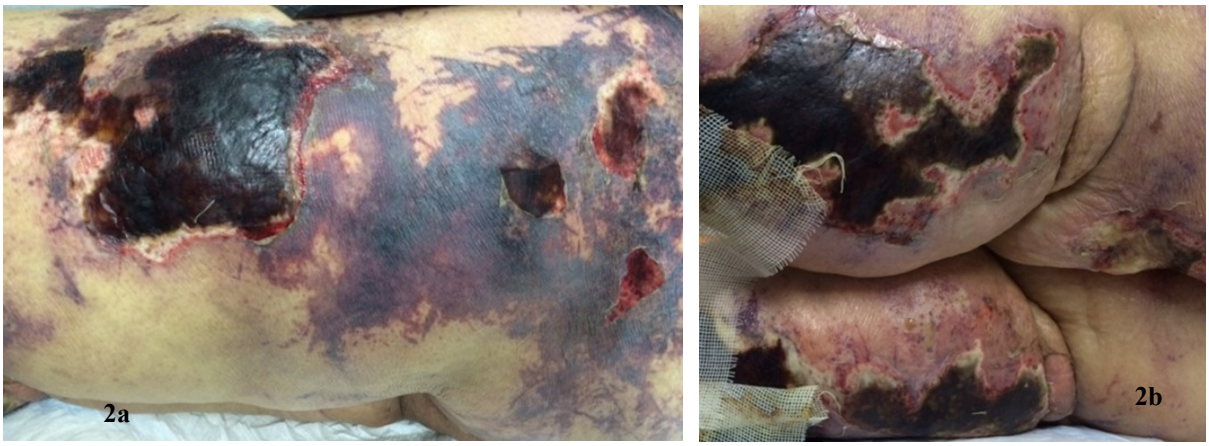

Figure 2a: Calciphylactic lesions on left thigh, 2b: Calciphylactic lesions on bilateral buttocks.

fied vessels in calciphylaxis restrict blood flow and create ischaemia. Hypoperfusion of the optic nerve leads to ischaemic optic neuropathy. Indeed ischaemic optic neuropathy was reported in two patients on long-term hemodialysis presenting with hypotensive episodes. Temporal artery biopsy in one of the patients showed extensive medial calcification without arteritis. The cause of the ischaemic neuropathy was thought to be due to both calcific uraemic arteriolopathy and hypotension. These two patients did not have cutaneous manifestations of calciphylaxis.[5]

Clinical data is limited on treatment for calciphylaxis and is mostly based on expert opinion and observational data. In general, supportive care with multidisciplinary approach is recommended. The specialties involved should include nephrology, dermatology, palliative care, nutrition, physiotherapy and wound care specialists. Pain is the main associating feature with calciphylaxis thus its management needs to be optimized. Combination of opioids and non-opioids including neuropathic agents is often used as pain in calciphylaxis may have a neuropathic component.[13] In our case, we used fentanyl infusion and gabapentin. Fentanyl dose was titrated up during haemodialysis as our patient experienced intense pain during dialysis. The involvement of palliative care team helped with symptom control.

In terms of disease-specific treatment, sodium thiosulphate was used successfully in small observational studies or case reports.[4, 14] A multicenter retrospective cohort study published in 2013 reported resolution in calciphylactic lesions in 26% and an improvement in 28% of the 57 patients treated with intravenous sodium thiosulphate in the last half hour of haemodialysis.[14] How the agent halts the progression of the disease is uncertain. There has been no studies on optimal treatment duration, however an improvement of pain within two weeks is thought to predict long-term response.[4] Recent literature reported successful treatment with intralesional sodium thiosulphate in four distinct cases of calciphylaxis. The skin lesions in their case series were active, violaceous and non-necrotic.[15] Intralesional sodium thiosulphate was not considered in our case as her lesions were extensive and progressed very quickly to ulcerated necrotic lesions.

In conclusion, this case illustrates systemic calciphylaxis in a middle-aged, morbidly obese, dialysis patient who eventually died despite multidisciplinary team approach and intravenous sodium thiosulphate treatment. She developed ischaemic optic neuropathy attributed by the repeated hypotensive insult. Prevention of this disease is therefore crucial

as it is difficult to treat. We recommend controlling the modifiable risk factors as preventative measures. Weight loss must be emphasized for obese dialysis patients. Secondary hyperparathyroidism should be managed through strict diet control and medications use. For those with uncontrolled secondary hyperparathyroidism and evidence of parathyroid adenoma, early treatment with surgical parathyroidectomy should be carried out. Blood pressure control must be optimum to prevent hypotension that could lead to optic neuropathy and blindness.

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Prenatal Ultrasound Diagnosis Of Cephalothoracomphalopagus Janiceps Monosymmetros.

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ABSTRACT

The role of antenatal ultrasound is established in detecting fetal well-being and abnormalities. Cepahalothoracomphalopagus conjoined twin is a rare occurrence and typical ultrasound features have been described in the literature. We report a case of cephalothoracomphalopagus conjoined twin diagnosed by ultrasound performed in a peripheral Maternal and Child Health Centre and later confirmed at a district hospital. The objective of this case report is to emphasize the possibility of fetal abnormalities even in low risk antenatal case at early gestational age and highlight the ultrasound features of this rare condition.

Keywords: Conjoined twin, conjoint twins, antenatal ultrasound, cephalothoracomphalopagus, prenatal diagnosis

INTRODUCTION

Cephalo-thoraco-omphalopagus is an extremely rare variety of conjoined twin where the twins are joined with a single head, neck, thorax and abdomen but have 4 limbs.[1] Majority of conjoint twins are not viable and are still birth and an additional third will not survive more than a day.[1] With routine use of antenatal ultrasound, an early diagnosis can be made. We report a case of Cephalo-thoraco-omphalopagus conjoined twin in a young primigravida who did not have any recognized risk factors for congenital anomalies and discussed about the incidence and causes of such disorder.

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CASE REPORT

A 29-year-old healthy, clinically uncomplicated primigravida, was first seen at the Maternal and Child Health clinic at Seria Health Centre, Brunei Darussalam for routine second trimester ultrasound as internationally recommended. [2] This was a spontaneous pregnancy with a married life of less than one year. The patient had no major medical illness, consanguinity or previous history of twin pregnancy. There was no significant family history of multiple gestations or any congenital anomaly. There was no history of smoking, drugs consumption, exposure to teratogenic medications or irradiations, assisted reproduction or infectious diseases during the pregnancy.

The initial ultrasound scan revealed an abnormal alive conjoined twin. The fetus had single large head with fused thalamus

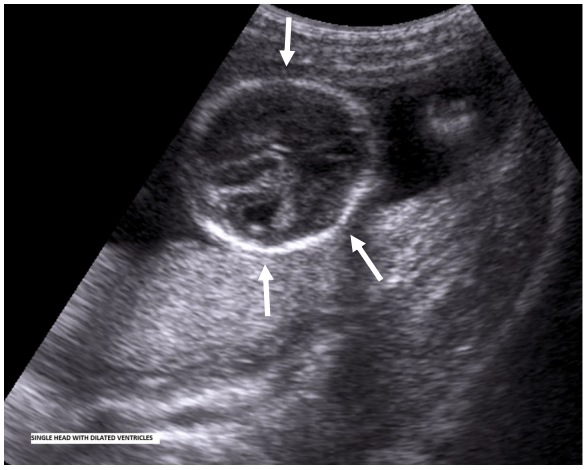

Figure 1: Ultrasound scan image showing a single large head with dilated ventricles (White arrows).

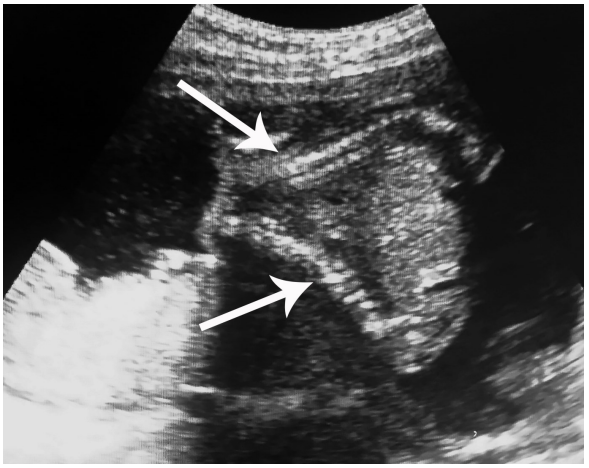

Figure 2: Ultrasound scan image showing conjoint twin with two separate spines (White arrows).

and dilated ventricles (Figure 1). There was a single thorax with two lower abdomens and pelvic girdles. There was complete independent cervico-thoraco-lumbosacral vertebral columns diverged inferiorly (Figure 2). The twin had a single neck (Figure 3). There were two pairs of arms and legs, with single placenta and polyhydramnios.

She was then referred to the district hospital for detailed ultrasound scan to be performed by the radiologist. In addition to the above findings that were confirmed, the conjoined twin revealed shared lungs, heart and stomach. The liver was wide and shared into two halves.

The ultrasound findings were explained to the couple and they were counseled extensively. The couple opted for termination of pregnancy. The patient was admitted under the care of the Obstetrician. The pregnancy was terminated at 21 weeks of gestation. The patient delivered vaginally, a female conjoined twins with birth weight of 750 grams. On examination of twins, the findings of ultrasound examination were confirmed including a single face with large head. Both babies had normal shoulders, arms, hands, legs and feet. Thorax and abdomen were fused. There was a single placenta with a single umbilical cord. Both eyes were normal, the tongue was enlarged with a small cyst of 0.5 cm hanging outside the mouth. Considering the sensitivity of the matter and parents request, no photographs were obtained or any postmortem examination conducted. amination conducted.

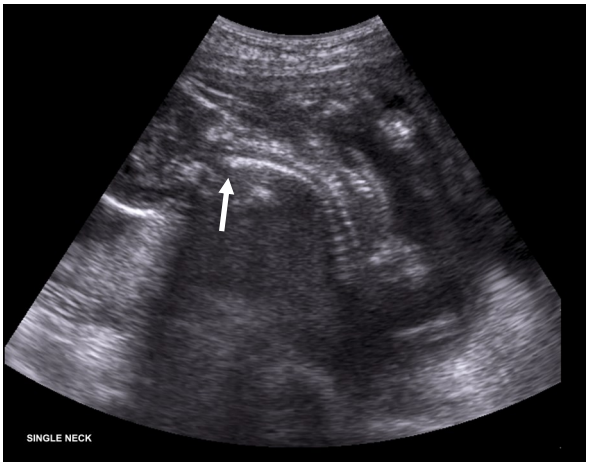

Figure 3: Ultrasound scan image showing conjoint

DISCUSSION

Twins are categorized into dizygotic twin and monozygotic twin. Dizygotic twin is a phenomenon resulting from fertilization of 2 ovules separately by 2 sperms. The monozygotic twin occurs due to fertilization of a single ovule to form one zygote, which then divides into 2 separate embryos. [3] The dizygotic twin is constrained by conditions such as heredity, race, maternal age, parity and history of as-

assisted reproduction. The monozygotic twin in turn does not depend on any condition, occurring independently and randomly. [3-5]

Conjoined twin is a variety of monozygotic twins which results from an incomplete division of embryonic disk after 13th day of conception. There is incomplete separation between both the embryos, which by design will occur in single amniotic cavity and same placenta. [3,6,8] This is associated with high risk of perinatal morbidity and mortality. [3,8]

There are several types of conjoined twins, which are named for the site of union followed by suffix *pagus* meaning 'fixed'. [4-6] There can also be overlap with more than one type involved. [5] Conjoint twins are classified by Spenser according to the site of union: Craniopagus-joined at cranium, Pyopagus-joined at sacrum and coccyx, Thoracopagus-joined at thorax, Thoraco-omphalopagus-joined from thorax to abdomen; Ischiopagus-joined at pelvic area, Cephalo-thoraco-omphalopagus- joined from cranium to thorax and abdomen (Figure 4). [4,6-8]

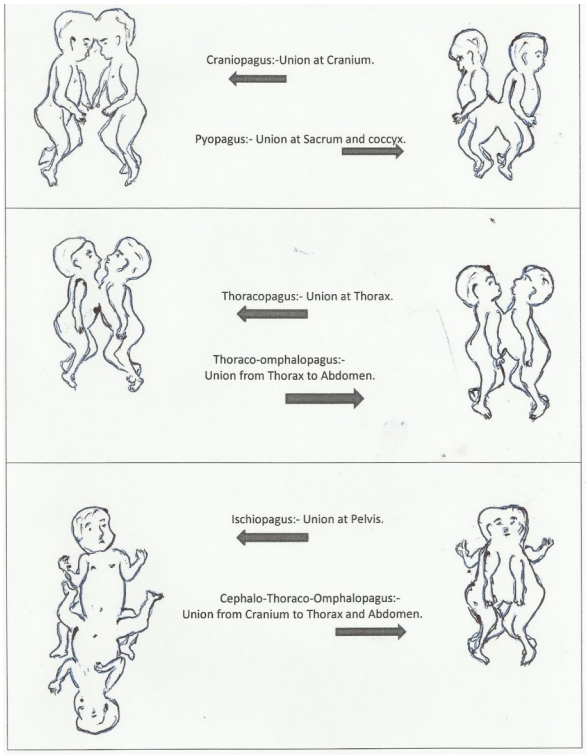

Figure 4: Spencer classification of Conjoint twins.

Although historically there have been many reported cases of conjoined twins through-out the centuries, the most famous case was of Chang and Eng Bunker born in Siam in 1811. [4,5] The incidence of conjoined twins is in the range of 1:50000 to 1:100000. [3,6,9] However the incidence rate of the rarer variety of cephalothoracomphalopagus conjoint twin is 1:3000000 pregnancies or 1:58 conjoined twins. [9,10] The ratio of females to males is 3:1. [4-6,8] Thus cephalothoracomphalopagus is a rarest type of conjoined twin pregnancy described as imperfect division of head, chest and abdomen at the area of umbilicus, but separated vertebral columns, limbs and pelvis.

The term janiceps is derived from the 2-faced Roman god named Janus. Janiceps twins are categorized into 2 subgroups: disymmetros and monosymmetros. In janiceps disymmetros the 2 faces are symmetrical and identical on a single head, in which the orientations of 2 notochord axes are perfectly ventroventral. In janiceps monosymmetros variety there is asymmetric union of 2 faces due to 1 poorly developed notochord. [3,9,10]

Our case is classified as cephalothoracomphalopagus janiceps monosymmetros which is the rarest type of conjoined twin with features described earlier. There have been few cases of conjoined twin reported in the late second and third trimester of pregnancy in the last ten years with the outcome of termination of pregnancy. [4,6,9] Another case of conjoined twin was diagnosed early in first trimester. [5] Our case was diagnosed at 19 weeks of gestation and the pregnancy was terminated at 21 weeks. This substantially reduced the psychological stress and anxiety

of the couple.

The antenatal diagnosis of conjoined twins is very important at early gestation of pregnancy in order to counsel the parents about interruption of pregnancy. The neonatal prognosis is extremely poor and surgical separation of the complex defects is usually not offered. [3] Conjoined twins can cause dystocia with the risk of rupture of uterus and quite often require cesarean section which may have negative consequences for the obstetrical future of the mother. [6] Before 24 weeks of gestation, the termination of pregnancy by vaginal route is opted, whereas after 24 weeks of gestation termination by hysterotomy is seen prudent. [3,10]

The present case study highlights two important points related to clinical practice. It is possible to detect serious congenital abnormalities on antenatal scan performed at peripheral health center and it can occur even in low risk cases.

CONCLUSION

In conclusion, Cephalothoracomphalopagus janiceps momosymmetros is extremely rare variety of conjoined twin and the prenatal diagnosis with typical ultrasound features at earlier gestation is very important in order to counsel the parents.

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A Rare Case Of An Isolated Central Retinal Artery Occlusion Following A Recreational Scuba Diving: A Case Report.

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ABSTRACT

Clinical manifestation of decompression illness after a scuba diving may vary widely. We report a rare case of a 29-year-old man with decompression illness that manifested as isolated retinal artery occlusion in a diver with a single shallow dive profile but missed the obligatory safety stop due to poor buoyancy control. He was treated successfully with one cycle of Treatment Table 5 followed by four cycles of Treatment Table 6 (US Navy Treatment Table) of hyperbaric oxygen therapy.

Key words: Retinal artery occlusion, scuba diving, arterial gas embolism

INTRODUCTION

Scuba diving is associated with a risk of decompression illness (DCI) due to formation of inert nitrogen bubbles under pressure that mainly affect the central nervous system. [1] It is caused by bubbles in blood or tissues during or after a sudden reduction in ambient pressure manifesting in a large range of signs and symptoms. In scuba diving, DCI mostly occurs in divers engaging in excessively long dive time, deep dive or if the mandatory `stops', which are pause during ascend to surface at the end of a dive to safely remove dissolved inert gas from the body, have been omitted. It encompasses two pathophysiological syndromes: pulmonary over-inflation syndrome (POIS) and decompression sickness (DCS). [1] Butler (1995) found that visual disturbances were seen in 7-12% of all DCS that include nystagmus, diplopia, visual field defects, scotoma, homonymous hemianopia, orbicularis oculi pain, cortical blindness, convergence insufficiency, central retinal artery occlusion and optic neuropathy. [2] We describe a rare case of an isolated central retina artery occlusion (CRAO) as a manifestation of decompression illness due to scuba diving, which is of medical interest. This case also highlights the possible occurrence of the incidence albeit a mere single dive and a relatively shallow dive profile which might have an

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implication on scuba diving safety and precautious.

CASE REPORT

A 29-year-old man presented to Hospital Universiti Sains Malaysia with progressive painless blurring of vision of the right eye associated with dizziness after two hours surfacing from a single recreational scuba diving. The dive was to a maximum depth of ten meters with a bottom time of twenty-five minutes. During ascending to five meters depth at the end of the dive he had thirty bar (435 psi) of air pressure left in the tank.[3] With the near empty tank of air he had trouble maintaining neutral buoyancy and went straight up to the surface without being able to perform the mandatory safety stop procedure. He did not complain of any limb weakness, numbness or any joint pain.

On physical examination, he was fully conscious with normal vital signs. His right eye acuity was 6/60 with a positive grade II relative afferent pupillary defect (RAPD). Optic nerve function such as light brightness and red saturation were 20% reduced. Posterior segment examinations of the right eye revealed flat retina with cherry red spot and pale macula (Figure 1). The cherry red spot is a contrast between edematous, pale retina and reddish choroid. The optic disc was pink, not swollen, had well-defined margin and the cup-disc-ratio was 0.3. However, no focal arterial narrowing and optic nerve lesions were seen. The left fundus was normal. Intraocular pressure was 10 mmHg on the left eye and 12 mmHg on the right eye. Other central nervous system examinations were normal.

A diagnosis of central retinal artery occlusion was proposed. The patient was treated with hyperbaric oxygen therapy. He was prescribed one cycle of Treatment Table 5 followed by four cycles of Treatment Table 6

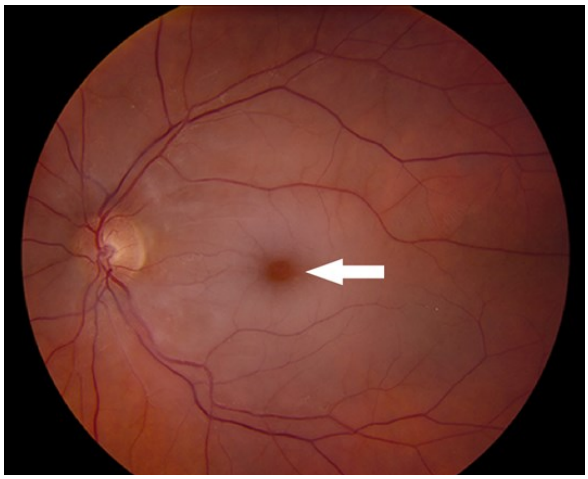

Figure 1: Right eye fundus photography of the diver showing cherry spot (white arrow) before hyperbaric treatment.

(US Navy Treatment Table) which was commenced seven hours after the onset of his symptom.[4] His right visual acuity had remarkably improved from 6/60 to 6/7.5 with no RAPD one day after completed the hyperbaric treatment. Light brightness and red saturation test were also comparable to the left eye and normal. Retina appeared healthy with flat macula and presence of vague fovea reflex. Three weeks after the event, he had no residual eye symptoms and his right eye vision had returned to 6/6 with normal ocular findings on examination.

DISCUSSION

Decompression illness results from both physical and biochemical sequelae of free phase inert gas precipitated by sudden a drop in ambient pressure. [5] In the case of recreational scuba diving not exceeding a non-decompression depth limit as in the case we reported, this is brought about by rapid ascend to surface as well as omitting the three minutes safety stop at five meters at the end of a dive. The safety stop in recreational diving is a standard practice to allow `off-gas' of excess nitrogen in the lung and soft tissue to prevent DCI. [3] Once DCS is precipitated, the bubbles have multiple physical and biochemical effects in the form of compression and

stretching of the surrounding structures as well as activation of complement cascade. [5]

Although scuba diving is considered a safe sport and the overall incidence of DCI in recreational diver of only 0.01-0.019%, the effect of CRAO as a manifestation of DCI has a significant function morbidity. [6] CRAO typically presents with painless, acute and often complete loss of vision and typical ophthalmologic changes occur within few hours or minutes of the event. However, in some cases the presentation may precede with prodromal visual disturbance symptoms and the severity is subtle if the supero-temporal branch is mainly involved. [6] The diagnosis is mainly by history with a dive profile that deviates from standard recommendation. Risk factors of DCI include high body fat content, previous history of DCI, dehydration, advancing age, patent foramen ovale, exercise, repetitive dive, multiple-day diving, deep diving and altitude exposure after a dive. [7] A comparatively shallow dive does not exclude the diagnosis entirely as evidenced from the case we reported. There is a similar report of the occurrence of arterial gas embolism in apnoea diving exercise in very shallow water with a depth of a mere 1.2 meter. [8] However, rapid ascend and omission of safety stop protocol should always alert a physician of a possibility of DCI. [9] The safety stop is a standard procedure in scuba diving to allow slow and adequate nitrogen release from tissues and the lungs. Other ophthalmic manifestations of decompressive sickness include redness of the eye from mask squeeze, orbital cellulitis, nystagmus, double vision and pain upon moving eye. [6]

The goal of treatment in CRAO is to increase retinal blood flow and to dilate its arteriole to improve blood supply to the retina, hence dislodging emboli and overcoming retinal spasm that may be present. [10] The definitive treatment of CRAO is hyperbaric oxygen therapy that promotes angiogenesis and fibroplastic activity of the hypoxic tissue. [10] In our patient, hyperbaric treatment was commenced relatively early with successful outcome.

CONCLUSION

In conclusion, a diagnosis of CRAO is a rare manifestation of DCI and should always be suspected in a diver with sudden painless monocular vision loss after a dive and a suggestive fundus examination. A detailed history of the patient's dive profile should be obtained and hyperbaric treatment should be initiated early.

DISCLOSURE OF INTEREST

The authors declare that they have no conflict of interest concerning this article.

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Imaging Guided Thoracic Epidural Catheter Insertion In A Morbidly Obese Patient Undergoing Elective Thoracotomy.

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ABSTRACT

A 26-year old morbidly obese male with body mass index of 39 kg/m^2 was scheduled for an elective left thoracotomy for large loculated empyema. During pre-anaesthetic assessment, he had predictors of a difficult regional anaesthesia upon back examination such as indistinct thoracic spinous processes and intervertebral spaces. We planned for a combination of radiological imaging-assisted regional anaesthesia (mid-thoracic epidural catheterisation) and general anaesthesia for him. Prior to the procedure, the skin-epidural space distance at level T5 was measured as 8.32 cm from his transverse computed-tomography. A pre-induction ultrasound localisation of mid-thoracic spinous process and interspinous space (T5-6) was done. Epidural space was identified at the needle length of 8.5 cm (0.18 cm more than the CT-scan derived skin-epidural space estimation) and catheterised successfully, general anaesthesia with one-lung ventilation ensued. Pre-emptive thoracic epidural analgesia instituted and surgery was uneventful. Multi-modal analgesia applied and he was discharged from Intensive Care Unit four days later.

Keywords: thoracic epidural, morbid obesity, computed tomography, ultrasound.

INTRODUCTION

The prevalence of obesity in Malaysia is approximately 20% and many of them will require anaesthesia at any point of their life.[1] Generally, an epidural catheterisation provides perioperative analgesia, reduction of postoperative respiratory and sympathetic-related complications associated with pain.[2] These beneficial profiles promotes a more steady and enhanced systemic recovery in comparison of administering a conventional intravenous opioid. However, localising the epidural space correctly in a morbidly obese patient can be technically challenging for the anaesthesiologist in ensuring effective analgesia and avoiding potentially catastrophic morbidity such as spinal cord injury. More so when it is done at the thoracic region, hence the usage of radiological imaging may improve the success rate of performing it. We report our experience of a successful mid-thoracic epidural catheterisation in a young

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morbidly obese patient undergoing an elective thoracotomy after a preoperative assessment of the skin-epidural space depth from thoracic CT-scan and pre-puncture ultrasound localisation of the thoracic spinous process and interspinous space.

CASE REPORT

A 26-year old morbidly obese male (BMI: 39 kg/m^2), scheduled for an elective left thoracotomy for large loculated empyema. The patient was evaluated two days prior to surgery. He suffered prior community acquired pneumonia complicated with left lung empyema, previous transient ischaemic attack and hypercholesterolaemia.

Preoperatively, he denied any symptoms of obstructive sleep apnoea but claimed had snoring. Pre-anaesthetic assessment of his vital signs were: heart rate of 80 beats/min, non-invasive blood pressure of 130/84 mmHg, pulse oximetry oxygen saturation level (SpO_2) of 98%. He was clinically comfortable and respiratory assessment was consistent with left lung empyema. Bedside airway test revealed predictors of difficult bag-valve-mask (BVM) ventilation such as excess adipose tissues on the cheeks and neck circumference of 42 cm but otherwise he had Mallampati Class II with unrestricted neck flexion and extension. Thoracic spinous processes and intervertebral spaces were not appreciated on back examination due to excessive subcutaneous fat. Lung function tests revealed restrictive lung disease and a fair arterial blood gas. Other blood investigations such as full blood count, coagulation and renal profile were within normal limits. We opted for radiological imaging assisted mid-thoracic epidural catheterisation and analgesia (TEA) with general anaesthesia (GA) and one lung ventilation (OLV) for this patient. Despite having a difficult thoracic epidural anatomy, this method was chosen for its known post-operative pain relief, respiratory and circulatory benefits in an obese patient. The patient was also counselled for patient controlled analgesia morphine in view of an unsuccessful attempt of thoracic epidural catheterisation and he consented to this. The radiologist assisted us by measuring the distance from skin to epidural space at level T5 from his transverse computed tomography (CT-scan) and it measured as 8.32 cm (Figure 1). Anti-aspiration prophylaxis consisted of tablet ranitidine 150 mg and tablet metoclopramide 10 mg were given the night and one hour prior to the surgery. A written and informed consent for anaesthesia was taken after explaining the anaesthetic modes and their perioperative implications.

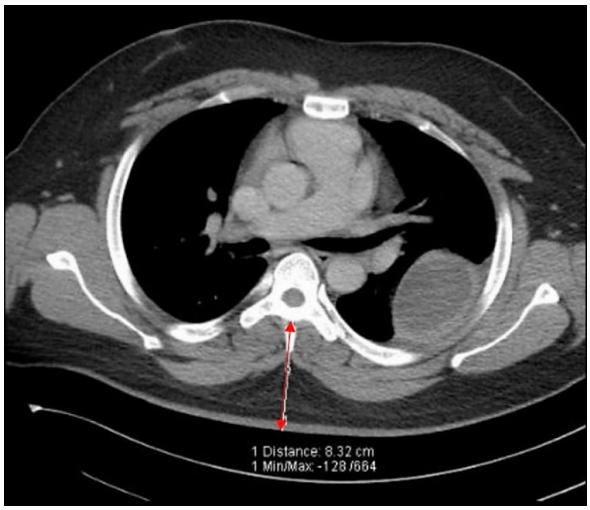

Figure 1**:** Transverse computed tomography of the mid-thoracic plane at level T5. Red arrow represents the perpendicular distance from skin to epidural space measuring at 8.32 cm.

On the day of the surgery, pre-induction monitoring were applied, these included five lead ECG, invasive blood pressure (inserted under aseptic technique at the left radial artery), pulse oximetry and capnography. Baseline vital signs were recorded: heart rate 85 beats/min, invasive blood pressure 134/82 mmHg and room air saturation was 98%. An 18-G intravenous cannula was in situ and Hartmann's solution was administered. On sitting up position, the mid-thoracic spinous process and interspinous spaces were visualised during pre-induction with ultra-

sound using a curvilinear probe (2-5 mHz) orientated transversely by tracking from the cervical (caudad direction) and lumbar region (cephalad direction) on the median plane. Level T5-T6 interspinous space was localised and marked at the midline. A paramedian sagittal oblique view was attempted but fail to visualize and identify the ligamentum flavum-dura matter unit. Under aseptic technique, the epidural space was located at the midline using 18-G Touhy needle of 8.8 cm length (from combined spinal-epidural set kit). The needle depth was 8.5 cm when the 'loss of resistance' to air was appreciated. Negative aspiration for blood and cerebrospinal fluid was confirmed, epidural catheter was inserted and placement was further confirmed with the 'hanging drop technique'. The epidural catheter was anchored to the skin at 13 cm with 4.5 cm of the distal end left in the epidural space.

He was placed on a troop elevation pillow and pre-oxygenated with 100% oxygen for five minutes. Induction, paralysis, two-handed BVM ventilation performed. Direct laryngoscopy showed Cormack and Lehane Grade I, a left-sided double lumen tube (DLT) inserted with confirmation by auscultation and fiberoptic bronchoscopy. He was positioned to the right lateral with adequate manpower and DLT placement was re-checked again with fiberoptic bronchoscopy. All pressure points were protected with silicone gel pads. Ropivacaine 0.37% of 3 ml aliquots were administered epidurally 10 minutes prior to surgical incision and every 10 minutes after surgery started with a total of 9 ml. General anaesthesia was maintained with sevoflurane and OLV commenced on the right lung.

No haemodynamic instability encountered, a cocktail of ropivacaine 0.1% and fentanyl 2 µg/ml infusion at 8 to 10 ml/hour was initiated at one hour after surgery started. Surgery was uneventful and lasted for two hours. He was reversed and extubated in a reversed Trendelenburg position and shifted to Intensive Care Unit (ICU) for observation. TEA was continued for three days with paracetamol and oral tramadol prescribed. Pain score was 0 to 2/10 with a satisfactory incentive spirometry of more than 2L achieved. He was discharged from ICU four (4) days later.

DISCUSSION

Patients planned for thoracotomy will routinely have a preoperative chest CT-scan, therefore an estimation of the CT-derived distance between skin to the epidural space can be estimated. Carnie et al described a concept to calculate the depth of needle insertion at the thoracic midline approach by using Pythagorean triangle trigonometry when perpendicular distance (measured from skin to the intended thoracic epidural space) and sin α (angle between the needle and thoracic vertebral body) are known.[3] They concluded that CT-derived depth appeared to be greater by the range of 0.03 to 0.49 cm than the actual depth. There were no correlations seen between either the CT-derived or the actual depth of the epidural space with age, weight, height or BMI. Sung et al used the same principles of trigonometry and found that there was a significant correlation between both the estimated CT-derived distance and the actual depth of the needle in performance of mid-thoracic epidural catheterisation.[4] In contrary, they demonstrated an actual depth of the needle reaching epidural space tended to have 1.25 times longer than the estimated distance on the CT-scan film. It showed a significant correlation between the actual length with both weight and BMI but not to age and height. In our case, the actual depth of the needle reaching the epidural space was 0.18 cm greater than the CT-scan derived distance between skin to the epidural space estimation. This finding is consistent with the study done by Sung et al. Practically, one would expect that the tissue of the back in a morbidly obese patient would be more compressible in supine position during CT-

imaging as compared to when they are sitting up during thoracic catheterisation. This potential differential compression based on the patient's position may support the fact that the actual depth of the needle reaching epidural space is longer than the estimated distance on the CT-scan film and anaesthesiologist should be aware of this.

Ultrasound imaging of the spinal region does not only identify the relevant landmarks but also able to provide an estimation of distance from skin to ligamentum flavum-dura matter unit (ultrasound depth), optimum insertion angle and insertion point of the epidural needle.[5,6] However, visualisation of the deeper structures such as ligamentum flavum -dura matter unit, epidural space and intrathecal space can be challenging in the morbidly obese patients. In our case, we used the ultrasound to facilitate the localisation of mid-thoracic spinous process and interspinous space as it was difficult to locate the deeper relevant structures. In obese patients, deeper structures are often obscured due to the beam attenuation of ultrasound waves which had to penetrate through a longer distance of soft tissues. Other reported factors that contributed to this poor imaging quality in the presence of excessive adipose tissue are: 1) the effect of phase aberration of sound field secondary to variable speed of sound in the overlying non-homogenous and irregularly-shaped fat layers and 2) the reflection of the ultrasound beam because of differing acoustic velocity at the fat-muscle interface.[7]

It is well reported that the ultrasound depth of skin to epidural space can be estimated if the ligamentum flavum-dura matter unit could be identified. Nishiyama showed a corrected shorter ultrasound depth ranging from 0.8 to 2.5 cm than the needle depth (distance from the skin to the tip of needle) for a thoracic epidural catheterisation in bariatric surgery among the morbidly obese.[8] Rasoulian et al found that the skin to epidural depth measured by an ultrasound had the tendency to underestimate the actual depth using needle among their thoracic surgery patients. This was probably secondary to probe-induced tissue compression or the intrinsic thickness of the ligamentum flavum.[9] However, Sahota et al demonstrated that ultrasound measured depth ranges from -14% to +17% of the actual needle depth, which was comparable in both sonographic transverse median and paramedian sagittal oblique plane.[10] The visualisation of the ligamentum flavum-dura matter unit and epidural space while performing a paramedian sagittal oblique view with the ultrasound was attempted in our case but to no avail, probably due to the presence of excessive adipose tissue. Applying different planes to estimate the ultrasound depth may be beneficial in those with poor sonoanatomy.

CONCLUSION

In conclusion, CT-derived distance between skin to epidural space with ultrasound localisation of the spinous process and interspinous space may be helpful as a guide and adjunct in mid-thoracic epidural catheterisation in morbidly obese patients for a better success rate and a favourable outcome.

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Answer: Parotid Lymphoepithelial cyst in HIV Infection

Parotid swellings of various types have been reported in HIV patients such as parotitis, benign lymphoepithelial lesions, inflammatory disorders, Kaposi sarcoma, lymphoma and neoplasm.[2] The pathophysiology of the cyst has been postulated to be due to the migration of HIV-infected cells into the parotid gland, which then triggers lymphoid proliferation promoting metaplastic changes in the salivary duct. The cellular proliferation causes ductal obstruction which further leads to cyst formation. The cyst serve as a reservoir of HIV-1 p24 and RNA copies that are sometimes 1000 times higher than plasma concentration.[1,2]

Management of these patients will involve multidisciplinary team. If the patient has already been diagnosed previously with HIV infection, then they should continue to be follow up at the nearest HIV disease centre. For those who are newly diagnosed, they should be referred for appropriate counseling and support services to reduce their risk of spreading the infection to others.

Pharmacotherapy with anti-retroviral drugs have shown to resolve certain lesions. Radiotherapy of both high and low-dose have been used to treat this lesion. However, there were high incidence of recurrence and malignant transformation. Although aspiration may help in diagnosing the lesion, it is not advisable to use that as a main treatment as the effects are not permanent and recurrence rate is high.[2,3] Doxycycline with sclerotherapy has been reported to respond well, which is a choice of treatment especially in children where surgery is avoided.

For asymptomatic patients with parotid cyst who do not want surgical excision, regular follow up can be recommended. However, patients should be informed of the high risk of malignant transformation. FNAC or biopsy is indicated for suspicious lesions. Enucleation of the cyst from the parotid tissue is associated with recurrence in some patients.[2,4] Superficial parotidectomy is recommended for patients who do not respond to medical treatment or those with recurrence or risk of malignant transformation.[1,2] In our patient, superficial parotidectomy was performed and patient has been free of recurrence.

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(*Refer to page 126*)

Answer: Presence of a supernumerary tooth obstructing the eruption of the permanent incisor

The cone beam CT scan of the area of interest showed evidence of a small tooth-like structure (supernumerary tooth) located between the crown of the unerupted permanent incisor and the root of the over-retained primary incisor.

The eruption of a maxillary incisor, which normally occurs between 7-8 years of age, is considered to be delayed if a) the contralateral incisor has erupted more than 6 months earlier; b) both incisors are unerupted and the lower incisors have erupted over a year previously or c) the eruption pattern does not follow the normal sequence e.g. the lateral incisor erupting before the central incisor[1]. Unerupted maxillary incisors have been reported to occur in 0.13% of the 5-12 year age group[2].

One possible cause of delayed maxillary incisor eruption is the presence of a physical obstruction such as supernumerary teeth. A supernumerary tooth is a tooth in addition to the normal tooth series. Supernumerary teeth have been reported to be associated with delayed eruption of the permanent incisors in 28% and 38% of the cases[3].

MANAGEMENT

Management of unerupted maxillary incisor often requires multi-disciplinary dental care involving Paediatric Dentist, Orthodontist and Oral Surgeon.

In this case, the delayed eruption of the maxillary left permanent central incisor was associated with an unerupted supernumerary tooth. The late presentation of the case had resulted in loss of central space due to midline shift of the contralateral maxillary central incisor and mesial drift of the maxillary left permanent lateral incisor. Furthermore, the root development of the affected incisor has matured, thus, the eruptive force that is required to cause normal eruption of the incisor has diminished and the affected incisor is less likely to spontaneously erupt even after surgical removal of the supernumerary tooth. Based on the Royal College of Surgeons of England's guidelines[1] on the management of unerupted maxillary incisors, the management of this case would include surgical removal of the supernumerary tooth, orthodontic re-creation of the space to allow for the eruption of the affected incisor into the arch as well as orthodontic traction to move the unerupted maxillary left permanent central incisor into the line of arch.

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Letter to Editor

Letter to Editor in response to the article by Wong et. al., on "Colonic diverticular disease in Brunei Darussalam" published in Brunei Int Med J 2017;12(6):191-5.

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I read with interest your original article by E Ru Wong et al. titled "Colonic diverticular disease in Brunei Darussalam" published recently. Always thought as a disease of the developed countries, it was really enlightening to know that in nearly one of five colonoscopy performed in Brunei Darussalam revealed the above diagnosis as a cause of abdominal symptoms.[1]

The author was right to point out to the reasons for the substantial increase in the prevalence of this often-obscure disorder i.e. lack of fibre intake, Westernisation of our Eastern diet and change in life style with increased alcohol, caffeine and nicotine intake. Humes D et al. pointed out that over 5% of adults aged 40 years and above will develop this sinister condition, but only up one quarter of them will ever be symptomatic.[2]

What is more worrying is the associated serious complications that includes intestinal obstruction, perforation, haemorrhage and formation of fistula.[2] This will eventually lead to an increase in abdominal related morbidity and mortality, and healthcare cost in already worsening worldwide economic climate.

Treatment will depend on the actual cause of the colonic diverticular disease will include diverticulitis, diverticulosis and diverticular disease.[3] It ranges from oral or intravenous hydration, lifestyle modification and antibiotics for less severe condition to life saving surgeries in more severe conditions including those associated with complications.[3]

Physician should increase their index of suspicion in diagnosing this great masquerade to attain early diagnosis and subsequently, prevent its' devastating complications.

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