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Factor XIII Deficiency and Thrombocytopenia Are Frequent Modulators of Postoperative Clot Firmness in a Surgical Intensive Care Unit

Sarah von Rappard[a] Corina Hinnen[b] Roger Lussmann[c] Manuela Rechsteiner[d] Wolfgang Korte[d]

[a] Department of Anesthesiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland;
[b] Department of Anesthesiology, Intensive Care, Rescue and Pain Medicine, Kantonsspital St. Gallen, St. Gallen, Switzerland;
[c] Institute for Anesthesiology and Intensive Care, Klinik Hirslanden, Zurich, Switzerland;
[d] Center for Laboratory Medicine and Hemostasis; and Hemophilia Center, St. Gallen, Switzerland

Keywords

Postoperative bleeding · Thrombeloastometry · ICU · Clot firmness · Fibrinogen · Platelet count · FXIII · Colloids

Summary

Objective: Fibrinogen and factor XIII (FXIII) have been shown to critically influence clot firmness in the intraoperative setting and thus likely influence intraoperative bleeding. We were interested to identify potential modulators of postoperative clot firmness in a tertiary care hospital surgical intensive care unit setting, independent of their clinical course during surgery. **Methods:** 272 day-shift consecutive patients were evaluated for whole blood clot firmness evaluated by the ROTEM® EXTEM thrombelastometric assay and various potential modulators of clot firmness upon arrival at the surgical intensive care unit (SICU). **Results:** Maximum clot firmness on the SICU was found to be independently influenced by the amount of colloids given during surgery as well as by platelet count, fibrinogen concentration, and FXIII activity at the time of SICU admission. In patients with lowest clot firmness, FXIII activity was the most important independent modulator of clot firmness; in patients with the highest clot firmness, platelet count and fibrinogen concentration were the most important modulators of clot firmness. Deficiencies (i.e., results below normal range) of these modulators of clot firmness were most prevalent for FXIII (activity < 70%: 45% of cases), which was significantly more frequent than thrombocytopenia (<150 × 10^9/l: 32%) or fibrinogen deficiency (<1.5 g/l: 6%). **Conclusions:** Postoperative clot firmness as evaluated by whole blood thrombelastometry (ROTEM EXTEM assay) is independently and frequently modulated though FXIII activity and the platelet count, while fibrinogen concentration is also an independent but much less frequent modulator. Different modulators show different influences, depending on the clot firmness being present. Colloids infused during surgery also independently modulate postoperative clot firmness. Based on our data, strategies can be developed to improving postoperative care of patients with bleedings or at risk for bleeding.

Introduction

Management of perioperative hemostasis has received increased interest in the recent past. Over the last 10 years, the number of publications relating to this topic has increased by approximately 3-fold.

Intraoperative and postoperative bleeding situations entail a significant risk of morbidity [1–3] and mortality [4–7]. Despite the obvious clinical importance, diagnostic procedures to identify perioperative coagulopathy are not well standardized. Single routine laboratory assays, such as the prothrombin time (PT), the activated partial thromboplastin time (aPTT), and the platelet count have been shown to be of very limited value to identify a perioperative coagulopathy [8–11]. Also, most authors failed to detect a relevant

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Fax +49 761 4 52 07 14
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Prof. Dr. med. Wolfgang Korte
Center for Laboratory Medicine St. Gallen and Hemostasis; and
Hemophilia Center St. Gallen
Frohbergstrasse 3, 9000 St. Gallen, Switzerland
wolfgang.korte@zlmsg.ch

association between the preoperative results of such (classical) assays and clinical outcome, e.g., subsequent transfusion requirements [9, 12–19].

Our group has shown in the past that specific markers determined preoperatively can be associated with unexplained intraoperative bleeding [16]. In line, we could later demonstrate that increased preoperative fibrin monomer (FM) concentrations that are associated with increased blood loss are likely secondary to reduced cross-linking capacity due to reduced factor XIII (FXIII) availability per unit of thrombin generated [20–22]. The hypothesis that early supplementation of FXIII would benefit such patients when undergoing surgery was later confirmed in a prospective, double-blind, placebo controlled trial [23].

The above mentioned observations came from the pre- and intraoperative setting. For overall clinical outcome, however, coagulopathy in the postoperative setting is not less important, and the European Society of Anesthesiology encourages individualized patient management, including viscoelastic tests [24]. We thus were interested to research what influences early postoperative clot firmness in the SICU. We explored different variables as potential modulators of clot firmness in the postoperative setting, such as volume of crystalloids and colloids given intraoperatively, as well as American Society of Anesthesiologists (ASA) classification, age, duration of surgery, fibrinogen concentration, hemoglobin concentration, FXIII activity, platelet count, as well as pH and temperature upon admission to the surgical intensive care unit (SICU). The outcome parameter was whole blood clot firmness quantified by thrombelastometry after activation by tissue factor. This assay is sensitive to changes in clotting factors as well as platelets and can be reliably measured by modern thrombelastometry systems [25–27], based on the original description by Hartert [28]. Other assays responsive to fibrinogen mainly are less appropriate as they include platelet-inhibiting substances, preventing determination of whole blood clot firmness.

Patients and Methods

The study was registered with and approved by the Institutional Review Board. Patients were recruited consecutively when arriving after surgery in the SICU during day time shift. Blood was sampled directly after admission to the SICU in 272 patients with an existing arterial (n = 244) or central venous (n = 28) access available. Patients transferred to the SICU had had general surgery (33% of patients), neurosurgery (30%), vascular surgery (11%), orthopedic surgery (11%), ear-nose-throat surgery (6%), urological surgery (4%), and various other surgical interventions, including trauma surgery (5%). No patients with cardiothoracic or with transplant surgeries were included. Laboratory parameters determined immediately were platelet count, fibrinogen concentration, FXIII activity, PT, INR, aPTT as well as the ROTEM® EXTEM assay. All measurements were performed according to routine standard operating procedures. Non-laboratory data (e.g. amounts of fluids administered) were obtained from the anesthesiology protocols. Whole blood maximum clot firmness (MCF) was determined by quantifying the maximum amplitude of the EXTEM assay run on a ROTEM thrombelastometry device (Tem International GmbH, Munich, Germany). In brief, the assay is performed by the inserting a vertically immersed plastic pin into the blood sample. The pin than rotates slowly back and forward through an angle of 4.75 °, with the rotation range influenced by the fibrin strands developing between the pin and the wall of the test cell. Increasing adhesive forces exerted on the movement of the pin are converted and transferred to a graphical display, plotting the results over time [27, 28].

Multivariate regression analysis with clot firmness as the dependent variable were performed in the whole population as well as in patients within the lowest and the highest quartiles of clot firmness. Using a stepwise approach instead of entering all variables in the model at once retained the same variables in the final model that were found to be independent predictors of clot firmness when all variables were entered. For variables showing statistically significant associations with clot firmness in the multivariate analysis, the respective frequencies of results found outside the normal reference range were calculated. Differences between deficiency frequencies were evaluated using the chi-square test. For variables showing independent, statistically significant associations with clot firmness in the multivariate analysis, cumulative influence on clot firmness was evaluated by Kruskal-Wallis test. All calculations were performed using MedCalc 17.2 (MedCalc Software, Ostend, Belgium).

Table 1. Influence of various parameters on clot firmness in the overall study population

Independent variables	r partial	p
Age	0.05233	0.4710
ASA class	0.02046	0.7782
Length of operation	–0.01710	0.8139
Fibrinogen	0.4011	<0.0001
Hemoglobin	–0.1192	0.0997
Colloids	–0.2285	0.0014
Cristalloids	0.05251	0.4695
pH	–0.005996	0.9342
Platelets	0.5321	<0.0001
Temperature (on admission to SICU)	0.02355	0.7458
FXIII	0.2986	<0.0001

ASA = American Society of Anesthesiologists; r partial = partial regression correlation coefficient.

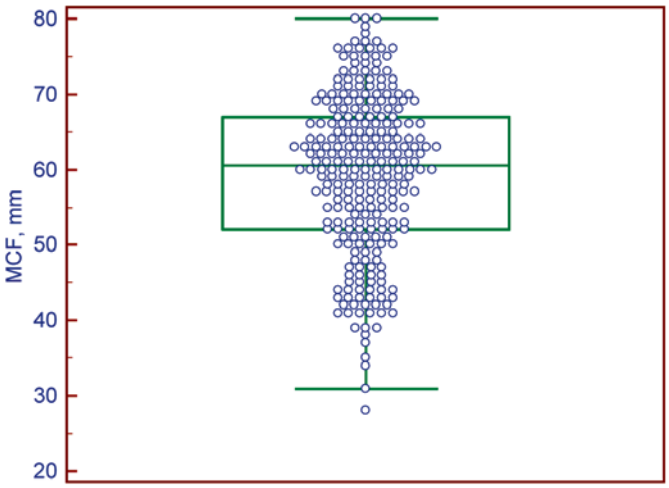

Fig. 1. Distribution of MCF results.

Results

160 male (59%) and 112 female (41%) patients were enrolled; the median age was 62 years.

Table 2. Influence of various parameters on clot firmness in the lowest quartile (<52 mm)

Independent variables	r partial	p
Age	–0.003702	0.9824
ASA class	0.09924	0.5533
Length of operation	0.007722	0.9633
Fibrinogen	–0.3663	0.0237
Hemoglobin	–0.09182	0.5835
Colloids	–0.1580	0.3434
Cristalloids	0.08155	0.6264
pH	0.04217	0.8015
Platelets	0.2829	0.0852
Temperature at SICU	–0.06913	0.6801
FXIII	0.4461	0.0050

ASA = American Society of Anesthesiologists; r partial = partial regression correlation coefficient.

Table 4. Influence of various parameters on clot firmness in the highest quartile (>67 mm)

Independent variables	r partial	p
Age	0.2397	0.1363
ASA class	–0.1101	0.4989
Lenght of operation	0.1884	0.2444
Fibrinogen	0.6031	<0.0001
Hemoglobin	–0.3302	0.0374
Colloids	–0.1783	0.2709
Cristalloids	0.008109	0.9604
pH	0.05406	0.7404
Platelets	0.6203	<0.0001
Temperature at SICU	0.2162	0.1802
FXIII	0.2100	0.1934

ASA = American Society of Anesthesiologists; r partial = partial regression correlation coefficient.

Table 3. Combination of deficiencies (FXIII, platelet count, fibrinogen) in the overall study population and the influence of combined deficiencies on MCF

	Patient frequency of combined abnormalities, %	MCF significantly different ($p < 0.05$) to
No deficiencies	44	1–3 deficiencies
Deficiencies	56	
One deficiency	33	0 and 2–3 deficiencies
Two deficiencies	20	0–1 deficiency
Three deficiencies	3	0–1 deficiency

In the overall multivariate analysis, postoperative fibrinogen concentration, postoperative FXIII activity, postoperative platelet count, and the volume of colloids given intraoperatively are significant, independent modulators of clot firmness in the SICU (table 1).

For patients in the lower quartile of clot firmness (25th percentile of the EXTEM MCF amplitude 52 mm; distribution of MCF (fig. 1)), FXIII activity was the strongest independent modulator of clot firmness, while the platelet count was not a significant modulator (but showed a strong trend). Fibrinogen concentration in this quartile showed a significant negative correlation (table 2) to clot firmness; but when three distinct outliers were removed, the correlation turned positive (see discussion); however, FXIII activity remained the strongest modulator in patients in the lower quartile of clot firmness.

In the highest quartile of clot firmness (75th percentile of the EXTEM MCF amplitude 67 mm), fibrinogen concentration and platelet count were significant and independent modulators of clot firmness while FXIII activity was not (table 4).

The frequencies of factor deficiencies or thrombocytopenia as well as their combined occurrences were evaluated (lower limits of the normal reference ranges were used as cut-off: 1.5 g/l for fibrinogen concentration, 70% for FXIII activity and 150×10^9/l for the platelet count).

When evaluating these three analytes separately, the proportion of patients with a decreased fibrinogen concentration (<1.5 g/l) was significantly smaller than the proportion of patients with thrombocytopenia ($<150 \times 10^9$/l), and thrombocytopenia was significantly less frequent than FXIII deficiency (<70%) (table 3, fig. 2). 6% of the patients had fibrinogen concentrations below 1.5 g/l (with no single measurement below 1 g/l), the median concentration being 2.53 g/l; the median platelet count was 189×10^9/l, with 32% of patients showing thrombocytopenia ($<150 \times 10^9$/l), and median FXIII activity was 72%, with 45% of the patients showing reduced FXIII activity < 70% (table 3). Thus, independently of its effect on clot firmness, FXIII deficiency is the most frequently observed deficiency in our study population (fig. 2).

Looking at combinations of deficiencies, no deficiencies of the three variables (FXIII, platelets, fibrinogen) were observed in 43% of patients, while 33%, 20% or 3% of patients showed reduction of one, two or all three mentioned variables. Figure 3 shows that MCF gradually significantly declines (table 3) as the occurrence of combined deficiencies increases.

Discussion

Postoperative bleeding is a potential life-threatening complication after major surgery of any kind [29, 30]. Thus, it is of great importance to identify potential, possibly modifiable, risk factors for postoperative bleeding. The risk and extent of peri- and postoperative bleeding depends on various factors, e.g., preexisting diseases, congenital or acquired coagulation disorders and their management as well as the surgical procedure itself [31]. If perioperative bleeding occurs, the risk of associated morbidity and mortality increases [29, 30, 32–34].

A number of studies have evaluated preoperative hemostasis assays as potential predictors of intraoperative blood loss. Most authors failed to find an association between preoperative results and subsequent blood loss or transfusion requirements [12–14].

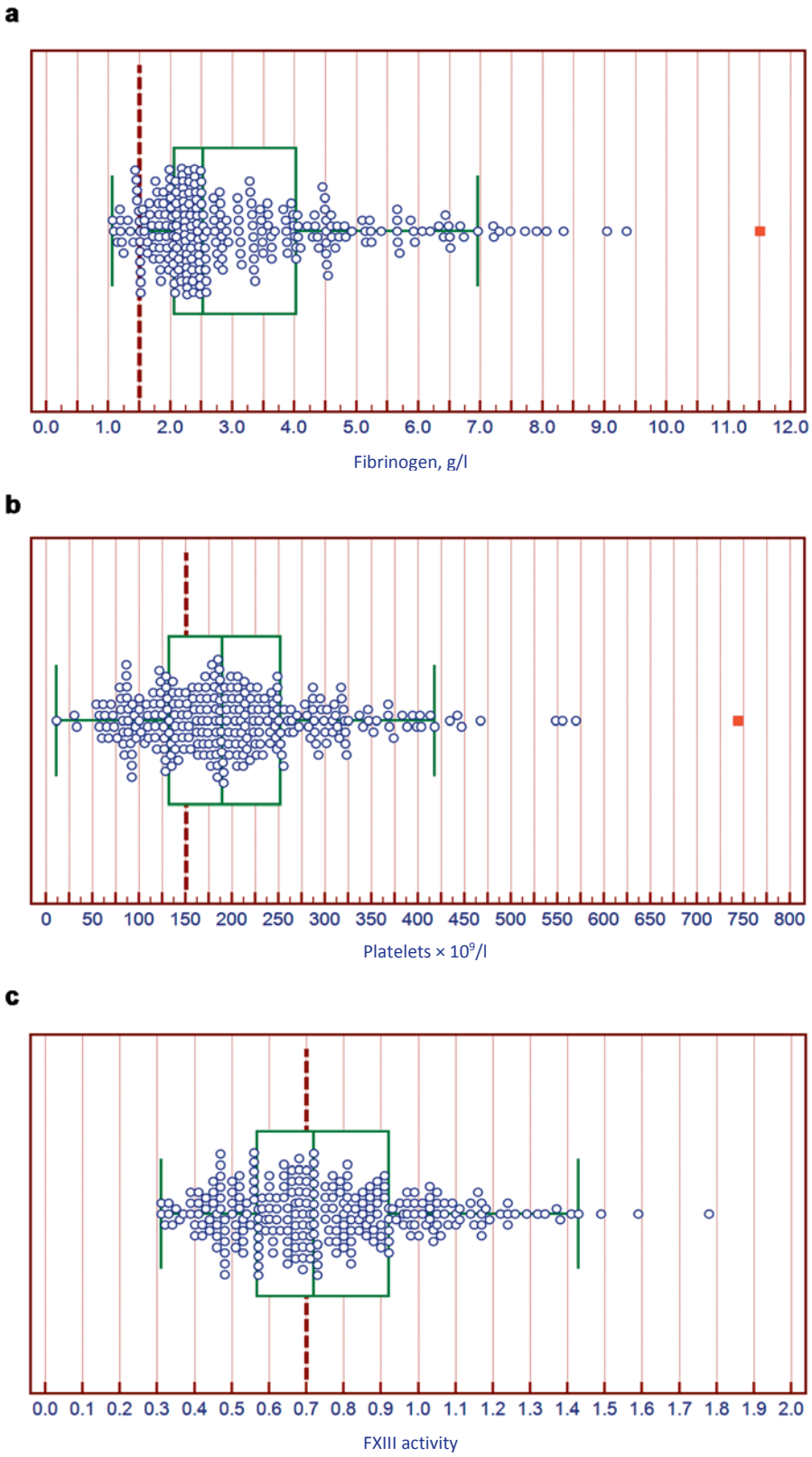

Fig. 2. Frequency of abnormalities of fibrinogen concentration, platelet count and FXIII activity. The brown dotted line represents the lower limit of reference range.

Our group has shown preoperative fibrin monomer concentrations to be associated with intraoperative bleeding, blood product support, and higher consumption of FXIII and fibrinogen [21]. We also showed that early substitution of FXIII in such high-risk patients results in intraoperative preservation of clot firmness as well as reduction of fibrinogen consumption and blood loss [23].

Given this knowledge from the intraoperative setting, we attempted to identify parameters influencing postoperative clot firmness and thus a potentially associated postoperative bleeding risk in

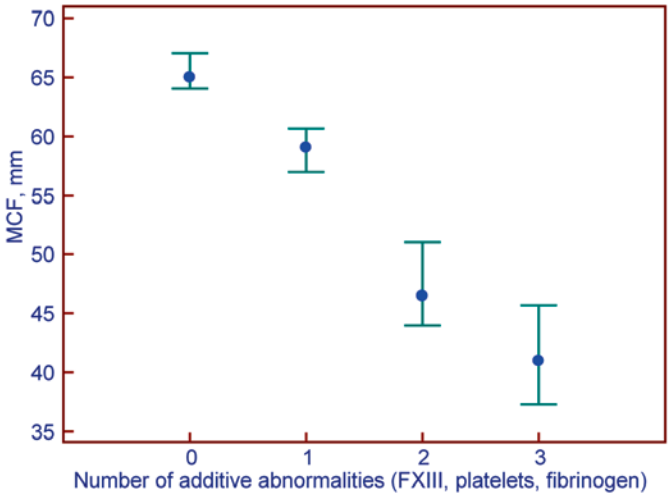

Fig. 3. Distribution of MCF depending of the number of abnormalities observed for FXIII, platelet count and fibrinogen (median with 95% CI).

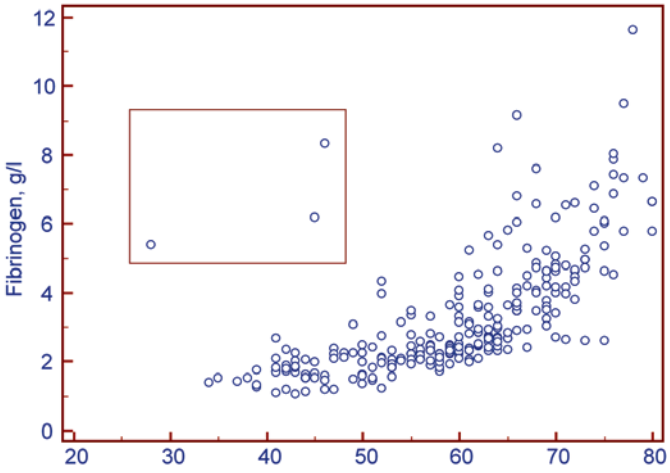

Fig. 4. The distribution of MCF compared to the fibrinogen concentration including three outliers (boxed, see text) is shown.

the SICU. Here we demonstrate that postoperative clot firmness upon arrival at the SICU is independently associated with FXIII activity, platelet count, fibrinogen concentration, and the volume of colloids infused during the preceding surgery. These parameters, being proven risk factors for decreased clot firmness (and thus a potentially increased risk for bleeding), have been shown to have significant impact on the respective outcome [35–39]. However, none of the other studies have – to our knowledge – evaluated postoperative clot firmness in a prospective and multivariate setting.

It was our goal to evaluate potential modulators of whole blood clot firmness as broadly as possible. Therefore, we choose to utilize the ROTEM EXTEM assay; this assay is activated using tissue factor in whole blood and has no inhibitors included (which is the case, for example, in the FIBTEM assay); it therefore comprises the extrinsically activated pathway as well as platelet influence.

In our study, clot firmness was independently associated with FXIII, platelet count, and fibrinogen. FXIII deficiency was the most frequent abnormality observed. Thrombocytopenia was significantly less common as was decreased fibrinogen concentration, which was rare overall (fig. 2a). All of the deficiencies were likely to be acquired.

An interesting and, to the best of our knowledge, novel observation is that in patients within the lowest quartile of clot firmness, FXIII activity is the strongest independent predictor of clot firmness (while this is not the case in patients within the highest quartile of clot firmness). After exclusion of classical outliers (that turned the association negative to begin with, fig. 4), fibrinogen concentration was positively associated with clot firmness, but to a lesser extent than FXIII. Interestingly, platelet count was not a significant predictor in the lowest quartile of clot firmness (although there is a trend).

On the other hand, for patients within the highest quartile of clot firmness, fibrinogen concentration and platelet count were significant predictors of clot firmness, while FXIII activity was not. This is in line with recent studies suggesting that high clot firmness levels (specifically in thrombocytopenia) are more influenced by the fibrinogen concentration than by FXIII activity (while the highest influence is obtained when combining both) [40].

Thrombocytopenia upon admission to an intensive care unit (ICU) or the development of a thrombocytopenia during an ICU stay has been shown to be associated with an adverse outcome with an increased complication rate and decreased patient survival [41–43]. Interestingly – and in line with our own clinical observations – it seems that the increase in platelet count rather than the improvement in platelet function after platelet transfusion increases thrombelastometric clot firmness [44].

Therefore, it seems reasonable to assume that the influence of different modulators on clot firmness, such as FXIII activity, platelet count and fibrinogen concentration, is not homogenously distributed in patients with different clot firmness levels; rather, it seems that the influence of these modulators is different at different levels of clot firmness. In other words, the importance of the various modulators of clot firmness seems to depend on the magnitude of the clot firmness present.

In addition, it has to be recognized that the influences of different modulators of clot firmness can combine – as indicated by our results that combination of various deficiencies show a more prominent impact on clot firmness compared to single deficiencies.

Another interesting observation was made in patients in the lowest quartile of clot firmness, where hemoglobin concentration was inversely associated with clot firmness in an independent and significant manner. Earlier research has shown that anemia is associated with increased (thrombelastometrically measured) clot firmness [45–47]. Thus, our finding is in line with these results – but also novel as our study demonstrates for the first time and in a multivariate analysis that the analogy, i.e., that lower clot firmness is associated with higher hemoglobin concentration, is also true.

As mentioned, FXIII showed the most prevalent changes (i.e., reduction in activity) of all modulators of clot firmness examined. There are ample clinical data indicating that decreased FXIII activity is associated with increased (surgical) bleeding [38, 48]. In such settings, FXIII deficiency might be clinically most important [38], possibly explained by the fact that a near linear decrease in clot strength is observed with decreasing FXIII levels [25]. Fibrinogen deficiency is clinically important if present [49]; and a decreasing fibrinogen concentration seems to be one of the earliest indicators of dilution and consumption [50–53]. However, fibrinogen deficiency was rare in this study. Thus, more epidemiological and comparative data on acquired fibrinogen deficiency – determined not only with viscoelastic testing but also with direct enzymatic and immunological assays in parallel – are therefore needed. Albeit that Yang et al. [54] and Gielen et al. [55] demonstrated the presence of a perpetual relationship between postoperative plasma fibrinogen level and the postoperative rate of bleeding, infusion of fibrinogen concentrate or cryoprecipitate did not reduce bleeding in these studies. As FXIII circulates in complex with fibrinogen (parts of it with high-affinity binding [56]) one might speculate that decreased fibrinogen concentrations are also a marker for a parallel decrease in FXIII. Our results, however, strongly suggest that this is not the case, at least not in the postoperative setting. Thus, a fibrinogen 'threshold' associated with excess bleeding or clinically relevant decrease in clot firmness still remains to be identified from a clinical point of view. This is important as the 'critical level of plasma fibrinogen' for postoperative patients has recently been explored with the FIBTEM assay (ROTEM device) [57–59]. But as FIBTEM results are not only depending on fibrinogen but also on other variables such as FXIII activity [58], more research is needed to determine whether other assays evaluating the same analytes would yield similar or different results [50, 54, 55, 60].

Besides the above mentioned procoagulant effect, the importance of FXIII in modulating the fibrinolytic response is increasingly recognized [42, 43, 61–63]. It is therefore tempting to speculate that this is another reason why addition of FXIII to a treatment strategy of postoperative bleeding might improve clinical outcome.

Some caveats have to be observed when interpreting our study results. First, this is a descriptive study with a surrogate (i.e., without a clinical) endpoint. However, as this surrogate endpoint has been correlated with relevant clinical endpoints in the past [64–68] and recently [69–71], it should allow generation of solid hypotheses to lay basis for further clinical studies. Also, this is a single center study, and the results may therefore be influenced by local specifics. But other groups have similarly found that FXIII deficiency is frequent in the perioperative setting [72], suggesting that our results correspond with those observed in other centers. Lastly, the hemostatic phenotype in the postoperative setting is likely to be the result of a variety of different influences. Knowing that it is impossible to research all potential influences on a surrogate marker or a clinical outcome, we believe that our approach of a multivariate analysis without preselection of the variables to include is a solid approach for a hypothesis-generating study.

Conclusions

Our prospective observational study, performed in the SICU of a tertiary care hospital, identified several modulators of postoperative clot firmness as assessed by tissue factor-activated whole blood thrombelastometry. FXIII activity, platelet count, fibrinogen concentration, and volume of colloids given intraoperatively are significantly and independently associated with overall postoperative clot firmness. In this patient population, FXIII deficiency is the most prevalent deficiency; and, at the same time, the most relevant modulator in patients with low clot firmness. Thrombocytopenia was also a frequent finding, though less frequent than (acquired) FXIII deficiency; thrombocytopenia is independently associated with clot firmness in patients with high clot firmness. Decreased fibrinogen concentrations postoperatively are rare; therefore, it remains uncertain which fibrinogen concentration can be considered to be 'sufficient' for adequate hemostasis. Combined deficiencies had a more pronounced effect on clot firmness than singular deficiencies. Further studies evaluating various analytes seem warranted in order to resolve the various effects of fibrinogen, platelets, and FXIII on clot organization in the perioperative setting.

Our data suggest that FXIII replacement and platelet transfusions might be early options to improve clot firmness in postoperative ICU patients as FXIII deficiency and thrombocytopenia are frequent findings. However, more clinical research is necessary in order to verify that outcome was improved.

Key Messages

Various studies have evaluated the association of various parameters with intraoperative clot firmness and blood loss.

In contrast, information about relevant properties and parameters as potential modulators of postoperative clot firmness and the risk of postoperative bleeding is scarce.

Postoperative clot firmness is independently associated with FXIII (which is the most important modulator in patients with low clot firmness), fibrinogen concentration, the platelet count as well as the amount of colloids infused during surgery.

In the postoperative setting, FXIII deficiency and thrombocytopenia are very frequent while fibrinogen deficiency is rare.

Authors' Contributions

S. von Rappard evaluated the data and drafted the manuscript.

C. Hinnen and R. Lussmann collected the clinical data and supervised the ICU part of the study.

M. Rechsteiner performed the laboratory work and collected the laboratory data.

W. Korte designed and coordinated the study, co-evaluated the data and revised the manuscript.

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WK has received research support, honoraria or travel support from CSL Behring, AxonLab, Haemonetics, Novo Nordisk.

The Center for Laboratory Medicine, where WK is an employee, holds or is a co-holder of patents on the determination of an intraoperative bleeding risk and the determination of FXIII by a thrombelastometric assay.

Disclosure Statement

Nothing to declare.

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