COMPARISON OF CONTRAST ENHANCED ULTRASOUND WITH DEXTROSE 50% AND NORMAL SALINE IN DETECTING SUPRADIAPHRAGMATIC CENTRAL VENOUS CATHETER MALPOSITION

DR. NOR AFIFAH BINTI IBERAHIM

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TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

LIST OF ABBREVIATION

CEUS	Contrast-enhanced ultrasound
CVC	Central venous catheter
CXR	Chest radiograph
HUSM	Hospital Universiti Sains Malaysia
ICU	Intensive Care Unit
PFO	Patent foramen ovale
POCUS	Point-of-care ultrasound
RA	Right atrium
RASS	Rapid atrial swirl sign
RV	Right ventricle
RVI PLAX	Right ventricle inflow parasternal long axis
SHDU	Surgical High Dependency Unit
SVC	Superior vena cava
TOF	Tetralogy of Fallot
US	Ultrasound

ABSTRAK

Latar belakang: Xray dada biasanya dilakukan selepas pemasangan kateter vena sentral (CVC) untuk memastikan kedudukan kateter yang betul. Namun begitu, prosedur standard ini akan menyebabkan kelewatan dalam penggunaan kateter selain mendedahkan pesakit kepada radiasi dan kos tambahan. Penggunaan ultrasound berkontras (CEUS) menggunakan larutan garam biasa telah digunakan sebagai satu alternatif kepada prosedur xray dada. Kajian terbaru pula telah dibuat untuk mengkaji kesesuaian cecair dekstros 50% sebagai alternatif bahan kontras untuk prosedur yang sama ini. Dekstros 50% telah dibuktikan boleh menghasilkan imej ultrasound yang lebih baik berbanding larutan garam biasa untuk mengesan masalah struktur jantung seperti patent foramen ovale. Oleh itu, kami ingin mengetahui sekiranya penemuan ini akan memberikan impak dalam kegunaan untuk mengesan malposisi kateter. Kami ingin menyiasat sekiranya terdapat perbezaan antara dekstros 50% dengan larutan garam biasa untuk tujuan tersebut.

Metodologi: Kajian ini adalah kajian rentas yang dibuat menggunakan teknik pensampelan mudah. Subjek yang dipilih merupakan pesakit didalam wad HUSM yang memerlukan pemasangan kateter vena sentral. Kami membandingkan antara larutan garam biasa dan dekstros 50% sebagai bahan kontras di dalam ultrasound berkontras untuk menentukan kedudukan sebenar posisi kateter vena sentral menggunakan kaedah penemuan Rapid Atrial Swirl Sign (RASS) ke dalam atrium kanan. Xray dada digunakan sebagai rujukan untuk memastikan posisi kateter yang betul.

Keputusan: Daripada 99 pesakit yang terlibat didalam kajian ini, terdapat 7 malposisi kateter vena sentral yang dikesan melalui xray dada. Hanya satu daripada 7 malposisi ini yang turut dikesan oleh ultrasound berkontras menggunakan larutan garam biasa dan dekstros 50%. Terdapat persetujuan tidak memuaskan antara kedua-dua bahan kontras dengan xray dada. Cohen’s Kappa coefficient untuk larutan garam biasa dengan xray dada adalah k=0.078 manakala untuk dekstros 50% dengan xray dada adalah k=0.049. Sensitiviti untuk kedua-dua bahan kontras mengesan malposisi kateter hanyalah 14% berbanding spesifisiti 97.5%.

Kesimpulan: Kesesuaian kedua- dua larutan garam biasa dan dekstros 50% untuk mengesan malposisi kateter adalah sama. Jika dibandingkan dengan xray dada, kedua-dua bahan kontras ini mendapat persetujuan yang kurang memuaskan. Xray dada masih lagi diperlukan untuk mengenalpasti kedudukan kateter vena sentral yang betul manakala CEUS berguna untuk memastikan kateter adalah di dalam saluran vena.

Kata Kunci: malposisi kateter, ultrasound berkontras,xray dada,larutan garam biasa, dekstros 50%

ABSTRACT

Background: Chest radiograph is performed after insertion of a central venous catheter to confirm its placement. However, this standard procedure delays catheter usage, exposing patients to radiation with added cost. Contrast-enhanced ultrasound (CEUS) using normal saline has been used in most previous literature as an alternative to chest radiograph. Recent studies have then explore the suitability of dextrose 50% as a contrast agent. It has been proven to generate a better ultrasonic image than normal saline to detect congenital heart condition such as patent foramen ovale. Hence, this study aims to demonstrate if this finding can significantly affect CVC malposition detection. We would like to investigate the possible difference between dextrose 50% and normal saline in detecting CVC malposition.

Methods: This is a cross-sectional study using convenient sampling. Subjects were chosen from the in-patient ward HUSM, who were indicated for central venous catheter insertion. We compared catheter malposition detection using dextrose 50% and normal saline as contrast agent by the observation of Rapid Atrial Swirl Sign (RASS) characteristic into the right atrium. Chest radiograph is used as the standard reference to confirm correct CVC position.

Results: From the 99 patients included in this study, 7 CVC malpositions were confirmed by chest radiograph. Only 1 of these malpositions was detected by both contrast agents. There was a poor agreement between both dextrose 50% (k = 0.049) and normal saline (k = 0.078) with chest radiograph. The sensitivity for both contrasts to detect CVC malposition was 14% with a specificity of 97.5%.

Conclusion: Normal saline and dextrose 50% are equivalent as contrast agents to detect CVC malposition. Both have a poor agreement with the chest radiograph. Chest radiograph is still indicated to confirm CVC malposition, but CEUS can be a useful tool to confirm the intravenous position of the catheter to facilitate its earlier usage.

Keywords: CVC malposition, contrast enhanced ultrasound, chest radiograph, normal saline, dextrose 50%

CHAPTER 1: INTRODUCTION

1.1 Contrast enhanced ultrasound (CEUS) to detect CVC malposition

Chest radiograph has been the reference standard to confirm the position of central venous catheter and to detect any possible complication from the procedure (Smit et al., 2020). More than 15% of complication rate were reported following insertion of CVC including catheter misplacement, pneumothorax, arterial puncture, and hematoma (Kamalipour et al., 2016).Visualisation of distal CVC catheter tip at the proximal to the right atrium or based on tip-to-carina distance are the anatomical landmarks used in chest radiograph as a confirmation of its placement (Weekes et al., 2016;Kang et al., 2021; Schuster et al., 2000). However, this standard procedure will expose patients to extra radiation, time consuming, with added cost for hospital care.

As ultrasound becomes more accessible, point of care ultrasound (POCUS) has been used as an alternative for this purpose. It involves directly identifying the distal CVC tip using supraclavicular ultrasound and transthoracic echocardiography (TTE) or visualising of turbulent flow into the right atrium using contrast-enhanced ultrasound (CEUS). Previous studies done showed that the time taken using ultrasound to confirm CVC placement was faster than chest radiograph (Baviskar et al., 2015; Maury et al., 2001; Vezzani et al., 2010). Not only that, Vezzani *et al.* (2010) also concluded that the ultrasound approach is much cheaper, €2.81 lesser than a chest radiograph. Because of these advantages, several studies have explored the usage of ultrasound, specifically using CEUS to replace chest radiograph in the role of catheter malposition confirmation.

In CEUS, contrast agents are flushed into the CVC port, and an echocardiogram will be performed simultaneously to visualise the onset and appearance of turbulent flow in the right atrium, referred as RASS (Rapid Atrial Swirl Sign). RASS characteristics are observed using first clear echocardiography view, either right ventricle parasternal long axis (PLAX), apical 4 chamber (A4C) or subcostal view. The appearance of RASS into or within the right atrium will be assessed as "immediate" (within 2 seconds), "delayed" (2 to 6 seconds), or absent (more than 6 seconds). Immediate RASS is defined when turbulence flow is observed within 2 seconds entering into or within the right atrium which indicates correct position of CVC (Che Rahim et al., 2021; Weekes et al., 2014). Delayed, absent or turbulence appearing first in the RV or migrating from tricuspid valve into RA indicates CVC malposition. The 2 seconds time frame used is based on previous studies by Vezzani *et al.* (2010) and Weekes *et al.* (2014).

1.2 Different contrast agent in contrast enhanced ultrasound (CEUS)

The concept of using a contrast agent in ultrasound has been introduced since the early 1960s, when injection of agitated saline was used as a contrast agent in echocardiography of the aortic root (Gramiak et al.,1968). The reason of using contrast agent is to enhance the ultrasound wave once it is administered in the vasculature, which allows marked amplification of the signals from the blood flow (Chung & Kim, 2014). Since then, various solutions have been tested and studied to improve the stability of the agent used to yield better ultrasound images. This includes using autologous blood, albumin, as well as dextrose solution to substitute normal saline (Calliada et al., 1998; Cukon Buttignon et al., 2004; He et al., 2017). All contrast agents have different characteristics and stability that influence the echogenicity, thus the image produced (Calliada et al., 1998)

1.3 Normal saline as contrast agent in contrast enhanced ultrasound (CEUS)

Normal saline has been widely used as the contrast agent to confirm CVC malposition. Weekes *et al*. (2014) reported that this method has 75% sensitivity and 100% specificity than chest radiograph. Later in 2016, Weekes *et al*. (2016) concluded no significant difference between CEUS using saline with chest radiograph for the same role. These two studies used non agitated normal saline.

Similar results were reported in other studies that used agitated normal saline. Blans *et al*. (2016) found that the sensitivity of CEUS using agitated saline to confirm CVC position was 98% as compared to chest radiograph. Likewise, Kamalipour *et al.*(2016) found that CEUS has 98% sensitivity and 69% specificity to detect CVC misplacement. Agitated saline as a contrast agent is prepared using 9 mL of saline and 1mL of air from two connected 10mL syringes and mixed using a 3-way stopcock until a homogenous mixture of air and saline is achieved (Kamalipour et al., 2016).

Transient ischaemic attack (TIA) is the recognized complication due to paradoxical microbubbles embolization during the injection of agitated saline to detect intracardiac shunt in patients with cryptogenic ischemic stroke. However, the exact incidence is still unknown and considered very low (Romero et al., 2009). Nevertheless, none of the studies published that used agitated saline to specifically detect CVC malposition reported any safety issues from the contrast agent used (Vezzani et al., 2010). Moreover, this study used non agitated saline; hence there is no concern regarding the risk of air embolism.

1.4 Dextrose 50% as contrast agent in contrast enhanced ultrasound (CEUS)

Recently, Li *et al.* (2018) concluded that dextrose 50% as a contrast agent in transthoracic echocardiogram yielded better ultrasonic features than normal saline to detect patent foramen ovale. They also found that the peak time of microbubbles production by dextrose 50% was longer than normal saline. In the study, they compare between agitated normal saline with agitated dextrose 50%.

With this concept, Che Rahim *et al*. (2021) investigated the feasibility of dextrose 50% as a contrast agent specifically to detect catheter malposition. They concluded that CEUS using non agitated dextrose 50% detected 1 out of 3 CVC malposition seen on chest radiograph and all correct CVC tip positions. The pilot study showed that using dextrose 50% is a reliable option for contrast agent. No significant hyperglycaemia incidence was recorded in both studies as only a small amount of dextrose 50% was used (5mL).

No similar studies has been done to compare the two solutions as contrast agent to detect CVC malposition. Therefore, this study aims to investigate the difference between dextrose 50% and normal saline in this role as demonstrated in previous literature.

CHAPTER 2: OBJECTIVES OF STUDY

General Objective:

To compare the RASS characteristic and detection of CVC malposition when using dextrose 50% or normal saline in CEUS with chest radiograph as the standard reference

Specifics Objectives:

1. To identify the RASS characteristics of dextrose 50% and normal saline

2. To determine the agreement between CEUS using dextrose 50% with chest radiograph in detecting CVC malposition

3. To determine the agreement between CEUS using normal saline with chest radiograph in detecting CVC malposition

4. To determine the agreement between normal saline and dextrose 50% in detecting CVC malposition

CHAPTER 3:MANUSCRIPT

Title: Comparison of contrast enhanced ultrasound with dextrose 50% and normal saline in detecting supradiaphragmatic central venous catheter malposition

Author: Nor Afifah IBERAHIM[1,2], Mohd Jazman CHE RAHIM[1,2], Shaik Farid ABDULL WAHAB[1,2], Chandran NADARAJAN[1,2], Siti Azrin AB HAMID[1,2]

[1]School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

[2]Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

Corresponding author: Mohd Jazman CHE RAHIM

Department of Internal Medicine, School of Medical Sciences Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

e-mail: iberahin@tcd.ie

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Background: Chest radiograph is performed after insertion of a central venous catheter to confirm its placement. However, this standard procedure delays catheter usage, exposing patients to radiation with added cost. Contrast enhanced ultrasound (CEUS) using normal saline has been used in most previous literature as an alternative to chest radiograph. Recent studies have then explored the suitability of Dextrose 50% as a contrast agent. It has been proven to generate a better ultrasonic image than normal saline to detect congenital heart condition such as patent foramen ovale. Hence, this study aims to demonstrate if this finding can significantly affect CVC malposition detection. We would like to investigate the possible difference between dextrose 50% and normal saline in detecting CVC malposition.

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No similar studies has been done to compare the two solutions as contrast agent to detect CVC malposition. Therefore, this study aims to investigate the difference between dextrose 50% and normal saline in this role as demonstrated in previous literature.

METHODOLOGY

This is a cross-sectional study conducted at Hospital Universiti Sains Malaysia (HUSM) from October 2020 until October 2021 including all patients aged 18 years old and above from medical general wards, intensive care unit (ICU) and surgical intensive care unit (ICU) who underwent internal jugular catheter (IJC) or subclavian catheter insertion. Those who have indwelling intravascular devices (cardiac pacemakers, defibrillators, existing temporary or permanent CVC), patients with inadequate US windows, diabetic ketoacidosis, and hyperglycaemic hyperosmolar syndrome were excluded from this study. Written informed consent was obtained from all the patients involved or their next of kin. Data on sociodemographic were also collected using a proforma checklist provided during screening. This study was approved by the Research Ethics Committee (Human) School of Medical Sciences (PPSP) University Sains Malaysia (JEPeM Code: USM/JEPeM/20060334)

Study Procedure

All central venous catheters were inserted by a trained medical officer using Seldinger technique under the standard aseptic protocol. Insertion of these catheters were done using ultrasound guidance with the patient lying in supine position. The CVC was either double or triple lumen of 15cm or 20cm catheters, depending on the indication and site of insertion. Indication for CVC insertion was established by the respective physicians in charge not involved in the study.

After CVC insertion, the assisting medical officer then flushed 5 mL of dextrose 50% through one of the CVC ports while the first investigator, a trained ultrasound fellow in critical care and emergency ultrasound performed echocardiography. The first investigator observed and determined RASS characteristic using the first clear echocardiographic view. The normal flow for any echocardiographic examination starts with the left ventricle parasternal long axis (LV PLAX) view then RVI PLAX view. If the RVI PLAX view is poor, we proceed with A4C view. If the A4C view is poor as well, we will use subcostal view. The ultrasound images were acquired using a handheld, battery-powered Vscan Extend™ by GE ultrasound machine. After the first image has been recorded, another 5 mL of normal saline was flushed into the CVC port with the same first investigator observing the RASS features and recorded the clip as per earlier protocol. We used 5mL of each contrast based on previous study protocol by Blans *et al*. (2016) and Che Rahim *et al.* (2021)

The appearance of RASS characteristics were assessed as immediate, delayed, or absent as well as site of onset (into RA, within RA or RV). Immediate RASS is defined when the turbulence flow is seen within the RA or enters the RA from the superior vena cava and immediately migrates toward the RV within 2 seconds (Che Rahim et al., 2021). The immediate RASS indicates that the CVC is in the correct position. Delayed, absent or turbulence appearing first in the RV or migrating from tricuspid valve into RA indicates CVC malposition. The timing of RASS detection after flushing was measured using a stopwatch. This image were stored to be reviewed by the second investigator. The ultrasound image acquisition would not interfere with the ongoing management of any patient. The second investigator (certified emergency physician in critical care US) then reviewed the recorded ultrasound clips to determine RASS characteristic. The second investigator was blinded to the RASS finding of first investigator. If there is any disagreement between the finding of first and second investigator, they will meet up and decide the final RASS finding after viewing the clip together.

After this catheter insertion, a routine chest radiograph was ordered. The chest radiograph was the gold standard to confirm CVC position. The third investigator, a senior radiologist then reviewed the post-procedure CXR. Correct position of catheter based on chest radiograph was determined using previously published study protocol. The optimal tip of the catheter should be at Zone 1 (3 cm above the carina on the right hemithorax), Zone 2 (3 cm below the carina on the right hemithorax), Zone 3 (brachiocephalic vein for left-sided CVCs), and Zone 4 (superior cavo atrial junction)(Che Rahim et al., 2021). This third investigator was blinded from the other investigators finding.

Statistical Analysis

All statistical analyses were performed using SPSS version 27. Descriptive statistics were used to summarise the sociodemographic and clinical characteristics of the patients. Categorical data was presented as frequency (n) and percentage (%). Numerical data was presented as mean (standard deviation (SD)) or median (interquartile (IQR)) based on their normality distribution. Kappa 2 raters test was used to determine the agreement between CEUS using dextrose 50% and normal saline with chest radiograph to detect CVC malposition. Kappa 2 raters test was also used to compare the agreement between normal saline and dextrose 50% to detect CVC malposition. We also calculate for sensitivity and specificity of both contrast to detect CVC malposition.

RESULTS

Clinicodemographic characteristics of participants

A total of 109 patients participated in this study. However 10 patients were excluded from data analysis due to incomplete data collection. 59 (59.6%) patients were male, and 40 (40.9%) were female. The mean age was 55.22. The mean average of blood pressure was 144 mmHg (systolic) and 71 mmHg(diastolic) with heart rate of 85.7 bpm. Central venous catheter was indicated for venous access in 55 patients (55%) while the other 44 patients were for haemodialysis access.

Forty-nine of the catheters inserted were internal jugular triple lumen, 43 were internal jugular double lumen while others were subclavian catheter triple lumen and triflow. The majority of these catheters were inserted on the right side (85.9%) as compared to the left side (14.1%). Twenty-nine patients were on inotropic supports and forty patients were on mechanical ventilation. Table 1 provides further details of patient's clinicodemographic characteristics.

Characteristics	**n / Frequency (%)**
Gender	
Male	59 (59.6)
Female	40 (40.4)
Age (years)	55 (16)[a]
Blood pressure (mmHg)	144 (26)[a] / 71 (15)[a]
Pulse rate (bpm)	85 (17)[a]

CVC indication	44 (44.4)
Haemodialysis	55 (55.6)
Venous	
CVC type	
IJC double lumen	43 (43.4)
IJC triple lumen	49 (49.5)
IJC Tri-flow	1 (1.0)
Subclavian	6 (6.1)
Side of insertion	
Right	85 (85.9)
Left	14 (14.1)
Inotropic support	
Yes	29 (29.3)
No	70 (70.7
Ventilatory support	
Yes	40 (40.4)
No	59 (59.6)

[a] Mean (SD)

Table 1. Clinicodemographic characteristics of patient (n=99)

RASS features

After each CVC placement, the first investigator observed the first clear echocardiographic view to determine RASS characteristic. The majority of echocardiographic window for RASS detection by both contrast was RVI PLAX (n=82) followed by subcostal (n=12) and A4C (n=5). This is shown in Table 2.

Immediate RASS within 2 seconds into or within RA indicates CVC is correctly positioned. Delayed, absent or turbulence appearing first in the RV or migrating from tricuspid valve into RA indicates CVC malposition .With normal saline, immediate RASS was detected flowing into RA in 66 patients and within RA in 26 patients. RASS was absent in the remaining 7 patients. By using dextrose 50%, 63 of patients has immediate RASS into RA, 27 within RA and 2 flowing within RV. RASS was absent in the remaining 7 patients. Table 3 outlined the distribution of RASS characteristic using each contrast agent.

ECHO View	**Normal saline n (%)**	**Dextrose 50% n (%)**
RVI PLAX	82 (82.8)	82 (82.8)
Subcostal	12 (12.1)	12 (12.1)
Apical 4 chamber	5(5.1)	5(5.1)

Table 2. Echocardiogram view

RASS features	**Normal saline n (%)**	**Dextrose 50%**
Immediate		
Into RA	66 (66.6)	63 (63.6)
Within RA	26 (26.3)	27 (27.3)
Within RV	0 (0)	2 (2.0)
Delayed	0 (0)	0 (0)
Absent	7 (7.1)	7 (7.1)

Table 3. RASS features using normal saline and dextrose 50%

CVC malposition detection

A true positive result was defined as CVC malposition detected using CEUS (absent RASS or not into RA) and confirmed by chest radiograph. A true negative result was defined as CVC to be in situ as observed by immediate RASS into RA and confirmed by chest radiograph. There was a total of seven CVC malposition confirmed by CXR. Four of these malposition catheter tips was too deep into the right atrium, one into the right brachiocephalic vein, one into the left brachiocephalic vein for right internal jugular catheter, and another one into the inferior vena cava. CEUS using normal saline and dextrose 50% only identified one of these misplaced CVC. This true positive involves the tip of catheter that was too deep in the right atrium. In this patient, RASS was absent in CEUS using normal saline while with dextrose 50%, RASS onset was observed in the RV.

Dextrose 50% detected nine CVC malposition while normal saline detected seven malposition. For each contrast, only one catheter was a true malposition. Two same patient was detected as malposition by both contrast but catheter tip was correctly positioned based on chest radiograph. Normal saline detected correct CVC tip placement in 86 of 92 patient with correct CVC placement as determined by chest radiograph. Meanwhile, dextrose 50% detected 84 from 92 correct CVC placement.

There was poor agreement between both normal saline (k = 0.078) and dextrose 50% (k = 0.049) with chest radiograph to detect CVC malposition as shown in Table 4 and Table 5.

In comparison with each other to detect CVC malposition, normal saline and dextrose 50% have fair agreement (k=0.321). Sensitivity of both contrast to detect CVC malposition is 14% and specificity of both contrast to detect CVC malposition is 97.5%. This is shown in Table 7.

	CVC Malposition detected on CXR		
	No	Yes	Total
CVC Malposition detected by CEUS with NS			
No	86	6	92
Yes	6	1	7
Total	92	7	99
Kappa Coefficient	0.078		

Table 4 Agreement of CVC malposition detected by CEUS using normal saline and CXR

	CVC Malposition Detected on CXR		
	No	Yes	Total
CVC malposition detected by CEUS with D50%			
No	84	6	90
Yes	8	1	9
Total	92	7	99
Kappa Coefficient	0.049		

Table 5 Agreement of CVC malposition detected by CEUS using dextrose 50% and CXR

	CVC Malposition Detected with D50%		
	No	Yes	Total
CVC malposition detected with NS			
No	86	6	92
Yes	4	3	7
Total	90	9	99
Kappa Coefficient	0.321		

Table 6 Agreement of CVC malposition detected with normal saline and dextrose 50%

DISCUSSION

Based on our study, both contrast agents have poor agreement with chest radiograph to detect CVC malposition. This showed that dextrose 50% is equivalent to normal saline, the commonly used contrast agent. This outcome is in accordance with the study by Li *et al.* (2018), which showed no significant difference in sensitivity to detect patent foramen ovale using either normal saline or dextrose 50%.

However, Dextrose 50% was suggested to have better ultrasonic features to detect patent foramen ovale based on the higher peak intensity recorded with longer peak time, effective duration, and duration of microbubbles produced as compared to normal saline (Li et al., 2018). In the study, the sensitivities of patent foramen ovale detected by Dextrose 50% was 100% compared to 83% by normal saline. Though not statistically significant, it suggests that dextrose 50% is more sensitive to detect left to right shunt. Fuller *et al.* (2021) reported a case of a patient with left to right shunting who had a negative bubble study using agitated normal saline but markedly positive when repeated with dextrose 50%.

Feinstein *et al.* (1984) also found that dextrose solution is better at detecting left to right shunt due to the smaller and more uniform microbubbles produced, giving better ultrasound signals (Fuller et al.,2021). Likewise, microbubbles produced by higher molecular weight of contrast agents had been found to be more stable (Malakan Rad, 2019). The molecular weight of dextrose (180g/mol) is in fact comparable to the commercially available contrast agent (188g/mol) and much higher than normal saline (58.44g/mol) (Malakan Rad, 2019)

Nevertheless, despite better ultrasonic images, no significant difference was observed between the two contrasts agents in terms of RASS characteristic to detect CVC malposition. The most probable justification for this finding is due to the difference in the outcome of the current study compared to the earlier studies mentioned. To our knowledge, previous studies only compared dextrose 50% with normal saline to identify intracardiac shunt, and no similar studies to compare these two agents specific to CVC malposition detection. RASS characteristic identified in this study was defined by the timing and location of turbulence flow that first appeared into right atrium. In comparison, the outcome of Li *et al.* (2018) was the timing of microbubbles entering the left atrium after emerging in the right atrium to indicate the right to left shunt (patent foramen ovale). Longer duration of microbubbles had no significant impact on our study, which focuses on the onset of the turbulence into the right atrium.

While both contrast agents are equivalent in terms of RASS characteristic detection, the poor agreement of saline (k = 0.078) and Dextrose 50% (k = 0.049) with chest radiograph for CVC malposition differ from the expected outcome based on previous studies. Normal saline and dextrose 50% also recorded a sensitivity of only 14 % and a specificity of 97.5% to detect CVC malposition. This is lower than previous studies by Weekes *et al.*(2014) and Blans *et al*.(2016), who documented sensitivity of 75% and 98% respectively. The finding of this study is even lower than Cortellaro *et al*. (2014), who reported 33% of sensitivity and 98% specificity using CEUS as compared to CXR.

A systemic review by Smit *et al.* (2018) also showed a higher pooled sensitivity of 68.2% with a specificity of 98.9%. They concluded that this large variation of sensitivity between each study reviewed was possible due to the inclusion of smaller sample size studies and studies with a low prevalence of positive cases or without positive cases. Nonetheless, this systemic review suggests that ultrasound is an accurate modality to detect CVC malposition(Smit et al., 2018)

Vezzani *et al.* (2010) recorded a good concordance between ultrasound and CXR with kappa agreement of 0.88, 96% sensitivity, and 93% specificity. However, they included a combination of both B-mode ultrasound and CEUS to detect CVC malposition. They concluded that the combined method could be an alternative to chest radiograph. B-mode was used to scan both the subclavian and internal jugular veins before scanning the right atrium, superior vena cava, and inferior vena cava to identify the tip of the catheter placement. In contrast, our study used CEUS alone; thus, a similar high specificity and sensitivity could not be accomplished to reach the same justification.

On the contrary, the findings of this study are in accordance with Kamalipour *et al*.(2016) and Cortellaro *et al*. (2014), which stated that CEUS should not become a direct alternative for CXR to detect CVC malposition. While Kamalipour *et al.* (2016) recorded close concordance between CEUS and CXR with good kappa agreement of 0.72 and sensitivity of 98%, but due to the specificity of only 69%, they believed that CEUS should be used as a triage method in an operation room rather than a substitution of CXR.

From the 99 patients included in the data analysis, only 7% of the CVC cohort were malposition. The prevalence of CVC malposition in this study is congruent with the published literature review, with a recorded prevalence of up to 6.7% (Smit et al., 2018). A systemic review by Ruesch *et al*. (2002) reported a prevalence of 5.3% of catheter malposition with jugular access and 9.3% with subclavian approach from 17 prospective, comparative non-randomised studies . As explained by Weekes *et al*. (2016), lower number of CVC malposition recorded than the expected prevalence in clinical practice can underpower the study.

From 7 confirmed malpositions, only 1 was detected by CEUS using normal saline and Dextrose 50%. In 6 other patient, immediate RASS into RA was recorded for both contrasts. However,none of the malposition that was not detected by CEUS was intra-arterial. Hence, we can postulate that the immediate RASS, where turbulence flow is visualised in the right heart, it can confirm the venous placement of the catheter (Gekle et al., 2015). Therefore, the catheter can still be safely used in an urgent situation before chest radiograph is acquired.

The 2-seconds cut-off point was used based on the earlier study by Vezzani *et al.* (2010). However, Meggiolaro *et al.* (2015) suggested a 500-ms yield cut-off value for better accuracy while Weekes *et al*. (2016) proposed a time frame within 1.1s for RASS detection. Meanwhile, Wilson *et al.* (2017) employed a simplified ultrasound protocol but still able to achieve high sensitivity of 86.8% and 100% specificity as compared to chest radiograph. In the study, CVC was interpreted to be in situ once turbulent flow was visualised immediately after injection without a specific time interval given. Omitting time intervals for RASS visualisation can be considered in future studies as opacification of the right atrium is already indicatives of intravenous position of the CVC tip itself.