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Role of POC INR in the early stage of diagnosis of coagulopathy

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ABSTRACT

Background: Acute bleeding requires fast and targeted therapy. Therefore, knowledge of the patient's potential to form a clot is crucial. Point-of-care testing (POCT) provides fast and reliable information on coagulation. Structural circumstances, such as person-bound sample transport, can prolong the reporting of the results. The aim of the present study was to investigate the diagnostic quality and accuracy between POCT INR diagnostics and standard laboratory analysis (SLA) as well as the time advantage between a pneumatic tube and a personal-based transport system.

Methods: Two groups of haemorrhagic patients (EG: emergency department; OG: delivery room; each n = 12) were examined in the context of bleeding emergencies using POCT and SLA. Samples were transported via a pneumatic tube system or by a personal transport service.

Results: INR results between POCT and SLA showed a high and significant correlation (EG: $p < 0.001$; OG: $p < 0.001$). POCT results were reported significantly more quickly (EG: 1.1 vs. 39.6 min; OG: 2.0 vs. 75.0 min; $p < 0.001$) and required less time for analysis (EG: 0.3 vs. 24.0 min; OG: 0.5 vs. 45.0 min; $p < 0.001$) compared to SLA. The time for transportation with the pneumatic tube was significantly shorter (8.0 vs. 18.5 min; $p < 0.001$) than with the personal-based transport system.

Conclusion: The results of the present study suggest that POCT may be a suitable method for the emergency diagnosis and may be used as prognostic diagnostic elements in haemotherapy algorithms to initiate targeted haemotherapy at an early point in time.

1. Introduction

Haemorrhage and coagulopathy are particularly relevant complications and are often connected to injuries, surgical interventions, serious diseases, anticoagulant medication or pregnancy/delivery [1,2]. The incidence of bleeding complications varies depending on the patient population and the severity of the disease [3]; for example, the incidence of clinically relevant coagulopathy is estimated to

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be up to 25% in polytraumatized patients [4,5]. Postpartum bleeding is a common obstetric complication and is the leading cause of maternal mortality worldwide, with an incidence of 3% [6,7]. In approximately 1.8% of all cases, a massive transfusion of foreign blood products is necessary [1].

Treating bleeding complications, rapid haemostatic optimization (interventional, surgical, mechanical or medicamentous) and targeted therapy are therapeutic goals and are therefore equivalent to those of coagulopathy treatment [8]. The earlier a coagulopathy is diagnosed, the earlier a targeted therapy can be initiated.

Although viscoelastic and aggregometric methods have a wider diagnostic spectrum [9,10], the international normalized ratio (INR) value is of particular importance for the diagnosis and therapy of coagulopathy in this context. Not only is it used to confirm the diagnosis of so-called "trauma-induced coagulopathy" [11–13], but it also allows for statements about a lack of extrinsic coagulation factors or the effect of anticoagulant medication [14].

Conventional laboratory coagulation diagnostics and INR determination are usually conducted in the central laboratory of a clinic. In various studies, the duration of analysis, which is known as "bleed-to-treat" time or "turnaround time", has been quantified; accordingly, an INR analysis in Germany takes a median time of 53 min [9].

Since a shorter analysis duration can allow for an earlier diagnosis and thus faster therapy initiation, there is a fundamental need for bedside diagnostics with a short analysis duration, such as test strip-based INR measuring devices. We hypothesize that the use of point-of-care INR devices to exclude pathologic INR values in bleeding patients are appropriate and provide comparable results to standard laboratory analyses. furthermore, we hypothesize that pneumatic tube transport has a time advantage over personal bound transport. Therefore, the aim of the present study was to investigate the diagnostic quality of test strip-based INR diagnostics and to quantify the time advantage in comparison with that of the pneumatic tube and personal transport.

2. Material and methods

This prospective, monocentric study was performed at University Hospital Frankfurt, Frankfurt, Germany, from August 26, 2018 until January 28, 2019. This study was approved by the local ethical review board (No. 279/17). The present study was registered at ClinicalTrials.gov (NCT03242525) and was conducted in accordance with the Declaration of Helsinki.

2.1. Study design

Two groups of patients were included in this study. One group included haemorrhagic patients from the department of obstetrics (obstetric group = OG), with the other group comprising patients admitted to the emergency department (emergency group = EG). Written consent was obtained from all participants or their legal representatives.

2.2. Inclusion criteria: Haemorrhage worth treating, >18 years

Exclusion criteria: No written consent from patient or legal representatives, known coagulopathy, previous anticoagulant therapy, heparin-induced thrombocytopenia (type I and II), antiphospholipid syndrome.

Primary outcome measure: Difference between two INR results of one blood sample determined by point-of-care testing (POCT) and standard laboratory testing (SL), as well as time intervals between probe transport by pneumatic dispatch system (EG) or transport service (OG) and result availability.

The recorded time points were as follows: T1 = from blood sampling until POCT results were available; T2 = from taking blood samples until standard laboratory results were available; T3 = duration of analysis for POCT measurements; T4 = duration of analysis for SL measurements; and T5 = time needed for sample transportation.

All samples were marked as emergency samples using a special cap. This allowed a prioritized transport without detours and direct sample analysis in the laboratory. The distance between the emergency room, the delivery room and the central laboratory is identical.

Secondary outcome measures: blood loss prior to blood sampling [ml], administered red blood count [ml] (RBC), fresh frozen plasma [ml] (FFP), platelet count [ml] (PC), fibrinogen [g], desmopressin [μg] (DDAVP), tranexamic acid [g] (TXA), and activated recombinant FVII [mg] (rVIIa).

2.3. Blood sampling and analysis

Venous blood samples were collected via an established venous catheter (≥18 G, Vasofix Safety®, B. Braun Melsungen AG, Melsungen, Germany). From each patient, a 1.8-ml sodium citrate collection tube (S-Monovette®, Sarstedt AG & Co. KG, Nümbrecht, Germany) for SL analysis and an additional 1.0 ml blood sample for POCT analysis using a 5.0 ml syringe (Injekt® Solo, B. Braun Melsungen AG) were collected at the same time. Coagulation analysis included the determination of speed and INR.

After blood sampling, a drop of blood was applied immediately to the test stripe of the POCT device following the manufacturer's instructions (CoaguChek Pro II®; Roche Diagnostics GmbH, Mannheim, Germany). The CoaguChek Pro II® is a portable device requiring an 8-μl sample volume. It measures the international normalized ratio (INR) based on an electrochemical reaction, as described elsewhere (http://diagnostics.roche.com). All measurements were performed according to the manufacturer's recommendations.

Samples for SL analysis were sent to the central laboratory via a pneumatic dispatch system (EG) or personal-based transport (OG) for automated analysis with an ACL TOP 700 (Hemostasis testing System, Werfen GmbH, Munich, Germany) in combination with PT

Re Combiplastin 2G reagents (Werfen). The results of SL measurements were reported via an electronic system used everywhere in the hospital.

2.4. Statistical analysis

An a priori calculation of the sample size was performed. A paired *t*-test and a power of 0.8 were used for this. With a calculated sample of n = 12 patients per group, confidence intervals with a precision of approximately ±0.5 SD can be expected. The data were analysed using SigmaPlot 12 and SigmaStat 3.5 (Systat Software GmbH, Erkrath, Germany). Depending on the distribution (determined via the Kolmogorov-Smirnov test), values were expressed as the mean ± standard deviation or the median (25/75 interquartile range), as appropriate. Spearman rank correlation and Bland-Altman analyses were used to determine associations between the results of SL and POCT. To analyse differences between duration of transport and duration of analyses, Student's t-test was used. All tests were two-sided. Based on internal data on the mean differences between the reporting of POCT results and conventional analysis, a group difference of 44 min was estimated. Using a paired *t*-test, a power of 0.8, a level of significance of p = 0.05, and a confidence interval ±0.5 SD to detect significant differences between both methods of analysis, each group was estimated to have n = 12 participants.

3. Results

During this study, the data of n = 24 patients were included and analysed. The OG and EG were of identical sizes (n = 12). The demographic data of both groups are depicted in Table 1. SL INR analysis from the EG was 1.06 (IQR: 0.98/1.13). The POCT result from the same group was 1.00 (IQR: 0.90/1.00). The Kolmogorov-Smirnov test did not indicate a normal distribution of the data. Spearman's correlation coefficient was r = 0.913. The results of both methods of analysis showed a significant correlation (p < 0.001) (see Fig. 1). There was no significant difference between SL and POC analysis for EG patients.

The median SL INR from the OG was 0.96 (IQR: 0.88/1.02), while the median POCT result was 0.95 (IQR: 0.90/1.00). The Kolmogorov-Smirnov test did not indicate a normal distribution of the data. Spearman's correlation coefficient was r = 0.826. The results of both analysis methods showed a significant correlation (p < 0.001) (see Fig. 1). In the overall collective, a Spearman's correlation coefficient of r = 0.785 was found. There was no significant difference between SL and POC analysis for OG patients.

To evaluate the concordance of the two measurement methods, a Bland-Altman plot was calculated and drawn. The graphical representation of the Bland-Altman plot (see Fig. 2) shows the differences of the individual measurements (y-axis) as a function of the INR average (x-axis). The mean value of the differences (mean) was 0.082 ± 0.190. Therefore, the results from POCT measurements were 0.082 ± 0.190 lower than the results obtained from standard laboratory analysis. The limits of agreement were in the range of 0.29–0.45.

In 18 cases, the POCT results were below the results from the standard laboratory and in 6 cases above. In one particular case, the INR measured in the standard laboratory was 2.61, while POCT revealed 1.6, leading to a difference of 1.01.

Fig. 3 shows the different time points evaluated to examine the primary outcome. Table 2 depicts the time intervals measured. In both groups, the availability of POCT results was significantly faster than that of laboratory results (EG: 1.1 vs. 39.6 min; OG: 2.0 vs. 75.0 min; p < 0.001). The time required for sample analysis was significantly shorter for POCT than for laboratory measurement (EG: 0.3 vs. 24.0 min; OG: 0.5 vs. 45.0 min; p < 0.001). The time for sample transportation via pneumatic tube system was significantly shorter than that for the personal-based transport system (8 vs. 18.5 min; p < 0.001). The Shapiro-Wilk test did not show a normal distribution of the data for timeframe analysis.

3.1. Analysis of secondary outcomes

The application of haemotherapeutics, coagulation factor concentrates and estimated blood loss were documented before, during and after laboratory results were obtained. Six out of 24 patients received haemotherapeutics. Table 3 depicts medication and blood loss subdivided into the OG and EG. The estimated blood loss was between 800 ml and 1300 ml. All patients but one received tranexamic acid. Three patients were treated with prothrombin complex concentrate (PCC), two patients were given fibrinogen, and one

Table 1
Demographic data.

	Emergency group (EG)	Obstetric group(OG)	Total
Count [n]	12	12	24
Age [years]	65 ± 19	31 ± 4	48 ± 22
Sex [%]			
Male	66.6% (n = 8)	0.0% (n = 0)	33.3% (n = 8)
Female	33.3% (n = 4)	100.0% (n = 12)	66.6% (n = 16)
Height [cm]	175 ± 10	170 ± 7	173 ± 9
Bodyweight [kg]	84 ± 26	69 ± 12	76 ± 21
BMI kgm2	27 ± 6	24 ± 4	25 ± 5

Demographic data of both groups. Results are depicted as mean ± SD or percentage or count and percentage.
BMI = Body mass index.
OG = obstetric group; EG = emergency group.

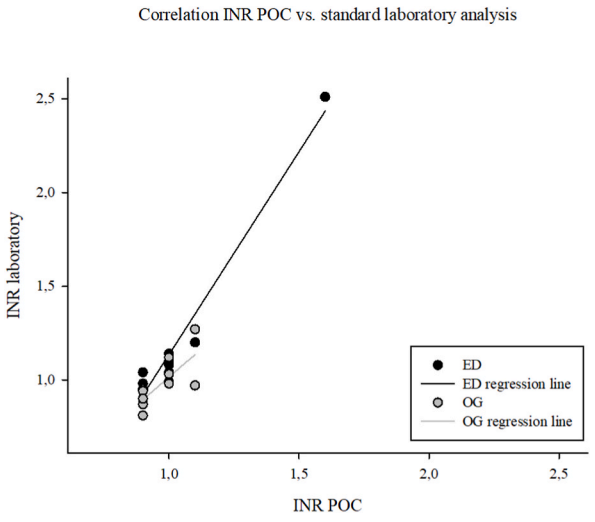

Fig. 1. INR results and correlationGroup
dependent correlation of POCT results and standard laboratory analysis of INR.
EG =
Emergency Department group
OG =
Obstetric group
X-axis: represents the results of POCT INR analysis.
Y-axis: represents the results of conventional laboratory INR analysis.

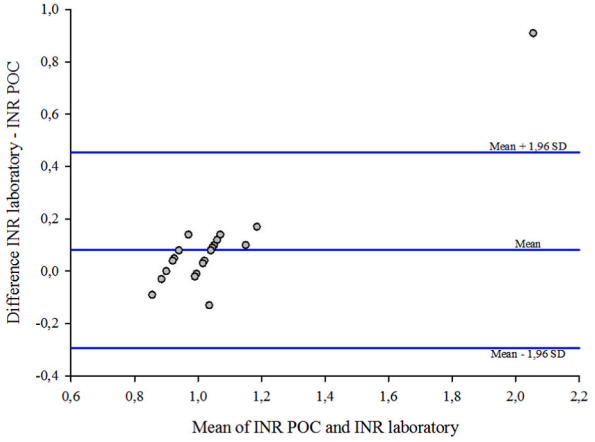

Fig. 2. Bland-Altman plot.
Analysis of differences between both measurement methods using a Bland-Altman plot.
Mean of the differences as well as the lower (mean – 1.96 SD) and upper (mean + 1.96 SD) border are drawn.
SD =
standard deviation; CI =
confidence interval; Bias =
0.082; SD =
0.191.

patient was treated with platelets.

4. Discussion

The early and targeted use of haemotherapeutic measures is of particular importance for the management of haemorrhages and coagulopathy [14–18]. POCTs have become increasingly important in this area in recent decades [19]. POC INR determination does not cover all areas of the coagulation cascade and has lower diagnostic accuracy than standard laboratory methods. While viscoelastic

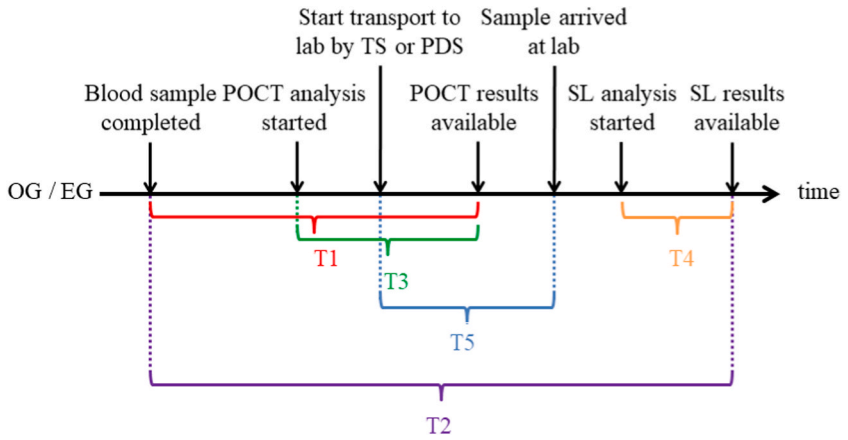

Fig. 3. Flowchart of analysed time intervals.
T1 =
Time interval between obtaining sample and POCT results are available (red)
T2 =
Time interval between obtaining sample and SL results are available (purple)
T3 =
Time needed for POCT measurements (green)
T4 =
Time needed for standard laboratory measurements (orange)
T5 =
Time needed for sample transportation (blue)
PDS =
pneumatic dispatch system; TS =
personal based transport service; lab =
laboratory; SL =
standard laboratory; POCT =
point of care testing; EG =
emergency group (emergency department); OG =
obstetric group.

Table 2
Time intervals.

Group	T1 [min.]	T2 [min.]	p-Value	T3 [min.]	T4 [min.]	p-Value	T5 [min.]	p-Value
OG	2.0 (2.0/9.0)	39.6 (34.0/56.9)	<0.001	0.5 (0.3/0.8)	45.0 (31.0/64.8)	<0.001	18.5 (14.5/33.0)	<0.001
EG	1.1 (0.4/2.4)	75.0 (58.3/108.5)	<0.001	0.3 (0.2/0.5)	24.0 (23.0/44.0)	<0.001	8.0 (3.3/10.1)	

Demographic data of both groups. Results are depicted as median (interquartile range).
T1 = Time interval between obtaining sample and POCT results are available.
T2 = Time interval between obtaining sample and SL results are available.
T3 = Time needed for POCT measurements.
T4 = Time needed for standard laboratory measurements.
T5 = Time needed for sample transportation

Table 3
Haemotherapeutics.

Group	No.	Est. bloodloss[ml]	RBC volume[ml]	PC volume [ml]	FFP [ml]	TXA[g]	Fib.[g]	PCC[I.E.]	rVII[mg]
OG	1	900	0	0	0	1	0	0	0
	2	1100	0	0	0	1	0	0	0
	3	1000	0	0	0	1	0	0	0
	4	1300	0	0	0	2	2	1500	0
EG	1	800	0	0	0	0	0	2000	0
	2	900	0	800	0	1	2	2000	0

Est. bloodloss = estimated bloodloss during observation. RBC = red blood count; PC = platelet count; FFP = fresh frozen plasma; TXA = tranexamic acid.
Fib. = fibrinogen; PCC = prothrombin complex concentrate; rVIIa = recombinant activated factor VIIa; EG = emergency group; OG = obstetric group.

or aggregometric methods allow a deeper insight into patients coagulopathic state they tie up human resources and require more time to deliver results. The significance, with regard to coagulopathies, is lower, but offers an initial indication of potential disorders, especially in emergency situations.

In therapy management, the INR is of outstanding diagnostic importance in the early phase care of haemorrhagic or coagulopathic patients. The INR may be suitable to assess the extent of trauma-induced coagulopathy [20,21].

Our results showed that POCT INR measurements were correlated with conventional laboratory values/results ($r = 0.826$), which has also been shown in studies with other patient populations [22–26]. Despite this correlation we observed a discrepancy in higher INR values. One patient presented an INR value of 1.60 in POCT measurement compared to a higher INR result in standard laboratory analysis of 2.51. Another explanation, supported by a correlation factor of $r = 0.826$, is a discrepancy between both methods in higher INR ranges. Nevertheless, it is a method to exclude trauma-induced coagulopathy (TIC) if normal results are detected. We demonstrated a good correlation for normative results between POC INR and standard laboratory. The causes of TIC are sometimes manifold and cannot be conclusively clarified by POC INR measurement. Further testing procedures are required. Nevertheless, the POC INR measurement can be seen as a clue that leads to further investigation in case of abnormal results.

In a review by Christensen et al. the POCT measurement method was declared accurate and reliable after the analysis of 22 studies [27]. Mitra et al. compared the INR values determined by POCT or conventional laboratory diagnostics in 72 acute traumatic and coagulopathic patients. A specificity of 88.2% and a sensitivity of 63.1% for POCT measurements were found compared to conventional laboratory analysis [28]. The authors compared their results with those of other studies and found that in the majority of these studies, no or only partially coagulopathic patients were included. In contrast to this study, they concluded that the INR values of actual coagulopathic patients measured by the POCT method were significantly different from laboratory results and therefore should not be used for therapy-relevant decisions in an acute situation. We could show that laboratory and POCT analyses were correlated in the acute setting in our cohort.

The POCT method for measuring the INR leads to a rapid assessment of a subarea of haemostasis and could therefore lead to faster therapeutic decisions in haemorrhagic patients. Investigating the time difference between the completion of blood collection and the availability of results of both procedures was another subject of the present study. Our results show a clear time advantage of the POCT method compared to conventional laboratory analysis. The two groups in the present study were selected with regard to the infrastructural conditions of the different hospital sections. Blood samples from the EG were sent directly via a pneumatic tube system, while the blood samples from the OG were sent to the central laboratory by a person-bound transport service. With a median time of 8 (IQR: 3.25/10.1) minutes, the pneumatic tube system was superior to the transport service (median time of 18.5 (IQR: 14.5/33) minutes). The entire process up to the POCT or conventional result provision took 1 (IQR: 0.4/2.4) or 39.6 (IQR: 34/56.9) minutes, respectively, in the EG and 2 (IQR: 2/9) and 75 (IQR: 58.3/108.5) minutes, respectively, in the OG. The clear time disadvantage of conventional coagulation analysis could also be demonstrated in other studies. Toulon et al. found a delay of 88 min (time span 29–235 min) compared to the POCT method [17]. Other studies found a time difference of 30 min [29], 53 min [30] or more than 1 h [31]. Reasons for differing durations could include transport times, processing times, the triage of blood samples in the laboratory (e.g., life-threatening, cito, routine), the amount of blood samples to be processed and the staffing of the respective laboratory. There is currently no evidence-based recommendation regarding the definition of an optimal or maximum time to provide results. A subgroup analysis of the American PROPPR study showed that a 15-min reduction in delay until the correction of a possible coagulation disorder or therapy of bleeding could achieve a reduction in mortality [32]. The “bleed-to-treat time” could be sufficiently reduced by POCT diagnostics [17,31,33,34]. A meta-analysis by Afshari et al. showed that the transfusion rate or the substitution rate of coagulation factor concentrates could be reduced by using viscoelastic POCT diagnostics [35].

Table 3 shows the substituted haemotherapeutic agents. The fact that the quantity of applied haemotherapy products in the total cohort is very small suggests that the study cohort we examined was haemorrhagic but not coagulopathic. For this reason, the use of blood products or coagulation factor concentrates was rare and heterogeneously distributed in the overall collective.

4.1. Limitations

The main methodological limitations are the cohort size and the restriction to two patient collectives. Cohort size was based on a case number analysis carried out in advance and the specifications of our local ethical committee. The limitation to two collectives should lead to a homogenization of the collective with regard to the causes of bleeding on the one hand and to two comparable groups of equal size with regard to the transport routes (pneumatic tube vs. personal transport) on the other hand. The low variance of results across groups and the comparable difference between the results of the methods examined indicate that the group sizes were sufficient. Another methodological limitation of this study is the lack of investigation of an association between INR values and clinical endpoints, such as blood loss or the administration of allogenic blood products Furthermore, POCT results differ in higher INR results compared to standard laboratory analysis limiting the validity. The strength of the result deviation is device-specific and varies in intensity. Viscoelastic or aggregometric methods allow a deeper insight in the patients coagulopathic state compared to a global test like INR and should be used in an ongoing treatment. To obtain a more complete picture of all patients, further studies should follow, including patients not included in this study due to exclusion criteria.

5. Conclusion

The consistent results obtained in the study suggest that strip-based test systems may be suitable methods for the emergency diagnosis of haemorrhagic patients because their measurement results are available significantly more quickly and seem to support the

use of point-of-care INR-devices to rule out pathological INR-values in bleeding patients. The test strip-based methods can be used as diagnostic elements in haemotherapy algorithms to implement fast and targeted haemotherapy that can positively impact the clinical outcomes of patients.

Author statement

Concept/design: FJR, CFW.
Data collection: FJR, CM, LJ, TL.
Data analysis/interpretation: FJR, M-LL, CM, LJ, TL, FP, KZ, CFW.
Drafting the article: FJR, MLL, CM, LJ, TL, FP, CFW.
Critical revision of article: FJR, M-LL, CM, LJ, TL, FP, KZ, CFW.
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Declaration of interest

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All other authors declare no conflicts of interests.

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Data availability

Data available upon request.

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