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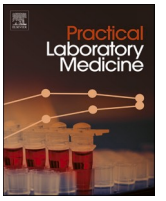

Reducing blood sample hemolysis in the emergency department using S-Monovette® in aspiration mode

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ABSTRACT

Background: Blood sample hemolysis continues to be a significant problem in clinical practice. *In vitro* hemolysis rates up to 77% have been reported in literature. The use of manual aspiration techniques for blood sampling has previously been shown to reduce the burden of erythrocyte injury in the pre-analytical phase compared to the vacuum collection technique. This study compares the hemolysis rates between two blood sampling methods: 5.0 ml BD Vacutainer® SST™ (BDV) and 4.9 ml S-Monovette® serum gel tubes in aspiration mode (SMA).

Methods: This was a prospective randomised controlled study conducted in an Emergency department (ED). A convenience sample of 191 adult patients, aged 18–90 years old, presenting at the ED and requiring blood samples for serum electrolyte was included in the study. Paired blood samples were obtained through an intravenous cannula from each patient with randomised order of blood draw using SMA or BDV. Patient data was obtained and hemolysis index (HI), serum lactate dehydrogenase (LDH), and serum potassium (K) levels measured.

Results: The adjusted mean HI (35.2 vs 21.5 mg/dL, $p < 0.001$), serum K (4.38 vs 4.16 mmol/L, $p < 0.001$) and LDH levels (259.6 vs 228.4 U/L, $p < 0.001$) were significantly higher in blood samples taken using BDV compared to SMA. The frequency of severely hemolyzed (>150 mg/dL) samples was also higher in blood collected using BDV (16.2%) compared to SMA (0%).

Conclusions: The burden of hemolysis in blood samples taken from IV cannulae can be effectively reduced with the use of manual aspiration using the S-Monovette® blood collection system as compared to BD-Vacutainer.

Abbreviations: BDV, BD Vacutainer®; SMA, S-Monovette® in aspiration mode; IV, Intravenous; ED, Emergency department; HI, hemolysis index; K, potassium; LDH, lactate dehydrogenase.

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1. Objectives

Clinical decision making is heavily dependent on laboratory diagnostics. Hence quality control systems that insure expeditious and accurate results are important in testing procedures upon which clinicians base their decisions. There is evidence to suggest that *in vitro* hemolysis, a major source of error producing unreliable laboratory test results, [1–3]. Hemolysis has been cited as the top pre-analytical factor affecting routine clinical chemistry tests [4–6]. Blood sampling techniques, sample transport, storage and handling can all result in pre-analytical hemolysis [2]. The causes of erythrocyte injury during the sampling process are also well described in previous studies and include the following: strong negative pressure during blood draw, forceful expulsion of blood into blood tubes, vigorous shaking of tubes, under-filled tubes, increased tourniquet time [2,7,8]. Unsuitable samples are frequently associated with inaccurate test results such as falsely elevated lactate dehydrogenase and potassium levels [9,10].

In a previous study conducted in another Emergency department (ED) in Singapore, the overall rate of hemolysis of blood specimen taken using various methods of blood sampling (vacutainer, syringe-needle, intravenous(IV) cannula) was reported to be 19.8% [11]. In our hospital, which also uses similar methods for venepuncture, overall hemolytic samples account for 14–28% of all samples taken. Outpatient clinics see the highest rates hemolysis of 23–28% and ED hemolysis rates are 18–19%. Reasons for the differences were not within the scope of this study.

Use of the IV cannula for drawing blood is known to cause higher proportions of hemolyzed samples compared to straight-needle direct venpuncture [4,7,12]. Hemolysis rates in blood drawn using IV cannula vary greatly from 1 to 77% with an average of 23% [12]. Despite all of the evidence against it, blood sampling using IV cannulae is still a prevalent practice, as it is the most practical approach in certain settings such as the Emergency Department or ICU where patients invariably require IV access for medications or transfusions.

The use of primary evacuated tubes such as the BD Vacutainer® system has also been shown to produce more lysis of samples compared to syringe aspiration. This is a result of high negative pressure, turbulent flow and high shearing forces so which erythrocytes are subjected during sampling [11,13]. On the ground, healthcare staff may prefer the needle-syringe method as it allows greater control over the negative pressure exerted to draw blood compared to vacuum blood collection [11]. However, the needle-syringe method increases the risk of needle-stick injuries to healthcare institution workers as it is an open system that requires injection of the blood obtained into test-tubes [14]. For obvious safety reasons, it is not encouraged in our institution. Also, cross-contamination from transferring blood out of the syringe from one tube to the next tube is an important factor to consider and can have a significant negative impact on sample quality [15].

The S-Monovette® system, particularly in aspiration mode, presents a practical solution to the above conundrum [16]. It provides a closed system allowing both vacuum and manual aspiration options in a single device. With a plunger incorporated into the test tube, the system acts like a syringe, allowing for controlled aspiration during a blood draw. It maintains a closed system, as the plunger can be detached from the test tube following blood collection, and the sample can then be sent directly to the lab for analysis.

A few studies have demonstrated the effectiveness of SMA in reducing blood sample hemolysis [13,17]. Notwithstanding these studies, vacuum systems continue to be prevalent and specimen hemolysis continues to be a significant problem in clinical practice. Some possible reasons may be reluctance to make systemic changes, lack of convincing local data and experience, or cost issues. The consequence is the necessity of repeated blood draws to obtain sufficiently accurate results from which patient assessment and disposition decisions can be made. This is not only wasteful and costly to the department but causes additional pain to the patient. The financial burden from blood sampling errors is significant and has been well documented [18,19].

While many cross-over and observational studies have been done, there has been no randomised controlled trial proving superiority of SMA over BDV. Our aim was to fill this gap and conduct a randomised controlled trial comparing the rate of hemolysis in paired blood samples from adult patients presenting to the ED, taken using the S-Monovette® blood collection system in aspiration mode and the existing BD Vacutainer® system.

2. Design and methods

This was a prospective randomised controlled study conducted in Sengkang General Hospital, a tertiary hospital in Singapore with annual ED attendance of approximately 103,000 patients.

We recruited a convenience sample of 192 adult patients, aged 18–90 years old presenting to the Emergency Department and requiring blood samples for serum electrolytes. Recruitment was conducted from 21 June to July 29, 2021 on weekdays between 8am and 4pm by the clinical research coordinators.

Two clinical research coordinators recruited eligible patients and obtained written informed consent. Block randomisation was performed to assign the order of blood draw (S-Monovette® or BD Vacutainer®) in each patient. An ED nurse or doctor then performed intravenous catheter insertion as per usual clinical practice and collected two blood samples directly from the IV cannula for the study, one using the BD Vacutainer® SST™ tube (BDV) and another using the S-Monovette® serum tube in aspiration mode (SMA) in addition to clinical samples required from the patient. A discard tube was used before each collection of study sample was made. For instance, if the order of draw was BDV then SMA, the IV cannula was inserted, a BDV discard tube was used followed by the BDV study tube then SMA discard tube followed by SMA study tube. The purpose of the discard tube was to negate the effect of sample hemolysis from blood drawn into the previous tube. The size of IV cannula (20G or 22G) and site of puncture (upper limb) was left to the discretion of the clinical staff performing the blood draw as per usual clinical practice.

Data was captured into a case record form by clinical research coordinators. Details of phlebotomist (e.g. designation, number of years of clinical experience), equipment used and blood sampling (e.g. IV cannula gauge, site of blood sampling, number of attempts)

and patient demographics (age, comorbid, difficulty of venous access) were recorded. The study samples were then anonymized, assigned a patient study number and sent to the laboratory via the hospital's pneumatic tube system as per usual institutional practice. The pneumatic tubes travel at a standard nominal speed of carrier transmission of 6 m/s and samples typically take less than 15 min to arrive in the laboratory.

Hemolysis index (HI), degree of hemolysis, serum K and LDH levels were compared and factors affecting hemolysis analyzed between the two methods (BDV and SMA). Ethical approval for the conduct of this study was obtained from the SingHealth Central Institutional Review Board (CIRB no 2019/2592).

Statistical Analysis was carried out by a statistician blinded to the treatment arms. Baseline demographics were summarized as mean (SD) and range for continuous variables and count (%) for categorical variables. The primary outcome for analysis was HI. Serum K and LDH levels were analyzed as secondary outcomes as these biomarkers are sensitive to erythrocyte injury [20]. Sample size calculation was conducted a priori. A sample size of $n = 160$ data pairs achieved 80% power to detect an effect size of $\delta = (\mu_1 - \mu_2)/\sigma = 0.22$ ($\delta \leq 0.20$ is considered small) at significance level $\alpha = 0.05$ using a two-sided paired *t*-test, where μ_1 and μ_2 are the respective BDV and SMA population means and σ is the standard deviation of the paired differences.

Both BDV and SMA measurements were taken on each patient, hence a general linear, mixed model repeated measures (MMRM) analysis of variance was employed. Sample values of HI, K and LDH samples were not normally distributed, however approximate normality of analysis residuals was achieved via logarithmic transformation, and consequently analysis results are summarized as geometric least squares (LS) means and ratios of means with 95% confidence intervals. Normality of residuals was verified visually via linearized Gaussian Q-Q plots. The variance covariance matrix was blocked by Patient ID, and the Kenward-Roger degrees of freedom approach was used. Patients were modelled as normally distributed random effects. Scatterplots, Boxplots and Bland & Altman plots of the data are presented in Figs. 1 and 2.

3. Results

Of 192 patients recruited for the study, 1 withdrew consent. Hence the final study population was 191 patients, (96 (50.3%) female and 95 (49.6%) male, mean age 46.2 ± 15.3 years (range: 21–85 years). There were 111 (58.1%) Chinese, 25 (13.1%) Indian, 35 (18.3%) Malay and 20 (10.4%) patients of other ethnicities. 149 (78.0%) IV cannulation attempts were described as easy, 36 (18.8%) as moderately difficult and 6(3.1%) as difficult. One patient underwent 5 attempts at IV cannulation before achieving a successful puncture while the other 190 patients required only 1 or 2 attempts.

The results of this investigation show that blood hemolysis is effectively reduced with the use of S-Monovette® blood collection system in aspiration mode compared to conventional BD Vacutainer® vacuum tube. In the SMA arm, no sample was severely hemolyzed according to our local laboratory specifications as compared to 16.2% in the BDV arm. If taking 30 mg/dL as the threshold for hemolysis as per the "EPiQ" study, SMA had a 4.3% hemolysis rate compared to 17.0% in BDV(17). The unadjusted mean HI (22.2 vs 40.1 mg/dL, $p < 0.001$). K (4.12 vs 4.41 mmol/L, $p < 0.001$) and LDH (226.8 vs 267.0 U/L, $p < 0.001$) levels were all significantly lower in SMA compared to BDV respectively.

Of the potential confounders included in the analysis— the only statistically significant main effects among the three endpoints were for gender, puncture site and size of IV cannula. After adjustment for these confounders, SMA continued to exhibit significantly lower adjusted mean HI (21.5 vs 35.2 mg/dL; $p < 0.001$), K (4.16 vs 4.38 mmol/L; $p = 0.002$) and LDH (228.4 vs 259.6 U/L; $p < 0.001$) relative to BDV.

The boxplots and Bland-Altman plots presented in Figs. 1 and 2 respectively also show a discordance of HI, K and LDH levels in paired blood samples taken from SMA compared to BDV. BDV show much higher proportions of samples HI, K and LDH readings that the upper limits of agreement within the Bland-Altman plots. Significant disagreement between the two blood sampling methods were confirmed using a one-sample *t*-test applied to the differences in HI, K and LDH levels, all with p values < 0.001.

4. Discussion

We carried out a randomised controlled study comparing the S-Monovette® and BD Vacutainer® SST II systems. The results of this study clearly show that SMA is effective in reducing blood hemolysis when compared to BDV (Figs. 1 and 2). Mean HI is almost halved with the use of SMA (Table 1). Statistically significant reduction in serum K and LDH levels were also demonstrated (Table 2). Similar findings have been demonstrated by other groups which have shown marked improvement in rates of hemolysis of blood drawn from IV catheters when the conventional vacuum blood collection system is replaced with the S-Monovette® blood collection system used in aspiration mode [13,17,21]. A study conducted to an ED in Italy showed a decrease of sample hemolysis rates from 29% to 2% after the introduction of the S-Monovette® blood collection system for blood drawn from intravenous catheters [13]. In a more recent "EPiQ" study done in an ED in Switzerland with 4794 subjects, introduction of the S-Monovette® system in place of the BD Vacutainer® SST II, resulted in the hemolysis rate of blood samples (HI > 30 mg/dL) to be reduced drastically (17.0%–4.3%) [17]. Both studies employed a cross-over design [17].

Hemolysis of blood samples affect various laboratory tests differently. Hemolysis is defined as the release of intracellular components of erythrocytes and other blood cells into the extracellular space of blood hence parameters most sensitive to hemolysis include K and LDH which are usually concentrated intracellularly. The most common parameter of concern in the ED is serum K levels as it directly affects patient safety and management. Clinically, only small variations in K levels are well tolerated (approximately 3.5–5.1 mmol/L). Both, hyper and hypokalemia may be life-threatening and need to be addressed.

Hemolysis is detected in serum and plasma by its red colour caused by hemoglobin either through visual inspection or through

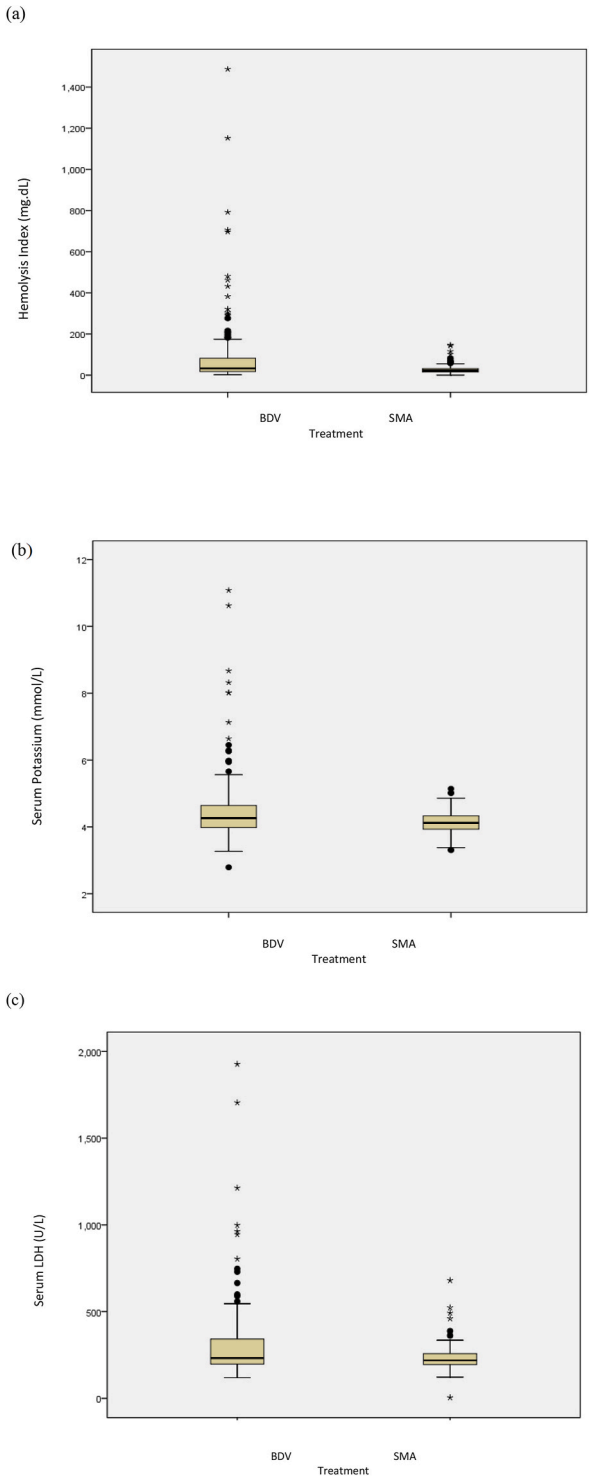
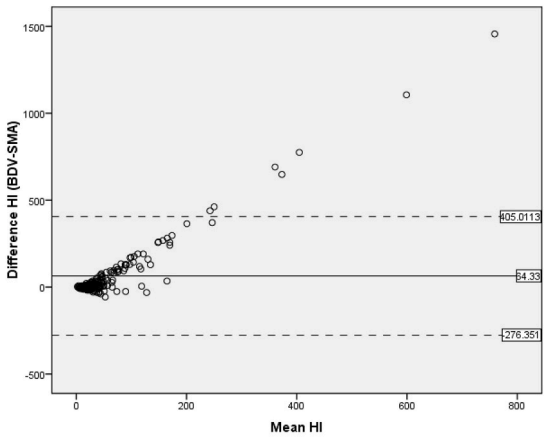
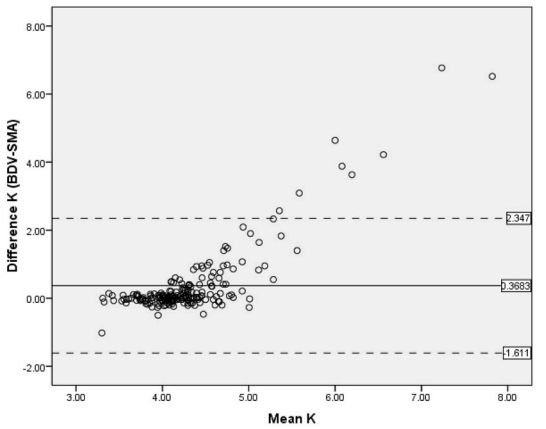


Fig. 1. Boxplots of (a) hemolysis index, (b) serum potassium and (c) lactate dehydrogenase levels in blood specimens drawn into BD Vacutainer® SST™ vacuum tubes (BDV) and S-Monovette® serum tubes used in aspiration mode (SMA).

(a) Hemolysis index



(b) Serum potassium



(c) Serum lactate dehydrogenase

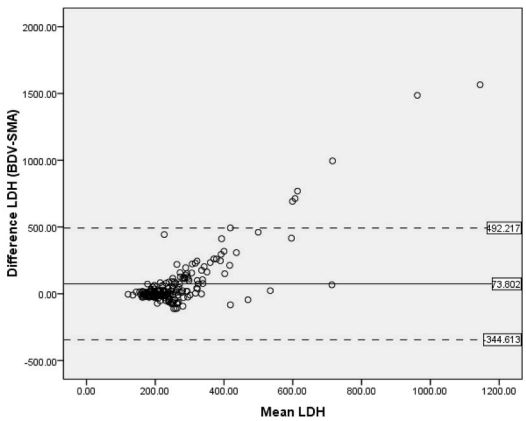


Fig. 2. Bland Altman plots of (a) hemolysis index, (b) serum potassium and (c) lactate dehydrogenase levels in blood specimens drawn into BD Vacutainer® SST™ vacuum tubes (BDV) and S-Monovette® serum tubes used in aspiration mode (SMA).

semi-quantitative measurement of cell-free hemoglobin concentration via photo spectrometry reported as the hemolytic index.

Thresholds of hemolysis, reporting systems and management of hemolyzed blood samples differ in different institutions and depends on various factors such as analyser used and method of determining degree of hemolysis [22–24]. Some institutions practice sample rejection beyond a set threshold. In our institution, all lab results are released to the physicians with an indication of whether the sample is mildly, moderately, or severely hemolyzed. It is then up to the attending physician to interpret the results of the test and determine if repeat sampling is required. Guidelines in management of hemolyzed samples exist but institutional practices continue to vary worldwide [25,26].

In our setting, patients with severely hemolyzed samples, as visually determined by the laboratory, require a repeat blood draw to accurately determine serum K levels. The rate of severe hemolysis is completely eradicated with the use of SMA (16.2% BDV and 0% SMA). As such, repeat blood draw could be avoided in 31 out of 191 patients if SMA were used in place of BDV. This not only improves patient satisfaction and comfort but also reduces ED throughput time and cost to the department.

Of all the factors listed, gender was significant. Males had to have higher rates of hemolysis than females. Recent studies in mouse models seem to demonstrate that the presence of testosterone increases erythrocyte susceptibility to injury although this effect has yet to be proven in human studies [27,28]. Even with adjustment for confounders, SMA still showed significant reduction of hemolysis rates.

The strengths of this study include its prospective, randomised, paired experimental design in which each patient acted as his own control. The study is also adequately powered to detect the level of difference in the primary outcome (HI). The limitations include the use of convenient samples instead of consecutive sampling. However, this was unavoidable due to the availability of study coordinators only during office hours. The laboratory staff and statistician were blinded to treatment arm (BDV or SMA) but blinding was not possible for other study team members, the phlebotomists and patients who were easily able to visually distinguish the two blood collection systems during blood sampling.

In vitro hemolysis remains prevalent in blood samples taken in the ED particularly in the pre-analytical phase. Blood sampling via IV cannula contribute to hemolysis. By virtue of its design, an IV cannula exerts greater shear stress during blood collection compared to a hollow bore straight needle due to the presence of valves inside the disposal, collapsibility of its tubing and the presence of hemolyzing effects of the lubricant present on the mandrel of the needle [29]. However, the routine use of IV cannula for blood sampling is likely to remain due to its practical and favorable implications for both clinicians and patients. As demonstrated by our study, one promising solution is the substitution of vacuum tubes with controlled aspiration. This can be done using a syringe to aspirate blood gently to reduce the pressure gradient between the veins, cannula, and collection device. However, transfer of blood sample from syringes to test-tubes increases the risk of needle-stick injury, nosocomial exposure to potentially contaminated blood and cross-contaminations between the tubes. The S-Monovette® system offers one practical solution to overcome all these problems.

Conversion to an alternative blood collection system may have its challenges especially in large institutions. With any new systems, there would be a requirement to get buy-in from all stakeholders to adopt the system, to train staff on the use of the new method and to ensure compatibility of existing laboratory equipment with the new blood collection tubes.

A myriad of factors needs to be addressed to reduce the burden of hemolysis. While many studies cite the ED as having the highest level of hemolysis [30], this is not the case in our institution. The central laboratory reported a hemolysis rate of 14–28% among all blood specimens received within a 6-month period. This goes to show that there is a role for improving blood sampling practices

Table 1
Baseline demographics.

Characteristics		Estimate (Mean ± SD) or n	Range or %
Age, years		46.2 ± 15.3	21 to 85
Gender	Female	96	50.3%
	Male	95	49.7%
Race	Chinese	111	58.1%
	Indian	25	13.1%
	Malay	35	18.3%
	Others	20	10.4%
Phlebotomist	Doctor	8	3.2%
	Nurse	183	95.8%
Experience, years		4.02 ± 4.31	1 to 12
Puncture side	Left	96	50.3%
	Right	95	49.7%
Puncture site	Antecubetal	62	32.5%
	Forearm	9	4.7%
	Wrist	8	4.2%
	Hand	112	58.6%
IV Cannula	20G	107	56.0%
	22G	84	44.0%
Difficulty in IV cannulation	Difficult	6	3.1%
	Moderate	36	18.8%
	Easy	149	78.0%
Number of attempts	1	162	84.8%
	2	28	14.7%
	5	1	0.5%

universally. Surveys among healthcare workers have shown gaps in knowledge about factors contributing to hemolysis regardless of experience level [31,32]. Continued staff training and education would enhance blood sampling practices.

In conclusion, this study confirms the existing body of evidence demonstrating the effectiveness of S-Monovette® in aspiration mode over vacuum mode in reducing blood sample hemolysis. Substituting primary evacuated tube with the S-Monovette® system as standard practice along with continued staff education would greatly enhance blood sampling practices and minimize the burden of hemolysis in clinical practice.

Study sponsor

Sarstedt AG & Co. KG, Germany.

Author contributions

Dr Eunizar Omar is the principal investigator of the study, designed, planned and supervised the conduct of the study and is the main and corresponding author for this paper.

A/Prof John Carson Allen Jr was the statistician that carried out all the analysis of the study results.

Mr Ahmad Khairil Bin Mohamed Jamil helped with the design, administration and conduct of the study on the clinical ground.

Dr Mohamad Fahamy Koenitz Bin Iskandar, Dr Sameera Ganti and Dr Kunzang Norbu helped with the conduct of the study on the ground as well as editing of the manuscript.

Ms Connie Tsang and Ms Jocelyn Yin assisted with the administrative elements, record keeping as well as recruitment and consent taking.

Dr Ong Siew Kim assisted with the laboratory aspects of the study and also critically reviewed and edited the manuscript.

Professor Marcus Ong Eng Hock was involved in the conceptualisation, design of the study as well as critically edited the manuscript.

Declaration of competing interest

This was an investigator-initiated study sponsored by Sarstedt AG & Co. KG, Germany, the company that produced S-Monovette®. The sponsor supplied study materials such as blood collection tubes and funded the costs incurred for running the laboratory tests performed for the study. Ms Connie Tsang received a part-time salary for this work. The remaining authors did not receive any honorarium for this study.

Data availability

The authors do not have permission to share data.

Table 2
Hemolysis index values, serum potassium and lactate dehydrogenase levels in blood specimens drawn into BD Vacutainer® SST™ vacuum tubes (BD-V) and S-Monovette® serum tubes used in aspiration mode (SM-A).

Blood Collection Technique	SM-A	BD-V	Ratio GMs (95% CI)	P-value
Number of patients	191	191		
HI values, %				
• 0–30 mg/dL (not hemolyzed)	70.2	47.1		<0.001
• 31–50 mg/dL	20.4	14.7		
• 51–75 mg/dL	6.3	8.9		
• 76–100 mg/dL	1.0	5.8	–	
• 101–150 mg/dL	2.1	7.3		
• 151–200 mg/dL	0.0	6.3		
• >200 mg/dL	0.0	9.9		
Degree of Hemolysis (from lab), %				
• No	42.9	28.8		<0.001
• Mild	53.9	42.9	–	
• Moderate	3.1	12.6		
• Severe	0	16.2		
[a]Geometric Mean HI (mg/dL)	21.5	35.2	1.64 (1.33, 2.02)	<0.001
Median HI (mg/dL)	23.0	33.0	–	<0.001
Highest Value of HI (mg/dL)	147.0	1487.0	–	–
[a]Geometric mean K (mmol/L)	4.16	4.38	1.05 (1.02, 1.09)	0.002
[a]Geometric mean LDH (U/L)	228.4	259.6	1.14 (1.05, 1.22)	<0.001

Legend: GM – geometric mean, HI – hemolysis index, K- serum potassium level, LDH – serum lactate dehydrogenase level.
[a] Adjusted for Gender, puncture site and size of IV cannula in general linear mixed model analysis of variance.

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