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The „EPiQ"-Study (Evaluation of preanalytical quality): S-Monovette® in manual aspiration mode drastically reduces hemolytic samples in head-to-head study

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ABSTRACT

Background: Hemolytic blood samples are the number one cause for specimen rejection at emergency departments. Triggered by unsuitable blood sampling material or incorrect handling and a related strong vacuum force, hemolytic samples often must be retaken. The objective of this study was to assess whether correct manual aspiration using S-Monovette® could reduce the number of hemolytic samples.

Methods: Between January and April 2019, a head-to-head study was conducted. Whereas in the first eight weeks, all specimens were collected using Vacutainer®, in the second eight weeks, blood was taken using S-Monovette® in aspiration mode. Specimens were categorized into five classes (0–30, 31–50, 51–75, 76–100, and 101+ mg/dl of cell-free hemoglobin) and for the statistical analyses, all samples exceeding 30 mg/dl were classified as hemolytic.

Results: Data were collected on 4794 blood specimens (Vacutainer®: 2634 samples, S-Monovette®: 2160 samples). While the percentage of non-hemolytic samples (HI of 0–30 mg/dl) was substantially higher for specimens drawn by S-Monovette® (95.7 %) than Vacutainer® (83.0 %), the opposite was true for all HI categories above 30 mg/dl. Importantly, the reduction of hemolytic samples took place immediately following the imposition of S-Monovette® and remained stable at a low level until the end of the study.

Conclusions: Based on our results, we conclude that switching to S-Monovette® in manual aspiration mode in the blood sampling process could be highly beneficial, not only from a financial point of view, but also with regards to reducing unnecessary tasks and stress for nursing staff and improving patient outcome overall.

1. Introduction

Imagine being taken to the emergency department (ED) of your local hospital because your health has deteriorated considerably since this morning. Given the unclear origin of your illness, the doctor instructs the nurse to take a blood specimen and have it analyzed in the laboratory. After waiting for approximately half an hour [1], the nurse informs you that the sample must be retaken because the first one was defective and rejected. Clearly, this negatively affects your mood, but furthermore it may delay your treatment and

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medical decisions. In addition, it enhances the workload for the nurse, and the laboratory, and in general consumes time and increases costs.

This short scenario not only highlights how, in a hospital, numerous events and processes are strongly interconnected, but, in particular, it stresses the importance of the preanalytical phase for a desirable patient outcome as illustrated in Fig. 1. Thus, errors or problems in the preanalytical phase can lead to harmful consequences for the patient at a later stage and certainly add costs in terms of material and human resources.

Between 70 % and 85 % of all healthcare decisions are based on at least one laboratory-based diagnostic [2,3]. Of these, around 0.3 %–0.8 % of all samples are rejected, whereas this number is considerably higher (2.2 %) at EDs [4,5]. Reasons for specimen rejection include insufficient quantity of sample for testing and clotted specimens [6–8]. However, by far the most common cause of specimen rejection at EDs is hemolysis (or haemolysis). The frequency of hemolyzed specimens from EDs ranges from 3 % to 12.4 % [4]. Hemolysis refers to the release of hemoglobin and other intracellular components into the surrounding plasma due to the ruptured cell membrane of erythrocytes. Hemolysis may occur *in vivo* caused by one of several medical conditions [9], or alternatively, it can occur *in vitro*. Although *in vitro* hemolysis can occur due to poorly handled and transported samples [10], the root cause of hemolysis *in vitro* is an improper sample drawing or, more specifically, an evolving strong vacuum force [11–13]. When blood is aspirated by vacuum, the difference of pressures between veins, catheter needles, valves and evacuated collection tubes leads to excessively high flow rates of blood and turbulences, heightening the chance of erythrocyte injury [14]. This difference is particularly problematic when combining vacuum tubes and intravenous catheters. Since the latter are almost unavoidable in EDs to improve efficiency and reduce the number of venipunctures, this explains why EDs in particular record hemolytic samples more often [15].

Hemolysis can affect the quality of the specimen in three different ways. First, due to the higher intra-cellular concentration of some of the cell constituents, the rise of intracellular constituents in the extra-cellular space can undesirably increase the concentration of these analytes, such as potassium and lactat dehydrogenase (LDH) [16]. Second, the strong absorption of light linked to the presence of hemoglobin, affects the measurement of various analytes in clinical chemistry. Third, due to chemical interference, the measurement of analytes can directly or indirectly be interfered with by blood cell constituents [17,18]. Thus, hemolysis strongly restricts the reliability and accuracy of laboratory testing and often requires a new blood sample.

With increasing degrees of hemolysis, more laboratory analyses are affected. For example, whereas the analysis of LDH is already affected starting from 15 mg/dl of cell-free hemoglobin, magnesium can be accurately measured up to a hemolysis concentration of 999 mg/dl [19]. As one of the analytes most important and frequently measured at EDs, the threshold value for the determination of potassium concentration has been recently lowered by Roche to 20 mg/dl, to ensure an accurate analysis and interpretation of potassium results [20]. This shows that even low levels of hemolysis have a significant impact on subsequent medical processes and actions, although fortunately the increasing sensitivity of analytical instruments allows for this lower threshold of detection.

Up till this point, no consensus for a critical hemolysis threshold has been defined. Clinically and analytically significant hemolysis values range from 30 mg/dl to 200 mg/dl [21]. According to Lippi, Cadamuro, von Meyer and Simundic [21], all results from samples with more than 100 mg/dl of cell-free hemoglobin should be ignored. Based on the latter guideline, all values exceeding 100 mg/dl are seen as explicitly hemolytic in the present study. Although the laboratory of the hospital involved in the study normally operates with a threshold of 40 mg/dl, a more conservative approach of 30 mg/dl was chosen. The purpose of this was to find out whether laboratory analyses with a lower threshold could benefit from manual aspiration.

In a comprehensive meta-analysis, Lippi, Cervellin and Mattiuzzi [22] show that manual aspiration (e.g., S-Monovette® blood

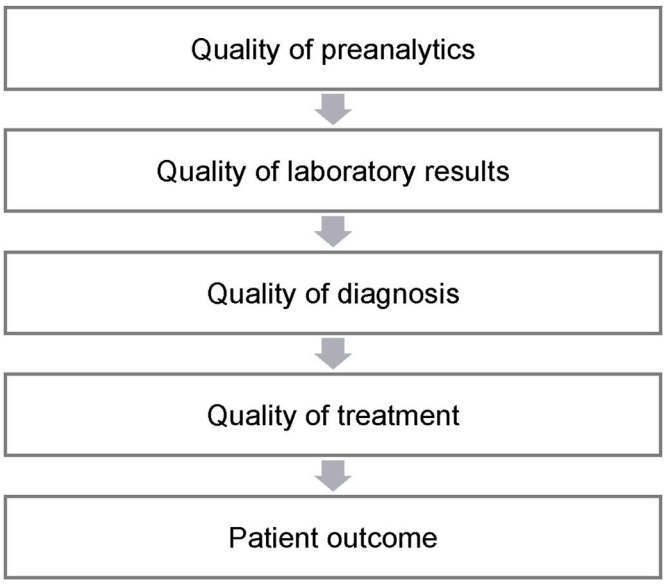

Fig. 1. Simplified process flow of the causal link between the quality of preanalytics and patient outcome.

tubes SARSTEDT AG, Nümbrecht, Germany) is effective in reducing hemolysis rates compared to vacuum tubes with predefined filling volumes. More precisely, a slow manual aspiration for drawing blood from intravenous catheters reduces both shear stress and a strong vacuum force as the primary sources of injured erythrocytes [14].

However, until now a large-scale and long-term study proving the superiority of manual aspiration using S-Monovette® appears to be missing. The present study aims to fill this gap.

2. Materials and methods

The present study was carried out in a major hospital in Western Switzerland, reaching nearly 13,000 inpatient and 350,000 outpatient treatments in the year 2019. Data collection took place between the 7th of January and the April 29, 2019. During this time, all blood samples from the emergency department were evaluated using Roche's Cobas® 6000, a state-of-the-art analyzing system, and their Hemolysis Index (HI 1 = 1 mg of free cell hemoglobin in 1 dl blood plasma) was determined.

In the first eight weeks (January 7, 2019–March 3, 2019) of the study, all specimens were collected using Vacutainer® (BD Vacutainer® Lithium-Heparin Gel, 4.5 ml). In the second eight weeks (March 4, 2019–April 29, 2019), blood was taken using S-Monovette® (SARSTEDT S-Monovette® Lithium-Heparin Gel, 4.7 ml) by applying manual aspiration only. All other pre-analytical processes, needle diameters, catheters and pneumatic transportation remained unchanged during the entire study.

Each morning of week 9 and 10, nursing staff were given the opportunity to attain a short instruction on how to apply S-Monovette®. In particular, it was pointed out to them that the aspiration process should be slow and careful until the desired fill quantity was reached. Compared to a manual aspiration and controlled vacuum, the Vacutainer® system works by a predetermined vacuum principle. The tube fills up automatically and the blood flow stops when the specified filling volume is reached.

All samples with a HI (mg/dl) higher than 30 were rated as hemolytic. Specimens were categorized into five categories: HI 0–30, HI 31–50, HI 51–75, HI 76–100, and HI 101+.

3. Results

Data were collected on 4794 blood specimens (Vacutainer®: 2634 samples, S-Monovette®: 2160 samples). Overall, 11.3 % of samples were rated as hemolytic because their concentration of hemolysis exceeded 30 mg/dl. This proportion differed considerably between specimens drawn by Vacutainer® (17.0 %) and S-Monovette® (4.3 %), meaning that, in proportion, there were four times as many hemolytic samples when using Vacutainer®. To get a more detailed understanding of how the number of samples in one category related to the tube used, we conducted a Pearson's chi-squared test, evaluating how likely it is that the observed difference between the number of hemolytic cases for Vacutainer® and S-Monovette® occurred by chance.

Statistical analyses showed a significant connection between tubes and hemolysis, indicating that S-Monovette® effectively reduced incidents of hemolysis, $\chi^2(4) = 209.794$, $p < .0001$. To determine in more detail across which categories the tube had an effect on the number of hemolytic samples, adjusted standardized residuals were converted into chi-squared values and checked for significance, as suggested by MacDonald and Gardner [23]. The critical p-value was corrected for this step to $p = .005$. Even when applying such a conservative approach, there was still a significant effect across all categories ($p < .001$). Fig. 2 shows that whereas the number of samples for HI 0–30 was drastically higher for S-Monovette® (95.7 %) than Vacutainer® (83.0 %), the opposite was true for all categories above 30 mg/dl (HI *31 – 50*: 5.0%$_{VT}$ vs. 2.5%$_{MV}$; HI *51 – 75*: 3.5 % $_{VT}$ vs. 0.8 % $_{MV}$; HI *76 – 100*: 1.9 % $_{VT}$ v. 0.5 % $_{MV}$; HI *101+*: 6.6 % $_{VT}$ vs. 0.6 % $_{MV}$).

Interestingly, as shown in Fig. 3, the reduction of hemolytic samples took place immediately following the imposition of S-Monovette® at week 9. Furthermore, it remained stable at a low level until the end of the week 16.

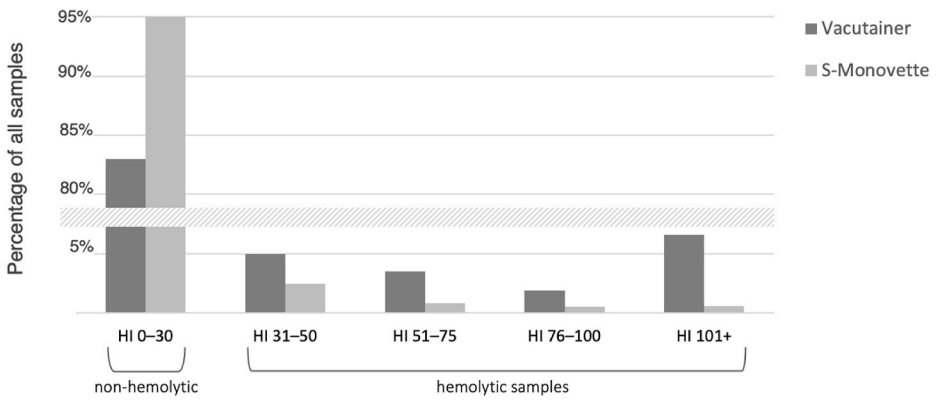

Fig. 2. Proportion of hemolytic and non-hemolytic samples in relation to the total number of blood specimens. Across all four hemolytic categories, the proportion of samples was smaller for S-Monovette®. HI = hemolytic index (e.g., HI 1 = 1 mg/dl).

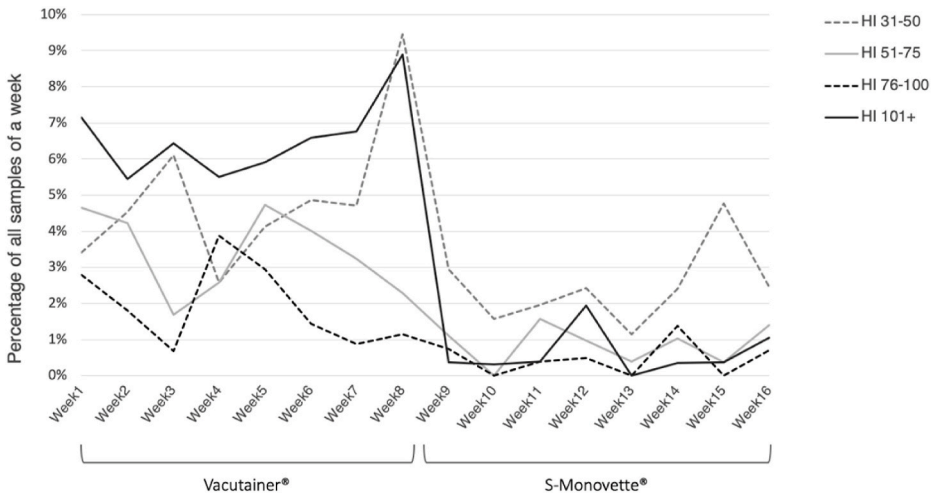

Fig. 3. Proportion of hemolytic samples (HI > 30) in relation to the total number of blood specimens of a week. Compared to the first eight weeks, the percentage of hemolytic samples is drastically reduced in the second eight weeks. This effect can be observed across all four categories.

4. Discussion

By far the most relevant cause for specimen rejection at EDs is hemolysis [24]. Mostly caused by an improper sample drawing and a related strong vacuum force combined with the use of intravenous catheters, hemolysis lowers the quality of the specimen. The necessity of retaking specimens causes undesired consequences, such as increased costs and expenditure of time. In addressing this challenge, the present study shows that, compared to Vacutainer®, S-Monovette® in aspiration mode drastically reduces hemolytic samples by a factor of four. This is in line with previous research showing the benefit of slow manual aspiration and a reduced shear stress, when compared with vacuum tubes [14].

Switching to S-Monovette® could thus be beneficial for several stakeholders affected by poor quality blood samples. For instance, patients such as the one in our introduction, would not need to wait for another sample. The procedure could be considerably less stressful without any unnecessary loss in time and postponed medical decisions, possibly resulting in a better patient outcome. Reduced stress may likewise be expected for the nursing staff, who could focus on other essential tasks. This assumption was strongly supported by the nursing team involved in the present research and especially their team leader. Staff members expressed the opinion that due to reduced number of hemolytic samples, there was a significant saving in time. More specifically, since the necessity of retaking blood samples had been drastically reduced and the laboratory results were not delayed by hemolytic samples, nurses reported having more time to focus on all their patients. Interestingly, the nursing staff further stated an improved collaboration with the laboratory. This seems logical since the laboratory was less frequently approached with redundant requests and thus a crucial source of frustration between the two teams was removed. The nurses' team leader underlined several times that while research projects often lead to resistance to change, this was not the case with S-Monovette®, despite a notable change in nurses' habits and equipment. All staff members have clearly seen the benefits and were in favor of a change to S-Monovette®.

Optimistically, similar effects such as savings in time and an increased focus on key responsibilities can be expected for laboratory staff and physicians. Both groups are negatively affected by delays due to hemolytic samples, caused by analogous reasons other than the nursing staff.

S-Monovette®, however, is not only associated with human benefits, but additionally would help to reduce costs. Depending on various factors such as employee salaries, the number of sample collections and the used material, monthly costs due to repeated measurement of hemolytic specimens are estimated between €67571 and €122077 for hospitals with 20,000 laboratory blood collections monthly [25]. Even though such a number must be treated with caution, it clearly indicates the financial importance of avoiding hemolytic samples. Interestingly, the cost of the material isn't the decisive factor for the significant cost savings, but accounts for within only a low, single-digit percentage range. Rather, it is the faster processes and time savings at EDs, as well as the potential reduction of reagents, that trigger important cost savings.

Limiting the findings of the present study, it is likely that nursing staff were aware of the experiment taking place. Although the exact hypothesis was not communicated in detail, the changes of material would have been obvious to them. Thus, they could have felt monitored and been extraordinarily motivated to perform well. In combination with the optional short instruction in week 9 and 10, it is clear that keeping the nursing staff blind regarding the change of material is not possible in such a study design. In addition, the employees only had the opportunity to attend training for S-Monovette® but not for Vacutainer®. It therefore seems unclear whether additional training for Vacutainer® would have diminished the positive effect. However, this criticism is put into perspective by the fact that the training for S-Monovette® was limited to appropriate handling with a focus on the use of slow aspiration. Further aspects for preanalytical aspects were not addressed. Furthermore, the staff had access to Vacutainer® guidelines at all times and were thoroughly familiar and experienced with the system, as it has been standard practice for over two decades. Most importantly, we

suggest that staff should be adequately trained in the use of S-Monovette® when it is first implemented, as misapplied manual aspiration can similarly create a strong vacuum force causing hemolysis. As another limiting factor, the study was conducted at a single center and at the ED only. As mentioned in the introduction, other wards have lower hemolysis rates and not all are as tied to the use of intravenous catheters as EDs. Thus, other wards might benefit less from a slow manual aspiration. Repeating the research as a multi-center study at several hospitals, on different wards, and by different investigators would further strengthen the scientific significance.

The present study has identified that regarding hemolysis rates, a slow manual aspiration using S-Monovette® is superior to vacuum tubes with predefined filling volumes, as demonstrated in the setting of our ED, which has important practical implications. Future research could focus on gaining a better insight into the beneficial effects on personnel, on patient reported outcomes and on the cost-effectiveness of evaluations.

Author contributions

All authors participated in writing, reviewing, editing and approving the manuscript. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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Declaration of competing interest

The funding organization played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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