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EDITORIAL

From Clinical Images to Publishable Case Reports

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A case report is one of the valuable articles in most medical-indexed journals. It is a scientific documentation of a single or more (traditionally less than 3) clinical case observation on the symptoms, signs, investigations, treatment, and follow-up showcasing the extensive medical review and knowledge (Carey, 2010). The ecosystem of submitting case reports for publication usually is practised among clinicians. Even though case report is found at the lower hierarchical level of evidence (Figure 1), it has its advantages, which are valuable to the medical literature (Burns et al, 2011; Nissen & Wynn, 2014), and clinical practices.

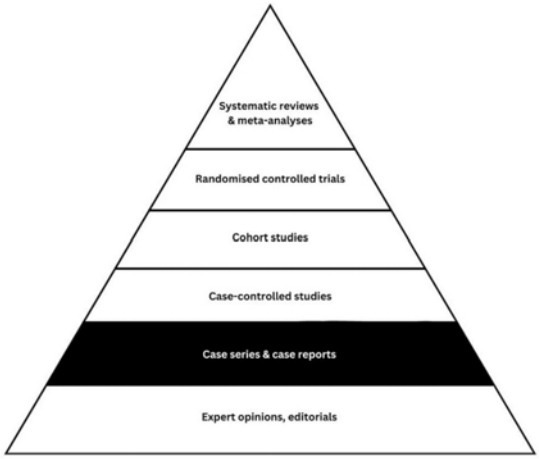

Figure 1 Level of evidence showing the hierarchical position of case reports

Nevertheless, the acceptance of a case report for publication can be challenging due to its level of hierarchal position, and low citation, which may affect the journal

performance. This has led a journal to limit the number of manuscripts accepted for publication under the case report section. The higher impact factor journals usually do not publish case reports anymore. Many factors determine the editors' decision in selecting case reports for those limited spaces. One critical aspect is the quality of the images included. This editorial explores the strategies to improve the acceptance of case reports by making informed choices and enhancing image-related strategies.

Perfect Angle

Manuscripts with images have a relatively higher chance of being accepted than those without. Thus, choosing not only the correct images but more importantly the perfect one is more critical. Nevertheless, most of the time, obtaining those 'perfect images' can happen by chance. Thus we need to be more prepared when we begin attending cases with the ending of publication, in mind. In the clinical ecosystem, every window of golden opportunity must be grasped, thus the practice of taking on-the-spot and live pictures is crucial. This is applied to the moment of seeing any patient in the clinic, wards and even during procedures for example intraoperative findings, in which it will not be repeated. In the era of modern technology, we can use high-resolution cameras to ensure the clarity and detail of the images, making it easier for readers to appreciate the highlights in the portrayed cases. Even though the requirements of images are always mentioned on the website, there are usually general rules that we can follow.

Quality

Some of the vital rules include getting a clear and sharply focused image with a clean background, deidentifiable patient and institution, and high-quality JPEG or TIFF files not more than 3 - 4 MB in size. The choice of getting excellent pictures includes using a point-and-shoot camera, a digital single-lens reflex camera and even more practically a good smartphone. When possible, we can include before-and-after images to demonstrate the impact of treatment or interventions, hence the readers can benefit from the case discussed. That is why, nowadays one of the practises is to get dynamic images or high-quality videos, especially on techniques and steps of procedure, so if needed, they can be converted into precious images. One more important rule in producing images is to maintain a consistent format for image labelling, captions, and sizing throughout the case report. We must not crop the original images as we opt to use image editing tools to improve the quality of such figures. Besides, the tools can also judiciously be used to enhance clarity, brightness, and contrast without altering the actual content. Together, we must include clear reference images within the text to guide readers to relevant visuals and explain the significance of each image in the context of the case. Markers such as arrows, asterisks, scales, abbreviations, and others are portrayed in the images so that the expression of specific findings or areas of interest can be delivered to the readers (Carleton & Webb, 2012).

Appropriateness

Besides the quality, the appropriateness of the images is very much dependent on the highlights. Some manuscripts require images of the clinical presentations (symptoms) or findings (signs), radiological images, intraoperative techniques, histological slides, or combinations of any. For example, if the case highlights a rare pathology, a microscopy slide (we identify as 'figures') with details of evidence that support the diagnosis is essential. On the other hand, if the symptoms are unusual or the signs are unique, most likely the histology slides are not required.

Anonymity

Another important requirement when taking pictures is to preserve the patient's anonymity. We must ensure that all images adhere to patient privacy regulations. It is highly crucial not to disclose any information that might reveal the identity of the patient. This includes other information such as the patient's unique signs, birthmark, or tattoo. The name and description of the institution must be anonymised as well, not only for privacy and confidentiality purposes but also to avoid any medicolegal risk. In addition, it will be helpful in the blinded review processes. Regarding consent, it is important to take note that some journals need that for all images, while some only for selected cases of exposed identity. Hence, it is good to prepare beforehand or keep track of the patient's contact number/follow-up date in case signatures are required later.

Self-Explanatory

However, the images must be clinically educational in a manner that they are vivid to the readers, as to what and which regions are involved (Figure 2). If we are showcasing a tumour from a large bowel, attempts must be made to anatomically align the structures to show that the portrayed organ is a large bowel and from where the tumour arises. In addition, the background must be clean as much as possible without degrading the quality or purity of the specimen. To make sure it is informative, a rule of thumb is to insert a ruler or tape for dimension (Figure 3).

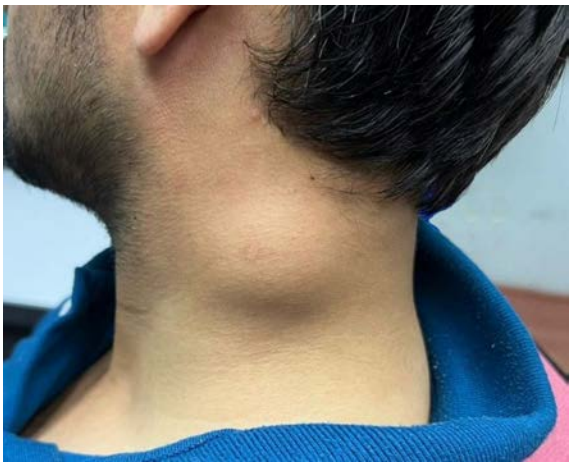

Figure 2 The image is not too zoomed which makes the identification of the landmark difficult

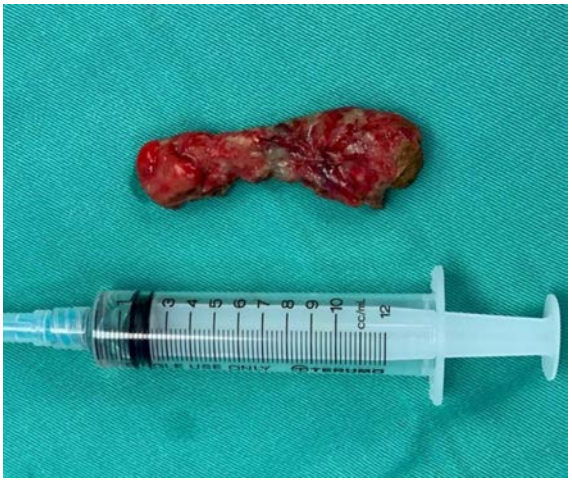

Figure 3 Specimens with a clean background (green towel) and a ruler (10-millilitre syringe) display informative and self-explanatory clinical images.

Get the Permission

In the event of published images, we must apply for written permission from the copyright holder (usually the former publisher) to reproduce the material and provide credit to the original source in the acknowledgement section. This is also applicable for published tables, and figures that we want to re-use in our manuscript. A credit line should appear in the legend for such figures. Or else, we can produce our images either by self-hand-

drawing or drawing applications or software. Besides, in the current era, images also can be produced using generative artificial intelligence (MQA, 2023).

Unsatisfactory Images

Occasionally, the best images to us may be unsatisfactory to the editor. We go for the best but at the same time, we must prepare for the worst unfavourable comments. Quite at times, the reviewers asked to replace it with a better-quality picture and most of the time, we do not have any other better. In such cases, where the images are not reproducible by tracing the old notes, by dwelling in the storage PAC system, or by going back to the pathology labs, we must admit to the reviewer, in the reply letter, that this is regrettably the best that we have. We can give the option of withdrawing the images/ figures as a last resort if they are not up to the quality of the reviewer. Most of the time, the editor will accept the initial submitted ones as the opinion of the reviewers, is still an opinion.

In conclusion, enhancing the acceptance of case reports relies significantly on the relevance, quality, and presentation of images. By selecting appropriate images, standardising their presentation, and adhering to ethical guidelines, authors can improve the chances of their case reports being accepted for publication.

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ORIGINAL ARTICLE

An Audit on Anaemia in Pregnancy Treatment in a Local Health Clinic

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ABSTRACT

Anaemia in pregnancy is one of the most common conditions encountered in antenatal follow-up at primary care. Some targets need to be achieved and managed by healthcare professionals, especially at the earliest possible time and optimal level of haemoglobin in the pregnancy period. Nevertheless, some patients may end up with severe anaemia that was not successfully treated even at term. Therefore, an audit was conducted among antenatal women in a local health clinic to assess the patient's haemoglobin level at booking and term, the management plan and to formulate strategies for improvement. This audit was conducted for two weeks using a universal sampling method in November 2022. All antenatal women who were already at term gestational period and attended the clinic during this period were included. The patients' sociodemographic and health characteristics, haemoglobin level at booking and term as well as management plan were recorded. The data were entered into the statistical software SPSS version 23 for analysis. A total of 115 antenatal women were recruited and 87% of them were able to achieve target haemoglobin at term. Twenty-three of them had concomitant iron deficiency anaemia since the pre-pregnant state. Associated factors for successful anaemia treatment were those without concomitant IDA, those without side effects on iron supplements and those who did not require changes in

the treatment course ($P < 0.05$). The majority of patients can achieve normal values of haemoglobin at term. Pre-pregnancy clinics to treat concomitant anaemia before pregnancy selective individualized iron supplementation to avoid side effects and maintaining the same medication groups would help treat more numbers of antenatal women with anaemia.

INTRODUCTION

Anaemia in pregnancy is one of the most common non-communicable diseases encountered in pregnancy (Frayne & Pinchon, 2019). Therefore, in the local healthcare setting, considering iron deficiency anaemia (IDA) is frequently encountered, all pregnant women will be prescribed instantaneously with haematinics starting the first visit and then step up further in subsequent follow-ups according to the haemoglobin level (Malaysia Ministry of Health, 2020). It is a standard operating procedure to monitor and document haemoglobin levels routinely during antenatal visits (Malaysia Ministry of Health, 2020). Medical doctors are expected to treat the anaemia antenatally through pharmacological and non-pharmacological methods.

Anaemia in pregnancy has many causes. One of the most common is IDA (Goonewardene et al., 2012). Despite several guidelines being adopted, there is still a high number of patients unable to achieve the optimum level of haemoglobin (Hb) near term (Hasneezah et al., 2020). Other causes include folate deficiency, vitamin B12 deficiency and concomitant thalassemia or haemoglobinopathies in pregnancy (Goonewardene et al., 2012). There are a lot of complications of anaemia in pregnancy for the mother and foetus. These include acute heart failure, low birth weight or intrauterine growth restriction, premature delivery, spontaneous miscarriages and intrauterine death (Lin et al., 2018). The most worrisome event is postpartum haemorrhage which can be prevented if the anaemia is treated before term (Omotayo et al., 2021). This strategy gives rise to the target of Hb 11 g/dL at 36 weeks gestational period (Malaysia Ministry of Health, 2020). Among risk factors of iron deficiency anaemia that can be screened in early antenatal booking include poor nutrition, young age, underlying stressors, concomitant menstrual disorder before pregnancy, multigravida or close spacing of pregnancy (Lin et al., 2018).

There are various causes of the failure to treat anaemia in pregnancy (Churchill et al., 2022). These can be divided into patient factors, healthcare provider factors and healthcare system factors. Patient factors include poor compliance to haematinics and diet advice, intolerance to iron, poor iron absorption as well as a psychological stressor or lack of a good support system (Churchill et al., 2022; Yadav et al., 2019). Doctor factors include delay in stepping up the iron treatment, poor in initiating oral or parenteral iron and failure to assess compliance as well as ignoring diet modification. Healthcare system factors include lack of one-to-one care, inability of medication at primary care level and poor holistic monitoring plan (Churchill et al., 2022; Yadav et al., 2019; Gilder et al., 2019).

Considering these multifactorial causes, it is important to identify and perform a cross-sectional audit to view this problem. From the results of the audit, the problems can be explored clearly and further modifications can be made from there. Therefore, the objectives of this audit were to assess the patient's haemoglobin level at booking and term, the management plan and to formulate strategies for improvement.

MATERIALS AND METHODS

An internal audit was performed in a local health clinic for two weeks duration starting from 25 October 2022 to 8 November 2022. A two-week study period was perceived as sufficient for data collection to include background characteristics of patients and retrospective documentation of antenatal

management of patients with anaemia. The objectives of this study were: (1) to describe the characteristics of antenatal women follow-up in the health clinic and their haemoglobin status, (2) to identify the associated factors for the antenatal women achieving normal haemoglobin at term and (3) to identify the predictors for treating the anaemia successfully. The data were collected from the antenatal book of the patient reaching 36 weeks within those two weeks. All relevant data were recorded manually in the audit form before being entered into the SPSS version 26.0 to be analysed. Descriptive analysis was used to describe the background of the antenatal women in the form of frequency, percentage and mean. Simple and multiple logistic regression was used to identify the associated factors and predict factors for achieving resolved anaemia at term gestational week.

This audit had been approved by the clinic administrative authority and managing specialist as well as an elective proposal by Kulliyyah of Medicine, International Islamic University of Malaysia.

RESULTS

A total of 115 patients' records were analyzed, in which the majority of patients were Malay, educated up to secondary school and still working (Table 1). The majority have the normal value of haemoglobin at booking and do not have iron deficiency anaemia. Surprisingly, despite available standard operating procedures, 67% of the antenatal women were treated with haematinic late in the third trimester and 13% of the cases were unable to resolve their anaemia at term.

Table 1 Characteristics of patient and antenatal parameters

Variables		Frequency (N)	Percentage %	Median	Range
Age				28.0	25
Race	Malay	97.0	84.3		
	Chinese	8.0	7.0		
	Indian	3.0	2.6		
	Others	7	6.1		
Gravida	One	35	30.4		
	Two	35	30.4		
	Three	25	21.7		
	Four	9	7.8		
	Grand multigravida	11	9.6		
Education	No	2	1.7		
	Primary	5	4.3		
	Form 3 (PMR)	2	1.7		
	SPM	45	39.1		
	STPM	3	2.6		
	Certificate	4	3.5		
	Diploma	25	21.7		
	Degree	28	24.4		
	PhD	1	0.9		
Work	Housewife	43	37.4		
	Work	72	62/6		
Hb at booking				12.3	8.20
Hb at term				12.0	7.50

IDA present	Yes	23	20.0		
	No	92	80.0		
Iron supplement initiation	1st trimester	27	23.5		
	2nd trimester	11	9.6		
	3rd trimester	77	66.9		
Types of iron supplementation	Sangobion	1	0.9		
	Obimin	1	0.9		
	Ferrous fumarate	4	3.5		
	Iberet	20	17.4		
	Zincofer	88	76.5		
	Maltofer	1	0.9		
Iron modification	Yes	22	19.1		
	No	93	80.9		
Experience side effects	Yes	18	15.7		
	No	97	84.3		
Hb treated	Yes	100	87.0		
	No	15	13.0		

Simple logistic regression proved that those antenatal women without iron deficiency anaemia (IDA) at booking, and good compliance with the same type of haematinics without changing the group were the ones that were statistically proven to be associated with successful anaemia treatment (Table 2). Nevertheless, the only predictor for success was those without concomitant IDA (Table 3).

Table 2 Associated factor for achieving normal haemoglobin at term vis simple logistic regression

Variables	P value	Crude odd ratio (OR)	95.0% C.I. for OR	
			Lower	Upper
IDA (without)	< 0.001	0.075	0.022	0.253
Change iron (no)	0.001	0.142	0.045	0.455
Iron side effects (no)	0.001	0.141	0.043	0.465

Table 3 Predictors for resolved anaemia at term

HbCorrected[a]		B	Std. Error	Wald	Df	Sig.	Exp(B) Lower bound	95% Confidence Interval for Exp(B) Upper bound	
Yes	Intercept	3.415	.575	35.310	1	<.001			
	[IDA = 1]	−2.573	.683	14.180	1	<.001	0.076	0.020	0.291
	[IDA = 2]	0[b]	.	.	0	.	.	.	.
	[ChangeIron = 1]	−0.612	1.368	0.200	1	0.655	0.542	0.037	7.924
	[ChangeIron = 2]	0[b]	.	.	0	.	.	.	.
	[Sideeffects = 1]	−1.417	1.448	0.958	1	0.328	0.242	0.014	4.139
	[Sideeffects = 2]	0[b]	.	.	0	.	.	.	.

DISCUSSION

Anaemia in pregnancy is common but challenging to manage at the primary care level. It usually requires early and effective management including self-empowerment by consuming a high-iron diet on top of daily haematinics prescribed by the managing team (Kumar et al., 2022). Nevertheless, there are always ways to improve the haemoglobin control by the healthcare team through education, training as well and by conducting the audit (Morrison et al., 2021).

The audit was conducted among 115 antenatal patients within two weeks. Zincofer® was the commonest haematinic prescribed in this clinic (76.5%) followed by Iberet® (17.4%), as shown in Table 1. Both Zincofer® and Iberet® contain 115 mg and 105 mg elemental iron respectively which are among the highest iron content among the oral pharmacological drugs available for treating anaemia in primary care clinics (Abu et al., 2020). They provide equivalent efficacy and side effects. However, Zincofer® has higher folic acid content, causing it to be highly chosen in this clinic setting. The trend is clear that most medical doctors would like to start haematinic with the highest iron content at the onset of the treatment, to treat the anaemia successfully (Lewkowitz et al., 2022). This study also detected a high tendency among medical doctors to start treatment in the third trimester (66.9%) compared to other trimesters, as shown in Table 1. Due to the short duration of time left prior to term gestational week, the highest iron content haematinic would be given.

However, this practice of starting haematinic only in the third trimester is against the standard practice of managing antenatal women in primary care (Malaysia Ministry of Health, 2020). Haematinics should be given since booking, regardless of the level of haemoglobin of the women. This is because, even though they are not anaemic, the requirement of iron in pregnancy is increased and they require at least 30 – 60 mg of elemental iron per day. Meanwhile, for the treatment, the requirement would be increased further to 60 – 120 mg of elemental iron (Means, 2020). Therefore, the inertia in initiating haematinic supplementation should be avoided. The absolute reason for this practice should be explored by the clinical specialists and at the health district office level through the assessment of the medical doctor's knowledge in managing antenatal women. This knowledge can be assessed through discussion in a clinical medical education (CME) or workshop session that should be conducted regularly.

Malaysia Ministry of Health (2020) had proposed a standard target to achieve normal haemoglobin levels at term gestation. However, not all healthcare providers are able to change such a benchmark into an achievable outcome. This study showed that around nine-tenth of these antenatal women were able to treat the anaemia at term and this is relatively a good achievement despite the failure to achieve 100% treatment among the women. Simple logistic regression (Table 2) reveals that compliance issues and prior diagnosis of iron deficiency before pregnancy were the main reasons why the anaemia was unable to be resolved within antenatal visits. Concomitant iron deficiency anaemia requires a higher dose of haematinic and therefore, will cause a barrier for sustainable treatment in pregnancy. Previous studies have shown that IDA is common among Malaysians as well as worldwide and requires appropriate modification in the treatment protocol (Abd Rahman et al., 2022; Breymann, 2015; Igbinosa et al., 2022; Di Renzo et al., 2022).

Compliance issues are another important factor in determining the outcome of the treatment (Rattanapiratanon et al., 2021). In this study, it was noted that almost one-fifth of the antenatal women required changes in the haematinics during the antenatal follow-up (Table 1). This was supported by 15.7% of the women experiencing intolerance to the

medication which required replacement of the initial haematinics. These changes require some time to adapt to the compliance and suitability of the drugs. Therefore, this study proved that those on haematinics without side effects and the need to change the drugs would have achieved resolved anaemia at term successfully compared to those who have with odds value of 0.14 ($P < 0.001$) (Gómez-Ramírez et al., 2018). In relation to this, a clear algorithm should be made available in the clinic for medical doctors to refer to in choosing the most appropriate hematinic since the beginning of antenatal care. The list of haematinics should also be revised by the clinic authority to provide more efficacious haematinic in future with fewer side effects (in subsequent budget plan).

Multiple logistic regression, however, identified that concomitant IDA status at booking was the only significant factor predicting the anaemia treatment outcome ($P < 0.01$). This has indeed been observed in other studies done previously (Abd Rahman et al., 2022; Breymann, 2015; Igbinosa et al., 2022; Di Renzo et al., 2022). Therefore, it is recommended for all medical doctors to assess and verify the past medical history of all antenatal patients including previous history of iron deficiency anaemia so that specific treatment can be tailored accordingly. The role of pre-pregnancy care and services should be emphasized and be carried out properly in the clinic together with a regular audit on its implementation.

LIMITATION

Our study was based on the clinical audit outcome in which proper sample size calculation was not required to be done. Therefore, the number of our samples might be considered low. Our study also was unable to capture diet history among patients, which is important to be screened to identify possible nutritional deficiency as the main cause of anaemia. Therefore, in future, a more structured clinical study should be conducted involving bigger sample sizes from a large number of health clinics within a longer study duration. Policymakers and higher authorities from the Ministry of Health should also be invited to be involved in the study to tackle this issue seriously.

CONCLUSION

Resolving anaemia at term gestational age is indeed challenging. Identifying IDA status at the early gestational period together with maintaining compliance with the same highly effective dose haematinic would make the achievement possible. It is recommended that optimal efficacy haematinic is used since early antenatal booking to avoid intolerance and side effects.

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ORIGINAL ARTICLE

Investigation of Phytochemicals and Antibacterial Activity of *Persicaria odorata* (L.) Methanolic Leaf Extract Against Selected Bacteria

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ABSTRACT

Multidrug-resistant microorganisms pose serious threats, especially to children from developing countries. Due to this concern, there is a greater need to develop potentially effective antibacterial agents from natural resources. This study aimed to investigate the phytochemical compounds of *Persicaria odorata* (L.) methanolic leaf extract and its antibacterial activity against selected bacteria. Agar well diffusion and broth microdilution were used to test gram-positive (*Staphylococcus aureus* and *Bacillus cereus*) and gram-negative bacteria (*Salmonella enterica serovar typhimurium* and *Shigella flexneri*). The bacteria were treated with *P. odorata* (L.) leaves extracted using methanol and diluted with 10% Dimethyl-sulfoxide (DMSO). *P. odorata* (L.) leaf extract was highly effective against *S. aureus* at a concentration of 1,000 mg/mL. Gram-positive bacteria had the lowest MIC and MBC values. The qualitative phytochemical analysis of the methanolic extract of *P. odorata* (L.) leaves indicated the presence of antibacterial compounds such as phenols, flavonoids, terpenoids, and tannins. In conclusion, *P. odorata* (L.) leaves which have been widely used in cuisines and traditional medicine also possess the potential to serve as an antibacterial agent.

INTRODUCTION

In the modernised era, infectious diseases caused by pathogens pose a significant societal burden worldwide. Another alarming issue is bacterial antimicrobial resistance (AMR) making antibiotic use futile or less effective against many common bacterial infections affecting animals and humans. Data on AMR from Malaysia, as well as other countries, have been analysed. The analysis demonstrated that five bacteria were each involved in more than 500,000 deaths in 2019: *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*. Three infectious syndromes (lower respiratory infections, bloodstream infections, and peritoneal and intraabdominal infections) caused more than 1 million deaths in 2019 and accounted for 75% of deaths due to bacterial infections (Ikuta et al., 2022). Developed and underdeveloped countries encountered similar challenges in managing the burden of infectious diseases, which can be transmitted from person to person through direct or indirect contact. Weak infection management practices may lead to the development of infectious diseases (Kourtis et al., 2019).

For millennia, traditional medicine that utilises natural resources such as plants and minerals has been widely used to treat illnesses and practised in maintaining patients' health. Approximately 1,200 species of higher plants have been reported to possess medicinal properties but only less than 0.1% of them have been studied (Manaf & Daud, 2016). Each part of the plant is enriched with primary and secondary active metabolites that contribute to a diverse biological activity that is either essential for therapeutic purposes or as precursors for drug synthesis (Manaf & Daud, 2016; A'attiyyah et al., 2018). It has been shown that alkaloid extracts from the leaves, stem bark, and root of *Ochrosia oppositifolia* have antibacterial activity against gram-positive and gram-negative bacteria (Mahmud et al., 2017), while usnic acid and atranorin were the most active chemical constituents to act as antibacterial agents from the lichens of *Ramalina dumeticola* and *Usnea rubrotincta* (Gunasekaran et al., 2016).

Persicaria odorata (Lour.) Soják, also known as *Daun Kesum*, is a perennial fresh culinary herb that belongs to the *Polygonaceae* family. The plant is found in Peninsular Southeast Asia and is widely recognized for its traditional use in medicines, cuisines, pharmacies, and cosmetics (Ridzuan et al., 2017). Leaves of *P. odorata* (L.) successfully treat digestive problems, including flatulence, stomach cramps, and indigestion (Mumtak et al., 2017). Earlier investigations have probed the restorative properties of *P. odorata* (L.), and the outcomes appeared helpful for its broad use as an essential remedial agent, including anti-inflammatory, antioxidant, antimicrobial, anticancer, and antifungal (Okonogi et al., 2016; Chansiw et al., 2019; Ridzuan et al., 2013; Putthawan et al., 2017; Yik et al., 2018). The plant can be of great value as an antibacterial agent for combating the threat posed by bacteria, particularly multidrug-resistant bacteria. This study may act as a starter for further research related to the biological function of *P. odorata* (L.) towards the human population.

The development of new drugs is different from the rapid emergence of various multidrug-resistant bacteria, increasing the burden on healthcare settings. Besides, harmful side effects due to exposure to synthetic drugs in a patient's treatment may lead to higher risk (Rather et al., 2017). Therefore, the need for advanced production of antibacterial derived from bioactive compounds from natural sources is crucial to combat the emergence of these hard-to-treat bacteria, especially in developing countries where the availability of antibiotics and the cost of therapy are critical constraints in public health settings. This study experimented on the antibacterial activity of *P. odorata* (L.) leaves in vitro against selected pathogens (*Staphylococcus aureus*, *Bacillus cereus*, *Salmonella enterica serovar typhimurium*

and *Shigella flexneri*). Moreover, screening for phytochemicals within the leaves was also done qualitatively.

MATERIALS AND METHODS

P. odorata (L.) Leaves Collection

P. odorata (L.) was purchased from the Wholesale Wet Market in Sungai Petani, Kedah (GPS coordinate: 5.642121, 100.490964), and species confirmation was done by submitting a voucher specimen (PID 070319-07) to the herbarium of the Forest and Research Institute, Malaysia (FRIM). The healthy leaves were picked out, washed thoroughly with distilled water, and then dried under the sun. Dried leaves were processed into a powder in an automated blender and then kept at room temperature in an airtight container.

Preparation of Concentrated Extract Stock Solution Using Maceration Technique

For three days at room temperature, 480 g of powdered *P. odorata* (L.) leaves were soaked in 4.8 L of 100% methanol (1:10 weight/volume) while continuously agitated at 70 revolutions per minute (rpm) on an orbital shaker to ensure proper mixing. Whatman filter paper no. 1 and then the white cotton cloth was used to filter the mixtures twice to eliminate any remaining particles. Exhaustive evaporation at 40°C under reduced pressure using a rotary evaporator was used to evaporate the filtrates further, yielding the concentrated extract. The resulting extract was transferred to a universal bottle, weighed using the following procedure, and kept at 4°C.

About 30 g (30,000 mg) of the extract was dissolved into 30 mL of 10% DMSO to obtain a final concentration of 1,000 mg/mL (Samsudin et al., 2018).

Qualitative Phytochemical Screening

Secondary bioactive metabolites are abundant in wild plants and play an important role in plant adaptation. Moreover, it has therapeutically active components in the form of medicines (Shakya, 2016). A phytochemical screening method was performed to detect the secondary metabolites found in the leaves of *P. odorata* (L.).

Phenols (Ferric Chloride Test)

One mL of the concentrated methanolic extract of *P. odorata* (L.) was spiked with a few drops of 1% ferric chloride. Developing colours in the blue, purple, violet, green, or red-brown range indicated the presence of phenol group compounds.

Flavonoids (Alkaline Reagent Test)

Two mL of a concentrated methanolic extract of *P. odorata* (L.) were treated with a few drops of a 20% sodium hydroxide solution (NaOH). After adding NaOH, the solution became a bright yellow.

Terpenoids (Salkowski Test)

First, 5 mL of *P. odorata* (L.) methanolic concentrated extract was mixed with 2 mL of chloroform and 3 mL of concentrated sulfuric acid. The positive result was based on the development of a reddish-brown hue.

Tannins (Ferric Chloride Test)

Two mL of a 10% ferric chloride solution were added to 2 mL of a methanolic extract concentrated from *P. odorata* (L.). Intense green, dark blue or black colouration indicated the presence of tannin in the extract.

Isolation and Confirmation of Bacterial Species

Staphylococcus aureus (ATCC 25923), *Bacillus cereus* (ATCC 11778), *Salmonella enterica serovar Typhimurium* (ATCC 13311), and *Shigella flexneri* (ATCC 12022) from the American Type Culture Collection were all employed as the four bacterial strains. Subculturing of *S. aureus* and *B. cereus* was performed on nutrient agar (NA) and sheep blood agar (SBA), whereas xylose-lysine-deoxycholate (XLD) agar was used for *S. typhimurium* and *S. flexneri*. Gram stain, biochemical test, and iMViC test were used to identify further the four bacterial strains.

To ensure viable bacteria were collected, a bacterial growth curve was performed by measuring the absorbance of each pre-cultured bacteria in Tryptic Soy Broth (TSB) at the wavelength of 600 nm (OD600) against blank (sterile TSB) for every half an hour using an ultraviolet spectrophotometer and the following formula was used for volume determination:

$$C1V1 = C2V2$$

C1 = The absorbance of TSB + bacterial suspension after overnight incubation
V1 = Volume of pre-cultured TSB that will be transferred to obtain a final volume of 50 mL
C2 = Fixed standard value (0.05)
V2 = Final volume (50 mL)

Furthermore, colony count using the spread plate method was also performed using a ten-fold dilution of the pre-cultured bacteria in Tryptic Soy Broth (TSB), and the mean of triplicate plates was calculated and recorded.

Antimicrobial Susceptibility Test (AST)

Bacterial colonies from NA were cultured by suspending three to five similar colonies in 4 mL of sterile Mueller-Hinton Broth (MHB), incubating at 37°C until the turbidity reached 1 to 2 × 10^8 colony forming unit/mL, or the equivalent of 0.5 McFarland standard. After adjusting the turbidity for 15 minutes, 100 µL of each four of the bacterial inoculums were added to Mueller-Hinton agar (MHA), spread equally over the surface of the medium, and rotated 60° to ensure equitable distribution. Sterile blue pipette tips were used to pierce two neighbouring wells in the agar. Pipetting into the well was 60 µL of the concentrated *P. odorata* (L.) extract solution and 60 µL of a 10% DMSO solution. A commercially available antibiotic paper disc that served as a positive control was aseptically put on the bacterial lawn. All plates were incubated for 24 hours of incubation at 37°C. The study was repeated thrice, and the findings were presented as the mean standard deviation.

Minimal Inhibitory Concentration (MIC)

Triplicate broth microdilution MIC was done in 96-well microtiter plates. Microtiter plate wells were numbered 1 – 9. 100 µL MHB was pipetted into wells 2 – 9. Subsequently, 100 µL of *P. odorata* (L.) leaves methanolic concentrated extract (1,000 mg/mL) was pipetted into well 1 and well 2. The stock solution in well 2 was serially diluted with MHB in a two-fold serial dilution by transferring 100 µL of solvents in well 2 into well 3 of the microtiter plate. The steps were repeated until well 9. 100 µL of solvents in well 9 were eliminated to standardize all well volumes. The final concentrations of extract in each well were 3.91, 7.81, 15.63, 31.25, 62.5, 125, 250, 500, and 1,000 mg/mL. At the same time, 100 µL of bacterial solution was pipetted into well 10 to serve as a positive control. Well 11 and well 12 were used for sterility testing by adding 100 µL of a stock solution of methanolic extract from the leaves of *P. odorata* (L.) and 100 µL of MHB, respectively, to make sure no apparent bacterial growth or contamination that might provide a false positive result. The microtiter plate cultures were incubated at 37°C for 16 – 24 hours.

Minimal Bactericidal Concentration (MBC)

The minimum bactericidal concentration (MBC) was determined by subculturing a loop full of bacteria from each dilution of the extract that showed no apparent bacterial growth in the MIC microtiter wells onto an MHA plate (MBC). The plates were kept at 37°C for 16 to 24 hours.

DATA ANALYSIS

IBM SPSS Statistics for Windows, Version 21.0, was used to analyse the data. All ASTs were performed in triplicate, and the results were reported as the mean SEM (SEM). An independent T-test was used to analyse the statistical significance of the zone of inhibition produced by the plant extract in comparison

to the positive control and the variations in antibacterial activity between the bacteria. When the P-value for the differences was less than 0.05, it was regarded as significant.

RESULTS

Phytochemical Analysis

Table 1 summarizes the qualitative phytochemical screening of chemical compounds in the 1,000 mg/mL methanolic leaf extract of *P. odorata* (L.).

Table 1 Results for qualitative screening of phytochemical compounds tested in 1,000 mg/mL of *P. odorata* (L.) methanolic leaf extract which was detected using colour changes

Phytochemicals	*P. odorata* (L.) methanolic leaf extract
Phenols	Present
Flavonoids	Present
Terpenoids	Present
Tannins	Present

Antimicrobial Susceptibility Test Using Agar Well Diffusion Method

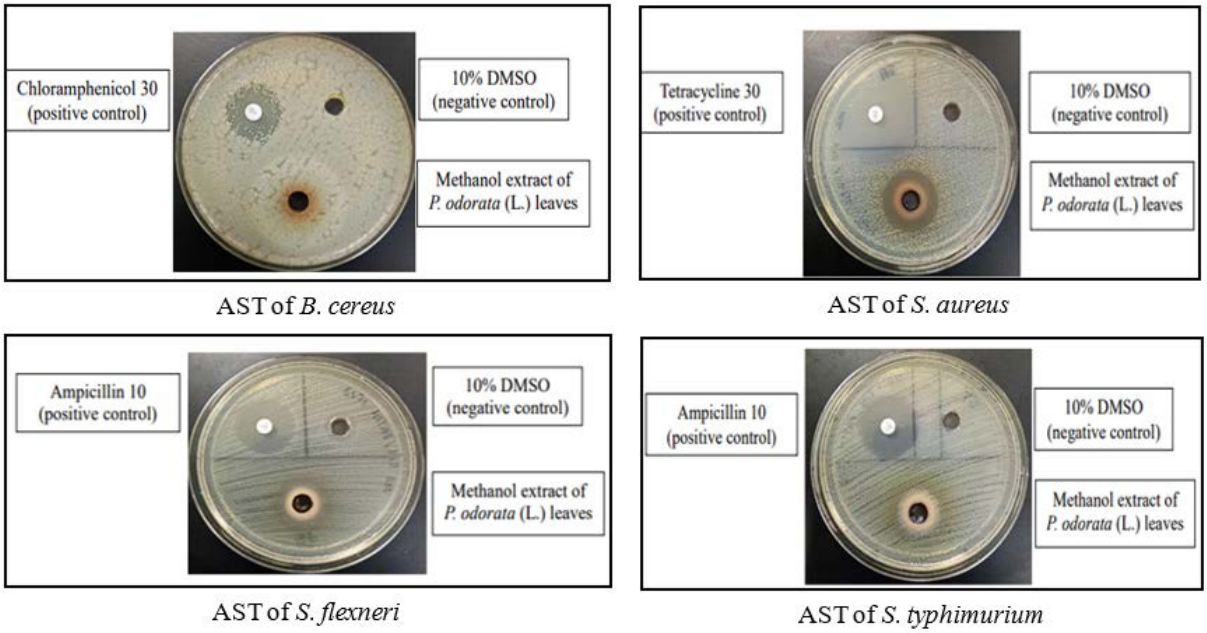
The mean inhibition zone diameter of the 1,000 mg/mL methanolic leaf extract of *P. odorata* (L.) against the selected bacterial strains was presented in Table 2 and shown in Figure 1.

Table 2 Diameter of inhibition zone of 1,000 mg/mL *P. odorata* (L.) methanolic leaf extract against selected bacteria

Bacteria	Zone of inhibition (Mean ± SEM**)					*P*-value*
	***P. odorata* (L.) methanolic leaf extract**	**Positive control**			**Negative control (10% DMSO)**	
		Tetracycline 30	**Chloramphenicol 30**	**Ampicillin 10**		
S. aureus	22.67 ± 0.67	37.33 ± 1.33	–	–	0	0.001
B. cereus	18.00 ± 0	–	20.33 ± 0.33	–	0	0.020
S. typhimurium	18.00 ± 0.58	–	–	27.00 ± 0	0	0.001
S. flexneri	17.00 ± 0	–	–	25.00 ± 0	0	0.000

* Independent T-test of inhibition zone between *P. odorata* (L.) methanolic leaf extract and positive control,
** Standard error of mean

Figure 1 AST using agar well diffusion method showing the absence of an inhibition zone by negative control (DMSO) and presence of inhibition zone by commercial antibiotic discs as positive control across all four bacteria isolates



MIC and MBC Using Broth Microdilution Method

The mean MIC and MBC values in Table 3 reveal that the *P. odorata* (L.) methanolic leaf extract was effective against the *S. aureus* and *B. cereus* at a 15.63 mg/mL concentration. The MIC/MBC ratio indicated the plant extract has bactericidal properties.

Table 3 MIC and MBC of *P. odorata* (L.) methanolic leaf extract against selected bacteria

Bacteria	*P. odorata* (L.) methanolic leaf extract (Mean ± SEM*)		MIC/MBC Ratio
	MIC (mg/mL)	MBC (mg/mL)	
S. aureus	15.63 ± 0	15.63 ± 0	1 (–)
B. cereus	15.63 ± 0	15.63 ± 0	1 (–)
S. typhimurium	250 ± 0	500 ± 0	0.5 (–)
S. flexneri	125 ± 0	500 ± 0	0.25 (–)

* Standard error of mean
(–) Bactericidal
(+) Bacteriostatic

DISCUSSION

This study obtained 13.21% of *P. odorata* (L.) methanolic leaf crude extract using the maceration technique. This technique used solvent-mediated extraction; the conventional method commonly utilised in small research settings, due to its convenience, expanded applicability, productivity, and low production cost (Azwanida, 2015; Safdar et al., 2017). Methanol was selected as an extraction solvent based on its excellent polar, protic solvent, and intermediate polarity characteristics. It produced a higher extraction yield than acetonitrile and extracted a wide range of phytochemicals (Nguyen et al., 2015). A smaller sample size with a longer contact time between the sample and solvent can increase the surface contact area of the sample with extraction solvent (Azwanida, 2015; Dzulkarnain & Abdul Rahim, 2014). Therefore,

the plant extraction technique was slightly modified to achieve a higher yield of the crude extract by soaking finely powdered *P. odorata* (L.) leaves in methanol for a longer period (i.e., three days) and continuous agitation at 70 rpm on an orbital shaker. DMSO is an organosulfur compound utilised widely as a polar, aprotic solubiliser miscible with water to dissolve an extensive number of polar and nonpolar small molecules. 10% DMSO (1:10 v/v) was prepared as it has relatively low toxicity against living cells (Da Violante et al., 2002; De Abreu Costa et al., 2017).

The present study subjected the methanolic extract of *P. odorata* (L.) leaves to qualitative phytochemical analysis. The results demonstrated the presence of phenols, flavonoids, terpenoids, and tannins (Table 1). The presence of secondary metabolites has contributed to diverse biological activity essential for therapeutic purposes or as precursors for drug synthesis (A'attiyyah et al., 2018). The antibacterial properties of polyphenols were reported to stem from their extreme ability to combine with various macromolecules. In contrast, terpenoids exerted antimicrobial activity due to their lipophilic characteristics, allowing direct penetration into the bacterial cells and disrupting protein biosynthesis, nucleic acid replication, and repair mechanisms (Zacchino et al., 2017). The mechanisms of plant phenolic antibacterial occur via the bacterial cell membrane or non-membrane disruption along with the synergism of the compounds with current antibiotics (Rempe et al., 2017). Meanwhile, flavonoids possess several antibacterial mechanisms with enhancement depending on their different structural configuration. Several antibacterial mechanisms proposed include inhibition of nucleic acid synthesis and cell membrane porin, disruption of the functional cytoplasmic membrane and energy metabolism, obstruction of biofilm production, and attenuation of bacterial pathogenicity in which these mechanisms were enhanced as the flavonoid contained hydroxyl groups on specific aromatic rings and hydrophobic substances (Xie et al., 2015). These findings were supported by a study in which the structural relationship of flavonoids with different structural configurations contributed to the enhancement of antibacterial activity, and alteration to these structures, such as methylation, led to the reduction of the antibacterial properties of flavonoids (Ahmad et al., 2015). Meanwhile, the antimicrobial activity of tannins is correlated with bacteria's extracellular enzyme metabolism obstruction and nutrient or substrate starvation, as well as the direct inhibition of oxidative phosphorylation in microbes' metabolism (Agyare et al., 2015). Total tannins exert their antibacterial effect by destroying the bacterial structure, such as malformed cell walls, detached cytoplasm, and strong affinity to aggregate between themselves (Li et al., 2016).

The AST (Table 2) revealed that the *P. odorata* (L.) methanolic leaf extract possesses the highest antibacterial activity against *S. aureus* (22.67 ± 0.67), followed by *S. typhimurium* (18.00 ± 0.58), *B. cereus* (18.00 ± 0) and *S. flexneri* (17.00 ± 0). The absence of an inhibition zone by negative control (DMSO) across all four bacteria isolates indicated nonparticipation of the solvent in the antimicrobial feature of *P. odorata* (L.) leaves (Figure 1). The *P. odorata* (L.) methanolic leaf extract demonstrated effective antibacterial activity, especially on gram-positive bacteria. Nevertheless, its activity was lowest against *S. flexneri* due to the unique structure of the gram-negative bacteria's outer membrane which acts as a powerful permeability barrier against antibacterial agents (Oikeh et al., 2017). In contrast, previous studies only reported the antibacterial activity of *P. odorata* (L.) leaves against gram-positive bacteria, which may be due to the lower concentration of *P. odorata* (L.) methanolic leaf extract, different AST methods and bacterial species used (Ridzuan et al., 2017; Chansiw et al., 2018). The MIC and MBC of the 1,000 mg/mL methanolic leaf extract of *P.*

odorata (L.) demonstrated potent antibacterial activity against the growth of gram-positive bacteria. The lowest concentration was 15.63 mg/mL for both *S. aureus* and *B. cereus* compared to gram-negative bacteria. (Table 3). Bacteriostatic effects were defined as MIC/MBC ratios more than four, whereas bactericidal effects were defined as ratios less than four. Thus, the current findings demonstrated that the *P. odorata* (L.) extract had a bactericidal effect on all four bacterial strains. A previous study with other bacterial species reported that the methanolic extract of *P. odorata* (L.) leaves also exhibited the most significant antimicrobial activities with MICs of 3.125 mg/mL and 12.5 mg/mL for *S. pyogenes* and *S. pneumonia*, respectively (Ridzuan et al., 2013).

Theoretically, the lower the MBC value, the greater the inhibition zone seen in antimicrobial susceptibility tests (Murray, 2015). However, the MBC values of 15.63 mg/mL obtained for the methanolic extract against the gram-positive bacteria in this investigation did not correspond with the inhibitory zone diameter employing a 1,000 mg/mL concentration of the plant extract as compared to the gram-negative bacteria. This result, however, is consistent with a previous study that utilised an ethanolic extract of *Syzygium aromaticum*. Gram-positive bacteria (*B. cereus* and *S. aureus*) exhibited lower MBC values and inhibition zones compared to gram-negative bacteria (*E. coli*) in a contradictory finding (Gonelimali et al., 2018).

The purpose of an antimicrobial susceptibility test is to determine the degree to which an organism is sensitive to or resistant to a particular antimicrobial agent. In this investigation, the well diffusion technique was utilised, in which the antimicrobial compound diffuses into the agar to inhibit the growth of the test organism. The interaction between the antimicrobial agent and the solid medium, as well as inactivation during diffusion, has been demonstrated to be one of the causes of low inhibition zone readings of the tested organism (Bonev et al., 2008). The Clinical and Laboratory Standards Institute also lists several factors that can affect the inhibition zone's diameter, including the susceptibility test medium, the concentration of the test organism, its rate of growth, the concentration of the antimicrobial agent, the antibiotic's diffusion rate in the agar, and the organism's susceptibility to the antibiotic. The creation of bacterial biofilm, on the other hand, has been shown in a prior study to potentially decrease the efficacy of antimicrobial activity because it serves as a significant barrier, blocking the entry of polar and charged antibacterial agents (Macia et al., 2014). *B. cereus* and *S. aureus* propensity to build bacterial biofilms may be one of the factors contributing to the low inhibition zone of the gram-positive bacteria.

CONCLUSION

The antibacterial activity against selected bacterial strains was discovered in the methanolic leaf extract of *P. odorata* (L.). The inhibitory or bactericidal effect was more potent against gram-positive than gram-negative bacteria. The presence of phenols, flavonoids, terpenoids, and tannins suggests that the phytochemicals of *P. odorata* (L.) leaves are responsible for the therapeutic property against infections, making the natural herbal extract a viable initial therapy source.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL ARTICLE

Malaysian Specialists' Involvement in Research: Attitudes, Barriers and Facilitators

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ABSTRACT

In Sabah, the research tradition still needs to be improved due to the need for more participation of specialists in the field of research. Their views and attitudes towards research still need to be improved and expanded. Therefore, this study aimed to assess the willingness of specialists to participate in research and their attitude towards research, as well as the barriers and facilitators in conducting research in government hospitals. This cross-sectional descriptive study was conducted among specialists in three government hospitals in Kota Kinabalu, Sabah using self-administered questionnaires. A total of 49 specialists responded to the questionnaires distributed. Only 44.9% of respondents were involved in research. All the respondents thought that research was advantageous to both patients and society. However, lack of access to expertise, software or statistical analysis and too much red tape in obtaining approvals were among the top barriers to doing research. The main facilitators were to receive acknowledgement of research achievement for their career advancement. In conclusion, most specialists have a positive perception towards research, but more than half of them were not involved in any research during this study.

INTRODUCTION

Medical research is critical to advancing patient care and is significant to the discipline. Disease surveillance, diagnosis, treatment and prevention advances rely heavily on quality research, and research also influences healthcare policies (Lavis et al., 2008; Pager et al., 2012; Sabzwari et al., 2009). However, research in the Malaysian healthcare system is still very new and developing, especially in Sabah. In addition, Malaysia faces difficulties in medical research, and most work is compromised due to flawed methodology, lack of research training and background of researchers. Thus, for health systems to be improved and better health outcomes to be achieved, robust national health research programmes are required.

Specialists are a key "driving force" and catalyst for expanding research in their institutions (Teh et al., 2013). Individuals' critical thinking abilities are crucial for research. A study from Taiping Hospital found that most specialists working in northern Malaysia believed that research benefits patients and society and helps their professional development. However, most are not involved in research, and one-third are unlikely to participate due to their current working conditions (Teh et al., 2013). Several studies have also examined attitudes and research interests among doctors in various specialities and sub-specialities.

Building the capacity to undertake research in health professional groups is a priority. The involvement of specialists in clinical research is essential to improve clinical services in healthcare facilities. This is because specialists play a significant role in policy-making and changing clinical practices for their respective departments and units (Lansang & Dennis, 2004). Thus, there are considerable difficulties to overcome. To successfully cultivate research culture in government hospitals, it is essential to understand and highlight the attitudes, barriers and facilitators faced by specialists so that future research is more in number, better in quality and more significant in impact. However, little is known about specialists' perceptions towards research. Therefore, this study aimed to understand better how attitudes, barriers and facility specialists in Sabah government hospitals in Sabah to do research.

MATERIALS AND METHODS

A cross-sectional descriptive study was conducted in three government hospitals in Kota Kinabalu, Sabah, which were Queen Elizabeth Hospital (QEH), Queen Elizabeth Hospital II (QEH II) and Sabah Women and Children Hospital (SWACH) between September 2015 and October 2015. This study included only those specialists working in government hospitals. Those who were non-personnel of government hospitals or visiting specialists were excluded. Clinical Research Centre distributed self-administered questionnaires in each hospital to their specialists. The questionnaire had been validated (Teh et al., 2013). No personal identifiers or personnel's personal information were collected. Informed consent was taken from the first page of the questionnaire. The questionnaire consists of five sections: (A) personal particulars, (B) attitude, (C) barriers, (D) facilitators and (E) comments and suggestions. All responses were presented categorically (yes/no and by ranking the importance of facilitators given without repeating the same number, from one as the most important to eight as the least important). In total, there were 33 questions, 10 questions for attitude, 15 questions for barriers and 8 questions for facilitators.

All data were analysed using IBM SPSS Statistics version 24. Data were expressed as descriptive statistics such as percentages and frequencies for attitudes and barriers and scoring for facilitators among specialists towards research. No inferential statistics are involved as study objectives are fulfillable with descriptive

statistics and limited respondents. This study was approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia (NMRR-15-1294-27149).

RESULTS

Among the 122 questionnaires distributed, 49 were completed, giving a response rate of 40.2%. Responses by three hospitals were QEH (28), QEH II (5), and SWACH (16). The demographic characteristics of the respondents are shown in Table 1. The study's respondents were mainly males (n = 31; 63.3%). Most respondents belonged to the 30 – 39 years age group (n = 23; 46.9%), and the mean age was 40 years old (SD 5.341).

Table 1 Demographic characteristics of respondents (n = 49)

	n	%
Gender add		
Male	31	63.3
Female	17	34.7
*Missing data	1	2.0
Age range		
30 – 39	23	46.9
40 – 49	19	38.8
≥ 50	2	4.1
*Missing data	5	10.2
Designation		
Head of department	15	30.6
Consultant specialist	15	30.6
Specialist	11	22.4
Specialist under gazettement	7	14.3
*Missing data	1	2.0
Directorate		
Surgical	13	26.5
Women and child health	10	20.4
Medical	9	18.4
Others	16	32.7
*Missing data	1	2.0

There were an equal number of heads of department and consultant specialists (n = 15; 30.6%). Most respondents worked in surgery (n = 13; 26.5%), followed by women and child health (n = 10; 20.4%). Most respondents received research training (87.8%) and had research experience (85.8%) in the past five years. However, only 44.9% currently had involvement in research (Figure 1). Attitudes towards research are given in Table 2.

Figure 1 Training and experience of the respondents and their current involvement in research (a) research training in the past five years; (b) research experience in the past five years; (c) current involvement in research

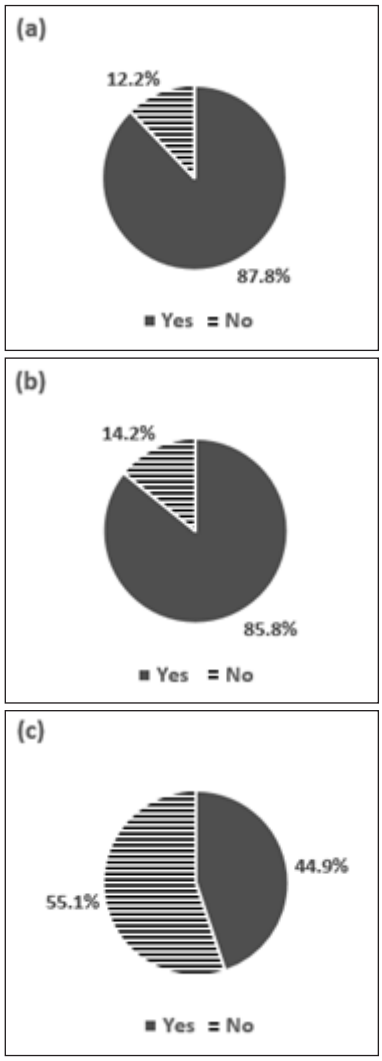

Table 2 Attitudes of specialists towards research (n = 49)

	n	%
I think research benefits patients and society	49	100
I think research helps to improve healthcare systems and policies	49	100
I think research helps in my professional development	46	93.9
I think research achievement given consideration in promotion exercise	35	71.4
I can carry out my clinical duties and do research at the same time	29	59.2
I think research is difficult and too time consuming	26	53.1
Research is in my job description	23	46.9
I think research could be harmful to my patients	7	14.3
I think research may affect my 'doctor-patient' relationship	7	14.3
I think research is a waste of time	1	2.0

All the respondents thought that research benefited patients and society (n = 49; 100%) and helped improve healthcare systems and policies (n = 49; 100%). Table 3 shows the perceptions of barriers to doing research. Lack of access to expertise, software or statistical analysis (n = 43; 87.8%) is the primary concern among specialists doing research in government hospitals.

Table 3 Specialists' views regarding barriers to research (n = 49)

	n	%
Lack of access to expertise, software or statistical analysis	43	87.8
Too much red tape in obtaining approvals (NMRR/NIH/MREC)	42	85.7
Lack of funds for research	41	83.7
Lack of mentors	39	79.6
The desire for work or life balance	36	73.5
Inconsistent number of doctors in my department	36	73.5
No coordinated approach to research in my department	36	73.5
Lack of access to journals and articles	35	71.4
Inadequate skills in research	34	69.4
Inadequate opportunities for training	34	69.4
It interferes with my daily work schedule, e.g., clinic duties, ward rounds, etc.	28	57.1
Lack of recognition from top management	27	55.1
Lack of encouragement and support from the department/institution	26	53.1
Research is not a priority in my department	25	51.0
Community distrust of research	12	24.5

The order of importance of facilitators is shown in Table 4. Recognition of research achievement for promotion was ranked as the most critical facilitator (score = 198), followed by professional development and peer recognition (score = 208).

Table 4 Importance of facilitators or motivators for research

	Score
Recognition of research achievement for promotion	198
For professional development and peer recognition	208
Financial incentives	211
Potential to benefit patients and institutions	223
Consideration for research scholarships	230
Seeing colleagues with research achievement	231
Ministry support to present at international conferences/scientific meetings	258
Getting CME credit	260

The lowest score reflects the most important facilitators or motivators.

DISCUSSION

This study provides valuable information on the attitudes, barriers and facilitators towards the research of specialists working in three tertiary hospitals in Kota Kinabalu, Sabah. Most respondents have attended research training such as Good Clinical Practice and protocol development training, whilst some had done research at their master's or PhD levels. Moreover, many respondents also have research experience as principals or sub-investigators in the past five years, which comprises doing research for their postgraduate requirement, involved in self-initiated or industry-sponsored research. Although the respondents may have adequate exposure and experience in research, their involvement at the time of this study was lower than half. This may result from the heavy workload that specialists deal with; once they begin working with patients, they cannot be more in research. In addition to that, specialists may think that research is not their primary job duties (Jowett et al., 2000).

In this study, most specialists positively perceive research, but more than half were not involved in any research. These results were in line with results from previous studies in Taiping (Teh et al., 2013) and studies from Caldwell et al. (2017) and Reali et al. (2021). Most believe that research benefits patients and society and thus improves the quality of care for patients and practices. Moreover, in recent years, several new guidelines for conducting research in the Ministry of Health (MOH) (2021), Malaysia's institutions and facilities were established, and a national funding programme was introduced to promote research culture in MOH.

Lack of access to expertise, software or statistical analysis was a significant barrier in conducting research, possibly due to statistician manpower shortage and inadequate funds to buy the statistical software. Moreover, too much red tape in obtaining approvals from the National Medical Research Register (NMRR), National Institutes of Health (NIH) and MREC, and lack of funds for research were also identified as the second and third most significant barriers. These perceived barriers have become the reason for the MOH management to document the level/frequency of research activity at the ministry level and to keep track of the approved and supported project, such as funding, to combat the arising issue National Institutes of Health (NIH), 2021). Furthermore, a few studies also identified that time, financial constraints, busy clinical practices, difficulties overcoming IRB hurdles, infrastructure support, lack of mentors and lack of interest as significant barriers to clinicians' involvement in research (Bakken et al., 2009; Jowett et al., 2000; Lloyd et al., 2004; Rosemann & Szecsenyi, 2004).

The top three excellent facilitators or motivators were recognition of research achievement for promotion, professional development and peer recognition, and financial incentives. This is consistent with the findings in Bakken et al.'s (2009) study. The results show that most specialists appreciate

research; however, in our practice, some specialists are still unaware of it being a professional obligation, unlike their colleagues in countries like the United Kingdom or America, with a much longer tradition in research, do. They are willing to participate in research mainly to improve their reputation and as an acknowledgement of their professional career.

CONCLUSION

In conclusion, this study provides valuable information for formulating strategies to increase specialist participation in research in government hospitals. Most specialists are trained and have experience in research, and they also believe that research benefits patients and society. However, not many engage in research due to barriers they face. This study also identifies key facilitators or motivators for specialists: promotion through recognition of research accomplishments. Therefore, MOH should pay attention to the barriers faced by specialists and facilitators, which motivate them to conduct research. Furthermore, steps and strategies should be implemented to reduce perceived barriers and increase awareness of research resources to improve the research environments.

CONFLICT OF INTEREST

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

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ORIGINAL ARTICLE

Causes of Visual Impairment and Types of Low Vision Aids Prescribed in Low Vision Clinic, Sibu Hospital, Sarawak

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ABSTRACT

This study was to determine the causes of visual impairment and to identify the low vision prescribing pattern among Low Vision Clinic (LVC) patients in the Sibu Hospital. This study was conducted retrospectively among 41 patients attending the LVC, Sibu Hospital. Patients' demographic characteristics, causes of low vision and blindness, and types of low vision devices prescribed were recorded and analysed for 21 (52.5%) males and 19 (47.5%) females. The mean age was 39.38 ± 17.98 years. The main causes of visual impairment were retinal dystrophies in 12 cases (30.0%) followed by neurological causes in 9 cases (22.5%), glaucoma in 8 cases (20.0%), and acquired macular disorders in 4 cases (10.0%). A total of 27 low vision devices were dispensed, 85.2% (n = 23) were near devices and 14.8% (n = 4) were distance devices. The most frequently prescribed low vision devices (LVD) were video magnifiers (37.0%), followed by hand magnifiers (22.2%), spectacle magnifiers (14.8%), telescopes (14.8%) and stand magnifiers (11.1%). The main leading causes of visual impairment in LVC Sibu Hospital were retinal dystrophies. Video magnifiers were the most common type of low-vision device prescribed. A prompt comprehensive screening is urged for family members with retinal dystrophies to detect the diseases early and hence timely exposure to low vision care and rehabilitation. Familial counselling on

inherited retinal diseases and better screening by primary eye care providers are required. Low vision services should be an integral part of the eye care systems in Malaysia.

INTRODUCTION

Visual impairment is known to affect an individual's visual system and functions (World Health Organization (WHO), 2019). Despite a decline in global visual impairment rates as shown in WHO data, low vision continues to be a significant public health concern requiring attention from all stakeholders (Ackuaku-Dogbe et al., 2016; WHO, 2019). Research indicates that vision rehabilitation can be beneficial for individuals with vision impairment (Binns et al., 2012; Ekpenyong & Ndukwe, 2010; John et al., 2021; Joshi et al., 2021; Omar et al., 2008). Since 2010, the Low Vision Clinic (LVC) at Sibu Hospital has provided services to patients referred by the Ophthalmology Department Sibu Hospital which covers the central region of Sarawak. This region includes Sibu, Kanowit, Selangau, Mukah, Dalat, Daro, Matu, Tanjung Manis, Kapit, and Song. Furthermore, LVC Sibu Hospital also received referrals from other suburban towns such as Julau, Machan, and Pakan. These patients would be assessed thoroughly and managed according to the Ministry of Health (MOH) Standard Operational Procedure (SOP) for low vision care service and undergo necessary visual rehabilitation in the LVC.

Previous studies on low vision and blindness in Malaysia were mainly conducted in the peninsular region and predominantly focused on Malay, Chinese, and Indian ethnic groups (Ibrahim & Razif, 2022; Mohidin & Yusoff, 1998; Omar et al., 2008; Omar, 2010; Rahman et al., 2020). Although some studies have explored the visual impairment among preschool and school-aged children, as well as among patients visiting the Ophthalmology Department in the southern and northern regions, there were no studies described visual impairment in the central region of Sarawak (Abu Bakar et al., 2012; Huong et al., 2022; Ting et al., 2021; Premsenthil et al., 2013). Moreover, no studies were done to investigate the low vision prescribing pattern in East Malaysia, which has unique and different ethnic compositions. This study aimed to identify the main causes of visual impairment and investigate the types of low vision aids that were frequently prescribed among patients who had attended LVC in Sibu Hospital.

MATERIALS AND METHODS

This study is a retrospective cross-sectional, observational study. All existing medical files in the Low Vision Clinic (LVC) Sibu Hospital were reviewed and retrieved from 1 January 2019 to 30 April 2022. The new referrals of low vision patients regardless of age that attended full low vision assessment by an optometrist and ocular diagnosis recorded and verified by an ophthalmologist were included in the study. Data retrieved were patient demographics that included age, gender, ethnicity, best-corrected visual acuity (BCVA) of the better eye, visual field (VF), main ocular diagnosis, and types of low vision devices (LVD) prescribed. The data were recorded in Data Collection Form which was adapted from the MOH Low Vision and Blind Registry Form and then transferred electronically into Microsoft Excel Spreadsheet. These data were anonymous with each patient being given a coded number identification with non-identified names/details.

Patients who fulfilled low vision and blindness definition according to the World Health Organization with irreversible and permanent visual impairment were included in this study (WHO, 2010). In our study, the severity of visual impairment and the causes of low vision and blindness were classified in accordance with the categories of the International Classification of Diseases Update, version 2010 (ICD-10). In this regard, visual impairment either moderate visual impairment (VA 6/18 to 6/60) or severe visual impairment (VA 6/60 to 3/60) was grouped

under the term "low vision" (WHO, 2010). Our patients' best corrected visual acuity (BCVA) was measured using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and Snellen Chart. Visual field loss was accessed concurrently to categorize the visual impairment in our study, in which low vision was defined as the BCVA in the better eye was less than 6/18, but equal to or better than 3/60, or a visual field loss less than 20° while blindness was defined if the BCVA in the better eye is worse than 3/60 or visual field less than 10°. The visual field was assessed using the Humphrey Visual Field Analyzer. The main ocular diagnosis referred to the particular disease that contributed to the irreversible and permanent visual impairment in a patient with various ophthalmic diseases that was verified by the ophthalmologist.

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 27 for descriptive analysis. Subjects' demographic data and clinical low vision data such as causes of visual impairment and types of low vision devices (LVD) prescribed were presented in a frequency and percentage table, bar graph, and pie chart, respectively. The study adhered to the principles of the Declaration of Helsinki and was approved by the Medical Research and Ethics Committee (MREC) of MOH Malaysia [NMRR ID-22-01742-XG9 (IIR)].

RESULTS

A total of 41 clinical records of patients attending LVC, Optometry Unit, Hospital Sibu were obtained in this study. Out of these, one was excluded as the subject showed visual acuity improvement which was better than 6/18 after glasses correction.

Age, Gender and Ethnicity Distribution

The mean age was 39.38 ± 17.98 years with a range of 7 – 75 years. Among the 40 subjects, more than half (n = 21, 52.5%) were male. This study showed that Native Iban (45.0%) was the predominant ethnicity among the LVC subjects, followed by Chinese (30.0%), Malay, and Melanau which contributed 12.5% each respectively (Table 1). Fifty-five per cent (n = 22) of LVC patients had low vision and the others (n = 18) were legally blind based on the aforementioned ICD10 definition (Figure 1).

Table 1 Demographics of the study sample

Variables	Number (n)	Percentage (%)
Gender		
Male	21	52.5
Female	19	47.5
Ethnicity		
Iban	18	45.0
Chinese	12	30.0
Malay	5	12.5
Melanau	5	12.5

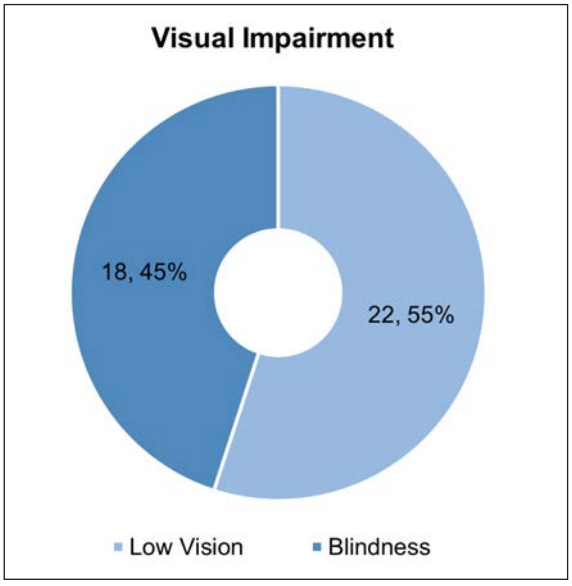

Figure 1 Category of visual impairment based on distance best corrected visual acuity (BCVA) and visual field (VF) in the better eye among the subjects

Ocular Pathology

The leading cause of low vision and blindness of our LVC was retinal dystrophies (n = 12, 30.0%); which included retinitis pigmentosa, Stargardt disease, albinism and macular scar. The second biggest cause was neurological causes (n = 9, 22.5%); which comprised visual impairment secondary to underlying neurological disorders, optic disc atrophy and congenital nystagmus. The third major cause was glaucoma (n = 8, 20.0%). It was followed by acquired macular disorders (n = 4, 10.0%); which consisted of age-related macular degeneration, pathological myopia and other macular disorders. Other causes were diabetic retinopathy (n = 3, 7.5%), retinal detachment (n = 3, 7.5%) and cornea opacity (n = 1, 2.5%) (Figure 2).

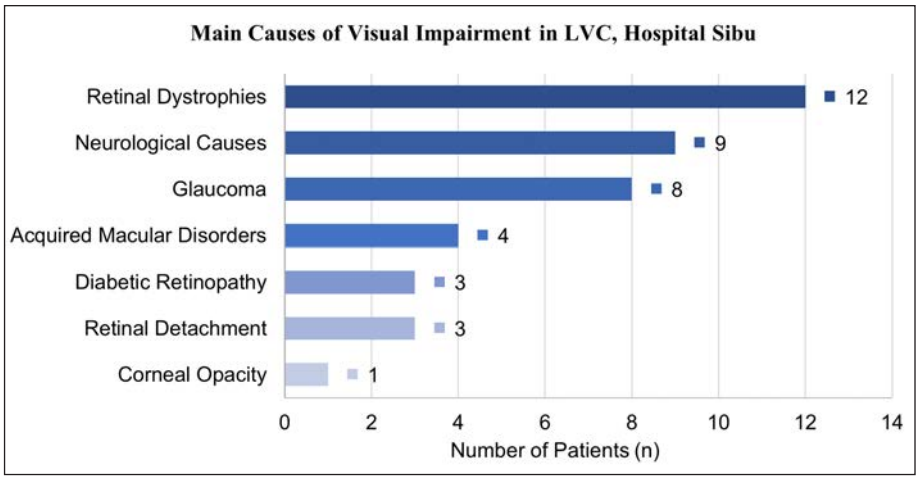

Figure 2 Main causes of low vision and blindness in LVC, Sibu Hospital

Low Vision Aids Prescribed

The data analysis showed that 23 LVC patients (57.5%) were prescribed LVD during the low vision assessment. Ten per cent of patients (n = 4) required more than one device to perform their daily tasks comfortably, hence they were prescribed more than one LVD. The most frequently low vision aids prescribed in LVC, Sibu Hospital were video magnifiers (n = 10, 37.0%), followed by hand magnifiers either illuminated or non-illuminated type (n = 6, 22.2%), spectacle magnifiers (n = 4, 14.8%), telescopes (n = 4, 14.8%) and stand magnifiers (n = 3, 11.1%) [Figure 3]. A total of 27 low vision aids were dispensed, 23 (85.2%) were near LVD and four (14.8%) were telescopes, the only distance LVD. Nevertheless, one-quarter of visually impaired patients (n = 10, 25%) were referred to an occupational therapist for orientation and mobility training. For comprehensive and optimal care of patients with low vision or blindness, our LVC collaborated with other disciplines such as the Department of Social Welfare Malaysia, a specialized school for visually impaired individuals, and also offered visual rehabilitation techniques including null point, eccentric viewing, Peli-prism prescription, and cerebral visual impairment therapy.

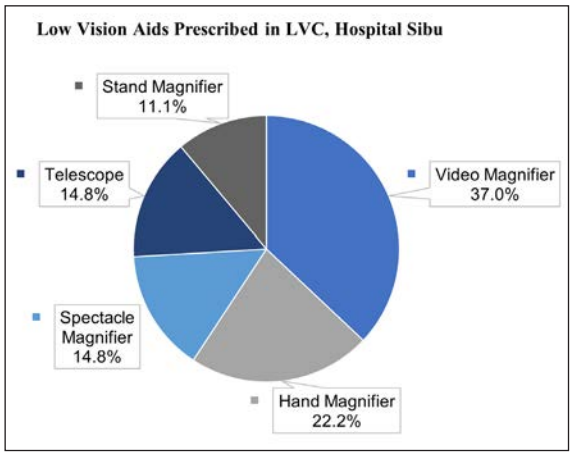

Figure 3 Low vision aids prescribed in LVC, Sibu Hospital

DISCUSSION

Gender and Ethnicity among LVC Patients

Males were predominant in LVC Hospital Sibu, which is in accordance with the literature (Huong et al., 2022; Ibrahim & Razif, 2022; Kim et al., 2010; Mohidin & Yusoff, 1998; Omar et al., 2008; Sapkota & Kim, 2017). This was possibly due to a lack of social support among females and they may have limited access to eye clinics in view of financial constraints and logistic issues. Similar results were revealed in developing countries such as India and Nepal (Olusanya et al., 2016; Xulu-Kasaba et al., 2020). On the contrary, a study by Chong et al. (2018) in Australia recorded a reverse result where female citizens were more likely to access low vision clinics. This indicated that efforts may need to be stepped up to enlighten the importance of low vision service and benefits among visually impaired patients, especially the female population. Regarding ethnicity, our study finding was close to the ethnic distribution of the central region of Sarawak as recorded by the Official Portal of Sarawak Data where Iban was the majority race (41.9%), followed by Chinese (25.3%), Melanau (16.1%), Malay (7.6%) and other local natives (1.9%) (Sarawak State Secretary Office, 2018).

We found that more of our patients in LVC suffered from low vision rather than blindness. Chotikavanich et al. (2018) reported the same finding with us that 54.1% of their patients had low vision while 27.4% of the patients were blind. A similar outcome was also described by other studies in the literature and the finding was in sync with the world's prevalence of visual impairment and blindness (Ackland et al., 2017; Joshi et al., 2021; Stevens et al., 2013).

The Aetiology of the Low Vision and Blind in LVC, Sibu Hospital

Retinal dystrophies contributed to the principal cause of low vision and blindness among our patients, followed by neurological causes and glaucoma. The result was compatible with the study of Omar et al. (2008) which reported that the main cause of low vision of their patients was retinal diseases (55.5%), followed by optic nerve diseases (23.1%). This high proportion of retinal disease was consistent with many previous studies conducted in either developing countries (Thailand, Iran and Jordan) or developed countries (Australia and the United Kingdom) (Abu-Yaghi et al., 2022; Chong et al., 2016; Chotikavanich et al., 2018; Pardhan & Mahomed, 2002; Qutishat et al., 2021; Ramezani et al., 2012).

Contrarily, UiTM Low Vision Clinic claimed that the leading cause of visual impairment among low vision patients was cataracts, which was a reversible and treatable ocular condition (Ibrahim & Razif, 2022). This observation discrepancy had been attributed to different visually impaired patients' entry criteria because LVC Sibu Hospital only accepted referrals of patients with irreversible and permanent ophthalmic diseases. Besides, a recent study by Huong et al. (2022) reported that the four leading causes of low vision and blindness in Miri Hospital, Sarawak were diabetic retinopathy (24.91%), glaucoma (24.54%), followed by retinitis pigmentosa (10.04%), and age-related macular

degeneration (6.32%). The study was a hospital-based study to investigate the prevalence and causes of low vision and blindness, however, our study was not population-based and only represented a small proportion of visually impaired patients who attended LVC in Sibu Hospital. Hence, we concluded that the result variations depended on geographic location, sampling or entry methods and clinic settings.

Provision of Low Vision Aids and Rehabilitation

The low vision aids were the essential gadget for the visually impaired patients to make use of the remaining functional vision to perform daily activities and consequently improve their quality of life. These were well documented in the literature (Binns et al., 2012; Ekpenyong & Ndukwe, 2010; Joshi et al., 2021; Kim et al., 2010; Omar et al., 2008). A small number of patients were referred to LVC Sibu Hospital possibly due to a lack of confidence in counselling regarding low vision care among the eye care personnel. They may have less exposure to low vision specialised fields and thus lack awareness of the available low vision service and their benefits. To date, most of the low vision care services were only available in government hospitals or provided via non-government organisations such as the Malaysia Association for the Blind (MAB), Sarawak Society for the Blind (SSB), Sabah Society for the Blind (SHSB) and St Nicholas Home, Penang. Nevertheless, there were very limited or almost no low vision services in the private eye centres. The LVC service often required extra consultation time and expenditure of low vision devices, thus the cost of practice was deemed as prevailing over the benefits. All these factors were speculated to influence the rate of LVC referrals.

Almost three-fifths of our LVC patients (57.5%) received low vision aids. Unfortunately, those not prescribed with low vision aids are due to the unfavourable residual vision. This was attributed to the majority of the patients being referred to LVC only if their vision was severely impaired due to advanced ocular conditions. Some of our patients were unsettled with LVD learning and training because they were sceptical about its advantages and partly in denial of having irreversible, permanent visual impairment. Moreover, the patients who stayed in remote areas tended to default to the low vision follow-up session due to transportation issues. It was well known that Sarawak was one of the few states that had the poorest accessibility to eye clinics caused of the geographical terrain (Chew et al., 2018; Huong et al., 2022; Yong et al., 2016). This significant issue indicated a need for further expansion of ophthalmological and LVC services to manage patients promptly and reduce preventable low vision and blindness even further, especially in Sarawak.

Video magnifier was the most popular LVD prescribed by our LVC because it was well-developed with technological advancement and became more accessible in the market. The device enabled low vision patients who generally had reduced contrast sensitivity to fully exploit the residual vision to read prints effectively by manipulating contrast, brightness and print size. Therefore, LVC patients mostly were pleased and delighted to use it because reading, writing and the performance of near tasks were their main concerns (Chotikavanich et al., 2018; Kim et al., 2010). Contrarily, many previous studies claimed that spectacle magnifiers were the most commonly used among their LVC patients as they were the cheapest and highly available in the market (Chong et al., 2016, 2018; Ekpenyong & Ndukwe, 2010; Ibrahim & Razif, 2022; Omar et al., 2008). Although utilisation of a basic and cheaper range of LVDs such as spectacle magnifiers, handheld and stand magnifiers was adequate for the visually impaired patients to maintain and improve their quality of life, they still might need a more advanced LVD to perform a different range of tasks daily (Omar et al., 2008).

Video magnifiers were generally more expensive and harder to access, especially among the socio-economic disadvantaged

population. However, the electronic magnifier prescription rate was unexpectedly found low in developed countries such as Australia and the United Kingdom although video magnifier was cheaply loaned or supplied at no charge to low vision and blind patients (Chong et al., 2018; Taylor et al., 2017). Yet the reasons for the low uptake of electronic devices regardless of their benefits of digital magnification, remained uncertain (Chong et al., 2018). Generally, near LVD was preferred among LVC patients especially those with a restricted visual field such as patients with retinitis pigmentosa, glaucoma, or diabetic retinopathy instead of a telescope for distance viewing due to its limited field of view and lighting (Chotikavanich et al., 2018). However, according to Kim et al. (2010), telescopes (39.2%) were the most prescribed LVD in South Korea compared to other types of LVD which were spectacle magnifiers (27.8%), hand-held magnifiers (22.7%), stand magnifiers (7.2%), and electronic magnifiers (3.5%) although overall more near LVD were prescribed (60.8%).

The issue of financial constraint indeed restricted low vision patients to utilise the pricey and yet extremely useful LVD. Therefore, the subsidization or any properly planned insurance scheme helped ameliorate the utilization of LVD and subsequently amplified the benefits of low vision care services among visually impaired patients (Dandona & Dandona, 2001; Ekpenyong & Ndukwe, 2010; Huong et al., 2022). In our centre, we tried to provide the appropriate LVD to our LVC patients with prioritization of their visual function and needs. For the social-economic disadvantaged patients, we tried to help by requesting funds from NGOs or some local politicians in Sibu. The sponsorship of the device was undoubtedly and tremendously helpful especially for school-age patients because it would improve and allow them to catch up with learning at school.

Besides, it is crucial and essential to improve public transportation and road conditions in extremely remote areas and suburban towns such as Kapit, Song, Matu, Daro and Dalat to promote access to ophthalmological and LVC services. Community programmes and awareness campaigns are important to educate the public on the significance of seeking early intervention for low vision and exposure to LVC services. Thereby, this allows more individuals with low vision and blindness to improve their quality of life and independence.

The management of visually impaired patients requires a multidisciplinary approach to achieve a better quality of life besides periodic review of ocular conditions by ophthalmologists and low vision care by optometrists (Chong et al., 2018; Joshi et al., 2021) Appropriate referrals to other disciplines were made available via LVC, for instance, review of activities of daily living, adaptive techniques and technology, orientation and mobility training by occupational therapists, referral to social welfare workers for financial assistance, a special school for Braille training, some non-government organisations such as Malaysian Association of the Blind (MAB) or Sarawak Society of the Blind (SSB) for white cane, handicraft and massage training. In addition, Baarah et al. (2018) suggested that pre-marriage medical counselling and guidance should be conducted concurrently to prevent visually impaired genetic diseases, and to manage patients with inherited ocular diseases.

We believe that our study is able to provide invaluable information to improve low vision care service and rehabilitation, national healthcare policies and insurance schemes on the provision of low vision aids. Enhancing visual rehabilitation and personalized care that meets the unique needs and circumstances of visually impaired patients enables them to perform daily routines effectively and independently.

Our study was primarily limited by its retrospective cross-sectional nature, the fact that the analysis is hospital-based and

the small number of patients. This may have resulted in a biased sample that might not be representative of the general population of patients with low vision. However, this report provides reliable and credible information about the causes of low vision and blindness and the LVD prescribing patterns as well-documented records and diagnoses by ophthalmologists nailed the accuracy of the data presented in this study. Additionally, consistency in low vision care services is guaranteed with standardized and reliable low vision assessments by optometrists. Overall, our study highlights the significance of screening for low vision and the need for appropriate interventions to improve the quality of life for the low vision and blind.

CONCLUSION

We concluded the predominant causes of low vision and blindness of our LVC patients were retinal dystrophies followed by neurological causes and glaucoma. Video magnifiers were the most frequently prescribed devices. More comprehensive screening is urged promptly for family members with retinal dystrophies to detect the diseases early and hence timely referrals to low vision care and rehabilitation services. We emphasized the importance of familial counselling and education on inherited retinal diseases and the need for better screening by primary care service providers, particularly in the context of rural and underserved populations. Moreover, policymakers and healthcare providers should prioritize integrated low vision and blind care services as part of comprehensive eye care systems to ensure optimal outcomes for visually impaired patients. A further multi-centre study can be carried out in Sarawak to investigate the quality of life among visually impaired patients with low vision device interventions.

CONFLICT OF INTEREST

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

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ORIGINAL ARTICLE

POUR-UP: Power of Urination in Relieving Urethral Pain During Flexible Cystoscopy in Males

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ABSTRACT

This study aimed to investigate the effectiveness of micturition (urination) during flexible cystoscopy in alleviating urethral pain in males. A single-blinded, randomized controlled trial was conducted with 103 male outpatients at a tertiary care hospital in Malaysia. Participants, aged 18–80, undergoing flexible cystoscopy were randomly assigned to either a control or interventional group. The interventional group was instructed to urinate during the procedure, while the control group received no such instructions. All patients received standard lidocaine gel before the examination. Patient discomfort was assessed using Visual Analogue Scores (VAS) at three points: before gel instillation (baseline), immediately after the procedure, and 15 minutes post-examination. Age, BMI, duration of the examination, and examiner experience were also recorded to explore their correlation with the immediate post-procedure pain score. The interventional group reported significantly lower pain scores immediately after the procedure ($p < 0.001$) and 15 minutes later ($p < 0.005$) compared to the control group. However, there was no statistically significant difference in age, BMI, examination duration, or examiner experience level between the two groups regarding the pain score immediately post-procedure. These findings suggest that urination during flexible cystoscopy can substantially alleviate urinary discomfort and lead to a significant reduction

in urethral pain in males. This approach may provide a valuable method to improve patient comfort during the procedure.

INTRODUCTION

Flexible cystoscopy examination is a routinely performed office procedure in any urological consultation. Since its introduction in 1984, it has become a common procedure with almost no/minimal reported side effects. In comparison with a rigid cytoscope, it has no blind spots, clear vision, and can be performed as an outpatient procedure for most diagnostic/surveillance procedures (Pillai & Sooriakumaran, 2009). Urethral pain or discomfort has been one of the most challenging factors that urologists have faced while performing this procedure (Krajewski et al., 2016). Many patients, particularly men, refuse this examination for this reason.

There have been many methods described in the literature on how to manage pain among patients undergoing CE, especially male adults. Instillation of local analgesic agents (LA) such as Lignocaine/Bupivaicaine/ Tetracaine gels as a gelatinous mix of lubricant and LA has been common practice for years (Akkoç et al., 2016; Patel et al., 2008). In recent years, many studies have been performed to explore the role of behavioral/psychological interventions to reduce urethral pain, for example, watching examination procedures via television (Patel et al., 2007; Zhang et al., 2011) or squeezing pressure balls while listening to music (Zhang et al., 2014; Raheem et al., 2015).

Techniques to reduce urethral pain during cystoscopy are still a controversial topic, as most studies use the patient's perception of pain. The role of urination in reducing urethral pain is relatively new, and the only randomized study that has been performed to support this idea was by Xie et al. (2020) with the concept that micturition should relax the sphincters, which in turn should open the urethral lumen wider, and reduce the painful sensation of cystoscopic examination.

The primary objective of this study is to assess the effectiveness of micturition (urination) during flexible cystoscopy in relieving urethral pain in males. Additionally, the study aims to identify any other factors that might contribute to a higher pain score among the Malaysian population during this procedure.

METHODOLOGY

Study Population

Male patients between 18 and 80 years old undergoing elective CE in Hospital Sultanah Aminah from May 2022 – Dec 2022 and requiring diagnostic/surveillance cystoscopy were recruited. Exclusion criteria included using analgesics within 24 hours of the study period, having a known urethral stricture, a history of urethral dilation, an acute urinary tract infection, an indwelling urethral catheter, and having existing urethral pain (including chronic pelvic inflammatory disease and interstitial cystitis).Patients as well as those who are unable to cope with pain assessment due to a mental disorder or who are treated as neurogenic bladder failure or bladder failure or who are unable to void on command were excluded from this study. Potentially vulnerable subjects were also excluded from the study (prisoners, cognitively impaired subjects, and critically ill subjects).

Randomization

After being reviewed by the medical officers-in-charge, by using Random Allocation Software, version 1.0.0, a random number is built, which then randomly divides patients into experimental and control groups with a 1:1 ratio. This process is carried out by another medical officer who is not involved in the subject's recruitment process. To ensure concealment of allocation, only sealed opaque envelopes were used. Only participants in the intervention group in the trial know the grouping; however, the data collectors (staff nurse who qualified to assess pain scores)

were blinded to avoid bias. The operator of the cystoscopy only knew the grouping of the patient when he opened the sealed envelope prior to performing the procedure.

Design

We performed a prospective, randomized, controlled trial (single-blinded) designed to compare pain scores between patients in the interventional and control groups. Patients who are deemed eligible to join this study underwent routine urinalysis to rule out the presence of any active infection. Prior to cystoscopy, a routine bladder scan was performed to ascertain a minimal volume of 100 ml of urine present so the patient was able to void on command. Patients in the test group were instructed to urinate during the procedure, while those in the control group were not given any instructions.

All cystoscopies were performed by experienced urologists, surgeons, or trainees who have a minimum of 2 years of experience in the field of urology. Pain scores are assessed using the Visual Analogue Score (VAS), where patients where are asked to mark their intensity of pain with a range from "0" indicating no pain, to "10" on the other end, indicating severe pain. Patient's pre-procedure pain score, immediate post-procedure pain score (after entering bladder), and 15 minutes post procedure pain score recorded by data collectors. In this study, a standard cystoscopy system, including 16F flexible cystoscopy (Olympus CYF-5A), a digital camera (Olympus OTV-S7), and color video monitor (Olympus OEV-191H), was used.

Intervention

All patients underwent preliminary bladder scans immediately prior to the procedure to ascertain that at least a minimum of 100 ml of residual urine was present in order to be able to void on command. Patients were positioned supine as per any cystoscopic examination. The area of interest was disinfected with routine antiseptic solutions. Prior to the examination, 10 ml of 2% lidocaine gel was instilled into the urethra and squeezed gently for a duration of 5 minutes. For the control group, the penis is stretched and the cystoscope introduced through the meatus with examiner's left hand while introducing a flexible cystoscope into the urethra with the guide of his left thumb and index finger. The cystoscope held with his right hand, with his thumb used to control the adjusting lever. Under direct vision and with the help of continuous irrigation fluid flow, the examiner observes the urethra, which is transmitted into video surveillance. Upon reaching the external urethral sphincter, the examiner stays 1 – 2 seconds and attempts to enter the bladder. Meanwhile, for the experimental group, similar steps repeated and patients were instructed to void upon reaching external urethral sphincter. Cystoscopy advanced to enter the bladder as the patient attempts to voids, when visual relaxation of sphincter happens completing the examination.

Collection of co-variate data

A few other data points such as age, height, weight, indication for examination, and duration of examination were also recorded. Performing examiners are distributed by random selection. This data was collected to support the secondary objective of this study.

Follow-up

Prior to discharge, patients were reviewed by the medical officer in charge, and the findings of the procedure were explained in detail. Follow-up is given to review the patient at one-month's duration to record any adverse effects. Routine clinic follow-up appointments were given according to the nature of the illness.

Data Analysis

Sample size of this study calculated based on two-sample t-test: $n = (2 * (Z\alpha/2 + Z\beta) / d)^2$. Where: n = sample size per group $Z\alpha/2$ = critical value of the standard normal distribution at a

significance level (α/2) Zβ = critical value of the standard normal distribution at the desired statistical power (1 – ß) d = Cohen's d effect size.

We used results from Taghizadeh et al. (2006) 2.82 ±1.2 VAS (presuming with minimally clinically important pain difference as 0.9 (Kelly, 1998). Given the effect size of Cohen's d = 0.5, and a two-sided 5% level t-test with a statistical power of 1 – ß = 80%, 32 patients would be needed to detect this group difference. We recruited 103 patients in this trial (n = 51 control, n = 52 interventional); recognizing a potential loss of analytical power due to patient withdrawals of 10%.

SPSS 20.0 software was used for all data analysis. Numerical data are presented as mean ± standard deviation (SD), median, and interquartile range (IQR). Categorical are presented as frequency and percentage. The mean pain score between the 2 groups (control and intervention) was compared using an independent t test. A p-value less than 0.05 was considered to be statistically significant. The correlation between factors is analyzed with Pearson correlation.

RESULTS

As shown in Table 1, 103 patients included in this study which were randomized into control, (n = 51) and interventional (n = 52). Mean age, BMI, and examination time are analyzed with an independent t-test showing no statistical significance among the control and interventional groups empowering our study population, which are similar in nature.

Table 1 Demography of study population

Variables	Control (n = 51) Mean (SD)	Interventional (n = 52) Mean (SD)	Mean diff (95% CI)	t-statistic (df)	p-value
Age (years)	59.37 (9.35)	59.00 (9.68)	–0.37 (-4.09,3.34)	–0.20 (100)	0.843
Body Mass Index	30.17 (2.45)	30.15 (3.49)	–0.14 (-1.19,1.17)	–0.02 (101)	0.983
Examination time (min)	14.61 (1.04)	14.67 (1.26)	0.07 (–0.39,0.52)	0.29 (101)	0.776

Between interventional and control groups, patients were equally examined by either Consultant, Surgeon, Senior or Junior trainee (Table 2). Statistical analysis by one-way ANOVA showed a p value that was not significant between and within groups, as shown in Table 3 below, the same as for all our other demographics in both groups.

Table 2 Examiner's experience among control vs interventional groups

Examiner's experience	Control group N (%)	Interventional group N (%)
Consultant	13 (25.4)	13 (25.0)
Surgeon	12 (23.5)	14 (26.9)
Senior trainee (UT2)	13 (25.4)	12 (23.1)
Junior Trainee (UT1)	13(25.4)	13 (25.0)

Table 3 Comparison between surgeons experience and pain recorded one-way ANOVA analysis

	Sum of squares	df	Mean square	F	Sig.
Between groups	0.289	1	0.289	0.229	0.633
Within groups	127.264	101	1.260		
Total	127.553	102			

The majority of our patients undergo cystoscopy as part of preoperative evaluation for bladder calculus, followed by a benign prostatic hyperplasia workup prior to surgical interventions. The third largest group of patients were those on regular surveillance for malignant neoplasm of non-muscle invasive bladder carcinoma/upper tract urothelial carcinoma after radical nephro-ureterectomy with bladder cuff excision. The other indications are tabulated in the bar chart below (Figure 1).

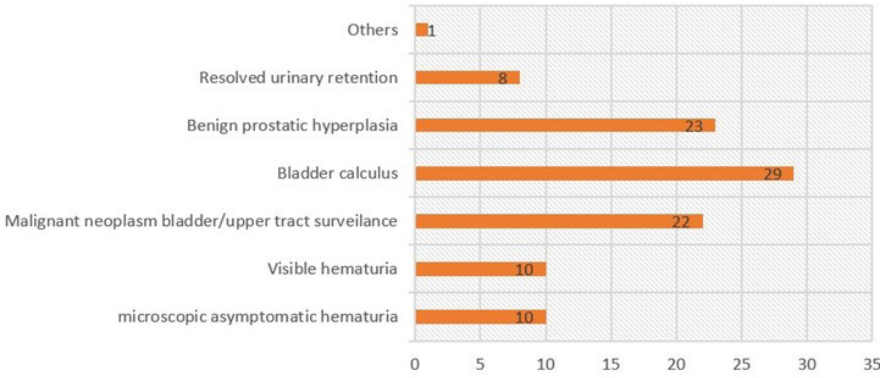

Figure 1 Indication for urethro-cystoscopy

In terms of VAS, neither group experienced pain at the start of the test (score = 0).Score at immediate post-procedure was lower among the interventional group: 4.35 ± 1.05, while the control group score was 5.20 ± 1.23, with a statistically significance difference of p = 0.00001. Similar findings noted for score 15 minutes post procedure whereby interventional group recorded score = 2.06 ± 1.02 while control group score = 2.63 ± 1.00 with statistically lower score with p < 0.005. Table 4 shows statistical analysis while box and whisker in Figure 2 showing interquartile range of both test and control group at 2 different time of pain score recordings.

Table 4 VAS difference Control vs Interventional at immediate and post procedure (15 min)

Visual analogue score (VAS)	Control mean (SD)	Interventional mean (SD)	Mean diff (95% CI)	t-statistic (df)	p-value*
Immediate	5.20 (1.23)	4.35 (1.05)	–-0.85 (–1.30, –3.97)	–3.72 (101)	0.00001
15 min post procedure	2.63 (1.00)	2.06 (1.02)	–0.06 (–0.96, –1.78)	–2.89 (101)	0.005

*Independent t-test

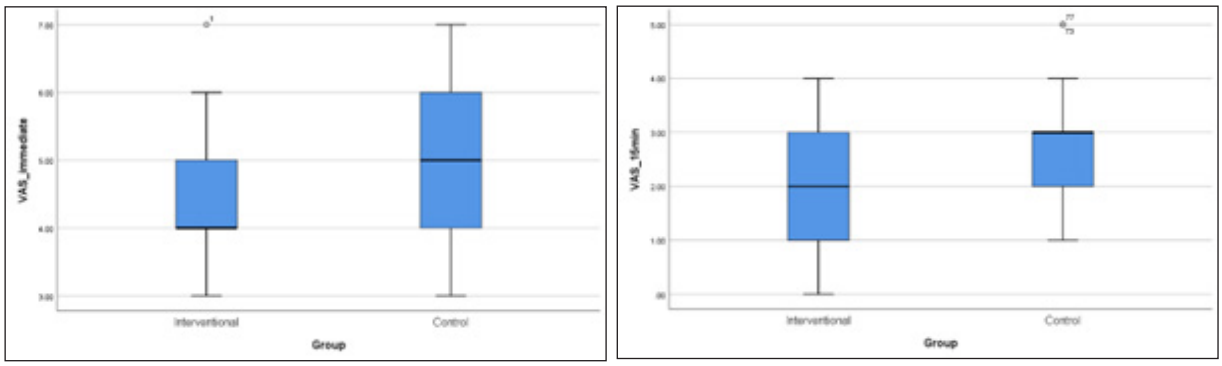

Figure 2 VAS comparison immediate and 15 minutes post procedure

Age, BMI, procedure duration (time), and operator experience are found to have no significant effect on pain score (VAS) at the immediate post procedure ($p>0.05$). Result of the Pearson correlation are tabulated in Table 5 below.

Table 5 Secondary factors associated with VAS (immediate)

	Pearson Correlation	Sig (2-tailed)
Age	0.187	0.06
BMI	–0.01	0.99
Time	0.127	0.20
Operator experience	0.057	0.570

DISCUSSION

Flexible cystoscopy is widely used in urological investigations for direct visualization of lower urinary tract pathologies. However, urethral pain and discomfort have been significant limitations, particularly in males undergoing this procedure. Previous studies have highlighted that the most painful part of flexible cystoscopy occurs when the scope tip passes the external sphincter (Taghizadeh et al., 2006; Chen et al., 2005), which is rich in nerve endings and comes into contact with the urethral mucosa.

Studies by Xie et al. (2009) demonstrated that during urine storage, the external sphincters remain contracted to maintain continence, and they relax during voiding. These findings have led to the exploration of various methods to reduce pain during cystoscopy. Non-pharmacological strategies, including psychological and behavioral techniques, have gained popularity, as they allow active control of the cerebral cortex through intentional urination, leading to relaxation of the external urinary sphincter and smoother passage of the cystoscope.

In our study, we aimed to replicate these findings within our local population as this may lead to better treatment modality for future references. We were successful in recruiting 109 patients to participate in this study. After recruitment, total of 6 patients were excluded from further data analysis. 4 patients from interventional arm withdrawn due to failure to void with instruction. This event might be related in the earlier phase of study whereby more medical personnels than needed were present that contributed shyness to perform needed act. The other 2 patients (1 from each arm) refused to undergo this procedure due to personal reasons. Degree of relaxation of sphincter is subjective to each performing surgeons however all agreed upon only to advance cystoscopy further once urine is seen gushing out at level of external sphincter in interventional arm. Verbal assurances, the bag squeeze technique, listening to music were allowed for both while maneuvers that might lead to sphincter relaxation (verbal order to relax sphincter, wiggling toes, cough, etc.) was not performed in control group. Retroflexion however not performed in any of the cases as we believed bladder pain might arise with friction of endoscope. We observed significantly lower pain scores in the interventional group compared to the control group immediately post-procedure (5.20 ± 1.23 vs 4.35 ± 1.05, $p = 0.000$) and 15 minutes post-procedure (2.63 ± 1.00 vs 2.06 ± 1.02, $p = 0.005$). Although statistically significant, we acknowledge that clinical difference of VAS 1 does not seem much in real world data. First experience with painful episode of cystoscopy examination will affect compliance of further surveillance follow up (Chen et al., 2005) and affects overall quality of life in patient care.

One of the strengths of our study is the even distribution of the study population between the interventional and control groups, with no significant differences in age, BMI, duration of examination, or examiner experience. This minimized bias and reduced the impact of confounding factors. Surprisingly, our analysis did not find any correlation between age, BMI, examination duration, examiner experience, and higher pain scores immediately post-procedure.

However, our study does have limitations. One limitation is the uncertainty regarding the degree of relaxation of the external sphincters in the control group. Objective assessment of sphincter relaxation using techniques such as electromyography (Xiyu & Bo, 2002) could be considered in future studies. Furthermore, a more comprehensive analysis of other potential confounding factors and their influence on pain scores could provide additional insights. It would be interesting to explore if there is any association between pain scores and race, considering that Malaysia is a multiracial country. This could be a potential avenue for future research.

CONCLUSION

In conclusion, our study supports previous findings that micturition during flexible cystoscopy significantly reduces urethral pain in males. This non-pharmacological approach, allowing active relaxation of the external urinary sphincter, shows promise in enhancing patient comfort during the procedure. Further research is warranted to explore additional factors and refine the techniques used to alleviate pain and discomfort during cystoscopy.

CONFLICT OF INTEREST AND FUNDING

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DISCLOSURE

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. Approval was obtained from Medical Research and Ethics Committee (MREC) and this study is registered as RSCH ID-21-01155-Z2F with National Medical Research Register (Malaysia) prior to recruitment. All participants signed consent agreeing to be involved in this study. There was no animal involved in this study.

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CASE REPORT

Parkinson's mimicker in Acute and Chronic Hepatic Encephalopathy

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ABSTRACT

Hepatic encephalopathy (HE) is a neuropsychiatric spectrum mainly caused by cirrhosis, portosystemic shunt, or portal hypertension. It may also mimic the presentation of Parkinson's disease, which can make clinical diagnosis a challenge. A 42-year-old man with underlying chronic hepatitis C with liver cirrhosis was initially admitted for chronic lower back pain. During admission, he appeared drowsy but was able to answer questions appropriately albeit with delayed and slow speech. He had bradykinesia without stigmata of chronic liver disease. Differentials at the time were hypoactive delirium and Parkinson's disease. Blood results were normal. Magnetic resonance imaging (MRI) of the brain showed bilateral symmetrical hyperintensities at the inferior temporal lobes, medial thalamus, cingulate gyri, head of caudate nuclei, posterior limbs of internal capsules and insula on fluid-attenuated inversion recovery (FLAIR) sequence. On the T1 weighted imaging (T1WI) sequence, bilateral symmetrical hyperintensities were seen at globus pallidi, cerebral peduncles and periaqueductal regions extending to superior cerebellar peduncles. Based on imaging, a diagnosis of acute chronic hepatic encephalopathy was made. The patient was treated conservatively in the ward and was discharged with persistent Parkinsonism. In patients with neurological abnormalities where hepatic encephalopathy

(HE) is least expected due to subtle symptoms, MRI could play an important role in eliciting the underlying cause, and extent of disease and for prognostication.

INTRODUCTION

Hepatic encephalopathy (HE) is a neuropsychiatric spectrum, mainly caused by cirrhosis, portosystemic shunt, or portal hypertension (Nizamani et al., 2018). It is associated with poor survival and a high recurrence rate without prompt initiation of adequate treatment (Vilstrup et al., 2014). Magnetic resonance imaging (MRI) can detect the extent of brain parenchymal injury and correlation to the patient's clinical status is the utmost importance (Nizamani et al., 2018). Herein we report a case of a 42-year-old man with underlying hepatitis C, with atypical presentation of Parkinsonism in a classic MRI imaging findings of acute on chronic hepatic encephalopathy.

CASE PRESENTATION

A 42-year-old man with underlying chronic hepatitis C with Child-Pugh A liver cirrhosis was admitted with an initial presentation of chronic lower back pain. He appeared drowsy and slow to respond, but was able to answer questions coherently. The neurological examination noted bradykinesia with no neurological deficit depicted. There were no stigmata of chronic liver disease either. No preceding history of fever or any notable neurological symptoms such as seizure, hemiparesis or behavioural changes. Social history revealed that the patient did not work in the mining industry. Vital signs, liver enzymes and hepatitis C virus (HCV) RNA tests were all normal. Magnetic resonance imaging (MRI) of the brain showed bilateral symmetrical hyperintense signal seen at inferior temporal lobes, medial thalamus, cingulate gyri, head of caudate nuclei, posterior limb of internal capsules and insula (Figures 1 and 2). These findings are typical in acute on chronic hepatic encephalopathy. There was no abnormal signal intensity involving the substantia nigra and red nuclei to suggest Parkinson's disease. The patient was treated conservatively with syrup lactulose in the ward and subsequently discharged well with persistent Parkinsonism.

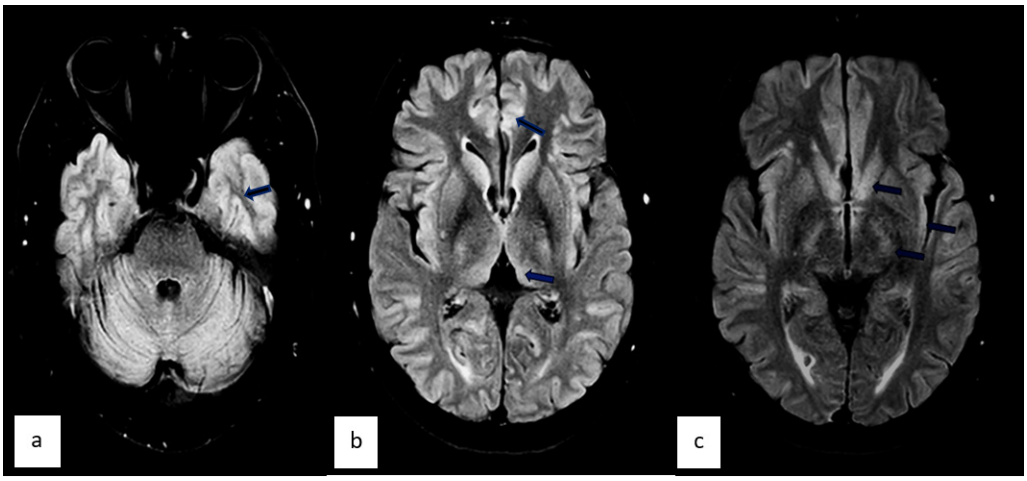

Figure 1 Axial FLAIR (a, b, and c) shows bilateral symmetrical hyperintensities at inferior temporal lobes, medial thalamus, cingulate gyri, caudate head, posterior limb of internal capsules and insula

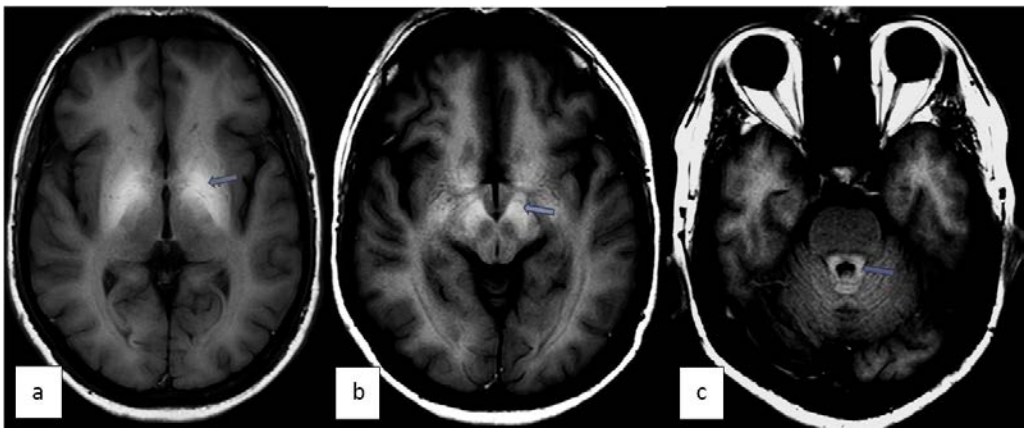

Figure 2 Axial T1W (a, b, and c) displays bilateral symmetrical hyperintensities at globus pallidus, cerebral peduncles and periaqueductal region extending to superior cerebellar peduncles

DISCUSSION

Hepatic encephalopathy (HE) is a neuropsychiatric spectrum, mainly caused by cirrhosis, portosystemic shunt, or portal hypertension (Nizamani et al., 2018). It is associated with poor survival and a high recurrence rate unless the underlying cause is successfully treated (Vilstrup et al., 2014). In a middle-aged patient with a rapid onset of symmetric Parkinsonism, hepato-cerebral Parkinsonism should be suspected (Noone et al., 2008). In the literature, the reported prevalence rate ranges from as low as 3.5 – 4.2% to as high as 21.6% (Burkhard et al., 2003; Tryc et al., 2013; Kang et al., 2011). Global hypokinesia and gait impairment are early Parkinsonian symptoms in cirrhosis, whereas dementia and resting tremors are uncommon symptoms (Noone et al., 2008).

Excess manganese within the brain is believed to be the cause of T1 weighted image (T1WI) hyperintensity on magnetic resonance imaging (MRI), which can be seen affecting bilateral globus pallidi and substantia nigra, which explains Parkinsonian manifestation (Noone et al., 2008; Rovira et al., 2008; McPhail et al., 2012). It coincided with autopsied brain tissue, where it affects the post-synaptic dopamine D2 binding sites, associated with high levels of manganese (Spahr et al., 1996).

Although the diagnosis of hepatic encephalopathy is almost always clinical, we can however appreciate the affected brain areas, in which different areas of distribution can be seen in acute and chronic hepatic encephalopathy. MRI is an important modality in aiding the diagnosis of hepatic encephalopathy. Fluid attenuated inversion recovery (FLAIR) sequence is sensitive to detect hyperintense white matter lesions which is a combination of reversible oedema and irreversible neuronal damage. This can be seen along the hemispheric corticospinal tract and subcortical hemispheric white matter (Rovira et al., 2008). Meanwhile, on diffusion-weighted imaging (DWI) sequence increased diffusion can be seen at hemispheric white matter, which suggests interstitial brain oedema (Rovira et al., 2008).

On magnetic resonance spectroscopy (MRS), an increased glutamine/glutamate signal is seen, caused by osmolar adaptation of intra-astrocytic accumulation of glutamine (Rovira et al., 2008). Diffuse cortical lesion involving the cingulate gyrus and insula cortex, with sparing occipital and perirolandic cortices is highly specific to hepatic encephalopathy, which may be explained by susceptibility towards hyperammonemic-hyperglutaminergic encephalopathy (Nizamani et al., 2018; Reis et al., 2020). Other sites involved include thalami, midbrain, and periventricular areas (Reis et al., 2020).

However, it is important to take note that any other hyperammonemic cause of encephalopathy also yields similar findings on MRI (Reis et al., 2020). Differences in frequency and imaging findings on MRI between acute HE and chronic HE were summarized, as shown in Table 1.

Table 1 Comparison of acute and chronic hepatic encephalopathy

Types of hepatic encephalopathy	Chronic hepatic encephalopathy	Acute hepatic encephalopathy
Frequency	Common	Rare
Aetiology	Chronic severe liver disease (cirrhosis)	Varies – hyperammonemia, infections, drug toxicities, parenteral nutrition
Imaging findings	T1WI hyperintensities involving: • Globus pallidus • Substantia nigra	FLAIR/DWI hyperintensities involving: • Mainly insula and cingulate gyri • Spares perirolandic and occipital regions • May involve basal ganglia, thalami, and periventricular regions MRS may show glutamate-glutamine peak
Cause of imaging findings	Attributed to manganese deposits	Hyperammonemia

Source: Rovira et al., 2008; McPhail et al., 2012; Spahr et al., 1996; Osborn et al., 2018

Manganese and ammonia are two of many compounds that are metabolized by the liver (Rovira et al., 2008). They may enter the brain and induce disturbances in neurological function (Rovira et al., 2008). It is widely accepted that ammonia is the main cause of hepatic encephalopathy, where it is deposited into astrocytes and causes brain oedema (McPhail et al., 2012). In turn, they will be converted into glutamine which causes neurological disturbance (McPhail et al., 2012). Manganese was already considered neurotoxic 150 years ago when industrial workers exposed to black oxide manganese developed unsteady gait and muscle weakness (Rovira et al., 2008). In this case, they typically exhibit extrapyramidal symptoms such as hypokinesia, rigidity and tremors (Rovira et al., 2008).

In cases of cirrhosis and portosystemic shunts, plasma manganese levels are increased and then transported to the brain, causing neuronal loss in basal ganglia structures and reactive gliosis (Rovira et al., 2008). At the toxic level, it affects mitochondria where it catalyzes dopamine oxidation mainly in globus pallidus, extending to substantia nigra (which has a high concentration of neuromelanin) (Goldman, 2014; Ratner & Feldman, 2005).

Acute disseminated encephalomyelitis (ADEM) is also a possible diagnosis for this patient, but it is rare in hepatitis virus infection (Lazibat & Brinar, 2013). While it can cause encephalopathy in the affected patients, their imaging features are very different as their distributions are asymmetric and may involve both subcortical and deep white matter and grey matter, like thalamus and basal ganglia in particular (Lazibat & Brinar, 2013).

Currently, the first choice treatment for HE is by administrating nonabsorbable disaccharides which is lactulose (Vilstrup et al., 2014). Rifamixin may also be given together with lactulose to reduce the risk of HE recurrence in a patient (Vilstrup et al., 2014). There are many other medical treatments available as mentioned by Vilstrup et al., however, it is not the main focus of this article. It was also reported that these symptoms are reversible once the patient is treated with portosystemic shunting or liver transplant (Noone et al., 2008), and only done if medical treatments are exhausted (Vilstrup et al., 2014). Some of the patients, however, may show good responses from taking Levodopa (Burkhard et al., 2003).

CONCLUSION

Hepatic encephalopathy is a sequelae of a failing liver, due to excessive unmetabolized plasma manganese and ammonia. In patients with neurological abnormalities where hepatic encephalopathy is least expected due to subtle symptoms, MRI could play an important role in eliciting the underlying cause and extent of disease and for prognostication.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in publishing this article.

CONSENTS

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

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CASE REPORT

Uterine Arteriovenous Malformation: A Near-Missed Fatal Misdiagnosis?

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ABSTRACT

Less than 100 cases of uterine arteriovenous malformations (AVM) have been documented. The true incidence remains unknown with 30% complicated by hypovolemic shock. Women who experience unexplained vaginal bleeding may consider this diagnosis. We chose to emphasize this case because, while being a rare disease, it could cause mortality if misdiagnosed. In this case, a 23-year-old lady, para 1+2 with a history of several miscarriages and curettage, complained of per vaginal bleeding more than 2 months after her suction and curettage on September 2018. Her second visit was managed as having retained the product of conception and another curettage was conducted. Despite this, the patient still has worsening vaginal bleeding which leads to her third visit. A bedside ultrasound was conducted and suspected uterine AVM. This was then further confirmed with contrast-enhanced computed tomography of the pelvis and pelvis angiography. Five Micronester coils and 10% Histoacryl adhesive were used to successfully embolize the uterine artery. This case report served as a valuable lesson on the importance of having a proper diagnosis and prompt treatment to avoid fatal misdiagnosis which could have disastrous consequences.

INTRODUCTION

Dubreil and Loubat published the first description of uterine arteriovenous malformations (AVM) in 1926 (Evans et al., 2017). In women who are not pregnant, AVMs are rare. Although less than 100 occurrences were reported, 30% of those people required blood transfusions due to hypovolemic shock (Polat et al., 2002; Manolitsas et al., 1994; Hasegawa et al., 2012). Therefore, women who experience unexplained vaginal bleeding may need to consider this diagnosis. We chose to emphasize this case because, while being a rare disease, it could cause mortality if misdiagnosed.

AVMs of the uterus can result in deadly vaginal bleeding due to intervillous space enlargement deep into the myometrium. This enables direct passage without the involvement of capillary vessels from the arterial system to the venous system (Evans et al., 2017; Farias et al., 2014). Uterine AVMs can be acquired or congenital. An anomaly in the embryologic development of early vascular structures gives rise to congenital uterine AVMs (Kwon & Kim, 2002). The causes of acquired uterine AVMs include pelvic trauma, surgery (including cesarean section and curettage), malignancy, and infection. Multiple feeding arteries, a central nidus of vessels with characteristics of both arteries and veins and numerous big draining veins are the structural features that distinguish structurally congenital uterine AVMs. Contrarily, acquired uterine AVMs are made up of one or more arteriovenous fistulas (AVFs) between the myometrial venous plexus and intramural arterial branches. Due to the similarity of their radiologic findings, congenital uterine AVMs and acquired uterine AVFs must be distinguished by the patient's medical history (Lalitha et al., 2015; Timmerman et al., 2000). We highlight a 23-year-old lady, post suction and curettage complicated with uterine AVMs which was successfully embolized and we discussed our management strategy for managing this fatal condition.

CASE REPORT

A 23-year-old lady, para 1+1 with a history of missed miscarriage in 2014 (required dilatation and curettage) and emergency caesarean section for breech in labour (2015), was admitted for a second miscarriage in September 2018. Suction and curettage were done with an estimated blood loss of 1.8 litres. However, two months later, the patient still complained of per vaginal (PV) spotting. The patient denied having any fever or abdominal pain. On bedside ultrasound examination, noted a thickened endometrial wall and elevated beta-HCG level. It then proceeded with second suction and curettage as it was initially presumed there were retained products of conception (POC) which was complicated with an estimated blood loss of 1.3 litres. After the procedure, the patient still complained of having per vaginal bleed (quarterly soaked 3 pads/day) and seek gynaecology consultation again when it worsened to fully soaked 2 pads/day.

Bedside ultrasound (Figure 1) was then repeated by the gynaecology team which noted there was a hypoechoic lesion at the left side of the uterine wall in the transabdominal scan and multiple short tubular-like hypoechoic structures seen at the uterine wall in the transvaginal scan. There was no residual product of conception (POC) detected. The constellation of these findings of a hypoechoic lesion surrounded by multiple tubular-like structures raised the suspicion of uterine AVMs. However, the overall findings and raised beta-HCG level also raised the suspicion of possible gestational trophoblastic disease. Hence, a computed tomography (CT) of the pelvis was done to assess further the hypoechoic lesion at the left uterine wall.

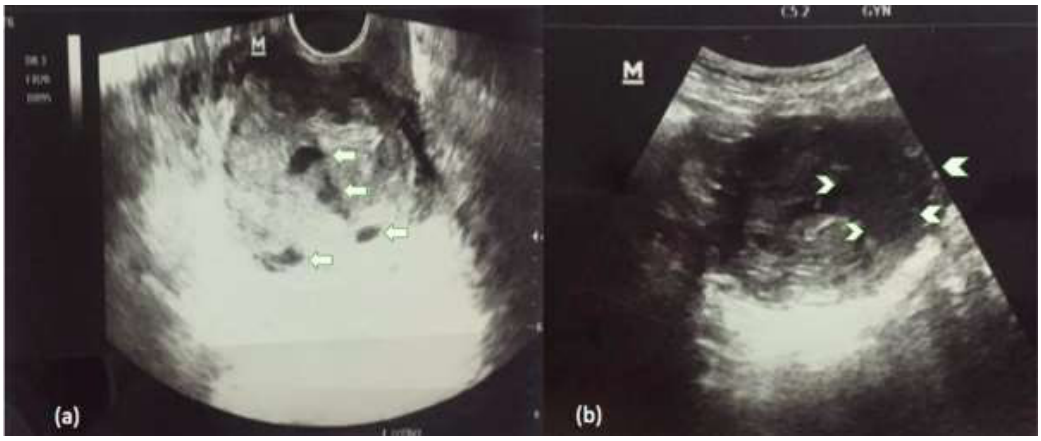

Figure 1 (a) Transvaginal scan shows multiple tubular hypoechoic structures at the uterine wall (white arrows). (b) Transabdominal scan shows a hypoechoic lesion noted at the left side of the uterine wall which raised the suspicion of uterine mass or if correlating with the tubular-like structure in (a), this raised the suspicion of a possible uterine AVM nidus (arrowheads)A contrast-enhanced CT of the pelvis (Figure 2) showed tortuous dilated vessels noted at the parametrium around the uterus with some seen traversing the hypodense lesion. There is a hypodense lesion arising from the left anterolateral wall of the uterus measuring 5.7 × 8.6 × 5.4 cm (AP × W × CC). No calcifications were noted within. Both ovaries are normal. The tortuous dilated vessels raised the suspicion of uterine arteriovenous malformation while the hypodense lesion may represent a uterine fibroid.

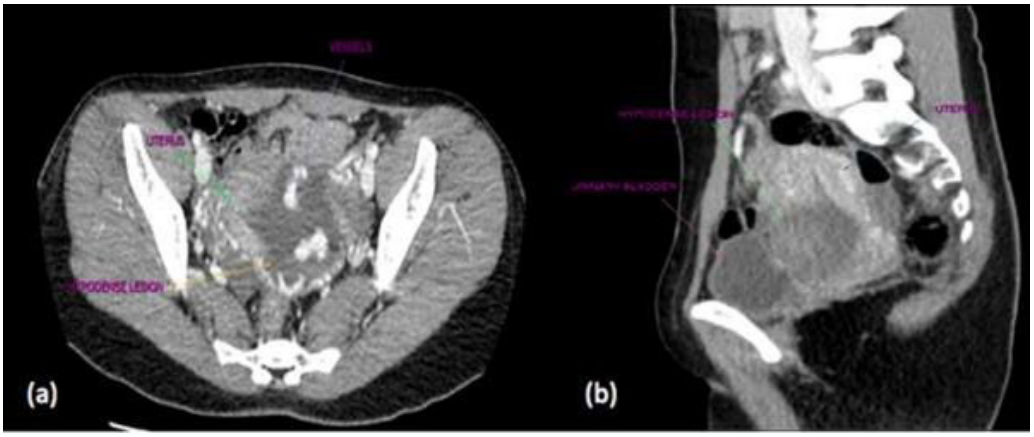

Figure 2 Contrast-enhanced CT of the pelvis at (a) axial view showing a hypodense lesion with tortuous dilated vessels seen traversing within. Dilated vessels are also seen at the parametrium around the uterus. The hypodense lesion pushed the uterus towards the right side. At sagittal view (b), the hypodense lesion was seen with its epicentre within the anterior uterine wall protruding into the uterine cavity

The decision to proceed directly with a diagnostic pelvic angiogram instead of a CT angiogram was made after the patient began to show worrying vital signs and haemoglobin level after the CT Pelvis. This was then followed by therapeutic embolization in the same setting after confirming the arteriovenous malformation in the pelvic angiogram. Pre-embolization (Figure 3a) noted arteriovenous malformation supplied by three feeding arterial branches from the left ascending uterine artery and drained into the nidus and uterine venous plexus. Post embolization (Figure 3b) with 5 Micronester coils and 10% Histoacryl glue noted successful occlusion of the left ascending uterine artery AVM. No AVM was seen at the right uterine artery.

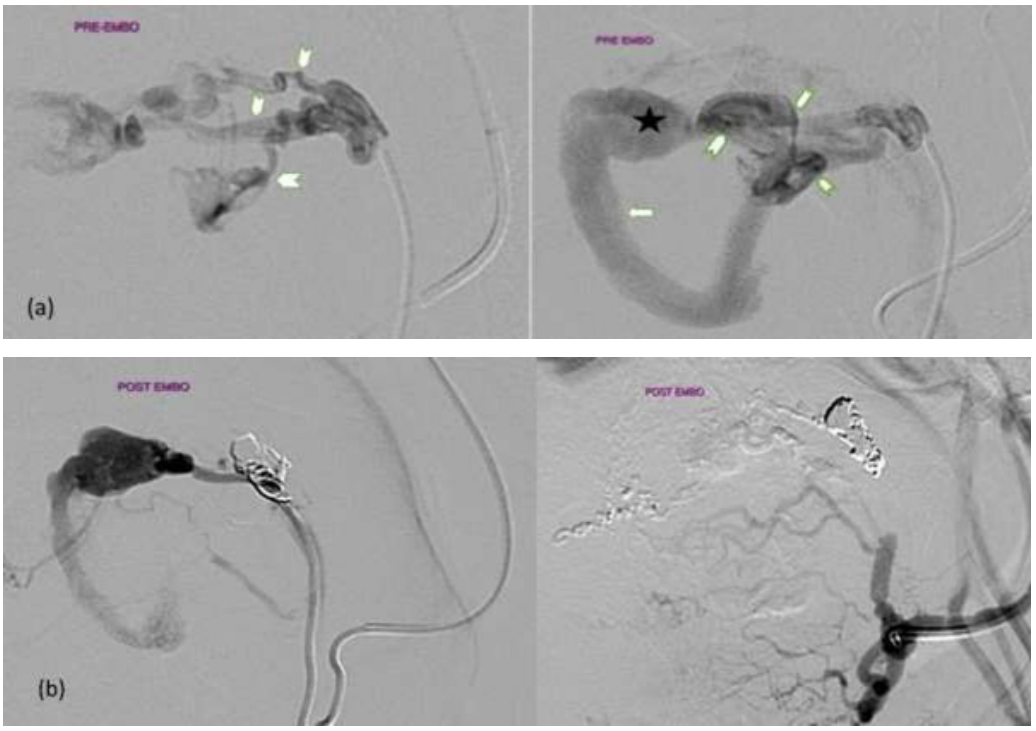

Figure 3 Pre-embolization images (a) showing three feeding arterial vessels (arrowheads) from the left ascending uterine artery draining into the nidus (star-shaped) and the venous plexus (arrow). Post- embolization images (b) showing a successful occlusion of the left ascending uterine artery AVM with 5 Micronester coils and 10% Histoacryl Glue. No AVMs were seen at the right uterine artery

DISCUSSION

The proposed incidence of 4.5% occurred at the mean age of 30 years old with 96% premenopausal and 4% postmenopausal. The most typical presenting symptom is menorrhagia. Some authors assert that the uterus may have enlarged with noticeable pulsation during bimanual examination. A vascular "steal" pattern with considerable blood shunting from the arterial to the venous circulation will appear in serious cases. This circumstance might lead to serious circulatory disturbance and cardiac insufficiency which may complicate large AVM (Evans et al., 2017; Farias et al., 2014). However, instead of menorrhagia, our patient just complained of prolonged vaginal bleeding. Her stomach and vulva/vaginal examinations were unremarkable as well. Our patient suffered massive blood loss in two separate suction and curettage events before she was confirmed to have uterine AVM. This is considered to be dangerous as the massive blood loss might turn into a catastrophic event of hypovolaemic shock or death secondary to uterine AVM (Evans et al., 2017; Polat et al., 2002).

Ultrasound is usually performed as the initial imaging assessment as it is easily accessible and non-invasive. As noted in our patient, the greyscale ultrasound shows subtle multi-foci of hypoechogenicity scattered within the thickened myometrium. Colour Doppler ultrasonography should show serpiginous/ tubular anechoic structures within the myometrium with rapid and turbulent blood flow in a mosaic pattern. Spectral analysis of the arterial vessels within the lesion might show high-velocity flow with a low resistive index (0.51 – 0.65) (Evans et al., 2017; Polat et al., 2002). However, unfortunately, no Doppler examination was done for our patient by the primary team.

Along with doing an ultrasound as a preliminary examination, pelvic magnetic resonance imaging and CT angiography

are crucial for supporting the confirmation of the uterine AVM diagnosis (Evans et al., 2017). Contrast-enhanced examinations will demonstrate the enhancement of the collection of serpentine vessels which will enhance as intensely as normal vessels in the arterial phase. These findings will be accompanied by evidence of early venous return which is signified by opacification of venous structures on the arterial phase images (Evans et al., 2017). Even though our patient did not have a CTA examination, the dilated and tortuous vessels traversing the hypodense lesion and within the bilateral parametrium regions seen in the contrast-enhanced CT of the pelvis, increased the degree of suspicion of an arteriovenous malformation. This suspicion was then further confirmed with a diagnostic pelvic angiogram and proceeded with therapeutic embolization in the same setting.

The recommended gold standard is an angiography, especially in patients who might eventually undergo embolization. Since 1986, surgical intervention for uterine AVMs has been replaced with embolotherapy, which is now widely accepted. The preferred course of treatment for patients with significant uterine bleeding or in whom fertility is not the primary concern is hysterectomy, particularly in post-menopausal women due to the 17% recurrence rate (Polat et al., 2002; Hasegawa et al., 2012).

It is still unclear whether the pregnancy is safe after uterine AVMs have been successfully embolized. Pregnancies following effective embolotherapy are uncommon. This is due to the decreased placental vascularization that occurs after embolotherapy, which causes an unfavourable pregnancy outcome (Evans et al., 2017). However, some studies showed there is a 27% success rate for pregnancies after post-uterine artery embolization (UAE). According to their findings, after embolization, sufficient collateral supply can form to support a full-term pregnancy. A retrospective analysis reveals that during 10 years, five unremarkable intrauterine pregnancies were successfully carried to term in 4 of 15 patients who underwent pelvic arterial embolization for traumatic uterine AVMs. They concluded that percutaneous embolotherapy is a secure and efficient treatment for traumatic uterine AVMs while maintaining the chance of a subsequent pregnancy (Evans et al., 2017, Lalitha et al., 2015; Timmerman et al., 2000).

The most frequent adverse reaction that results from myometrium temporary ischemia is pelvic discomfort. The pain might occur right away and can last anywhere between 12 and 24 hours. As a result, it is typical for patients to need an overnight stay with proper pain management following the treatment. Post-embolization syndrome, which lasts a few hours to a few days and includes fever, discomfort, malaise, and nausea, is another common morbidity in the UAE. The syndrome frequently develops following the embolization of any solid organ and is assumed to be an immune-mediated reaction. Approximately 50% of patients are said to experience it, but controllable with analgesics, antipyretics, and anti-inflammatories (Memtsa & Homer, 2012).

A more severe complication is uterine infection, and patients may experience rapid onset severe pain, vaginal discharge, and/or bleeding. Since infection can sometimes result in systemic sepsis and necessitate hysterectomy, it must be aggressively treated. Rarely, sepsis-related deaths have also been reported. Fortunately, it is a rather uncommon complication that only occurs in less than 1% of cases (Memtsa & Homer, 2012). Pulmonary embolism is an uncommon but potentially fatal consequence of UAE that is hypothesized to be caused by a transient hypercoagulable state that is similar to but less severe than that seen during surgical procedures. Before undergoing UAE, it is wise to conduct a thromboprophylaxis risk assessment because the incidence is thought to be 1 in 400 (Memtsa & Homer, 2012). The ovaries are most likely to be affected by off-target organ embolization. Although the vaginal artery typically develops

as a distinct branch of the internal iliac artery, it occasionally may share a common trunk with the uterine artery or form anastomoses within the broad ligament. In such cases, the vagina is susceptible to embolization-induced ischaemia, which can cause sexual dysfunction and/or dyspareunia (Memtsa & Homer, 2012). Despite everything stated above, multicentre trials consistently demonstrate that the rate of major adverse events following UAE is significantly lower than that of more conventional surgical interventions like myomectomy and hysterectomy (Memtsa & Homer, 2012).

Although most of the complications start to occur within the first month post-procedure; long-term monitoring is also required to identify any developing complications and determine whether or not the therapy was successful. In large clinical trials, the standard follow-up is 3, 6, 12, 21, or 24 months, and then annually after that. In one of the studies done, the patients were followed up with phone calls for 6 months, at which time patients returned to the department for follow-up imaging. The most accurate way to document interval change is through imaging modality continuity. If the patient had ultrasound imaging done before the procedure, the same method of re-assessment should be used for post-procedure imaging follow-up. However, till now there are currently no clear recommendations for long-term follow-up (Carrillo, 2008).

CONCLUSION

In conclusion, uterine AVMs are still uncommon since they are only identified in symptomatic individuals who are pregnant or have recently experienced a miscarriage. The rarity of this disease and the scarcity of relevant literature have caused a lack of awareness among medical professionals, which eventually may lead to a fatal misdiagnosis. This case may have been considered a near–missed situation when the patient was presumed to have retained the product of conception during her second visit for persistent per-vaginal spotting. Fortunately, her third visit with worsening symptoms triggered a high clinical suspicion of this disease and extensive imaging studies were conducted. The patient was then successfully treated before more catastrophic complication occurs. Therefore, from this case report, we have gained a valuable lesson on the importance of having a proper diagnosis and prompt treatment to avoid fatal misdiagnosis which could have disastrous consequences.

CONFLICT OF INTEREST

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

CONSENTS

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

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