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Value-based medicine and precision medicine in anaesthesia

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Evidence-based medicine has become the part and parcel of the practice of medicine nowadays.[1] It integrates patient preference with evidence and clinicians' experience, leading to the improvement in the length of life.[1] However, concern arises that it does not consider quality of life; hence, the concept of value-based medicine has become increasingly popular. Value-based medicine incorporates patient-perceived values that emphasise quality of life.[2] In addition, it also considers the cost of intervention, the goals of which is to improve the quality of health care and efficient use of resources.[1] The concept was first introduced by Brown *et al.*,[3] who defined it as "the practice of medicine incorporating the highest level of evidence-based data with the patient-perceived value conferred by health care interventions for the resources expended."[4]

Value-based medicine has many benefits, including lower costs and better outcomes for patients, better care efficiencies and controls, higher patient satisfaction, and eventually, better overall health for society. Patients' perceived value includes improvement in quality of life and/or length of life.[3] Length of life can be measured objectively by various means; however, quality of life is much more difficult to measure and define. The focus should shift from quantity of life as measured by lifespan to quality of life as measured by health span.[5] Financial value includes the medical costs, and the overall costs involved for society, such as caregiver and employment costs. Value is defined as the ratio of quality or outcomes over cost.

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Precision medicine is a medical treatment tailored to the patient's individual characteristics, such as disease susceptibility and drug metabolism.[6] Advanced genomic studies and deep machine learning allow deeper understanding of a patient's disease to develop more targeted therapy. Patients can be classified into subgroups that differ in their susceptibility to specific treatments or diseases, and the medical management will focus on treatment that is beneficial to the patient. Precision medicine's strength lies in its ability to guide health care professionals to make appropriate decisions in providing the most effective treatment to a particular patient. As a result, it will lead to improved quality of care while reducing the need for unnecessary diagnostic testing and therapies.

Anaesthesiologists have always been at the forefront of patient safety, and we utilise precision medicine in the daily management of our patients. All drugs administered to the patient are tailored to each patient's characteristics and attributes. Therefore, translating the modern-era definition of "precision medicine", which is interpreting a large amount of clinical data for critical and timely decisions in the delivery of anaesthetic and critical care, is a strength of the anaesthesiologist.[7]

What is the role of anaesthesiologists in delivering value-based medicine and precision medicine? Anaesthesiologists play an important role in improving the health outcomes of patients via approaches throughout the perioperative periods.[5] Preoperatively, visits can be used to proactively improve outcomes via optimisation of patients' health status such as weight reduction and smoking cessation, which may reduce perioperative complications. Proactive medicine becomes more important than reactive medicine.[5] Continued patient engagement perioperatively would likely lead to improvement in the patient's overall health status. Encompassing the patients' responsibility toward their health and continued engagement to stay healthy could be an important approach to improve health outcomes at population level. All preoperative patient data including blood and tissue can be fed into an artificial intelligence-driven algorithm, which can then be used as predictive analytics to stratify the patient's risk. The predictions could benefit clinical teams in anticipating and preventing any significant events perioperatively such as stroke, myocardial infarction, acute kidney injury, bleeding arrhythmias, cognitive decline, and sepsis.

As anaesthesiologists provide care for a wide spectrum of patients, targeted interventions could be implemented to each identified group of patients, *e.g.*, based on the American Society of Anaesthesiologists' physical status score.[8] Identification of patients who will benefit from targeted interventions, for example, patients who need better presurgical preparation may improve outcomes. Stratification of patients to different risks (*i.e.*, low *versus* high risk) allows for the standardisation of processes for care that could improve hospital efficiency. In addition, per-

sonalised care could be delivered based on patients' comorbidities and surgical complexity. Anaesthesiologists can be leaders as perioperative physicians in driving value-based care and precision medicine with the triple aims of (1) improving patients' experience of care, (2) improving health population, and (3) reducing costs.[8] This can be achieved through continued interaction with the patients as well as collaborative relationships with our surgical and medical colleagues and deep machine learning experts.

Algorithms of delivery of care such as enhanced recovery after surgery (ERAS) protocols have been used to improve perioperative outcomes and reduce costs.[9] As such, a value-based model protocol has been suggested that can be used similarly. This has been developed in 2,122 patients undergoing bariatric surgery and is incorporated in the perioperative management, in addition to the ERAS model.[10] Patients' perceived value includes excess weight loss, better control of comorbidities, quality of life improvement, and positive experience, while clinicians' perceived value is the optimisation of clinical parameters via engagement of patients to reduce hospital stay and readmission rate. Incorporation of patient-perceived value in the outcome of the surgery improves compliance with the therapy, which results in better outcomes for the patients and reduces cost. The model has been shown to be sustainable and can be replicable in the perioperative management of other conditions.

As medicine is a constantly evolving profession, changes are inevitable. Changes in the health care environment could be due to societal changes, which include changes in demographic changes (greater elderly demographics), social changes (higher expectations of medical care, greater emphasis on patients' safety, and work-life balance), and technological changes (advances in technology). Value-based medicine and precision medicine are the change that all health care providers should embrace for overall better health for society.

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Effectiveness of video tutorial on compliance of medical officers to sequence of intubation protocol in simulated Covid-19 patients

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Abstract

Introduction: The use of full PPE, aerosol box, and video laryngoscope are recommended when performing intubation on a Covid-19 patient. However, this technique may be difficult for medical officers unfamiliar with the intubation protocol sequence, especially for those with less experience in anaesthesia. Video tutorials may play a vital role in improving the technique. This study evaluated the compliance of medical officers in our anaesthesia department to the intubation protocol and the effect on compliance before and after viewing the video tutorial on the protocol.

Methods: A total of 70 medical officers (n = 70) in the Department of Anaesthesia, Hospital Universiti Sains Malaysia, Kelantan participated in this study. The participants performed the intubation protocol sequence on a simulated Covid-19 mannequin. Participants then viewed a video tutorial after their initial attempt and repeated the intubation sequence afterward. The outcomes measured include the proportion of participants compliant with the intubation protocol, the association

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between years of experience and compliance, and the compliance score before and after the video tutorial.

Results: There was no significant association between years of anaesthesia and compliance score (p = 0.058). A large proportion of the subjects were compliant (n = 57, 81.4%). There was a significant difference between initial and repeated compliance score post-video tutorial ($p < 0.05$).

Conclusion: Years of experience in anaesthesia was not a determining factor for compliance with the intubation protocol sequence on simulated Covid-19 patients. However, the video tutorial played a significant role in improving compliance with the intubation sequence.

Keywords: Covid-19, intubation, protocol, video laryngoscope, video tutorial,

Introduction

Covid-19 is a highly contagious disease and the highest viral load is found in sputum and upper airway secretions.[1] Personnel that performs tracheal intubation on Covid-19 patients may be exposed to the disease as the procedure may cause aerosolization and contaminate the airway of the operator along with the personal protective equipment (PPE) and parts of the exposed area of the body.[2] Performing tracheal intubation in such patients may be difficult when wearing eye goggles, face shields, or using an aerosol box.[3] However, some authors and guidelines recommend using the box as part of the protective strategy in handling Covid-19 patients.[3,4]

Experts also recommend using a video laryngoscope (VL) for the initial attempt of tracheal intubation in these patients for optimum intubation.[5,6] The use of a VL decreases the risk of contamination as it creates a distance between the operator and the patient's face.[7] Different VLs may perform differently depending on the setup and work.[8] In our setup, the Insighters© VL (iS3 type , Shenzhen Insighters Medical Technology, Shenzhen, China) was used by anaesthetists to handle Covid-19 patients who required tracheal intubation for ventilator support. Video tutorials are one of the tools used for teaching; well-designed and assessment-focused tutorial videos improve outcomes, especially in university settings.[9]

Simulated training and workshops improve performance outcomes of health care providers[10] and the use of mannequin training in simulations also aid in management strategies, improving performance, and skill retention.[11] Hence, the

use of video tutorials may improve performance post-tutorial, which can easily be assessed.

The anaesthetist must be familiar and compliant with the protocol involving the steps to tracheal intubation of Covid-19 patients when using the VL and aerosol box. Determining the compliance with the intubation protocol for anaesthetists in our department using VLs, specifically the Insighters VL, which is primarily used to handle Covid-19 patients in our setup, has been crucial during the Covid-19 pandemic outbreak.

Methods

This study, designed as a pre- and post-interventional study, was approved by the Medical Research and Ethics Committee (JEPEM) of Universiti Sains Malaysia (USM/JEPeM/20120687). Recruitment was open to all anaesthesia trainees in our institution within the Department of Anaesthesia, who were invited to participate in the study through serial announcements within the department. Inclusion criteria included medical officers with any experience in anaesthesia who consented to participate in the study.

The sample size was estimated using GPower software. Since there have been no previous studies looking at the effectiveness of video tutorials on intubation protocol compliance for Covid-19 patients, we assumed that the proportion of outcome post-intervention was at least 50% with an alpha value of 5%, power of 80%, and attrition rate of 20%, giving a desired sample size of 70. Seventy anaesthesia trainees were recruited for this study. All participants consented to participate in the study and attended the intubation station, which included the Insighters VL, an aerosol box, and a simulated Covid-19 patient (mannequin). Years of experience in anaesthesia for each trainee was recorded.

Each trainee then performed the intubation sequence using the Insighters VL pre-video tutorial. Each trainee was allowed only one session for attempt at the simulation station. All trainees were required to don full PPE with face shields for the simulation. An assistant was provided to aid in preparing the intubation equipment and to assist during the intubation. Participants were allowed a maximum of 2 attempts to intubate the mannequin. The researcher marked the subjects' performance based on the checklist steps in the pre-intubation, during intubation, and post-intubation phase (pre-video tutorial). The intubation sequence ended after the trainee successfully intubated the mannequin, connected the endotracheal tube to the self-inflating bag, and was able to provide

ventilation. After the initial intubation sequence was completed, the trainee then immediately viewed the video tutorial. After fully viewing the video tutorial, the trainee repeated the intubation sequence and the researcher marked the subjects' performance based on the same checklist (post-video tutorial).

The participants' compliance to the intubation sequence protocol was then scored based on the pre- and post-video tutorial by a single assessor, who was one of the researchers in this study during all the sessions. Each step completed during the intubation sequence was given a score of one point for a total score of 22 points. Compliance was checked by awarding points based on the steps completed during the intubation sequence and according to the correct sequence. A score of less than 80% was defined as non-compliant with the intubation protocol sequence, while a score of 80% or more was defined as compliant with the intubation protocol sequence. Initial compliance was regarded as the completion of the sequential steps based on the checklist for pre-intubation, during intubation, and post-intubation before the trainees viewed the video tutorial.

Our study assessed the compliance of trainees to successfully follow the correct steps from pre-intubation until completion of the procedures, including successful intubation and ventilation via self-inflating bag, where the total score achieved was the determinant of success. However, there have been no previous studies that incorporated a scoring system for checking adherence to the specific steps. Our study defined completion of at least 80% of the steps of the protocol as compliant since no other reference could be quoted.

Results

Seventy subjects were enrolled in the study and included in the final analysis. Baseline demographic for all participants showed the mean age of subjects recruited was 34.1 years (SD = 1.626) of age. They were predominantly female (*n* = 42, 60%). Of the 70 participants, trainees with < 2 years of experience were the minority (*n* = 5, 7.14%), followed by trainees with 2–4 years (*n* = 27, 38.57%), and > 5 years of experience (*n* = 38, 54.29%).

The results showed that trainees with < 2 years of experience had a mean compliance score of 17 (SD = 1.58), while trainees with 2–4 years and > 5 years of experience had an almost similar mean compliance score with 18.4 (SD = 1.28) and 18.7 (SD = 1.34), respectively. Table 1 shows that the majority of trainees were compliant with the intubation protocol (*n* = 57, 81.4%). Trainees with < 2

Table 1. Association between years of anaesthesia and initial compliance score (*n* = 70)

Years of experience	Initial compliance		
	Compliant, *n* (%)	Non-compliant, *n* (%)	*p*-value
< 2 years	2 (40)	3 (60)	0.058[a]
2–4 years	22 (81.5)	5 (18.5)	
> 5 years	33 (86.8)	5 (13.2)	
Total	57 (81.4)	13 (18.6)	

[a]Fisher's exact test

Table 2. Comparison on initial and repeated compliance score (*n* = 70)

Variable	Mean (SD)				
	Initial	Repeat	Mean difference (95% CI)	Statistic (df)	*p*-value
Initial-repeat	18.5 (1.39)	21.2 (1.14)	2.67 (2.48, 2.89)	25.6 (69)	> 0.000a

[a]Paired t-test

years of experience had the largest proportion of non-compliance (n = 5, 60%). Trainees with 2–4 years and > 5 years of experience had the largest proportion of compliance, with only a small proportion being non-compliant (*n* = 27, 18.5%) and (*n* = 38, 13.2%), respectively.

The association between years of anaesthesia and compliance to the sequence of intubation protocol was evaluated (Table 1). Our findings showed that the association between years of experience in anaesthesia and compliance score was not statistically significant ($p = 0.058$).

An evaluation of initial *versus* repeated compliance score was carried out (Table 2). The results showed that initial compliance score (mean = 18.5) *versus* repeated compliance score (mean = 21.2) were found to be statistically significant at p-value < 0.05.

Discussion

Covid-19 is a highly contagious disease, easily transmissible via aerosol-generating procedures, posing a risk to health care workers if necessary precautions are not

taken.[2] The medical officer must not only fully adapt to the use of full PPE, but also be well-versed in the standard intubation protocol sequence along with the use of the aerosol box and VL, which may be difficult if the officer is not familiar or compliant with the protocol.[3-5]

Trainees with long years of experience, especially in the field of anaesthesia, may be more competent in terms of skills and knowledge, including the intubation protocol and technique for dealing with Covid-19 patients. However, there is no standard definition on the exact years of experience to denote whether trainees are novices, experts, or truly experienced, or specific criteria to denote that an officer has sufficiently mastered the use of certain VLs or techniques. Our study showed that most of our department's medical officers were compliant with the intubation protocol (n = 57, 81.4%) compared to those who were non-compliant.

Our study found no significant association between years of anaesthesia experience and intubation protocol compliance (p = 0.058). This suggests that although experience is crucial, adequate training on the intubation protocol among trainees regardless of years of experience may be sufficient to allow them to be familiar and compliant with the protocol. Despite the indication that years of experience may not be a significant factor for compliance, our study does indicate that medical officers with < 2 years of experience had the largest proportion of non-compliance (n = 5, 60%). However, since the number of trainees with more than 2 years of experience comprised the majority of participants, the proportions were skewed. Thus, another properly planned study is required to assess this.

Binstadt *et al.* and Kuduvalli *et al.* conducted a study that showed that simulated training and mannequin simulation improved performance and skills.[10,11] We found that the video tutorial and mannequin simulation improved the medical officers' performance in handling the VL as well as their compliance with intubation protocol on simulated Covid-19 patients significantly (p < 0.05). This suggests that video tutorials are an essential tool to be incorporated into training protocols.

Our study had several limitations. First, subjects recruited in this study were from a single institution. Hence, this study may not represent the true population of medical officers or trainees in anaesthesia departments globally. Second, the compliance score used in our study was not based on existing literature, as to our knowledge, no studies have been conducted regarding intubation sequence compliance. Our study was the first to incorporate a specific compliance score on intubation protocol for Covid-19 patients. The results of this study may not represent true compliance with the intubation protocol.

The third limitation involves the intubation protocol sequence used as a standard protocol at our institution. Our department drew up the protocol for intubating Covid-19 patients from various recommendations and articles from the World Health Organization, British Journal of Anaesthesia, and New England Journal of Medicine. Different institutions incorporate different elements in their intubation protocol. Hence, our study may not be representative of other institutions. Finally, our study did not include blinding of the assessor and may therefore be at risk of bias.

Conclusion

The video tutorial significantly improved the compliance to the intubation protocol. Years of experience in anaesthesia did not significantly affect compliance to intubation protocol for Covid-19 patients.

Declarations

Ethics approval and consent to participate
This study involving human participants, materials, and/or data have been performed in accordance with the Declaration of Helsinki, had informed and explicit consent, and was granted approval by the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM), study protocol code USM/JEPeM/20120687.

Competing interests
Dr. Rhendra Hardy Mohamad Zaini and Dr. Wan Mohd Nazaruddin Wan Hassan serve as Section Editors of Malaysian Journal of Anaesthesiology. Neither has been involved in any part of the publication process prior to manuscript acceptance; peer review for this journal is double blind. The remaining authors state no conflict of interest.

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Appendix

Checklist for compliance check on of intubation protocol sequence (1 point for each step completed in the correct sequence). Maximum 2 attempts for intubation on mannequin.

Pre-intubation steps	**Yes/No**
Use full protective personal equipment (PPE) as appropriate	
Prepare endotracheal tube (ETT) with J-shaped stylet; (lubricate with jelly and insert stylet into ETT)	
Mentioned left hand to handle Insighter and right hand to handle ETT	

Intubation steps	**Yes/No**
Mentioned Insighter prepared from outside of the aerosol box and participant will bring the device inside the box through left opening	
Insighter blade inserted into the mouth centrally	
Glide the blade slowly until able to visualize the epiglottis	
Just lift the blade gently to fully visualize the airway opening/vocal cord	
Prepared ETT will be passed by assistant to the participant through the box right opening	
ETT should be held transversely and not vertically prior to insertion	
ETT inserted from the right side of mouth	
Glide the ETT above the Insighter's blade as pushing it inwards	
Once ETT pass through the vocal cord, push out the upper stylet from ETT with the right thumb	
Push the ETT further inside as appropriate to desired level	
Take out the Insighter and put it beside patient at the left side	
Stabilize the ETT by holding it with the left hand	

Intubation steps	**Yes/No**
Take out the stylet from the ETT with the right hand	
Cuff inflated with the help of assistant	
Connect the ETT with self-inflating bag/ventilator	

Post-intubation steps	**Yes/ No**
Detach the Insighter blade while it's still within the aerosol box	
Blade should be put inside a plastic bag	
Mentioned assistant to take the plastic bag containing the blade for decontamination	
Clean the scope with alcohol swab before it is taken out from the aerosol box	

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Monocyte distribution width in the detection of sepsis and prediction of mortality in critically ill patients

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Abstract

Introduction: Sepsis is the leading cause of intensive care unit (ICU) admission. Delayed recognition of sepsis is associated with increased morbidity and mortality. Monocyte distribution width (MDW) represents the width of a set of monocyte volume values, which increases as infections progress in severity. This study evaluated the diagnostic and prognostic accuracy of MDW and white cell count (WCC) for sepsis and mortality.

Methods: This was a prospective cohort study of 100 patients who were grouped into sepsis and non-sepsis according to the Sepsis-3 definition. MDW and WCC were collected on admission to ICU and for the subsequent 3 days.

Results: On admission, MDW was diagnostic of sepsis with an AUC of 0.86 (95% CI, 0.7–0.94) with a cut-off threshold of 20.97. Serial MDW on days 1 and 2 were also shown to be predictive of sepsis. MDW has a high sensitivity of 92.1% (95% CI, 82.4–97.4%) but a specificity of only 68.8% (95% CI, 50.0– 83.9%). The positive predictive value and negative predictive value of MDW using the new cut-off threshold in this study

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were found to be 83.6% (95% CI, 73–91.2 %) and 81.5% (95% CI, 61.9–93.7%), respectively.

Conclusions: MDW is an effective screening tool in the detection of sepsis upon admission to the ICU. As part of the differential in some complete blood count analysis machines, MDW provides a cost-effective and widely available test at present. Early detection of sepsis allows initiation of sepsis care bundle and better clinical outcomes.

Keywords: biomarker, blood cell count, critical illness, death, sepsis

Introduction

Sepsis is one of the leading causes of mortality in hospitals and hence a major financial burden on the Malaysian health care system. The intensive care unit (ICU) mortality rate was 18.6% with the all-cause mortality in severe sepsis at 42.3%.[1] Delay in initiating sepsis protocol as per surviving sepsis guidelines is associated with worse sepsis-related clinical outcomes, such as hospital and ICU lengths of stay, morbidity (*e.g.*, organ failure), and mortality.[2-5] The medical field is in dire need of a widely available and cost-effective test that is able to effectively differentiate septic from non-septic patients. This prevents the delay in initiating the sepsis care bundle and antimicrobial therapy in order to reduce or prevent sepsis-related clinical outcomes. White cell count (WCC) has an 88% sensitivity for sepsis detection but unfortunately with a downfall of low specificity.[6]

To date, available biomarkers of sepsis, such as procalcitonin (PCT) and C-reactive protein (CRP) are typically used to confirm the presence of sepsis after the initial encounter in the emergency department (ED), but with limitations of cost and availability.[7] As infections progress to sepsis, the size of the white blood cells increases. Circulating immune cells, particularly monocytes and neutrophils, are rapidly activated. This is reflected by the change in their size and shape,[8,9] and the release of chemokines and cytokines for the recruitment and activation of other immune cells in the body.[10,11] Another postulation is that sepsis causes the release of larger, immature monocytes into the circulation, leading to an increase in immune cell size.[12]

Early studies on the utility of monocyte distribution width (MDW) for sepsis detection have shown promising results in emergency departments[6,13] and ICU populations.[14,15] However, to the best of our knowledge, there have been limited studies investigating the prognostic value of MDW. Since MDW measurement is one

of the haematologic parameters of complete blood count (CBC), it does not incur an added cost and is available widely as part of the CBC measurement. Hence, we investigated its utility as a diagnostic marker for sepsis in our local ICU settings. The primary objective of the study was to compare the serial level of MDW and WCC in sepsis and non-sepsis patients in ICU in the first 3 days of admission. The study also compared the diagnostic ability of MDW in sepsis and the prognostic ability of MDW in 30-day mortality.

Methods

This study was a prospective cohort conducted between December 2020 and March 2021, on patients admitted to ICU of Sultan Ahmad Shah Medical Centre (SASMEC) in Kuantan, Pahang, Malaysia. Inclusion required patients having CBC in their initial evaluation within 24 hours of admission to IIUM Medical Centre. Subsequently, patients were reviewed over 3 days for evidence of sepsis. This study was registered with the Kulliyyah of Medicine Research Committee (KRC) and obtained approval from the IIUM Research Ethics Committee (IREC) on June 20, 2020, IREC number 2020-079. All patients admitted during the study period were screened for eligibility to be included in the study and written consent was taken from the patients or their relatives. This study enrolled adults, aged 18 years and above, whose evaluation included a CBC with differential upon admission to ICU. Exclusion criteria included patient refusal to join the study, readmission to ICU within 12 hours, and prior study enrolment.

CBC and MDW were evaluated in all patients as part of the routine investigations collected daily in the ICU. Blood samples were collected in K_2-EDTA anticoagulated tubes and analysed within 4 hours using UniCel DxH 900 (Beckman Coulter, Inc., Brea, CA, USA) with volume, conductivity, and scatter technology. In short, signals obtained by bioelectrical impedance analysis of cell volume, conductivity, and light scatter can evaluate the morphological changes in monocytes. MDW represents one standard deviation from the mean of the monocyte distribution. Maintenance and calibration of the equipment were performed according to the manufacturer's instructions. Quality of the assay was constantly monitored through the internal and external quality assurance programme.

Demographical data of the patients were recorded. Routine blood investigations, which included CBC with differential, were taken for all patients on admission. MDW and WCC were recorded as day 0. Patients were subsequently grouped into sepsis and non-sepsis groups based on Sepsis-3 Criteria. Patients were categorized as sepsis when there was a clinical suspicion of infection (with or without positive

culture) and a Sequential Organ Failure Assessment (SOFA) score of 2 and above; otherwise, they were grouped into non-sepsis. For patients with pre-existing medical illness, for example, chronic kidney disease, an increase in SOFA score of at least 2 above the baseline score was taken if the baseline parameter was available. If baseline value was not known, a non-renal SOFA score was taken into consideration. Infection was defined according to related clinical signs and symptoms supported by suitable imaging findings and relevant biomarkers for infection and positive cultures. Patients were reviewed for evidence of sepsis subsequently on day 1, day 2, and day 3, where MDW was recorded.

Statistical analysis

The sample size required in this study was calculated based on estimation in the diagnostic test method by Obuchowski[16] and the data from a study by Piva *et al.*[14] with an area under the curve (AUC) of 0.7 for MDW in critically ill patients with sepsis upon admission to ICU. In order to estimate an AUC of 0.7 with 95% confidence, degree of precision of estimate 0.1, and power of study of 90%, the required sample size was a minimum of 79 subjects with at least 19 septic patients.[16] Analysis was conducted using STATA/SE 12.0 (StataCorp, College Station, TX, USA). Continuous variables were presented in mean (standard deviation, SD) or median (interquartile range, IQR) depending on the normality of data distribution. Categorical data were presented as frequency and percentage. Independent Student t-test or Mann-Whitney U-test were used to compare mean differences between groups for numerical variables. To investigate the association between categorical variables, we employed Pearson's chi-square statistical test or Fisher's exact test.

Analysis using receiver operating curve (ROC) was utilised to measure the inherent validity of MDW as a diagnostic test. From the ROC, complete information on the accuracy of the diagnostic capability was obtained, which included sensitivity, specificity, threshold value, positive predictive value (PPV), and negative predictive value (NPV). For better visualisation, a ROC plot was generated to display the complete information of the trade-off between the sensitivity (true positive rate) and 1-specificity (false positive rate) across a series of threshold values. The global performance of MDW as a diagnostic test was summarized by the area under the ROC curve (AUC). As for identifying the optimal threshold cut-off point, we utilised the Youden index, which maximizes the vertical distance from the line of equality to a point on the ROC curve. The Youden index provided a maximum correct classification of sepsis or non-sepsis patients in our study.

Results

A total of 104 patients admitted to the ICU were screened for eligibility. Four patients were excluded from the study because they did not meet the inclusion criterion of the age 18 years and above. Eventually, a total of 100 patients were enrolled into the study and grouped into sepsis and non-sepsis according to Sepsis-3 definitions. There were no deviations from the study protocol and data from all 100 participants were analysed. Figure 1 shows the flow of recruitment in our study. Out of a total of 100 admissions, the prevalence of sepsis in this ICU population was 66%.

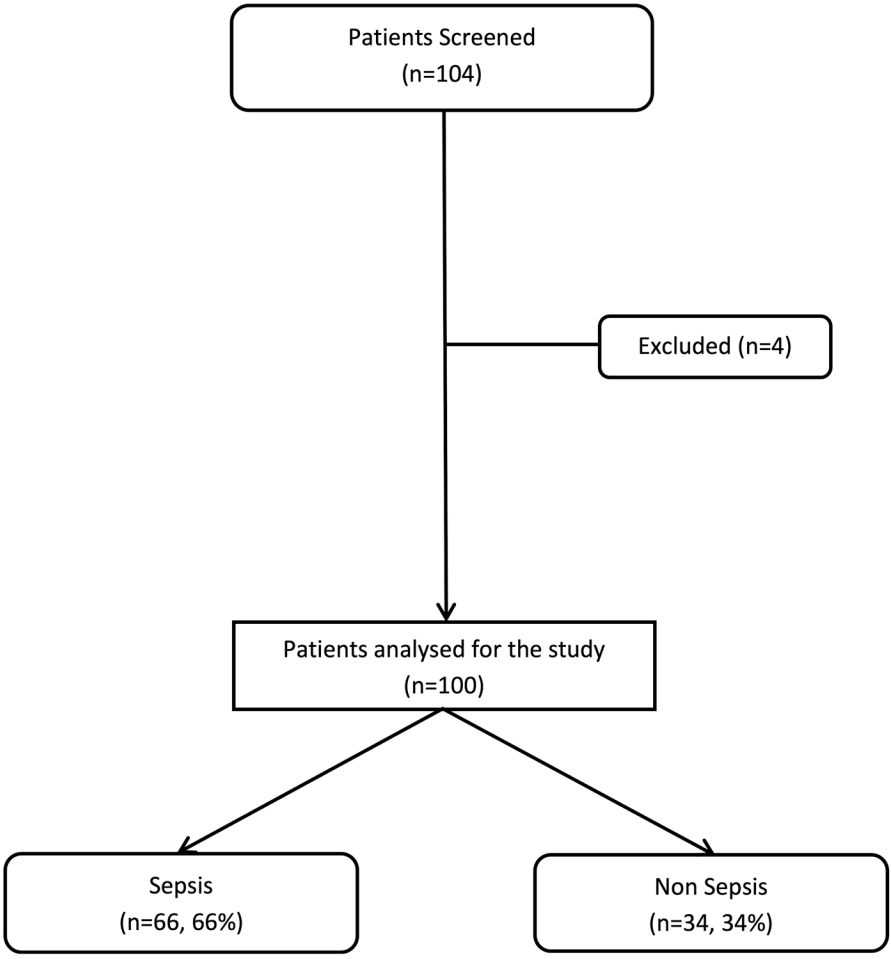

Fig. 1. STROBE flow diagram for patient recruitment into sepsis and non-sepsis groups.

Demographic, clinical characteristics, and outcome

Table 1 illustrates the background characteristics of the patients in this study. Hypertension was the leading pre-existing medical illnesses among the patients (72%), followed by diabetes mellitus (56%) and renal disease (40%). Of these three comorbidities, diabetes mellitus was found to be significantly higher in the sepsis group with a *p*-value of 0.0032. The sources of sepsis in 66 patients (63.4%) were primarily of respiratory origin (*n* = 33, 50.0%), followed by gastrointestinal (*n* = 14, 21.2%), with the rest from blood, soft tissue, and urinary tract.

Table 1. Patients' demographic, clinical features, and outcomes

Variable	**All (*n* = 100)**	**Group**		***p*-value**
		Non-sepsis (*n* = 34)	**Sepsis (*n* = 66)**	
Age	64 (56.5–70)	64 (55–70)	64 (57–70)	0.43
Gender				
Male	60 (60)	18 (30)	42 (70)	0.30
Female	40 (40)	16 (40)	24 (60)	
Ethnicity				
Malay	91 (91)	31 (34.1)	60 (65.9)	1.00
Chinese	9 (8)	3 (37.5)	5 (62.5)	
Indian	1 (1)	0 (0)	1 (100)	
Comorbidity				
Chronic obstructive pulmonary disease	2 (2)	0 (0)	2 (100)	0.55
Bronchial asthma	2 (2)	1 (50)	1 (50)	1.00
Chronic lung disease	3 (3)	0 (0)	3 (100)	0.55
Renal disease	40 (40)	11 (27.5)	29 (72.5)	0.26
Liver disease	1 (1)	1 (100)	0 (0)	0.34
Hypertension	72 (72)	23 (31.9)	49 (68.1)	0.49
Diabetes mellitus	56 (56)	14 (25)	42 (75)	0.03
Others	40 (40)	15 (37.5)	25 (62.5)	0.55

Variable	All (*n* = 100)	Group		*p*-value
		Non-sepsis (*n* = 34)	Sepsis (*n* = 66)	
Source of admission				
Operating theatre	19 (19)	13 (68.4)	6 (31.6)	0.001
Emergency department	40 (40)	13 (32.5)	27 (67.5)	
Ward	41 (41)	8 (19.5)	33 (80.5)	
APACHE II score	16.6 ± 6.9	13.1 ± 6.4	18.4 ± 6.6	< 0.0001
SOFA score	3 (2–5)	2 (0–3)	4 (3–6)	< 0.0001
Death within 30-days	23 (23.0)	3 (8.8)	20 (30.3)	0.02
In survivor (*n* = 77)				
Length of ICU stay (days)	7.03 ± 9.32	3.76 ± 4.26	9.23 ± 11.1	0.003
Duration of hospital stay (days)	24.9 ± 28.6	19.9 ± 28.7	28.3 ± 28.4	0.21

Data expressed as mean ± SD, n (%), or median (lower quartile–upper quartile). APACHE II: Acute Physiological and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment

The mean Acute Physiological and Chronic Health Evaluation (APACHE) II score in the sepsis group, 18.4 ± 6.6, was statistically higher than the non-sepsis group, 13.1 ± 6.4 ($p < 0.0001$). The SOFA score in septic patients was also higher than in non-septic patients, 4 (3–6) *versus* 2 (0–3), $p < 0.0001$. Twenty-three of the 100 patients died within 30 days of ICU admission, higher among the sepsis group (20, 30.3%) compared to the non-sepsis group (3, 8.8%), ($p = 0.002$). Patients with sepsis stayed longer in the ICU compared to non-sepsis; however, there was no difference in the duration of hospital stay.

Serial profile of MDW and WCC between sepsis and non-sepsis

Figure 2 shows the serial profile of MDW and WCC between sepsis and non-sepsis from admission up to 3 days. MDW was higher during the first 3 days in patients with sepsis compared to non-sepsis (repeated measures ANOVA, $p = 0.001$). MDW decreased from day 1 to day 3 by 1.73 in the sepsis group (95% CI, -3.29 to -0.18) with a *p*-value of 0.028, compared to the non-sepsis group, which increased by 2.35 (95% CI, -0.55 to 5.27) with a *p*-value of 0.113 (Fig. 2). On the other hand, WCC was not different in patients with sepsis compared to non-sepsis ($p = 0.630$ with repeated measures ANOVA).

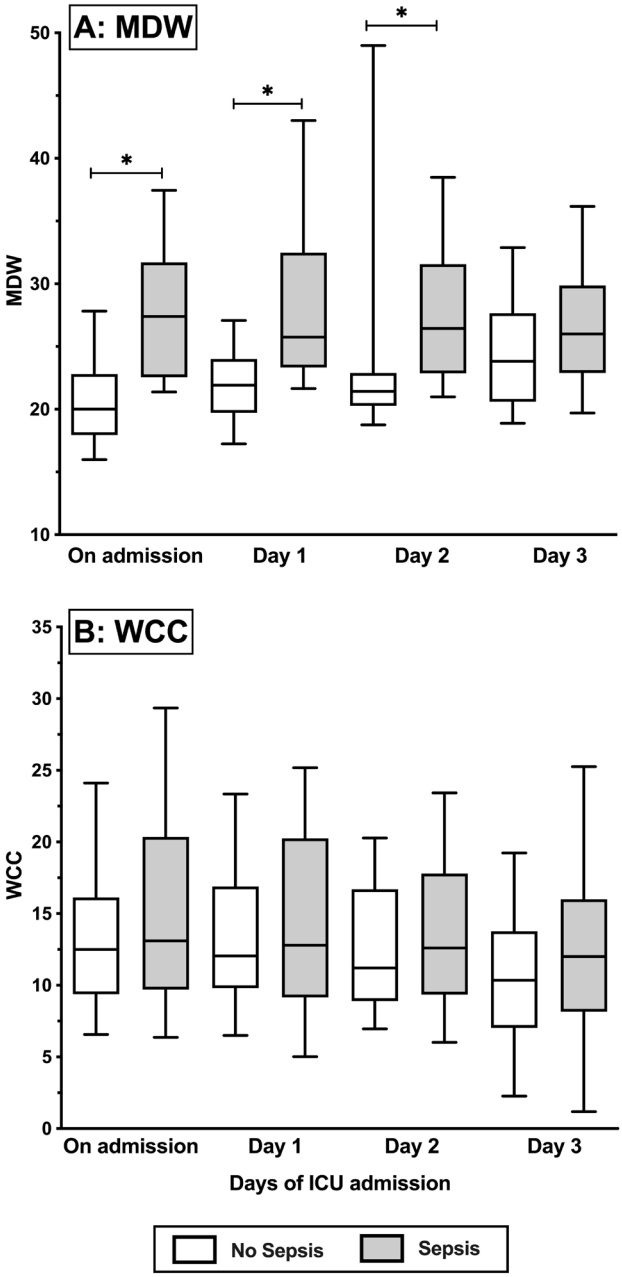

Fig. 2. Serial profile of monocyte distribution width (MDW) and white cell count (WCC) from admission up to 3 days.

Diagnostic performance of MDW for sepsis

MDW measured on ICU admission and during the first 2 days (on 0 hour, 24 hours, and 48 hours) were diagnostic for sepsis, whereas MDW on day 3 (on 72 hours) was not diagnostic (Fig. 3 and Table 2). The estimated AUC, optimal cut-off point, sensitivity and specificity are shown in Table 2. On ICU admission, the AUC of MDW for diagnosis of sepsis was 0.86 (95% CI, 0.77–0.94) with a cut-off threshold of 20.97 based on the Youden index. MDW had a high sensitivity of 92.1% (95% CI, 82.4–97.4%) but a specificity of only 68.8% (95% CI, 50.0–83.9%). Using the new cut-off threshold, the PPV and NPV of MDW were found to be 83.6% (95% CI, 73–91.2 %) and 81.5% (95% CI, 61.9–93.7%), respectively.

On the other hand, WCC measured on admission and throughout the first 3 days was not diagnostic of sepsis (Fig. 3). The AUC of WCC on admission for sepsis was 0.58 (0.47–0.70). The combination of WCC and MDW did not increase the AUC for MDW alone (AUC of 0.82 [0.74–0.91], χ^2 statistic = 0.74, p = 0.39).

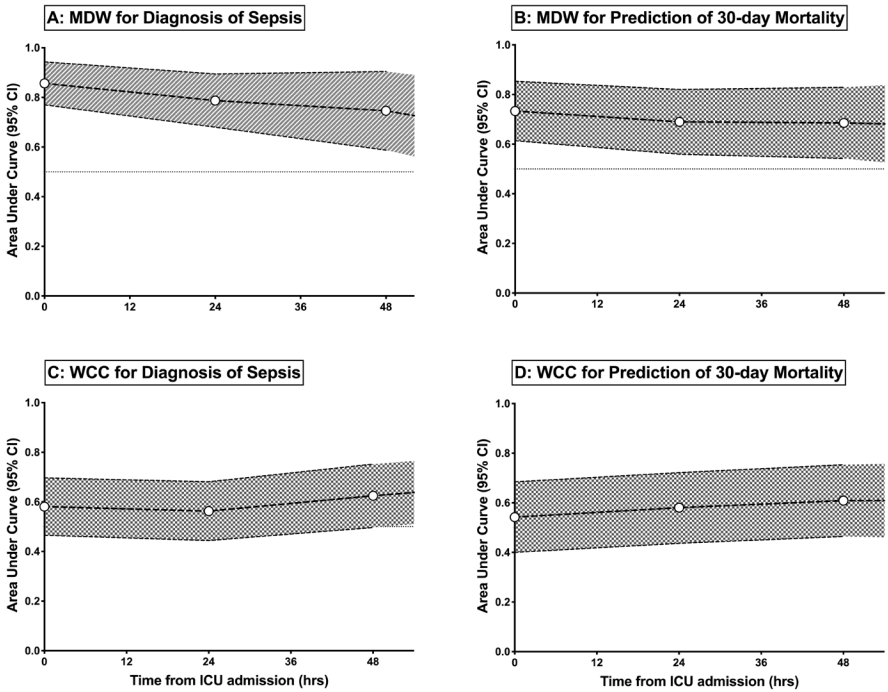

Fig. 3. Area under curve of the receiver operating characteristic curve of MDW for diagnosis of sepsis (A), prediction of 30-day mortality (B), and WCC for diagnosis of sepsis (C), prediction of 30-day mortality (D) from admission up to 3 days.

Table 2. AUC and optimal cut-off point for diagnosis of sepsis

BM	Day	AUC (95% CI)	Optimal cut-off point	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)
Diagnosis of sepsis					
MDW	0	0.86 (0.77 to 0.94)	20.97	92.1 (82.4–97.4)	68.8 (50.0–83.9)
	1	0.79 (0.68 to 0.89)	24.01	69.7 (55.9–81.2)	77.8 (57.7–91.4)
	2	0.75 (0.59 to 0.90)	22.90	76.0 (61.8– 86.9)	81.3 (54.4–96.0)
	3	0.63 (0.44 to 0.82)	20.69	88.9 (75.9–96.3)	40.0 (12.2–73.8)
Prediction of mortality					
MDW	0	0.74 (0.61 to 0.85)	25.97	73.9 (51.6 – 89.8)	68.1 (56.0–8.6)
	1	0.69 (0.56 to 0.82)	23.86	84.2 (60.4–96.6)	53.1 (40.2–65.7)
	2	0.69 (0.54 to 0.83)	22.31	93.8 (69.8–99.8)	38.0 (24.7 – 52.8)
	3	0.67 (0.48 to 0.86)	30.01	50.0 (21.1–78.9)	88.4 (74.9 – 96.1)

BM: biomarker; AUC: area under the curve

Prognostic performance of MDW for 30-day mortality and survival analysis

Twenty-three patients (23%) died within 30 days of ICU admission. Due to the limited number of deaths in the study, a greater number of patients would be needed to predict mortality significantly. Nevertheless, the analyses were performed to simulate the expected findings and MDW measured on admission up to 3 days were indeed predictive of death within 30 days, whilst WCC was not (Fig. 3). The optimal cut-off points of MDW, based on the limited data, for prediction of 30-day mortality are shown in Table 2. Kaplan-Meier survival analysis of MDW measured on admission for 30-day mortality showed lower survival for patients with MDW above the cut-off point of 25.97 compared to those with below the cut-off point (log-rank test, $p < 0.0001$, Fig. 4). After correction for age and SOFA score, Cox regression analysis showed a hazard ratio of 4.08 (1.55 to 10.75), $p = 0.004$. While the above data may not represent the population due to the limitation, a similar finding is expected to be reproduced in future studies with an appropriate sample size.

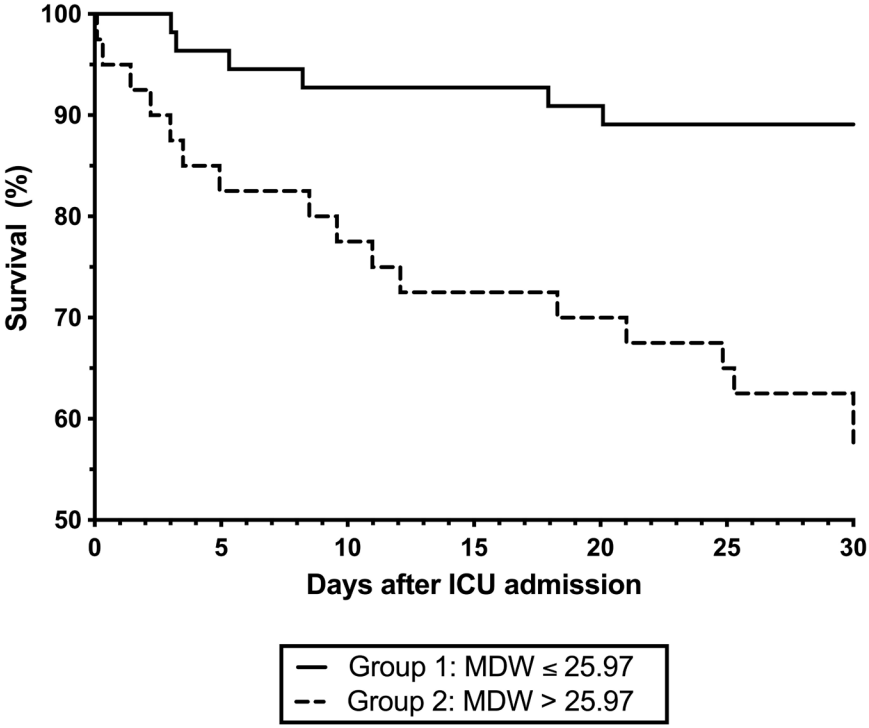

Fig. 4. Survival analysis curve for monocyte distribution width (MDW) on admission (log-rank test, $p < 0.0001$)

Discussion

This study showed that 66% of patients recruited had sepsis, with higher severity scores compared to those with no sepsis. MDW measured on ICU admission was diagnostic of sepsis with an AUC of 0.86 (95% CI, 0.7–0.94) with a cut-off threshold of 20.97. In addition, MDW on days 2 and 3 was also diagnostic. With the limited number of deaths among the sepsis patients to significantly predict 30-day mortality in this study, MDW above the cut-off value of 25.97 was associated with increased mortality. Patients with MDW greater than 25.97 were 4 times more likely to die within 30 days of ICU admission compared to those with a lower than the cut-off point. These results are highly hoped to be simulated in future studies with a larger sample size. On the other hand, the same data showed WCC on admission and throughout 3 days were not diagnostic of sepsis nor associated with increased mortality.

Early studies investigating the utility of MDW for sepsis detected were conducted by Crouser and team back in 2017 and 2019.[6,13] They showed that MDW alone and in combination with WCC were effective in the early detection of sepsis in the ED. Early detection of sepsis allows initiation of sepsis care bundles, wherein delay in treatment is associated with higher morbidity and mortality. However, more studies emerged in the past 2 years that compared MDW with other sepsis biomarkers such as CRP and PCT in ED populations,[17-19] infectious disease units,[20] and ICU settings.[14,15]

The prevalence of sepsis in our ICU population was high, comparable to our local data[21,22] but higher than other studies.[6,13,14] Given that most septic patients especially benefit from ICU admission for standardized care, we concur that the ICU population is the most appropriate for sepsis biomarker evaluation. Of all the comorbidities, diabetes mellitus showed a positive correlation with sepsis, $p = 0.03$. Diabetes may alter the immune system and is associated with a higher risk of community-acquired pneumonia, biliary disease, cutaneous infections, and aspiration pneumonia during hospitalisations, leading to an elevated risk of developing sepsis.

Volumetric increases are an early manifestation of immune cell response to infections and hence have shown potential as a sepsis biomarker. Of all the volumetric metrics in CBC, MDW was found to best discriminate sepsis in the ED population based on AUC with a 97% NPV of a normal MDW.[6] It was postulated that MDW outperformed other parameters because circulating monocytes are the first to respond to infections, leading to an acute increase in the monocyte size. MDW was predicted to provide added value to sepsis predictability on initial presentation. Moreover, CBC with differential is routinely taken in all patients admitted to ICU to screen for acute disease and help guide in the differential diagnosis. Traditionally, WCC is the first laboratory parameter to point to severe infections with a high sensitivity of 88% but poor specificity.[13]

In this study, we showed that the diagnostic performance of MDW in sepsis detection according to Sepsis-3 definitions was found to be excellent (AUC of 0.86), which is comparable to other studies.[6,14,20] Of interest, two studies investigated the utility of MDW for sepsis detection in critically ill patients. In a pilot study involving 96 ICU patients in Italy, MDW was shown to be higher in those with sepsis, and on-the-day sepsis was diagnosed in those without sepsis on admission.[15] In another larger study involving 506 critically ill patients, MDW value increased with increasing severity of sepsis to septic shock compared to those without sepsis. It was diagnostic of sepsis, with an AUC of 0.785 and a cut-off point of 24.63.[14]

The study also showed a positive correlation between MDW and PCT ($r = 0.543$) and CRP (5 = 0.509).[14] When compared with other biomarkers, the AUC of MDW was comparable to PCT but better than CRP in the detection of sepsis in the ICU.[14]

Similarly, two other studies showed comparable AUC of MDW and PCT between 0.82 to 0.87 in 260 patients in the infectious disease unit,[20] and in 1,517 ED patients.[18] The advantage of MDW is that it is available at no extra cost on some particular models of the routine CBC analyser machine, hence making it a convenient and cost-effective alternative for early sepsis predictability when PCT is not available, especially in primary centres. WCC performed poorly in our study as a biomarker of sepsis and hence should not be used as a sole diagnostic tool, similar to the findings of a previous study.[14] We also showed that the combination of WCC and MDW added no benefit in Sepsis-3 diagnosis, consistent with other studies.[17,18]

In addition, we showed that the MDW cut-off threshold for sepsis was 20.97. With that, MDW had a sensitivity of 92.7% and NPV of 81.5% in the screening of sepsis. The discrepancy between the cut-off point identified in our study and other studies could be explained by several reasons, including the different clinical settings (ED *versus* infectious disease unit *versus* ICU), the different calculation methods, and the type of anticoagulant used for blood sample collection (K_2-EDTA *versus* K_3-EDTA). The effect of the anticoagulant on MDW values has been described in the instrument's manual. In short, blood samples collected with K_2-EDTA are associated with lower MDW levels than those collected with K_3-EDTA. Hence, the manufacturer strongly recommends not to use the same cut-off points for different anticoagulants to avoid the risk of false-positive or false-negative results. In this context, the cut-off points of our study and those of Piva *et al.*[14] showed a discrepancy (20.97 *versus* 24.63) despite the same ICU setting, the same calculation method by Youden index, and the same K_2-EDTA anticoagulant in blood sampling. The cut-off threshold from studies using K_3-EDTA ranged from 21.5 to 23.5[18,20,23] compared to 19.8 to 24.6 for K_2-EDTA.[13,14,17] Another study on MDW in healthy blood donors has suggested a reference interval of approximately 16 to 23,[23] which is different from the manufacturer's recommendation. In a nutshell, these suggested that MDW was highly affected by the underlying medical conditions and characteristics of the study population.

Previously, Crouser *et al.*6[6] suggested in their limitations that the nature of the infectious agents could have important implications on MDW. However, Piva *et al.*14[14] showed that MDW was not affected by the aetiology of sepsis, be it Gram-positive or negative bacteria, fungal or viral infections, or even COVID-19 infection. On the contrary, PCT showed the highest value in Gram-negative bacteria but low values in fungal and viral sepsis, particularly severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We were unable to evaluate this due to the lack of microbiological evidence in our study, as most cultures may have been negative due to the delay in testing.

Our study also compared the trend of MDW in both sepsis and non-sepsis groups after admission to ICU. We found that MDW in septic patients dropped by 6% from 28.38 to 26.64 within 48 hours, with $p = 0.028$. We posit that this fall may reflect on the response to the sepsis care bundle and may be used as a prognosticating tool. This is supported by the findings from Piva *et al.*[14] wherein MDW in sepsis survivors decreased from a median of 29.14 (IQR: 26.22–32.52) on the first day to 25.67 (IQR: 22.93–30.28) on the end of the stay. In contrast, MDW in patients who developed ICU-acquired sepsis increased from a median of 21.33 (IQR: 19.47–21.72) to 29.19 (IQR: 27.46–31.47).

Another interesting point to highlight from Woo *et al.*[17] is that MDW should be interpreted with caution according to the patient's immune status. The AUC of MDW in immune-competent patients was higher than that in immune-compromised patients (0.73 *versus* 0.66). Their overall MDW performance was rather disappointing compared to other studies due to the relatively high proportion of immune-compromised patients (more than 50% of the overall population). Therefore, future studies should consider excluding immune-compromised patients to improve the diagnostic accuracy of MDW in sepsis.

Even with the limited number of mortality cases in this study, our study was able to demonstrate that MDW within the first 3 days was consistently predictive of 30-day mortality. Of interest is the early measurement of MDW in the prediction of mortality, as this can be used for risk stratification. Piva *et al.*[14] showed that, in non-survivors with sepsis, MDW was significantly different from the first to last value, whereas there was no difference in those who survived. Even after adjusting for age and severity score, patients with MDW above the cut-off point were 4 times more likely to die compared to those with those below the cut-off point. To the best of our knowledge, we are the first to report on the utility of MDW to predict mortality in the Malaysian ICU population.

Limitations

We acknowledge several limitations in this study. First, there is no gold standard for the diagnosis of sepsis to date; thus, the possibility of misclassification cannot be excluded, and this inevitably limits the biomarker's accuracy. Second, investigators were not blinded to the PCT and CRP values ordered as the standard of care, which may have led to bias and overestimation of the prevalence of sepsis, and again, the accuracy of the biomarker. Third, missing data from some patients may have also skewed the biomarker's accuracy. The use of a single biomarker (MDW) in this study is also a limitation.

Recommendations
This study was conducted with the aim of paving the way for further research on MDW in guiding sepsis management in Malaysia. More research is necessary to compare MDW in sepsis in multiple centres locally or internationally, with larger sample sizes to produce a more reliable and accurate representation of the Malaysian population, and even the global population. Future studies should also be conducted to compare MDW with other biomarkers, such as PCT and CRP. Ultimately, it would be important to determine how the availability of MDW could guide sepsis management in the ICU and its implication on sepsis-related clinical outcomes, such as ICU length of stay, morbidity, and mortality.

Conclusion

In summary, MDW is an effective screening tool to detect sepsis and predict mortality upon admission to ICU. As part of the differential in CBC, MDW provides a cost-effective and widely available test at present. Therefore, MDW may be use as a biomarker for early detection of sepsis, allowing early initiation of sepsis care bundle and improved clinical outcomes.

Declarations

Ethics approval and informed consent
Informed consent was obtained from all individuals included in this study prior to enrolment. The local Institutional Review Board deemed the study exempt from review. This study had been registered with the Kulliyyah of Medicine Research Committee (KRC), and had obtained approval from the IIUM Research Ethics Committee (IREC) on June 20, 2020, IREC number 2020-079.

Competing interests
Dr. Azrina Md Ralib serves as Deputy Chief Editor and Dr. Mohd Basri Mat Nor serves in the Advisory Board of Malaysian Journal of Anaesthesiology. Neither has been involved in any part of the publication process prior to manuscript acceptance; peer review for this journal is double blind. The remaining authors state no conflict of interest.

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Case report
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Successful emergency separation of premature omphalopagus conjoined twins: an anaesthetic experience

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Abstract

Anaesthesia for early emergency separation of premature conjoined twins is extremely rare as surgery generally done electively between 2 to 4 months of age. However, urgent separation may be needed due to life-threatening complications. We report a case of successful early separation of premature omphalopagus twins at 36 weeks of gestational age with a combined weight of 2.7 kg. To the best of our knowledge, this was the lowest weight yet reported of successful surgical separation in Malaysia. Early separation was indicated as extrauterine twin-to-twin transfusion with unbalanced blood shunting through the porto-systemic anastomoses within the shared liver parenchyma potentially risked impending life-threatening organ failures. Anaesthesia for the separation of premature conjoined twins in the emergency setting requires extensive multidisciplinary discussion and planning. Factors predicting difficult anaesthesia in this case were the twins' size and age as well as duration of anaesthesia. Two separate anaesthetic teams were required

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with all team members well versed in the operative workflow. Simultaneous airway management, prevention of hypothermia, and vigilant haemodynamic monitoring are key to successful anaesthesia in premature conjoined twin separation.

Keywords: extrauterine twin-to twin-transfusion, premature conjoined twins, separation surgery

Introduction

Conjoined twins (CT) are a rare phenomenon of monochorionic, monoamniotic twins. The prevalence of CT varies geographically and socioeconomically. The incidence varies from 1 in 50,000 to 1 in 10,0000 live births, with only 50% being liveborn.[1] CT are classified based on the site of attachment, where five types of CT are commonly identified: thoracopagus (thorax), omphalopagus (abdomen), pygopagus (sacrococcygeal junction), ischiopagus (pelvis), and craniopagus (skull). Omphalopagus CT have the best chances of survival if successfully separated. For a successful outcome, surgical separation of omphalopagus CT is often performed electively when the twins reach an acceptable age and weight, after extensive preparation and planning. Preparation includes examination of the twins with different imaging protocols and multidisciplinary team discussion. Here, we report the successful separation of premature omphalopagus CT weighing 2.7 kg at day 17 of life. The separation was done in an emergency setting due to life-threatening extrauterine twin-to-twin transfusion. Anaesthesia for premature CT separation surgery, especially in an emergency setting, imposes enormous challenges to the anaesthesiologist perioperatively.

Case presentation

A pair of premature symmetrical omphalopagus CT were born at 33 weeks and 5 days of gestation, via emergency caesarean section in a hospital distant from our centre. They were boys with a combined birth weight of 3 kg. The babies, designated as “twin A” (TA) and “twin B” (TB) (Fig. 1), were symmetrically conjoined from xiphisternum to below the umbilicus with normal head and neck, limbs, spine, and urogenital systems.

Both babies developed respiratory distress syndrome shortly after birth, received surfactant, and were mechanically ventilated for 72 hours. Initial echocardiography revealed two structurally normal and separated hearts, but dex-

Fig. 1. Omphalopagus conjoined twins A and B.

trocardia and a patent foramen ovale in TB. At day 6 of life, TA developed oliguria and hypotension requiring inotropes, and TB was noted to be hypervolaemic and polyureic. Extrauterine twin-to-twin transfusion was suspected and a contrast-enhanced computed tomography of the chest and abdomen was performed. The scan reported symmetrically conjoined twins, with shared liver parenchymał and small bowel, with possible complex biliary anatomy. The presence of cross-circu-

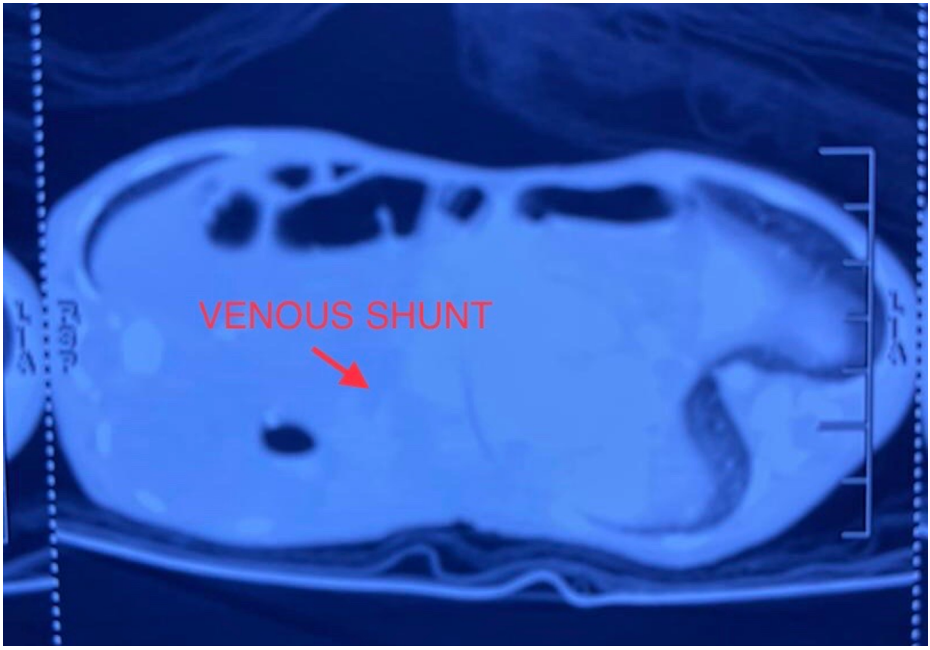

Fig. 2. Computed tomography of the abdomen showed venous vessels traversing the fused liver parenchyma.

lation between the twins was confirmed based on the presence of venous vessels traversing across the fused liver parenchyma (Fig. 2).

At day 13 of life, TA deteriorated, requiring bolus doses of fluids and increment in inotropic support, whereas TB became hypertensive and polyureic. The decision to transfer the babies to our centre for possible emergency separation was made after multidisciplinary discussion. A repeat echocardiography in TB revealed global hypokinesia and impaired systolic function, therefore intravenous (IV) adrenaline and IV milrinone were started preoperatively. The warning signs of imminent renal failure in TA and cardiac failure in TB prompted a multidisciplinary decision to proceed with the operation on day 17 of life, at a combined body weight of 2.7 kg, despite the high risk of morbidity and mortality. Written informed consent was obtained from the parents, specifying saving the baby with the better chance of survival should conditions arise where such a decision became necessary.

All team members involved were briefed on the flow of anaesthesia and surgery a day before surgery. The blood bank unit was alerted on the complexity of the case. Two anaesthetic teams were established and two operation rooms with an interconnecting door were used. Two sets of colour-coded equipment including the

anaesthetic machine, monitors, and induction carts were prepared. The identification tag of each team member was colour-coded to differentiate their roles.

The twins were transferred to the operation theatre in an incubator. Both babies faced each other in the semi lateral position. The drug dosage calculated for each baby was half of the combined body weight. They had femoral double lumen catheters inserted from the neonate intensive care unit (NICU), and were monitored with electrocardiogram, non-invasive blood pressure, and two sets of peripheral oxygen saturation.

Anaesthesia induction began in TB due to his cardiorespiratory instability. Following induction with sevoflurane 1% and IV fentanyl 1 mcg/kg, continuous positive airway pressure (CPAP) was applied with mask oxygenation and atracurium 1 mg administered for intubation. TB was intubated at the first attempt with a size 3 uncuffed endotracheal tube (ETT) using the C-MAC video laryngoscope (Karl Storz, Tuttlingen, Germany). During this time, CPAP and mask oxygenation with 1% sevoflurane in 100% oxygen was concurrently provided for TA. The same drugs and ETT size were used for TA. The ETTs were well secured with adhesive plasters to prevent ETT displacement during positioning or transfer. Anaesthesia was maintained with 0.2–1% sevoflurane in a 50% air-oxygen mixture, atracurium bolus doses, and IV fentanyl and morphine for analgesia.

IV and intraarterial line insertions were challenging. Catheterisation of the right internal jugular vein (IJV) for TA was achieved with ultrasound guidance. However, attempts of left IJV cannulation for TB were unsuccessful, hence achieved via venous cutdown by the surgeon. The twins' intraarterial blood pressure, central venous pressure (CVP), and temperature were continuously monitored

The total procedure time was approximately 7 hours, and they were separated 66 minutes after surgical incision. The surgery was performed with the twins in supine posture throughout the surgery. There were fluctuations in blood pressure and episodes of transient oxygen desaturation intraoperatively. The latter was managed by maintaining mean arterial pressure (MAP) above 35 mmHg for TA and above 40 mmHg for TB. The fused area of the liver was separated and the large abnormal vein ligated. TB was then transferred to the connecting operating room after separation. The diaphragmatic wall defect was repaired and abdominal wall defects were closed with Lyoplant® (B. Braun Melsungen AG, Germany). TA was infused with 5% dextrose and 0.45% normal saline solution as maintenance drip, and sterofundin 2% dextrose for TB. The twins' blood sugars were monitored. Estimated blood loss for TA was 30–50 ml; 20 ml of packed cells and 20 ml of fresh frozen plasma were transfused. The amount of packed cell transfusion for TB was equal to the amount of blood loss of 16 ml. Total fluids given for TA was 15 ml (10

ml/kg) of sterofundin while TB received 107 ml (approximately 70 ml/kg) of human albumin 5%.

Hypothermia was prevented intraoperatively by use of the radiant heat warmer, warming mattress, forced warmed air, fluid warming devices, and warm fluids. Core body temperature dropped to 35°C during line insertion, but remained above 35°C throughout surgery.

Postoperatively, both babies were transferred to the NICU ventilated. Urine output in TA normalised (1 ml/kg) within 12 hours postoperatively. TB developed anuric acute kidney injury within 18 hours postoperatively, which improved on postoperative day 2. Both babies were alive and well at the time of reporting.

Discussion

There is a recorded total of 25 CT separations performed in Malaysia since 1981. This is the third CT separation in our centre, and the first premature emergency separation due to extrauterine twin-to-twin transfusion. Each surgery involving CT has its unique circumstances, and its success depends on the site(s) of conjunction, organs shared, age and weight of patients, associated malformations, general condition of the twins, occurrence of serious illness in one twin or specific physiologic conditions, and the experience and skills of the attending team.[2] Our twin babies had liver fusion with venous shunt, and diaphragmatic defects.

Surgical separation is best done electively between 4 and 11 months of age.[3] Operative survival is 50% in the neonatal period, as opposed to 90% if surgery is performed after 4 months of age.[4]

Emergency situations warranting immediate separation include the presence of a stillborn twin, intestinal obstruction, rupture of an omphalocele, heart failure, obstructive uropathy, and respiratory failure.[2] In this case, urgent separation was indicated to avoid complications from significant circulatory crossover, resulting from extrauterine twin-to-twin transfusion, which potentially threatened the lives of both twins. TA developed CT extrauterine transfusion syndrome, with anuria despite creatinine levels within normal limits.[5] Despite the usual occurrence of vascular shunts and cross-circulation in CT, only a few cases of haemodynamically significant unbalanced circulatory shunting have been reported.[5] The extent of shared vasculature affects drug pharmacokinetics and pharmacodynamics, as well as fluid and blood administration. Prior to completion of surgical separation,

CVP in TA was maintained at 5–6 mmHg to minimize cross-circulation to TB. TA required packed cell transfusion for hypotension secondary to volume depletion. The use of inotropes was individualized, where TB was started on milrinone and adrenaline for impaired cardiac contractility, whereas adrenaline and noradrenaline were commenced in TA.

The perioperative management of CT requires extensive planning and teamwork with a multidisciplinary approach. The anaesthetic management for this case of CT was challenging due to their size and age at surgery. The younger the baby, the more immature the organs, especially the liver and kidneys, and thus the greater the challenges of all aspects of anaesthesia.[6] Their smaller size posed problems in terms of monitoring, vascular access, temperature control, and positioning.

Constant vigilance and monitoring were essential, and in this case experts of various fields including the neonatologist, nephrologist, and cardiologist were involved perioperatively. Advances in diagnostic techniques, meticulous anaesthetic management with careful intraoperative monitoring, improved surgical techniques with minimal blood loss, postoperative care with particular attention to potentially labile cardiovascular parameters,[4] and most importantly, prior experience, all contribute to the improved survival for CT separation.

Conclusion

CT separation is best managed by an experienced multidisciplinary team, functioning in a tertiary referral centre where a full range of medical and surgical specialties are available. The timing and planning of CT separation should be individualized based on the need for emergent separation and the degree of organ fusion. Anaesthesia for premature CT separation is very challenging and requires meticulous attention to details.

Declarations

Informed consent for publication

The guardians provided written informed consent for the publication of the images and clinical data contained in this case report.

Competing interests
None to declare.

Funding
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Ultrasound-guided caudal epidural anaesthesia for MRI-targeted transperineal prostate biopsy

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Abstract

Magnetic resonance imaging (MRI)-targeted transperineal prostate biopsy allows a more precise sampling of suggestive lesions. We describe a series of 10 cases for MRI-targeted transperineal prostate biopsy, of which 8 were successfully performed under ultrasound-guided caudal epidural anaesthesia. With the appropriate local anaesthetic volume and concentration, caudal epidural provides ideal conditions for this day case procedure.

Keywords: prostate biopsy, ultrasound-guided caudal epidural

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Introduction

Prostate cancer is the second most diagnosed cancer in men, with approximately 1.4 million new cases worldwide annually.[1] This high incidence is related to advances in prostate cancer screening including increasing public awareness, the use of prostate-specific antigen (PSA) testing, and improvements in prostate biopsy (PBx) techniques[2]. As a result, PBx is one of the commonest procedures performed by the urologist, with several surgical and concurrent anaesthesia techniques developed over the last few decades.[3]

A PBx technique that has recently generated interest is magnetic resonance imaging (MRI)-targeted transperineal prostate biopsy, which allows the clinician to target precise areas suggestive of cancer whilst avoiding those without any visible lesions on the MRI, thereby reducing the number of unnecessary biopsies and sampling errors.[4] MRI-targeted PBx has a similar or better ability to detect clinically significant cancer than standard biopsy techniques.[5,6]

The importance of effective anaesthesia for PBx regardless of technique cannot be understated. Men who undergo PBx have considerable psychological distress caused by the fear of cancer itself in addition to the anticipated procedural pain around a sexual organ and the anal route of penetration.[7] It is therefore now considered mandatory for anaesthesia to be administered during PBx. Over the years, various anaesthetic techniques have been described, including intrarectal lubricant agents, periprostatic nerve blocks, pelvic plexus blocks, pudendal nerve blocks, caudal blocks, intraprostatic anaesthesia, and general anaesthesia.[3]

In this article, we describe a case series on our experience in the use of ultrasound-guided caudal epidural anaesthesia for MRI-targeted transperineal PBx in a tertiary centre. To the best of our knowledge, there has been no description so far of utilising ultrasound-guided caudal epidural anaesthesia for this PBx approach.

Case series

We obtained informed consent from all patients included in this interventional case series as well as ethics approval from the Ethics Committee of Gleneagles Hospital Medini Johor. We describe the management of 10 cases of MRI-guided prostate biopsy with single shot caudal anaesthesia between August 2021 to January 2022.

The inclusion criteria were male adult patients, American Society of Anesthesia (ASA) physical statuses 1, 2, and 3, and scheduled for day case elective MRI-targeted

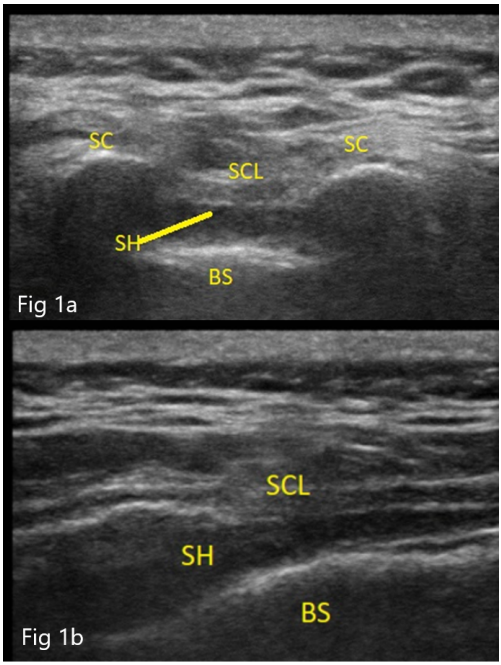

Fig 1. (a) Sonoanatomy in the tranverse view: base of sacrum (BS), sacral cornua (SC), sacral hiatus (SH) and sacrococcygeal ligament (SCL). *(b)* Sonoanatomy in the longitudinal view: BS, SH, and SCL.

transperineal PBx. The exclusion criteria were contraindications for neuraxial block, *e.g.*, antiplatelet therapy and inability to lie in prone position.

All patients had an intravenous cannula inserted and monitored with pulse oximetry, 3-lead electrocardiogram, and non-invasive blood pressure. Patients were then placed in the prone position. The procedures were performed by 3 experienced anaesthesiologists who routinely perform ultrasound-guided regional anaesthesia.

A scout scan was done to identify the anatomical landmarks and caudal epidural space target. A high-frequency linear probe (HFL38, Sonosite Inc. 6–13 Mhz) was placed in the transverse view across the sacrum to visualize the sacral median crest. The probe was slid caudal to view the base of the sacrum (BS), sacral cornua (SC), sacral hiatus (SH), and sacrococcygeal ligament (SCL) (Fig. 1a). The probe was then rotated to a longitudinal orientation to view the SH and SCL (Fig. 1b).

The equipment for caudal epidural anaesthesia is depicted in Figure 2a. The technique was performed under full aseptic technique. After skin infiltration with 2% lignocaine, a 50 or 100 mm Sonoplex needle (Pajunk, Geisingen, Germany) was inserted using the in-plane approach to pierce the SCL (Fig. 2b). An Infiniti Plus™ Disposable Needle Guide (CIVCO, Coralville, IA, USA) was used to improve the

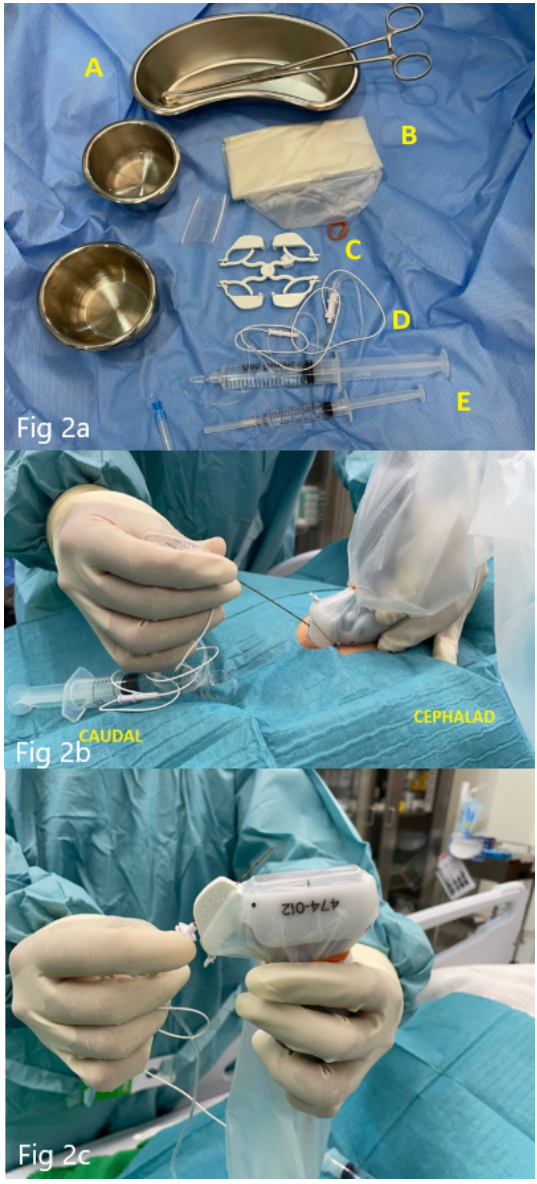

Fig. 2. (a) Kidney dish (A), ultrasound probe cover (B), CIVCO needle guide (C), Pajunk Sonoplex 50 mm/100 mm block needle (D), and local anaesthetic solutions (E). *(b)* Block needle point of insertion. (c) Fifty mm block needle placed in the needle guide.

procedural efficiency by aligning the block needle into the ultrasound beam (Fig. 2c). The advancement of the needle tip into the caudal epidural space was confirmed by ultrasound (Fig. 3). After negative aspiration, a few millilitres of the local anaesthetic (LA) solution were injected, while observing for the expansion of the epidural space. An LA solution of 17 to 20 ml was injected into the caudal space.

The patient was then turned supine and placed in lithotomy position as per surgical procedure. S1 dermatome hypoesthesia to pinprick was tested in to indicate sensory loss and initial success of the block. The transperineal PBx was performed using the iSR'obot™ MONALISA (Biobot Surgical, Singapore) robotic prostate biopsy navigation system. Five to 20 samples were taken depending on the evaluation of the urologist. If the surgeon noted that the patient was unable to keep still during the procedure, the anaesthetic technique was converted to general anaesthesia. The caudal block was considered successful if there was not a need to convert to general anaesthesia. One to 2 mg of midazolam was administered to all patients as anxiolysis.

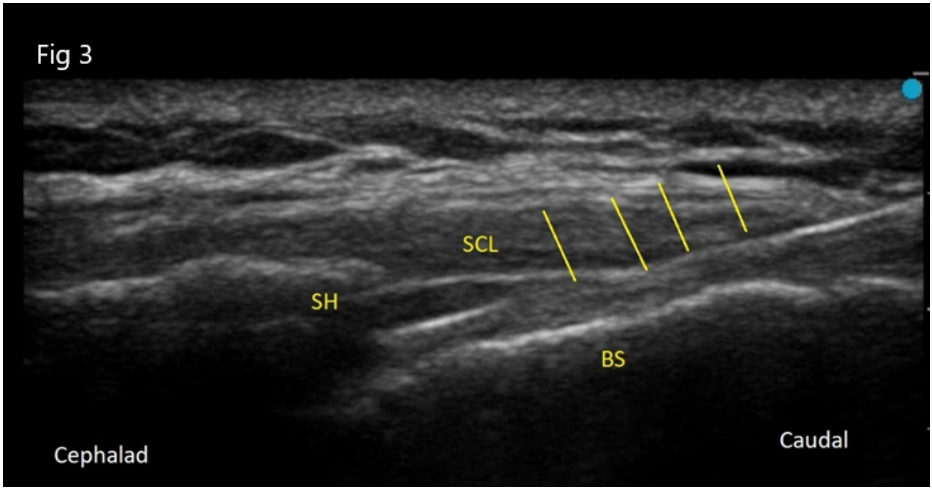

Fig. 3. Needle directed into the caudal space with ultrasound guidance. Base of sacrum (BS), sacral hiatus (SH), and sacrococcygeal ligament (SCL).

Table 1. Demographics and interventions for all patients included in the case series

No.	Age	ASA	Comorbidities	LA solution	Total volume	Complications
1	71	2	HT, IHD	0.2% ropivacaine	20 ml	Nil
2	75	3	HT, CHF with EF: 30%	0.2% ropivacaine	20 ml	Nil
3	71	3	HT, DC	0.2% ropivacaine	20 ml	Nil
4	52	1	Nil	1.5% lignocaine	20 ml	Converted to GA
5	72	2	Asthma	0.5% ropivacaine	20 ml	Nil
6	75	2	HT	1.5% lignocaine	17 ml	Nil
7	51	2	HT, smoking	0.375% ropivacaine	20 ml	Nil
8	73	2	HT	0.375% ropivacaine 2% lignocaine	10 ml 10 ml	Converted to GA
9	72	1	Nil	1.5% lignocaine	20 ml	Nil
10	74	2	HT, smoking	1.5% lignocaine	20 ml	Nil

ASA: American Society of Anaesthesia physical status; LA: local anaesthesia; HT: hypertension; IHD: ischaemic heart disease; CHF: chronic heart failure; EF: ejection fraction; DC: dilated cardiomyopathy; GA: general anaesthesia

Demographics and interventions for all patients are summarized in Table 1. In all cases, the duration of the surgical procedure was 20–45 minutes. Two of the 10 patients had to be converted to general anaesthesia. The 8 successful blocked patients did not report any discomfort whilst the procedure was performed. After the procedure was completed, the patients were observed in outpatient recovery. All patients were discharged home on the same day, and none experienced any serious complications warranting extended hospital stay or admission.

Discussion

In the last few decades, there has been progressive improvement in anaesthetic techniques that have led to PBx being a more accepted procedure. Indeed, studies have shown that anxiety around PBx is predominantly linked to symptoms rather than the actual diagnosis, with pain being closely related to high anxiety levels irre-

spective of biopsy outcome.[8] This underlines the importance of effective anaesthesia for the different approaches of PBx according to the urologist's preference.

We worked with a single consultant urologist in our centre who performs MRI-targeted transperineal PBx surgery. We believe that this allows for less confounding factors in our case series and for standardisation of biopsy technique.

The characteristics of the ideal anaesthesia technique for PBx are sufficient relaxation of the anal sphincter to allow manoeuvring of the rectal probe, prevention of pain during biopsy needle insertion ensuring immobilisation of patient during the procedure, low cost, and low incidence of side effects to ensure suitability for outpatient surgery.[9]

Our initial default anaesthetic technique was general anaesthesia. However, we quickly realised that this was less than ideal for elderly males presenting often with multiple comorbidities. In addition, there were other potential problems of general anaesthesia in this population including postoperative drowsiness and nausea/vomiting resulting in delayed discharges.

To mitigate these problems, we considered using various sedation techniques. Procedural sedation theoretically holds several advantages over general anaesthesia, including the maintenance of adequate spontaneous ventilation and cardiovascular function.[10] However, we also rapidly discovered issues with adequate pain control and immobilisation during PBx requiring increasing depth of sedation and its associated problems.

Spinal anaesthesia was also considered. Despite achieving dense sensory and motor blockade for the procedure, we found that this was again less than ideal for outpatient surgery, with delays in the return of motor function and prolonged urinary retention. Even with advances in spinal anaesthesia for ambulatory surgery with the use of agents such as hyperbaric prilocaine, the time to discharge can still take up to approximately 4 hours following administration.[11] Spinal anaesthesia saddle block technique could mitigate some of these issues; however, we found that the onset time for a saddle block with patients needing to be in a sitting position is comparable to the onset time of a caudal epidural injection, which is approximately 5 to 10 minutes. A major advantage of a caudal epidural injection in this regard is that once the injection has been performed, patients could be moved onto the lithotomy position and draped for surgery while the block is taking effect, as compared to a saddle block technique where the patient is required to be in a sitting position to achieve a true saddle block.

Caudal blocks have previously been described for transrectal ultrasound guided prostate biopsy, but not for a transperineal approach.[12] This approach allows the blocking of sacrococcygeal nerves, effectively providing anaesthesia to the perianal region, rectum, prostate gland, and perineum. The pudendal nerve arising from the ventral rami of spinal nerves S2 to S4 to innervate areas of the rectal canal, anus, perineum, and external genitalia is blocked by a caudal epidural injection, making this a suitable technique for anaesthesia in transperineal approaches to PBx.[13]

Despite being well described and more commonly used in paediatric anaesthesia and interventional chronic pain management, caudal epidural anaesthesia is less commonly used in adults. In fact, failure due to incorrect needle insertion has been reported to occur in up to 38% of cases, largely due to anatomical variation caused by ageing.[14] Ultrasonographic examination allows the clinician to appreciate these anatomical variations, reducing the number of attempts as well as improving success rates.[15] We have therefore utilised ultrasound in all our caudal epidural injections allowing us to achieve a success rate of 80% in this series. In our case series, 2 cases required conversion to general anaesthesia due to a failed caudal block, owing to the LA solution being erroneously injected into the SCL rather than within the caudal space. Nevertheless, our aim in this case series is to demonstrate that this anaesthesia technique is feasible for outpatient transperineal prostate biopsy surgery.

Therefore, an obvious obstacle to this anaesthetic technique is the requirement of operator training and experience in the use of ultrasound as well as the availability of the equipment itself. Knowledge in sonoanatomy of the SC, SC, and the SCL is crucial in the performance of this block, given the anatomical variations adult patients can present with.

When successful, however, caudal epidural anaesthesia achieves many of the aims of the ideal anaesthetic for transperineal PBx. This technique provides good analgesia and relaxation of the anal sphincter, with minimal side effects and minimal motor blockade of the lower limbs.

Sympathectomy causing hypotension is unlikely and the risk of dural puncture, particularly in adults, is extremely low, consistent with previous studies looking at the use of caudal blocks for transrectal PBx and anorectal procedures.[12]

Post-procedure urinary retention can be brought upon by caudal epidural injections, which not only interferes with patient comfort, but also necessitates insertion of a urinary catheter while also delaying postoperative urodynamic testing occasionally required by our urologist. Our initial experience did indeed demonstrate this side effect with the use of longer acting LA agents such as ropivacaine, resulting

in approximately 70% urinary catheterisation rate.

We are currently using a shorter acting LA, such as lignocaine, which resulted in a significant reduction in urinary catheterisation rates, but without any compromise on postoperative analgesia. In our experience, 17–20 mL of a shorter acting LA such as 1.5% lignocaine significantly reduces the risk of postoperative urinary retention. The volume of LA used for this indication can be further refined as we have more data on sensory block height. Further studies are therefore required for this.

Conclusion

Our case series has shown that ultrasound-guided caudal epidural anaesthesia is a feasible option for outpatient, MRI-targeted transperineal PBx procedures. With the appropriate LA volume and concentration, we believe that this technique provides ideal conditions for this surgical procedure with minimal side effects while allowing early ambulation and discharge.

Declarations

Ethics approval and informed consent
The authors declare that informed consent by all patients has been taken with due diligence. Ethics approval by the Gleneagles Hospital Medini Johor ethics committee has been confirmed.

Consent for publication
The authors declare to have received informed and sufficient consent from the patients to use their clinical information and images in the article.

Competing interests
Dr. Shahridan Mohd Fathil serves as Deputy Chief Editor of Malaysian Journal of Anaesthesiology. Dr. Mohd Fathil has not been involved in any part of the publication process prior to manuscript acceptance; peer review for this journal is double blind. The remaining authors state no conflict of interest.

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Case series
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Wolff-Parkinson-White syndrome: anaesthetic care for meningioma excision

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Abstract

In Wolff-Parkinson-White (WPW) syndrome, the presence of an accessory pathway between the atrium and ventricle predisposes the patient to paroxysmal supraventricular tachyarrhythmias, which may progress to ventricular fibrillation and sudden cardiac death. Several drugs that are used perioperatively may alter the cardiac conduction velocity and refractory period. This fact, interacting with factors such as increased sympathetic tone (*e.g.*, anxiety, pain, or seizure) or haemorrhage, leads to tachycardia, where shortened R-R interval predisposes the heart to re-entrant tachyarrhythmias. We reported and highlighted the perioperative issues while anaesthetising a 15-year-old boy with WPW syndrome for craniotomy and excision of parietal meningioma.

Keywords: craniotomy, general anaesthesia, intracranial surgery, meningioma, Wolff-Parkinson-White syndrome

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Introduction

Wolff-Parkinson-White (WPW) syndrome is a subtype of a ventricular pre-excitation syndrome caused by the presence of an anomalous accessory pathway (bundle of Kent) between the atrium and ventricle. The most significant anaesthetic risk in these patients is the development of haemodynamically unstable tachyarrhythmias, which may progress to ventricular fibrillation and sudden cardiac death. Currently, there is no validated scoring system that predicts the risk of tachyarrhythmias under anaesthesia. Its anaesthetic management is challenging, more so in neurosurgery, where specific neuroanaesthesia goals may be at times in conflict with haemodynamic considerations. Here, we present the successful anaesthetic management of a patient with WPW syndrome for the excision of a large parietal meningioma.

Case presentation

A 15-year-old boy was admitted to the cardiology ward for a workup of WPW syndrome after presenting with chest discomfort, syncopal attack, and breathlessness that subsided on their own. His presenting electrocardiogram (ECG) showed the classical type A WPW pattern: shortened PR interval and delta waves with widened QRS complex without right ventricular hypertrophy, while his 24-hour Holter showed several episodes of non-sustained supraventricular tachycardia, for which no intervention was required. In the cardiology ward, he developed one episode of a generalised tonic-clonic seizure. Following that, an urgent contrasted computed tomography of the brain (Fig. 1) was performed, revealing a large left parietal meningioma (10.2 x 8.8 x 8.5cm) with adjacent skull hyperostosis. He was posted for elective left craniotomy and excision of parietal meningioma. During preanaesthetic consultation, he was asymptomatic and fit-free, with a baseline heart rate of 74–83 beats/min. His blood investigations were normal. The echocardiogram did not show evidence of Ebstein anomaly or valvular pathology. After the cardiologist consults, he was not started on antiarrhythmic drugs, and we were cautioned to avoid tachycardia intraoperatively. The patient and his guardian were adequately counselled on the high cardiac risk and reassured. The patient was kept fasted, and an intravenous (IV) fluid was started to keep him euvolemic. No premedication was given to avoid obtundation of his neurological status.

We took all the necessary precautions to avoid tachycardia and arranged vital drugs to treat complications together with stringent monitoring, which were very important for a favourable outcome in this patient. In the operating room, an arterial line was inserted while the patient was still awake, and a self-adhesive

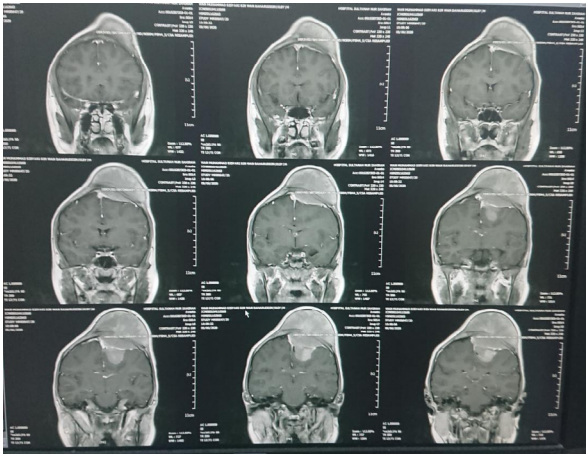

Fig. 1. A contrast-enhanced computed tomography of the brain (sagittal view) shows a large, left parietal meningioma measuring 10.2 x 8.8 x 8.5 cm with adjacent skull hyperostosis.

defibrillator pad was applied at the anterior-lateral placement prior to induction. A crash cart with relevant antiarrhythmic drugs (adenosine, esmolol, lignocaine and amiodarone) was also available in the operating room. Cardiac-stable induction was performed, with target-controlled infusion (TCI) remifentanil infusion [Minto model, effect site-targeted concentration (Cet) up to 6 ng/ml], titrated dose of IV propofol (total 120 mg), and IV rocuronium 50 mg. Care was taken not to hyperventilate the patient, and intubation was performed at the deep plane of anaesthesia. Intubation proceeded without any untoward events. The patient was put on a ventilator, and sevoflurane in an oxygen and air mixture was started. This was followed by obtaining additional IV access, a central venous line, and Foley's catheter insertion. Prior to head pinning, scalp block was performed at bilateral supratrochlear, supraorbital, zygomaticotemporal, and auriculotemporal nerves using landmark technique, with 3 ml of 0.25% bupivacaine (adrenaline free) per site. TCI remifentanil was then increased to Cet 6 ng/ml, and the Mayfield clamp was applied by the surgeon. Before starting the surgery, IV esmolol 10 mg was given to attenuate the sympathetic surge.

Intraoperatively, there were two episodes of sinus tachycardia (maximal heart rate of 110 beats/min): at scalp dissection and the period of rapid blood loss during meningioma excision (Fig. 2). During the first episode, which was probably due to intense pain stimuli, analgesia was managed by increasing TCI remifentanil to Cet of 6 ng/ml, and supplemental bupivacaine was infiltrated by the surgeon directly at the surgical site. In the second episode, which was probably due to ongoing blood loss, fluid resuscitation was initiated with crystalloids, packed red blood cells, and blood components. In both instances, we managed to return the patient's

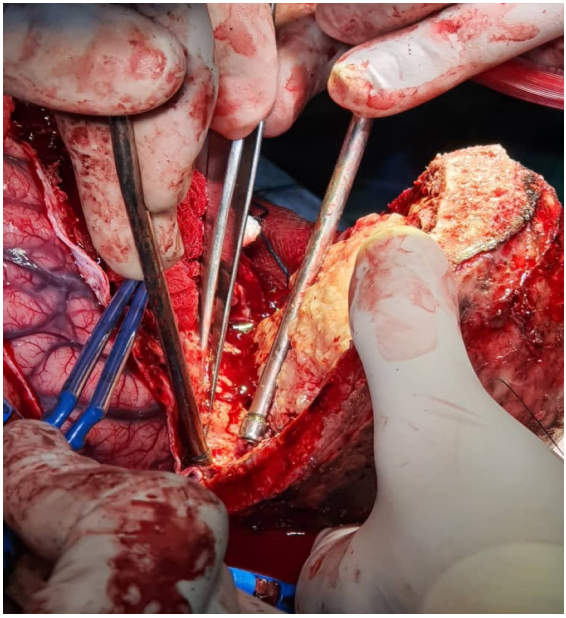

Fig. 2. The second episode of tachycardia occurred during excision of the meningioma, where there is a possibility of ongoing and underestimated blood loss.

heart rate to his baseline without any episodes of malignant supraventricular tachycardia and significant haemodynamic instability. The meningioma was successfully removed after 3 hours. After surgery, IV sugammadex 2 mg/kg was given, and the patient was extubated. Extubation was controlled and smooth. Postoperatively, his pain was managed with a titrated IV dose of fentanyl and morphine. He remained stable in the recovery and was transferred to the neuro intensive care unit (ICU) for monitoring. He was reviewed by the cardiologist in the neuro ICU and was given an electrophysiology study (EPS) appointment.

Discussion

Most patients with WPW syndrome may remain asymptomatic throughout life, but these patients are at risk of paroxysmal supraventricular tachycardia, atrial fibrillation, and sudden cardiac death during the perioperative period. Due to the rarity of this condition, the incidence of patients with WPW syndrome presenting for surgery is unknown, but ECG screening in the general population showed that asymptomatic WPW occurs in 0.7–1.7 patients per 1,000 population, where a further 1–1.8% are symptomatic.[1,2] For symptomatic patients, the most common presen-

tations include palpitations, chest pain, and dyspnoea. Our patient presented with chest discomfort, syncopal attack, and breathlessness, which were self-limiting but warranted a workout because of recurrent symptoms in a previously fit young man.

The normal atrioventricular (AV) node utilizes a calcium-dependent slow inward current, while the accessory pathway in WPW syndrome patients utilizes a sodium-dependent fast inward current for electrical impulse transmission. The lack of physiological delay in transmission of the sinus impulse via the abnormal accessory path*, i.e.*, the bundle of Kent, results in a short PR interval. Ventricular excitation, formed by the two impulses, results in a fusion beat seen as a "delta wave" with prolonged QRS complex in a typical ECG of WPW syndrome. WPW syndrome is traditionally classified into type A and type B. On ECG, type A resembles a right bundle branch block with right ventricular hypertrophy and posterior myocardial infarction, whereas type B resembles a left bundle branch block with left ventricle hypertrophy.[3] Our patient's ECG showed a type A pattern but without right ventricular hypertrophy. The cardiac anomaly most frequently associated with this problem is Ebstein's anomaly, but not in our patient, as his echocardiogram was normal.

Most anaesthetic drugs and techniques tend to change the physiology of AV conduction. The principle guiding perioperative anaesthetic management in this patient was to utilize agents with the least effect on myocardial contractility, conduction velocity, and refractory period with minimal circulatory depression.[4] Specific to the neurosurgical population, the selected agents must provide a rapid central nervous system recovery. In addition to the correct use of anaesthetic agents, a proper plan of the anaesthetic technique, teamwork, and vigilant monitoring are key to surgical success.

The effect of most anaesthetic drugs on conduction speed and the refractory period has been studied, principally derived from anaesthetic management during EPS.[4-6] Anaesthetic agents proven to be devoid of effect on cardiac conduction are fentanyl, remifentanil, alfentanil, propofol, etomidate, cis-atracurium, and rocuronium.[7] In fact, propofol has been shown to normalize WPW conduction in one case series.[8] For inhalational agents, sevoflurane, isoflurane, and nitrous oxide have been proven to be safe. Anaesthetic agents that are proarrhythmic (halothane), have intrinsic sympathomimetic properties (ketamine, desflurane, meperidine), or cause tachycardia either due to histamine release (causing reflex tachycardia, such as thiopentone and atracurium) or vagolysis (such as pancuronium) should be avoided. Specific to neurosurgery, such as in this case, fentanyl, propofol, and rocuronium were used during induction, and the anaesthesia maintained with remifentanil and sevoflurane in oxygen and air. Desflurane, with its potentially

detrimental effect on cerebral haemodynamics, was avoided in our patient. For the reversal of neuromuscular blockade, sugammadex, a selective reversal binding agent devoid of autonomic properties, was used.[9] Neostigmine, which increases parasympathetic activation and hence delays myocardial conduction speed and prolongs the refractory period, was avoided. Furthermore, anticholinergics such as atropine and glycopyrrolate, which are coadministered with neostigmine, were avoided due to their vagolytic properties.

Induction is a high-risk procedure in WPW syndrome, as 20% of tachyarrhythmias occur during induction of anaesthesia, and 10% develop ventricular fibrillation. For this patient, the intubation was performed smoothly and gently by the anaesthetist within a short intubation time. Monitoring in this patient was achieved by serial 12-lead ECG, defibrillator cardiac monitor, invasive arterial waveform analysis with pulse pressure variation as well as systolic pressure variation reading and bispectral index monitor.

Skull pinning is an intense and stimulating part of neurosurgery. Several methods have been proposed for its management, such as deepening the anaesthetic agents, opioids such as fentanyl or remifentanil, beta blockers such as esmolol or labetalol, scalp block, or avoidance of skull pinning where possible. In patients with WPW syndrome, sympathetic activation increases the conduction speed through the accessory pathway, putting them at risk of tachyarrhythmia. The scalp is richly vascularized. As a result, the risk of cardiotoxicity and local anaesthetic systemic toxicity (LAST) is higher. Levobupivacaine, which has a higher (safer) cardiovascular collapse:central nervous system ratio, yet has a reasonable duration of action, should be the local anaesthetic of choice, but it was unavailable for our patient and only an epinephrine-free preparation was used. Adrenaline is a potent vasoconstrictor with the potential advantages of prolonging block duration, reducing the risk of LAST, and reducing bleeding. However, its use for scalp block is associated with a biphasic response: an earlier, brief episode of hypotension caused by beta-2 adrenoceptor-induced systemic vasodilation, followed by hypertension and tachycardia due to beta-1 and alpha-1 adrenoceptor activation, causing increased dromotropy, inotropy, and vasoconstriction—both of which were detrimental in our case.[10]

Treatment of perioperative hypotension is crucial. Phenylephrine (an alpha-1 agonist) should be the vasopressor of choice. Phenylephrine, with its resultant reflex bradycardia, has been shown to abolish pre-excitation in one case series. Furthermore, phenylephrine does not affect intracerebral vasomotor tone since the alpha-1 receptor is absent in the brain vasculature.[11] Euvolemia should be instituted to minimize vasopressor use. In this case, fast response on catching up of the blood losses with fluid and blood products avoided any episodes of precip-

itated intraoperative tachyarrhythmia. In urgent situations with supraventricular tachycardia, especially with atrial fibrillation and atrial flutter, direct current shock is the treatment of choice, for which the defibrillator pad was readily attached preinduction. Patients developing atrial fibrillation with haemodynamic stability should be treated pharmacologically. In contrast, haemodynamically unstable patients should be treated by cardioversion with 150–200 J. Digoxin and verapamil should be avoided, as these antiarrhythmics have been shown to enhance anterograde conduction through the accessory pathway.

Hyperventilation, with its resultant hypocapnia, lowers the conduction threshold and should be avoided. Furthermore, it is not favourable in the neurosurgical patient as it impairs cerebral perfusion. In this patient, extubation response can be detrimental. Few reports in the literature show that tracheal extubation under deep anaesthesia may reduce the incidence and complications. However, it often causes airway obstruction and risks an unprotected airway. Particularly in the neurosurgical patient, assessment of neurological recovery mandates extubation in an awake patient. Few case reports have implemented laryngeal mask airway insertion after tracheal extubation, which may minimize the stress response while providing a patent airway during emergence from anaesthesia (Bailey procedure). However, in our patient, only after transferring him to the ICU bed, supplementation of adequate multimodal analgesia, gentle suctioning of oral airways, and keeping the remifentanil at a lower dose, did we cut off the gas before he regained full consciousness until extubation.

Conclusion

Successful anaesthetic management of patients with WPW syndrome depends on factors such as cardiac stable anaesthesia, avoidance of tachycardia and sympathetic surge, and ability to manage haemodynamically significant tachyarrhythmia. Scalp block using adrenaline-free local anaesthetics is an attractive method of analgesia.

Declarations

Informed consent for publication
This case report was published with the written consent of the patient and his mother.

Competing interests
Dr. Vanitha Sivanaser serves as Section Editor of Malaysian Journal of Anaesthesiology. Dr. Sivanaser was not involved in any part of the publication process prior to manuscript acceptance; peer review for this journal is double blind. The remaining authors state no conflict of interest.

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Platelet-rich plasma injection for symptomatic relief of disability associated with traumatic knee arthritis: a case report

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Abstract

Multimodality is the mainstay of osteoarthritis (OA) treatment and intra-articular platelet-rich plasma (PRP) injection is gaining acceptance due to its regenerative properties and being minimally invasive. We present a young woman with Kellgren-Lawrence grade 3 post-traumatic OA in the left knee who refused surgery and opted for pain clinic follow-up. Five PRP injections in intervals of 4 to 9 months were administered in the past 2 years in addition to oral analgesia when necessary. Five ml of PRP was prepared via the double-spin open method and injected under ultrasound guidance to the left knee joint. Visual analogue scale (VAS) for pain was recorded at pre-procedure, and at 1-week and 1-month post-procedure. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was recorded at pre-procedure and 1-month post-procedure. PRP injection successfully reduced the VAS from 5 to 3 at both 1-week and 1-month post-procedure, and resulted in a WOMAC reduction of 54% with improvement in all WOMAC subscales at 1-month post-procedure. Our case showed that PRP injection demonstrated a positive effect on pain relief and physical function improvement in traumatic knee OA.

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Keywords: knee osteoarthritis, platelet-rich plasma injection

Introduction

Knee osteoarthritis (OA) is a multifactorial, common, progressive joint disease which causes chronic pain and functional disability. The global prevalence is 16% with an incidence of 203 per 10,000 person-years, thus contributing to a major global health burden.[1] While multimodality is the mainstay of OA treatment, intra-articular platelet-rich plasma (PRP) injection is gaining acceptance.[2,3]

Case presentation

A 35-year-old woman with a history of left upper tibial plateau fracture treated with internal fixation and subsequent implant removal in 2010 initially presented to the Orthopedic Department with progressive left popliteal fossa swelling after a fall and unable to flex her left knee for 5 months in late 2018. She had also been diagnosed with smear-negative pulmonary tuberculosis and completed antituberculosis treatment in 2019. The diagnosis was extensive OA in the left knee with osteomyelitic changes in the tibia and femoral condyles. Arthroscopic debridement and synovial biopsy of the left knee were performed in January 2019. The tissue and synovial fluid cultures were both negative. As she was not keen for total knee replacement, the patient was then referred to the Pain Clinic in June 2019 for chronic pain in the left knee pain with an average visual analogue score (VAS) of 8 on movement. For analgesia, she was prescribed oral celecoxib 200 mg once daily and paracetamol 1 g when necessary.

The option of PRP injection was offered to her in February 2020. A total of 4 injections in intervals of 4 to 9 months were administered until September 2021. At this juncture, the average pain score on movement had dropped by 3 points from 8 to an average of 5, accompanied with reduction in the need for daily oral analgesia. Her functional improvement was not objectively documented.

During the clinic visit in June 2022, she reported VAS of 0 at rest and 5 upon movement. Her weight had increased from 48 kg in 2019 to 58.2 kg. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was 37/96, equal to 39%. She scored 7/20 in the pain subscale, 2/8 in the stiffness subscale, and 28/68 in the physical function subscale. On examination, she was able to ambulate without assistance with a slight limping gait. The knees were not swollen, erythematous, or

warm. There was no tenderness upon palpation of both knees. The right knee had a full range of motion. Left knee flexion was 90° with extension of -10°, which showed a fixed flexion contracture. Weight-bearing X-ray showed Kellgren-Lawrence Grade 3 OA changes.

We proceeded with the fifth PRP injection. Five ml of PRP were obtained from the patient's own 20 ml venous blood with the double-spin open method using the centrifuge machine. The first spin was 25,000 revolutions per minute (RPM) for 8 minutes in a serum clot activator tube and the second spin was 20,000 RPM for 8 minutes in a plain vacuum tube. PRP was administered to the left knee joint under ultrasound guidance with Stimuplex A 22-G, 80 mm needle (B. Braun, Melsungen, Germany) under aseptic condition. The procedure was uneventful. Post-procedure, the left knee was passively flexed and extended to allow the PRP to spread throughout the joint. She was then discharged with oral celecoxib 200 mg capsule when necessary (5 doses/month) and oral paracetamol 1 gm when necessary (5 doses/month).

Upon review after 1 week of the procedure, she reported a VAS of 0 at rest and 3 upon movement in the left knee. At 1-month post-procedure, her VAS scores were the same. The WOMAC score was 17/96, equal to 17.7%. The pain subscale was 4/20, the stiffness subscale was 1/8, and the physical function subscale was 12/68. This showed a 54% improvement from the pre-procedure score with better scoring in all subscales. There were no reported post-procedure side effects (pain, bleeding, stiffness or swelling) at the injection site. At the last follow-up, the patient reported being able to jog twice a week for weight reduction, which she was not able to do previously. However, there was no significant improvement on the range of motion in the left knee. Table 1 summarizes the results for VAS and WOMAC.

Table 1. Results for the VAS pain scale and WOMAC score

Pain scale		**Pre-procedure**	**1-week post-procedure**	**1-month post-procedure**
VAS for pain	At rest	0	0	0
	Upon movement	5	3	3
WOMAC	Pain	7/20	-	4/20
	Stiffness	2/8	-	1/8
	Physical function	28/68	-	12/68
	Total (%)	37/96 (39)	-	17/96 (17.1)

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

Discussion

The growing burden of OA highlights the need for a proactive approach in its management. However, the Malaysian Clinical Practice Guidelines (CPG) on the Management of Osteoarthritis, published in 2013, recommended a linear step-up algorithm and has not been updated to date.[2] Each approach is only introduced after failure of previous management with persistent OA symptoms. A revised consensus by Yeap at el. has suggested a multimodal approach as the mainstay of OA management, which includes pharmacological and non-pharmacological intervention.[2] Treatment must be individualized to fulfil the patient's expectation. Non-pharmacological treatment included patient education, weight loss, exercise programs, knee unloading, and soft braces/knee sleeves. Pharmacological management included symptomatic slow-acting drugs for OA, topical and oral non-steroidal anti-inflammatory drugs, paracetamol, short-term weak opioids, intra-articular hyaluronate, and intra-articular corticosteroids (IACS).[2]

Regenerative treatment in the form of intra-articular PRP and mesenchymal stem cell injections have also been included in the injection-based therapy as a potential joint remodeling approach.[3] Surgical intervention, either total or partial knee replacement, is recommended for patients with severe knee OA. Bourne *et al.* showed that one-fifth of patients were not satisfied with the outcome of total knee arthroplasty; the artificial implant has a lifespan of only 10 to 15 years, which is not suitable for young patients.[4]

In 2017, an update on PRP for treatment of OA was reported by the Health Technology Assessment Section of Ministry of Health Malaysia.[5] PRP is defined as a mixture of autologous plasma that has highly concentrated platelets and associated growth factors including hepatocyte growth factors, vascular endothelial growth factors, platelet-derived growth factors and transforming growth factors with other bioactive components derived after whole blood centrifugation and separation.[6] These have been shown to promote cell recruitment, proliferation, and angiogenesis and further induce a regenerative response by balancing the anabolism and catabolism in the damaged structures, including cartilage, and altering the microenvironment of OA disease progression.[7] PRP injection to the knee joint is minimally invasive, may assist in the repair of the injured tissue, and is currently a management option for knee OA. PRP has many other known applications in dentistry, dermatology, ophthalmology, plastic, maxillofacial, and cardiothoracic surgeries.[4,7]

PRP is gaining wide acceptance due to its minimal adverse effects compared to exogenous compounds.[7] The double-spin open method is the preferred method of preparation due to its lower cost and better platelet yield as compared to the

single-spin method.[8] Nevertheless, the optimal centrifuge parameters have not been concluded yet.[8]

A recent comprehensive consensus guideline on knee pain assigned a level 1 recommendation to safety and efficacy of intra-articular PRP for knee pain and improvement in function.[3] Studies have shown that improvement for pain and function decline starting at 6 to 9 months post-PRP injection; the optimal frequency of PRP injections remains unclear. Huang *et al.* showed that at 12 months post-intervention, all patients had significant improvement in terms of VAC and WOMAC compared to pre-procedure.[9] The group that received 3 injections per month showed better results than those with 1 and 2 injections per month, but there was no significant improvement in terms of range of motion of the knee among the 3 groups and between pre-intervention and at 12 months post-intervention.[9] However, Patel *et al.* suggested that a single injection was as effective as double PRP injections for 6 months in terms of pain improvement.[10] In our case, the interval of PRP injection was determined by the status of the patient's physical function and pain score.

We chose PRP instead of IACS because PRP has demonstrated better improvement over IACS in longer follow-up.[11] In their randomised controlled study, Elksniņš-Finogejevs *et al.* showed that both injections improve the short-term pain scores with knee function in those with mild to moderate OA.[11] There was no significant difference in pain reduction between the 2 types of injection up to the 6-month follow-up.[11] This may be attributed to the benefit of PRP in regenerating the joint micro-environment rather than just controlling the inflammation.[7,10] PRP injection also shows significant pain reduction compared to intra-articular hyaluronate with moderate evidence.[3]

WOMAC was used in our case report due to its disease-specific, self-administered characteristics, which help to measure pain and physical disability for people with knee and hip OA. Hmamouchi *et al.* has suggested a 16% reduction of the total WOMAC score from baseline, which is a clinically important difference and is associated with slightly better improvement on the transition scale.[12] We successfully reported a baseline WOMAC score of 39 % that decreased to 17.7 % which is a reduction of 54% post-PRP injection.

Conclusion

PRP injection demonstrated a positive effect on pain relief and physical function improvement associated with knee OA. However, more randomized controlled studies are needed to standardize PRP preparation and to determine optimal injection intervals for management of knee OA.

Declarations

Informed consent for publication
Informed consent for publication was obtained from the patient.

Competing interests
None to declare.

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Continuous spinal anaesthesia, an underutilised neuraxial technique in current anaesthesia practice: a timely reminder

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Abstract

Continuous spinal anaesthesia (CSA) is a cardio-stable technique used in high-risk patients undergoing surgery. However, this technique appeared to decline over the last decades due concerns of complications that arise from using this technique, such as post-dural puncture headaches and neurological deficits. We report two cases of elderly patients, one at high cardiac risk and one with dementia and multiple comorbidities, under CSA for orthopaedic surgery with no reported complications. CSA is an adequeate anaesthetic technique with a low failure rate and complications. Proper technique should be taken into consideration to increase the success rate for this procedure.

Keywords: continuous spinal anaesthesia, high-risk, orthopaedic surgery

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Introduction

Continuous spinal anaesthesia (CSA) is currently a less popular mode of anaesthesia. CSA is suitable for frail populations with fixed cardiac output and severe respiratory disease. Compared to other neuraxial and general anaesthesia techniques, CSA is acknowledged for its flexibility in dosage titration and increment, rapid onset, and indefinite block duration with haemodynamic stability.[1,2] Intraoperative hypotension is independently associated with poor non-cardiac surgery outcomes.[3]

Neurotoxicity, particularly cauda equina syndrome, was its most significant drawback in the United States in the 1990s. Further research revealed that high local anaesthetic concentration and maldistribution around spinal roots are the culprits.[4] Other downsides of CSA include difficult catheter insertion, the risk of anaesthesia failure due to catheter occlusion, post-dural punctuate headache, infection, hematoma, and catheter fracture. Lack of experience, expertise, and equipment prevent some anaesthetists from performing CSA. CSA popularity is re-emerging, and a newer study described using thoracic CSA for high-risk patients undergoing major abdominal surgery in Italy.[5] Nevertheless, thoracic CSA requires expertise due to its potential cardiac, respiratory, and spinal cord complications, which needs further analysis to prove its advantages.[6]

Cases

We performed CSA on two elderly patients with intertrochanteric fractures using the Pajunk IntraLong CSA set (Pajunk, Geisingen, Germany) (Fig 1), which is technically easy to perform, even for beginners. The IntraLong is the only CSA set available in Malaysia. Table 1 summarises their background. Both cases were performed by a resident anaesthesiologist who was using the IntraLong set for the first time under the consultant's supervision.

The following were steps in performing CSA for the above cases:

1. A spine sonography using transverse interspinous view (static guidance) was performed to measure the depth to the epidural space.

2. Case 1 was placed in sitting position, while Case 2 was placed in right lateral position (patient could not sit upright due to contracture). After cutting the skin, a 21-G 90-ml Sprotte needle was inserted.

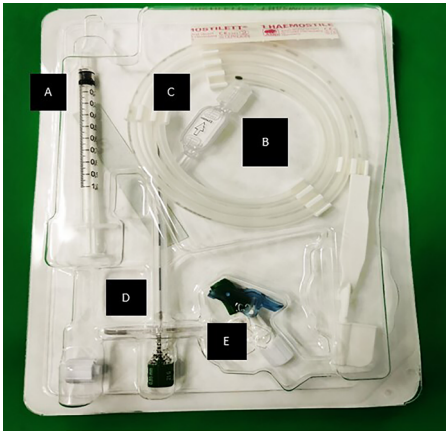

Fig. 1. Pajunk IntraLong. (A) 1 ml Luer syringe. (B) IntraLong spinal catheter (25-G with closed tip and three lateral openings) (C) Filter (the filling volume is approximately 0.35 ml). (D) IntraLong needle (Sprotte) 21-G (atraumatic tip minimises the chance of post-dural punctuate headache and reduces the chance of shearing off the catheter, also allowing easy catheter threading. (E) Clamping adapter.

Table 1. Background history of the two cases

Case information	**Case 1**	**Case 2**
Background history	85-year-old male, ASA III with coronary artery disease and HT. CFS score of 3.	87-year-old female, ASA III, with thoracic scoliosis and interstitial lung disease with mild bronchiectasis, HT, and type II DM, vascular dementia, L5/ S1 spondylolisthesis, L1 and L5 vertebra old compression fracture without neurological deficit. CFS score of 7.
Physical examination and investigations	Physical examination was unremarkable. Echocardiography showed global hypokinesia with a reduced ejection fraction of 30%. Chest X-ray revealed cardiomegaly. Revised cardiac risk index of 1 with 6% 30-day mortality, myocardial ischaemia, and cardiac arrest.	Physical examination was unremarkable. HRCT of the thorax showed interstitial lung disease with mild bronchiectasis.
Operation	Proximal femoral nailing	

American Society of Anaesthesiologists (ASA); clinical frailty scale (CFS); high-resolution computed tomography (HRCT); HT: hypertension; DM: diabetes mellitus

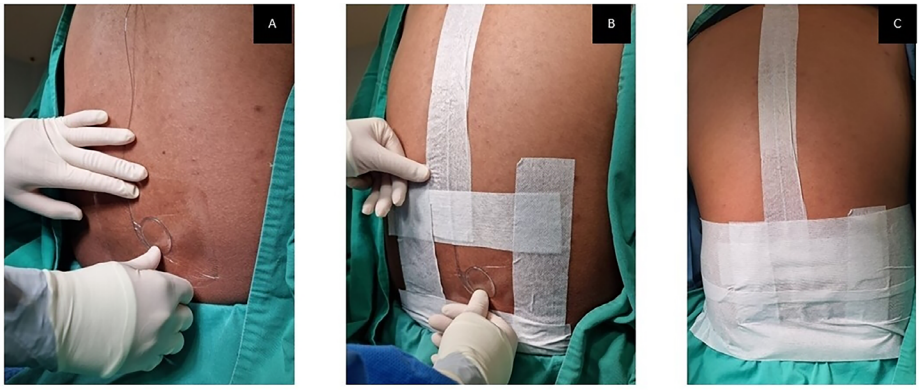

Fig. 2. (A-C). Spinal catheter was securely anchored with 3M® hypafix tape. The dead space volume, which includes the adapter, catheter and filter, is 0.9 ml.

3. The stylet was removed with demonstrable free-flowing cerebrospinal fluid (CSF). The length of the needle to reach the subarachnoid space (skin-to-space) was noted.

4. The spinal catheter was inserted using the catheter-through needle technique to adequate length. Next, the needle was removed from the skin carefully without pulling out the stylet guide wire. Then, the catheter was pulled out to the marking at the skin with 3 cm left in the subarachnoid space. Both the needle and stylet guide wire were carefully removed; no adjustment to the catheter should be performed thereafter.

5. The catheter was attached to the clamping adapter and bacterial filter, which had been primed with heavy bupivacaine 0.5%.

6. The catheter was secured with visible dressing at the insertion point and 3M hypafix surround the dressing frame (Fig. 2).

7. An initial bolus of 1 ml heavy bupivacaine 0.5% was given.

8. Assessment was made with pinprick for sensory block and modified Bromage scales for motor block.

9. Further top-up doses of 0.5 ml heavy bupivacaine 0.5% were given at 10 minutes intervals to achieve T10 dermatome.

The LA dosing for CSA may vary according to local protocol. The total spinal volume for both cases was approximately 1.5 ml. The key to safe practice is to

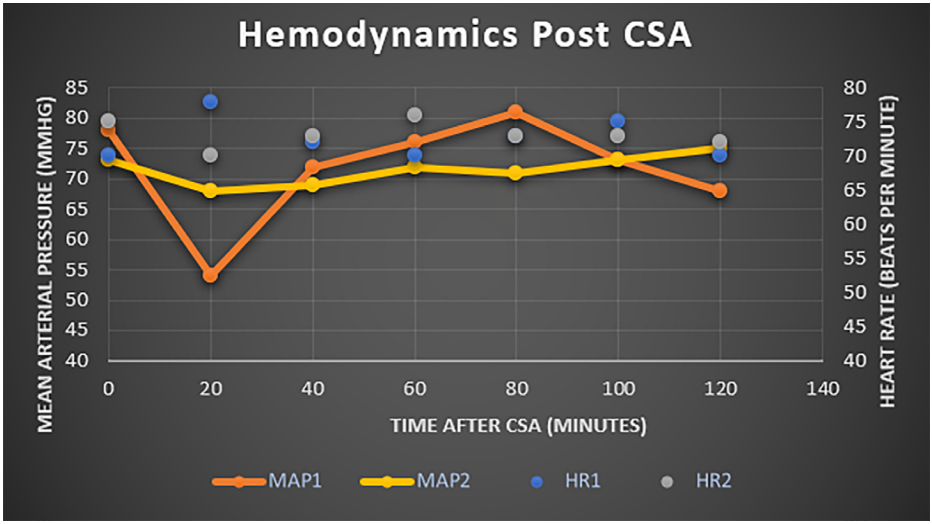

Fig. 3. Intraoperative blood pressure and heart rate trends. MAP1: mean arterial pressure of Case 1; MAP2: mean arterial pressure of Case 2; HR1: heart rate of Case 1; HR2: heart rate of Case 2.

administer the initial bolus in low volume[7] to avoid profound hypotension followed by small top-up doses during the interval. The titratability of CSA enables a more haemodynamically stable anaesthetic than that produced by a single shot spinal anaesthesia. This is the main advantage in patients with cardiovascular respiratory comorbidities whereby neuraxial anaesthesia remain the safest option. The duration of surgery was approximately 1.5 hours for both cases. Figure 3 showed the trends of intraoperative, non-invasive blood pressure (BP) and heart rate (HR) for both cases. Case 1 had one episode of transient hypotension (BP = 80/50 mmHg) which resolved with intravenous 6 mg of ephedrine. The patient's BP subsequently remained stable throughout the surgery. Prior to removing the spinal catheter, both cases received intrathecal top up 0.5 ml heavy bupivacaine 0.5% plus 25 mcg fentanyl. They reported pain scores of 1 at the sixth hour after surgery.

Recommendations to perform CSA

The following are some recommendations to perform CSA: utilize ultrasound for spine sonography to locate the intervertebral space and intrathecal depth, gently advance the catheter into the subarachnoid space, use the CSF gravity test to confirm catheter placement, and avoid cephalad local anaesthetic (LA) spread by using isobaric or hyperbaric bupivacaine. To minimize the risk of neurotoxicity, avoid using LA which exceeds the recommended concentration. To prevent infection and ensure patient safety, label the spinal catheter and remove it after usage, and use

bacterial filter with strict aseptic technique during handling.[8] The CSA catheter may be utilised with caution as a postoperative analgesic modality. Alessandro *et al.* showed that intrathecal levobupivacaine 1.25 mg per hour administered via spinal catheter was associated with reasonable postoperative pain control in hip and knee replacement surgeries.[9] To reduce the risk of catheter breakage during removal, withdraw the catheter gently and as close to the insertion point with the patient in flexed position. Several of the above recommendations and tricks were adopted from the accidental dural punctuate case scenario.[10] CSA can also be performed by alternatively using a combined-spinal-epidural set or Tuohy epidural set (B. Braun Melsungen AG, Germany), if the CSA IntraLong set is not available.

Conclusion

CSA is an effective method of delivering titratable neuraxial blockade. The potential benefits of CSA compared with other titratable neuraxial anaesthetic techniques include faster onset, improved haemodynamic stability, and low intraoperative failure rates. We strongly recommend developing a comprehensive local protocol with supervised training to encourage younger trainees to familiarise themselves with CSA.

Declarations

Informed consent for publication
We confirm that both patients consented to the use of the clinical data and images contained in this report. MyJA Informed Consent for Publication form was submitted along with the manuscript.

Competing interests
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