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ORIGINAL ARTICLE

Point of Care Analysis of Hematology in the Operating Theater - a Prospective Observational Study of Accuracy and Feasibility

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SUMMARY

Background: **Major surgery entails the risk of severe hemorrhage, and an optimized substitution with red blood cell (RBC) and platelet (PLT) transfusions necessitate rapid test results for RBCs/hemoglobin (HGB)/hematocrit (HCT), and PLTs. The HemoScreen (PixCell Medical, Yokneam Ilit, Israel) is an automated point-of-care hematology analyzer employing image analysis and single-use cuvettes. This study aimed to investigate the correspondence between the HemoScreen and standard laboratory testing (SLT) using the Sysmex XN-9000 in patients undergoing major surgery and to evaluate the feasibility in the operating theater.**
Methods: **A total of 145 blood samples from 91 adult patients were sampled during abdominal and orthopedic surgery and analyzed on both cell counters. Coefficient of variation (CV) was calculated, Passing-Bablok regression analysis was performed, and Bland-Altman plots were constructed. User experience was assessed through a questionnaire.**
Results: **The HemoScreen showed imprecision with a CV below 5%. Passing-Bablok regression showed positive proportional and negative constant errors for HGB and HCT, a positive proportional error for PLTs, but no difference for RBCs. Bias in the Bland-Altman plots with limits of agreement: RBCs 0.09 x 10^{12}/L (± 0.20 x 10^{12}/L), HGB 1.1 g/L (± 8.4 g/L), HCT 0.4 % (± 2.6%), and PLTs 28.8 x 10^{9}/L (± 33 x 10^{9}/L). The analyzer was scored easy to use with shorter turnaround times compared to SLT.**
Conclusions: **The HemoScreen is feasible and provides rapid test results with acceptable accuracy for the evaluated application but the two methods cannot be regarded as interchangeable based on the results in this study.**
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INTRODUCTION

Bleeding is a potential complication during any surgical procedure, and severe uncontrollable hemorrhage poses an immediate threat to the patient's life [1, 2]. The management of bleeding in the operating theater include surgical control and resuscitation with crystalloid and/or colloid fluids, but also transfusion of red blood cells (RBCs), fresh frozen plasma (FFP), and platelets (PLTs) in order to maintain circulation and hemostasis.

Optimal substitution with blood products calls for swift and accurate monitoring of blood components, including RBCs, hemoglobin (HGB), hematocrit (HCT) and PLTs [2,3]. Analysis of PLTs and RBCs is usually performed in a centralized hospital laboratory using large automated cell counters which may lead to long test turnaround times (TAT) [4]. Point-of-care testing (POCT) offers an advantage with faster TAT and analyzers for measuring of HCT and HGB have been available for years [3-5].

The HemoScreen (PixCell Medical, Yokneam Illit, Israel; hereafter POCT hematology analyzer) employs viscoelastic focusing where flow-cytometry and digital imaging is combined to perform a complete blood count. Repeated photographic images are analyzed by a computer software to identify cells types. The automated analysis takes 3 - 6 minutes and provides a complete blood count, standard red cell characteristics, mean platelet volume (MPV), and five-part differential [6,7]. Evaluations of the analyzer in laboratory settings has demonstrated high correlation between results obtained with the POCT hematology analyzer and standard laboratory testing (SLT) [6,7]. Use of POCT for analysis of HGB, HCT, and PLT count with short TAT in patients with potential risk of massive hemorrhage could contribute to improved management. However, there is very limited data available regarding use of the POCT hematology analyzer in an operating theater in patients undergoing major surgery.

This prospective study aimed to investigate the correspondence between the POCT hematology analyzer and the hospital laboratory full blood count instrument for analysis of RBCs, HGB, HCT, and PLTs in patients undergoing major surgery with risk of significant blood loss. Other aims were evaluation of the feasibility of the POCT hematology analyzer in an operating theater, users experience and their learning curve, and comparison of TAT.

MATERIALS AND METHODS

This prospective observational bed-side study was approved by the Uppsala ethical review board (DNR 2019-00469) and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study was performed at Uppsala University Hospital on a study population consisting of 91 patients undergoing planned major surgery in the central operating theaters during the period 02-27-2019 to 04-12-2019.

The study cohort

Eligible study participants were continuously identified from the operating program and asked to participate when arriving at the preoperative assessment unit after receiving verbal and written information. Inclusion criteria were adults (> 18 years old) undergoing major surgery who provided written informed consent. Exclusion criteria were children (< 18 years old), hemolyzed specimens, visibly clotted specimens, venous specimens with < 1 mL blood, specimens older than 6 hours from phlebotomy when first analysis occurs and when time of testing with predicate and the evaluated analyzer exceeded a 2-hour interval.

Samples

Blood samples from patients were first taken at the start of the surgical procedure from indwelling arterial or venous catheters using 4.0 mL K_2ETDA tubes (BD Vacutainer tube 454410, Becton Dickinson, Franklin Lakes, NJ, USA). The POCT hematology analyzer was placed in close proximity to the operating room and samples were analyzed there before being delivered to the hospital laboratory and analyzed on the Sysmex XN-9000 (Sysmex Sverige AB, Kungsbacka, Sweden; hereafter referred to as SLT), the standard instrument at Uppsala University Hospital for complete blood count test. The SLT analyzer is a large fully automated multiparameter blood cell counter [8] which uses direct current sheath flow, fluorescence flow cytometry and impedance to determine the parameters of a complete blood count, six-part differential, and reticulocyte count [9].

The test procedure during the data collection thoroughly followed the instruction for use provided with the POCT hematology analyzer. Transfers of blood from the K_2ETDA tubes were performed after gently mixing of the samples by end-to-end inversion of the tubes at least 10 times, immediately followed by penetration of the rubber membrane using an adapter with a dispensing cup (provided by PixCell Medical). By inverting and firmly pressing the tubes 2 - 3 times against a flat surface the dispensing cup filled with blood whereupon the dedicated capillary sampler unit was used to acquire 40 μL of blood. The sampler unit with the specimen was mounted into the disposable cartridge unit containing the necessary reagents before insertion into the POCT hematology analyzer which then ran an automated program analyzing the blood.

Quality control

Control samples (R&D Systems, Minneapolis, MN, USA) for three levels were analyzed with the POCT hematology analyzer every day during data collection before sampling and analysis of blood specimens from patients. Calibration and quality control of the SLT analyzer was carried out by laboratory personnel in accordance with instructions provided by the manufacturer.

Intra-sample variability

Results from analysis of control samples were used to calculate total coefficient of variation (CV, according to ISO-3534-1) for each level and analyte. Blood samples from patients (n = 10) were analyzed three times consecutively on the POCT hematology analyzer on the same day in order to measure within-day variation.

Table 1. Demographic values for the study population.

Characteristics	Categories	
Gender (n)	females	36 (39.6%)
	males	55 (60.4%)
Age (years)		65 (15)
Weight (kg)		78 (15)
Type of procedure (n)	hepato-biliary-pancreatic surgery	42
	lower gastrointestinal surgery	15
	urological surgery	13
	orthopedic surgery	10
	spinal surgery	4
	upper gastrointestinal surgery	3
	explorative laparotomy	3
	vascular surgery	1
Estimated blood loss during surgery (mL)		478 (605)

The age, weight, and estimated blood loss during surgery are presented as means and standard deviation (SD).

Feasibility and turnaround times

The times for sampling of blood specimens, analysis and obtention of results with the POCT hematology analyzer, delivery to the central laboratory, and obtention of results with SLT were noted and used for estimation and comparison of TAT.

For evaluation of the analyzer's feasibility, user experience and learning curve, assistant nurses at the operation theater, under supervision from an instructor, performed the complete testing procedure. Following analysis, staff members were asked to complete a short questionnaire where they were asked to report the number of completed analyses, estimate the time required for analysis and score their experience regarding learning procedure and user-friendliness on a scale from 1 to 5, where 1 equaled "easy" and 5 equaled "hard". The operators were also asked to score the extent in which they agreed with the following statement: "HemoScreen is a suitable device for point of care testing of blood count in the operating theater", on a scale where 1 equaled "I disagree" and 5 equaled "I agree".

Statistical analysis

The coefficient of variation (CV, according to ISO-3534-1) for the POCT hematology analyzer, Passing-Bablok regression, and the correlation between the two cell counters were calculated together with construction of Bland-Altman plots using Excel (Microsoft, Redmond, WA, USA).

RESULTS

A total of 145 blood samples were analyzed from 91 patients whose characteristics are summarized in Table 1. All samples were analyzed on both the POCT hematology analyzer and by SLT. A single blood specimen was collected from 37 patients, and from 54 patients a second blood sample was obtained towards the end of the surgical procedure. Mean values and differences between the first and second samples are presented in Figure 1.

Precision

Control samples were analyzed on the POCT hematology analyzer for each of the three control levels every day during collection of blood samples and in total 33 times for each control level. The first batch of tubes (LOT PIX190405) was analyzed on 23 separate days and the second batch of tubes (LOT PIX190605) was analyzed on 10 separate days. One result from analysis of the low control level was subsequently excluded due to detection of an air bubble. The mean total CV (%) for the control samples with low values were 2.18 for RBCs, 3.53 for HGB, 2.63 for HCT, and 4.1 for PLTs. The mean total CV (%) for the control samples with normal values were 1.52 for RBCs, 2.34 for HGB, 1.92 for HCT, and 2.7 for PLTs. The mean total CV (%) for the control samples with high values were 1.84% for RBCs, 2.48% for HGB, 1.94% for HCT, and 3.0% for PLTs. Control samples were also analyzed for each of the three control levels on the SLT. The results from analysis of each batch are presented in Table 2. Specimens from 10 patients were analyzed three times each

Table 2. Coefficient of variation (CV) for control samples with low, normal, and high concentrations.

PIX190405	Mean and SD	CV (%)	Mean and SD	CV (%)	Mean and SD	CV (%)
RBC * (106/µL)	2.56 (0.06)	2.14	4.53 (0.07)	1.64	5.71 (0.08)	1.40
HGB † (g/dL)	7.4 (0.3)	3.49	14.6 (0.3)	2.36	20.0 (0.5)	2.36
HCT ‡ (%)	18.9 (0.5)	2.47	36.2 (0.6)	1.75	50.9 (0.8)	1.63
PLT § (109/L)	67 (3.5)	5.2	241 (6.3)	2.6	534 (16.9)	3.2
PIX190605	Mean and SD	CV (%)	Mean and SD	CV (%)	Mean and SD	CV (%)
RBC * (106/µL)	2.57 (0.06)	2.22	4.62 (0.06)	1.40	5.45 (0.12)	2.28
HGB † (g/dL)	7.4 (0.3)	3.56	15.3 (0.4)	2.33	19.9 (0.5)	2.59
HCT ‡ (%)	18.2 (0.5)	2.78	37.1 (0.8)	2.08	48.8 (1.1)	2.25
PLT § (109/L)	70 (2.1)	3.0	249 (7.1)	2.8	537 (15.5)	2.9
Sysmex 92	Mean and SD n = 45	CV (%)	Mean and SD n = 41	CV (%)	Mean and SD n = 42	CV (%)
RBC * (106/µL)	2.42 (0.02)	0.09	4.45 (0.04)	0.93	5.33 (0.05)	0.89
HGB † (g/L)	60.3 (0.52)	0.87	126 (0.58)	0.58	167 (0.96)	0.58
HCT ‡ (%)	17.4 (0.27)	1.57	36.1 (0.48)	1.34	47.1 (0.64)	1.35
PLT § (109/L)	92.7 (8.5)	9.2	257 (6.2)	2.4	560 (9.7)	1.73

The table shows values with expected ranges and the results are presented as means and SD and CV (%) for each of the two batches that were used.
*** - Red blood cells, † - Hemoglobin, ‡ - Hematocrit, § - Platelets.**

and the mean CV (%) was 1.66% for RBCs, 2.10% for HGB, 2.07% for HCT, and 2.5% for PLTs.

Correspondence between the two methods

The equation for the Passing-Bablok regression for RBC count (10^{12}/L) was $RBC_{POCT\ hematology\ analyzer} = 1.025 \times RBC_{SLT} - 0.012$; r = 0.985. The 95% confidence interval (CI) for the slope was 0.992 to 1.058 and for the intercept -0.131 to 0.176. The Bland-Altman plot of the comparison between the two cell counters is presented in Figure 2. Bias in the Bland-Altman plot was 0.09 x 10^{12}/L for the RBC count, and the limits of agreement (LoA) were ± 0.20 x 10^{12}/L. There was no trend in the bias for the RBC count over the range of measurements.
The equation for the Passing-Bablok regression for HGB values (g/L) was $HGB_{POCT\ hematology\ analyzer} = 1.101 \times HGB_{SLT} - 11.43$; r = 0.971. The 95% CI for the slope was 1.057 to 1.153 and for the intercept -16.15 to -5.534. The Bland-Altman plot of the comparison between the two cell counters is presented in Figure 2. Bias in the Bland-Altman plot was 1.1 g/L for the HGB values, and the LoA were ± 8.4 g/L. There was a trend in the bias for the HGB values over the range of measurements.
The equation for the Passing-Bablok regression for HCT values (%) was $HCT_{POCT\ hematology\ analyzer} = 1.127 \times HCT_{SLT} - 4.588$; r = 0.962. The 95% CI for the slope was 1.070 to 1.182 and for the intercept -6.63 to -1.16. The Bland-Altman plot of the comparison between the two cell counters is presented in Figure 2. Bias in the Bland-Altman plot was 0.4% for the HCT values, and the LoA were ± 2.6%. There was no trend in the bias for the HCT values over the range of measurement.
The equation for the Passing-Bablok regression for PLT counts (10^9/L) was $PLT_{POCT\ hematology\ analyzer} = 1.137 \times PLT_{SLT} - 0.663$; r = 0.983. The 95% CI for the slope was 1.102 to 1.174 and for the intercept -8.53 to 8.69. The Bland-Altman plot of the comparison between the two cell counters is presented in Figure 2. Bias in the Bland-Altman plot was 28.8 x 10^9/L for the PLT counts, and the LoA were ± 33 x 10^9/L. POCT hematology analyzer - SLT bias was all positive except for PLT levels between 188 x 10^9/L and 300 x 10^9/L, where three of the values were negative. There was a trend in the bias for the PLT values over the range of measurement.

Comparison of turnaround times

The TAT, between sampling of blood from a patient in the operating room to an obtained result with the POCT hematology analyzer, presented as median value was 12 minutes (interquartile range, IQR = 5 minutes). The time required for sample preparation and analysis on the POCT hematology analyzer was 6 minutes (IQR = 0 minutes).

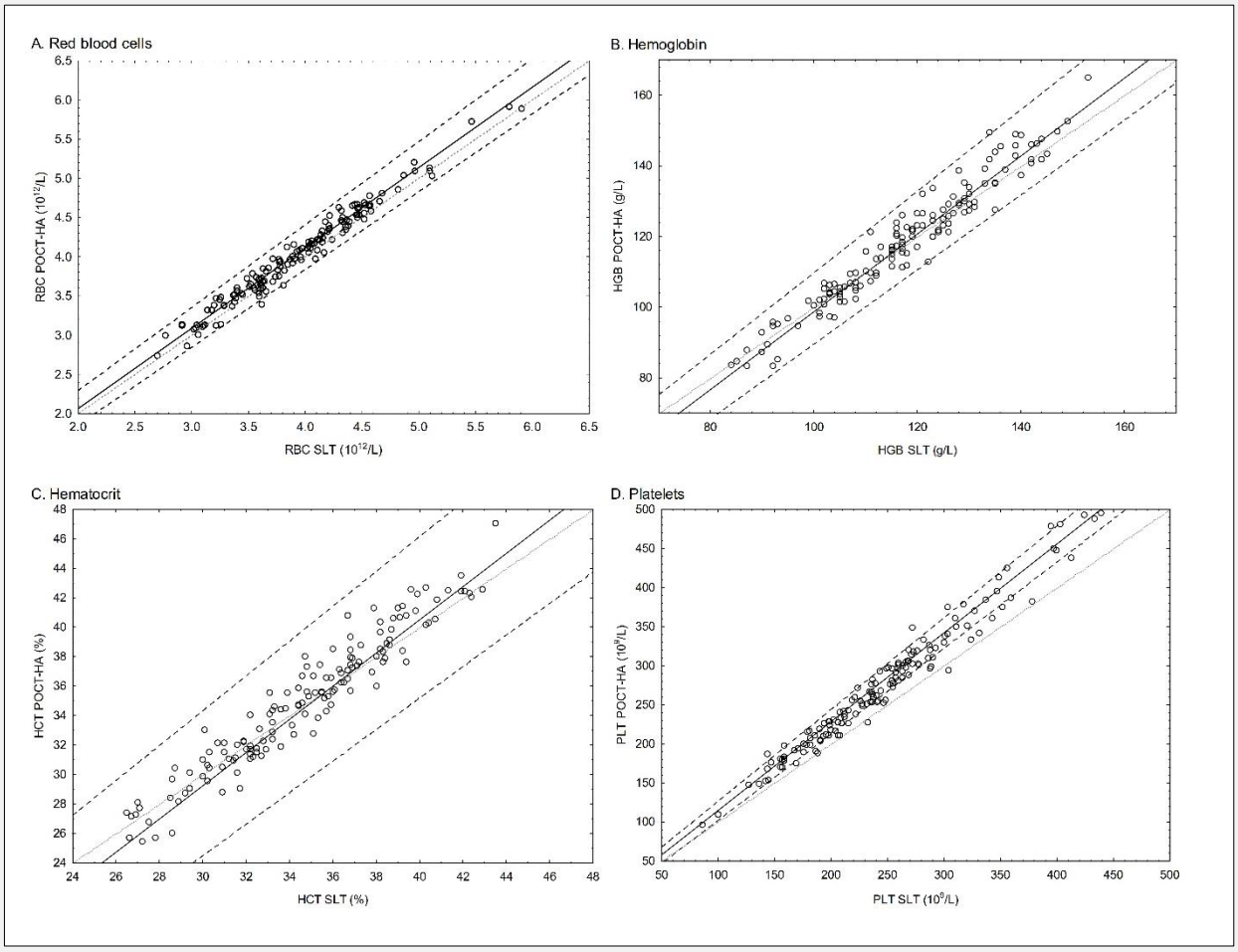

Figure 1. Scatter plots of red blood cell count (RBC, 10^{12}/L), hemoglobin (HGB, g/L), hematocrit (HCT, %), and platelet count (PLT, 10^9/L) readings from the two analyzers.

The solid lines show the Passing-Bablok regression line with 95% confidence intervals. Grey line is the line of identity where x = y. POCT HA - point-of-care hematology analyzer, SLT - standard laboratory testing.

DISCUSSION

This study shows that blood count performed in an operation theater corresponds to measurements in a central laboratory. The RBC, HGB, HCT, and PLT results obtained with the POCT hematology analyzer and SLT correlated strongly. The difference between the analyzers were minor for RBCs but for PLT count the POCT hematology analyzer tended to overestimate the values and for analysis of HGB and HCT, the estimated agreement interval for the analyzer may in some situations be considered wide.

Results from the POCT hematology analyzer and SLT for RBCs, HGB, HCT, and PLTs showed high correlation ($r > 0.96$) for all four analytes in this cohort of patients undergoing major surgery. Previous studies in hospitalized and intensive care patients reported similar or stronger correlations [6,7].

No constant or proportional error between the results from the analyzers were seen for RBC count, which corroborate the findings in previous studies [6,7]. The POCT hematology analyzer tended to underestimate HGB and HCT at very low ranges, but overestimated them in the higher ranges which differs from previous findings [7]. For PLT count a positive proportional error was seen suggesting a degree of overestimation which may become substantial for PLT counts in the higher ranges. This is in agreement with results in an earlier study [7] but in contrast to findings in an ICU cohort [6]. Nevertheless, in total, there is a high degree of cor-

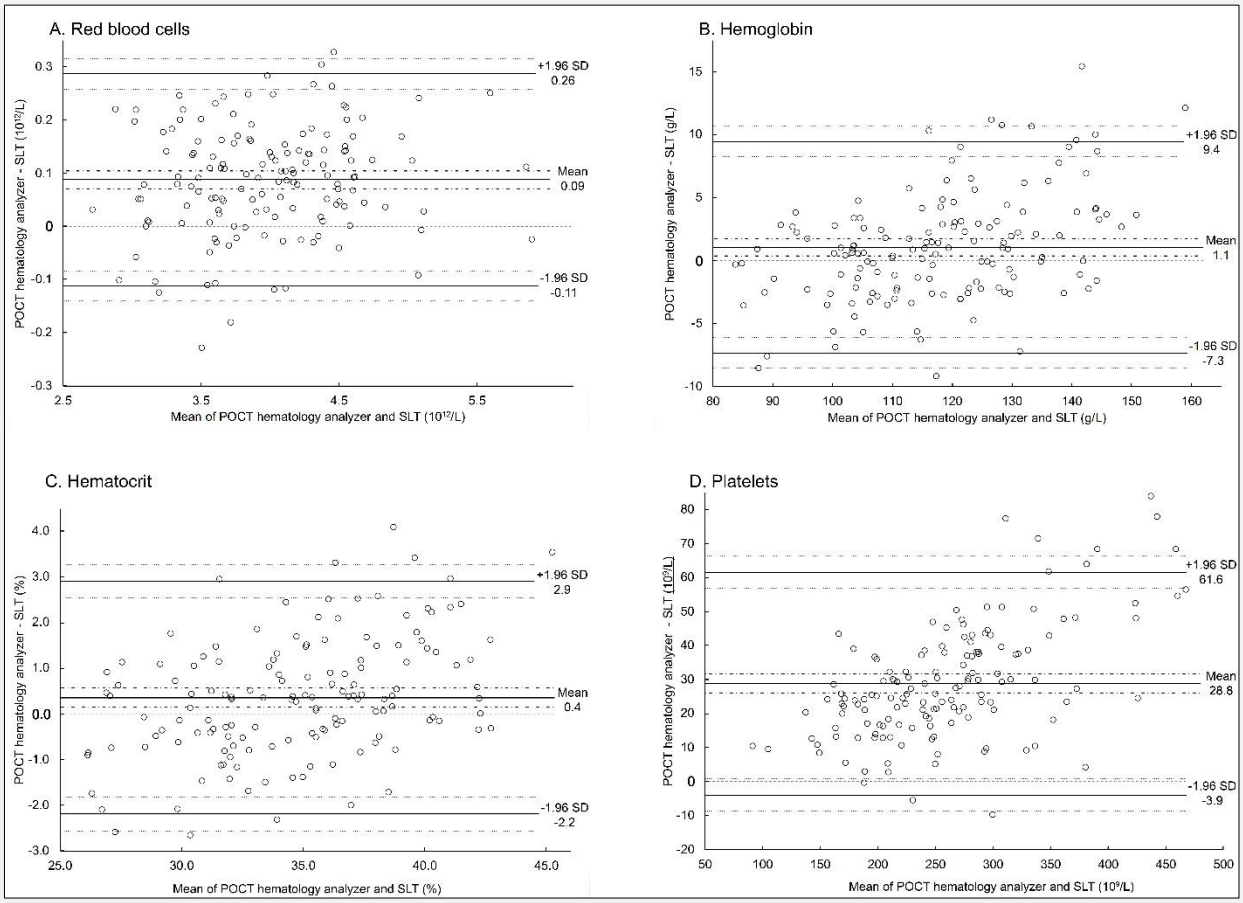

Figure 2. Bland-Altman plots for red blood cell counts (10^{12}/L), hemoglobin (g/L), hematocrit (%), and platelet counts (10^{9}/L).

The means of the two analyzers are plotted against the differences between the two analyzers. The horizontal lines show the mean difference between the two analyzers with 95% confidence intervals and limits of agreement with 95% confidence intervals.

relation between the results from the POCT hematology analyzer and SLT.

When investigating agreement between the analyzers for RBC, HGB and HCT values, the POCT hematology analyzer mean bias is low and without clinical significance. However, the wider limits of agreement for HGB and HCT could be too wide in the lower ranges that were not studied in this report. The analyzer tends to overestimate the PLT counts with a considerable degree of bias that increases as PLT values becomes higher. This could potentially lead to a risk of undertreatment in the clinical setting. However, the bias tends to decrease at mean PLT values around 250 x 10^9/L, possibly indicating clinically acceptable precision at the levels used as triggers for treatment with PLT concentrate. This remains to be studied, especially since the calculated agreement interval is wide and the obtained results do not include PLT values below 86 x 10^9/L. Interestingly, in previous reports, PLT counts were overestimated for higher values by the POCT hematology analyzer but underestimated for low values. The same study also observed a smaller mean bias (4.4 x 10^9/L) [6]. The differences in results might in part be due to different PLT levels in the lower ranges, where the aforementioned study included a higher number of samples with a mean PLT value below 100 x 10^9/L [6]. Based on the results from each analyzer and the estimated level of agreement, the differences between the instruments appears too significant for the methods to be regarded as interchangeable.

In this study and a previous study, the calculated total mean CV for control samples was below 5% for all four analytes [6]. Also, the mean CV calculated from patient blood specimens was well below 5% for all four analytes and lower than formerly reported [7]. The CV for a large cell counter, in this study the Sysmex XN-9000, has been reported to be lower for the investigated analytes both by the central laboratory at Uppsala Universi-

ty Hospital and others [8]. Thus, the POCT hematology analyzer displays a CV somewhat higher compared to a larger cell counter, but still at levels considered very good [10] and thus clinically acceptable.

In this study, the mean TAT from sampling of blood to an obtained result from the POCT hematology analyzer was much shorter compared to SLT. The operating theater was located in close proximity to the central laboratory and in an acute situation blood samples can be delivered there within a minute. Thus, it might be more appropriate to compare the response time from the POCT hematology analyzer with the time between delivery of samples to the laboratory and acquired results. Also, the POCT hematology analyzer was not used bedside in the operating room, which would have meant a reduction in TAT. Still, taking these circumstances into consideration, the TAT for the POCT hematology analyzer can be assumed to be substantially shorter compared to SLT. This is of importance since the goal of transfusion therapy is to maintain the oxygen binding capacity of the blood and maintain coagulation. Surgical bleeding treated with crystalloids leads to decreasing HGB, RBC, and PLT levels that can be monitored by POCT hematology analyzer with fast TAT. This reduction in TAT would offer a great advantage in the management of patients with severe hemorrhage, requiring administration of both packed RBCs and PLT concentrate, and it may also contribute to an improved utilization of the limited resources in the blood bank [6]. The POCT hematology analyzer was perceived as a suitable device and very easy to operate after only a brief introduction, and the quick learning curve may have been too steep in order to assess through the questionnaire used in the study. These results corroborate the ones in a previous study.[7]

Strengths and limitations

This was a prospective observational study that included a large number of samples and also evaluated the analyzer in a clinical setting, where it was operated by non-expert users without former laboratory experience. Therefore, many of the conditions in this study to a high degree resembles the intended use for a POCT hematology analyzer.

This study also has limitations. The majority of analyzed blood samples were from patients with PLT counts within the normal range, and for HGB and HCT, the absolute majority of results were significantly above the transfusion trigger. This is of course a disadvantage when aiming to investigate the threshold values that are considered clinically important when managing a hemorrhaging patient. As this was a prospective study and the estimated bleeding during the surgical procedure could not have been known at the time of consent, nor are severely anemic or thrombocytopenic patients usually subject to planned major surgery, at least not before receiving adequate amounts of packed RBCs or PLT concentrate.

Clinical implications

The POCT hematology analyzer is easy to use and provides rapid results for parameters important in the perioperative management of a patient with risk of bleeding, making it well suited for use in the operating theater. Another possible application may be use in the emergency department since it also rapidly can provide a five-part differential count, which might be valuable in the management of patients with suspected neutropenic fever. Due to its simplicity and low maintenance, the analyzer could also be of value in a primary care setting, especially community health centers located in sparsely populated rural areas where the time and cost related to transports are important factors.

Future studies

To investigate the accuracy of the POCT hematology analyzer when analyzing blood samples from severely thrombocytopenic and anemic patients, future validation studies could be performed on blood samples from hematology patients in an inpatient setting. It seems appropriate to also investigate the correspondence between the analyzer and standard laboratory testing regarding differential blood count while conducting such a study.

CONCLUSION

The POCT hematology analyzer is feasible and can provide rapid results with acceptable accuracy for analysis of RBCs, HGB, HCT, and PLTs in the operating theater. Based on the test results included in this study and the PLT count in particular, the two methods cannot be regarded as interchangeable.

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Declaration of Interest:
The authors declare that they have no conflicts of interest relevant to the manuscript.

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