Novel approaches in management of perioperative coagulopathy

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INTRODUCTION
The cause of perioperative bleeding is often multifactorial, and its dynamic nature (i.e., major deterioration in a matter of minutes) calls for rapid diagnosis and immediate interventions. Perioperative coagulopathy involves both procoagulant and anticoagulant proteins as well as cellular components (e.g., platelets and endothelium). Relatively long turn around time (TAT) for conventional hematological testing (>30–60 min) is adequate for managing chronic disorders, but it is crucial to have a faster TAT (<15–20 min) in perioperative, critically ill patients [1–4]. Laboratory-guided hemostatic component therapy has been shown to decrease blood component usage and overall costs of transfusion compared with unrestricted transfusion [5,6,7**]. However, the practice of hemostatic transfusion widely varies depending on locally available hemostatic components and their costs [7**,8,9], coagulation testing [point-of-care (POC) vs. central laboratory] [2,3,10], and patient demographics [11*] in addition to surgical and anesthetic techniques [12]. In cases of major bleeding, allogeneic blood and plasma components are considered to be life-saving, but a number of inherent risks is
KEY POINTS

- Hemostatic component transfusion guided by laboratory coagulation assays or viscoelastic testing (ROTEM and TEG) can lead to less blood usage, and overall cost reduction.

- Fibrinogen concentrate is a new alternative to cryoprecipitate in the treatment of congenital afibrinogenemia or hypofibrinogenemia.

- Bleeding associated with vitamin K antagonist therapy can be acutely reversed with PCC, which contains therapeutic amounts of prothrombin, FVII, FIX, FX, protein C, and protein S.

- Targeted replacements of fibrinogen, and vitamin K-dependent factors in perioperative (often dilutional) coagulopathy are feasible under thromboelastometry guidance, but additional data are needed for their efficacy and safety against conventional transfusion.

- Antifibrinolytic therapy with tranexamic acid is effective in both congenital and acquired coagulopathy, and it can be administered via topical, oral, and intravenous route.

- Associated with allogeneic blood transfusion [13–15]. The indications, hematological effects, and potential side-effects of each component should be well understood to optimize the safety and efficacy of hemostatic interventions. In this review, we present an overview of the recent advances in coagulation monitoring, and discuss clinical implications of blood components and hemotherapeutic agents.

LABORATORY-GUIDED HEMOSTATIC THERAPY

The evaluation of coagulopathy is conventionally performed using prothrombin time [(PT) or international normalized ratio; (INR)], activated partial thromboplastin time (aPTT), fibrinogen level (Clauss method), and platelet count. These tests are universally available although the reference (normal) ranges vary among different assay reagents, methods, and devices. These tests are performed in isolated plasma (PT, aPTT, and fibrinogen), or in anticoagulated whole blood (platelet count). Laboratory-based testing offers excellent quality control for the devices and assays, so that reliable test results can be reported according to laboratory practice regulations and guidelines. However, typical TAT for these tests is about 30–60 min, and it could take longer when tests are repeated to confirm abnormal results (e.g., severe hypofibrinogenemia). Some laboratories have dealt with these logistic issues by modifying the stat test procedures. Chandler et al. [3] recently demonstrated that TAT for PT and fibrinogen can be reliably shortened to 14 min (range, 6–28 min) using a rapid centrifugation (2 min), and extended calibration ranges. Although it is possible to obtain several coagulation test results in a timely manner, the complex interactions of different coagulation elements (e.g., platelets and enzymatic factors) cannot be appreciated from isolated tests (i.e., no platelets in PT/aPTT). Further, hyperfibrinolysis can be triggered in a complex coagulopathy during major trauma and surgery, but profibrinolytic tendency is not readily detected by PT/aPTT or fibrinogen level [16]. Some of these limitations of traditional laboratory testing can be overcome by the use of viscoelastic coagulation testing in whole blood.

VISCOELASTIC TESTING

Thromboelastometry (ROTEM, TEM Innovations, Munich, Germany) and thrombelastography (TEG; Haemonetics, Niles, Illinois, USA) are the currently available viscoelastic test devices. Clot formation is assessed in whole blood by measuring the tensile (viscoelastic) force development between the cup and the immersed pin (Fig. 1). The viscoelastic signal is highly dependent on endogenous thrombin generation, fibrin polymerization, and fibrin interactions with platelet glycoprotein IIb/IIIa receptors. In cases of systemic fibrinolysis, early clot degradation by plasmin can be observed [17] (Fig. 2). As recently reviewed elsewhere [17–19], both ROTEM and TEG offer similar types of tests, and yield closely related clotting measurements, but these two systems are not interchangeable because of different types of reagents and blood samples (fresh whole blood or recalcified citrated blood) (Table 1) [19–24]. Heparinase cups are specifically requested for TEG, but the reagents for EXTEM, FIBTEM, and APTEM for ROTEM contain hexadimethrine (polybrene), which neutralizes heparin. In terms of the reference ranges, it is recommended that local values are set according to the specific patient population that is, adults or children, ethnicity, and disease types [20,25,26].

The most notable advance in hemostatic management using viscoelastic testing is a fibrin-specific clot assessment. The FIBTEM assay on the ROTEM allows a rapid assessment (TAT <5–10 min) of fibrin polymerization in whole blood, and it correlates with plasma fibrinogen levels [27–30]. In combination with EXTEM, FIBTEM can delineate hypofibrinogenemia from isolated thrombocytopenia, both of which decrease the overall clot strength (Fig. 2).
Hypofibrinogenemia is assumed by the reduced $\alpha$ angle ($<52^\circ$) on kaolin-TEG assay [31]. However, the TEG result is more likely to be interpreted as thrombocytopenia even if hypofibrinogenemia is the predominant cause of reduced clot strength [24]. The functional fibrinogen assay has been recently introduced for TEG, but few clinical data are available on the cut-off value for fibrinogen replacement [23].

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Fibrinolysis is suspected when the decrease of the amplitude over 1 h is more than 15% of the maximum amplitude on TEG or ROTEM (Table 1, Fig. 2). This is confirmed by using APTEM on ROTEM because the reagent contains aprotinin, which inhibits plasmin-induced fibrinolysis in vitro [16–19]. No confirmatory test for fibrinolysis is currently available for TEG, and platelet-induced clot retraction may be misinterpreted as fibrinolysis [32].

Early diagnosis of hypofibrinolysis is important because ongoing fibrinolysis can exacerbate bleeding, and adversely affects therapeutic responses to hemostatic interventions including fibrinogen and recombinant activated factor VII (rFVIIa) [33–35]. Although preoperative fibrinolysis states may be corrected with an antifibrinolytic agent, hyperfibrinolysis by viscoelastic testing underlie the severity of traumatic injury, and it is associated with high mortality (70–88%) [36,37,38].

Fibrinogen concentrate

Cryoprecipitate has been the mainstay therapy for fibrinogen replacement in congenital and acquired fibrinogen deficiency in North America. Human plasma-derived pasteurized fibrinogen concentrate (RiaStap; CSL Behring, Marburg, Germany) has been recently approved for the treatment of congenital afibrinogenemia or hypofibrinogenemia [43]. Fibrinogen concentrate has been indicated for the treatment of perioperative bleeding in many European countries where cryoprecipitate is unavailable [7,39,40,41,42]. In contrast to cryoprecipitate and plasma, fibrinogen concentrate is stored at room temperature for 30 months [43]. In addition, it can be reconstituted at bedside, and administered regardless of the blood type [44]. The fibrinogen content in each vial of fibrinogen concentrate is standardized (900–1300 mg per vial), whereas fibrinogen content is variable in the cryoprecipitate or plasma. The efficacy of fibrinogen concentrate (1 g in 50 ml) should be equivalent or superior to cryoprecipitate (~225 mg in 15 ml) [45], and far superior to plasma (~250 mg in 100 ml) [46].
In perioperative patients, fibrinogen replacement can be guided by the FIBTEM assay \cite{7,40}. Görlinger et al. \cite{40} reported that a 25 mg/kg dose of fibrinogen in an 80-kg patient (total 2 g of fibrinogen) generally results in a 4 mm increase in FIBTEM-MCF. They have generalized this finding according to the body weight (Table 2).

Solomon et al. \cite{47} reported that FIBTEM-MCF was increased by 1 mm after the average fibrinogen dose of 7.6 mg/kg in adult cardiac surgical patients.

**FIGURE 2.** Normal EXTEM tracing is shown on the panels (a). Plasma fibrinogen level is presumably normal (>150 mg/dl), but thrombocytopenia is suspected on the panel (b). Thrombocytopenia and hypofibrinogenemia are suspected on EXTEM, and simultaneous FIBTEM on the panel (c) confirms hypofibrinogenemia. Systemic fibrinolysis is suspected on the panel (d) (ML: maximal lysis 100%), which can be confirmed by APTEM. Residual heparin or low coagulation factor levels are suspected on the panel (e), which can be confirmed by HEPTEM. Refer to Table 1 for reference ranges. Adapted with permission from \cite{17}.

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*Cardiovascular anesthesia*
The dose can be approximated by the following formula:

\[
\text{Dose} = \frac{[\text{target FIBTEM-MCF (mm)} - \text{current FIBTEM-MCF (mm)}]}{\text{Weight (kg)}} \times 140
\]

For example, if the FIBTEM-MCF were 4 mm in a 70-kg patient with clinical bleeding, and the target FIBTEM-MCF were 8 mm, the dose of fibrinogen can be calculated to be:

\[
\text{Dose} = (8 - 4) \times 70 \div 140 = 2 \text{ g}
\]

Per 1 g of fibrinogen administration, plasma fibrinogen is increased by approximately 25–28 mg/dl (median) in the adult bleeding case due to acquired hypofibrinogenemia [48,49].

In order to convert the dose of fibrinogen to the number of pooled units of cryoprecipitate, the calculated dose of fibrinogen is multiplied by a factor of 5 (assuming 1 g of fibrinogen in five pools of cryoprecipitate):

\[
\text{Pools of cryoprecipitate} = \frac{(8 - 4) \times 70 \div 140 \times 5}{10} = 10 \text{ U}
\]

It is important to realize that FIBTEM-MCF can be affected by hematocrit, but the correlation between FIBTEM-MCF and fibrinogen level tends to improve under anemic state [30]. The target values of FIBTEM-MCF have been in the range of 8–10 mm [7**,8,42], and FIBTEM-MCF of 10 mm approximates plasma fibrinogen of 200 mg/dl in post cardiopulmonary bypass (CPB) cases [30]. Clot firmness at 10 and 15 min after clotting time (CT) are designated as A_{10} and A_{15} respectively (Fig. 1), and these parameters can be used for early decision-making in severe coagulopathy [7**,40,42]. The optimal target ranges of FIBTEM-MCF (alternatively A_{10} or A_{15}) should be locally determined by considering the pertinent patient population (e.g., neonate) [8,9], the extent of vascular injury and bleeding risk (e.g., replacement of aorta) [41**], and by clinically evaluating therapeutic responses to available fibrinogen-rich components [45,47].

Fibrinogen concentrate is a plasma-derived product, but the risks of pathogen transmission, immunological, and allergic reactions are extremely low due to purification and pathogen inactivation processes [50,51]. Thromboembolic complications associated with fibrinogen concentrate are rare, but the estimated rate of thrombosis is presumably

<table>
<thead>
<tr>
<th>Dose of fibrinogen (mg/kg)</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (g) for 80-kg patient</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Δ Fibrinogen level (mg/dl)</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>200</td>
</tr>
<tr>
<td>Δ FIBTEM-MCF (mm)</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
</tr>
</tbody>
</table>

**Note:** The calculation is based on the assumption of normovolemia (blood volume of ~80 ml/kg body weight) and a hematocrit of about 30%. Actual fibrinogen recovery may vary due to volume status, extent of hemorrhage, and changes in hematocrit. No sufficient data exist for patients with a body weight less than 20 kg or more than 80 kg. MCF, maximum clot firmness.
3.48 events per $10^5$ treatment based on 1,034,389 g of the usage over 22 years [52]. The use of fibrinogen concentrate is potentially hazardous in disseminated intravascular coagulation (DIC) [5].

### PROTHROMBIN COMPLEX CONCENTRATE

In acquired bleeding conditions, fibrinogen may not be the only factor that needs to be replaced. After fibrinogen replacement, other procoagulant factors and platelet count (or function) may remain abnormal, contributing to persistent microvascular bleeding [53,54]. Testing of agonist-specific platelet aggregation requires a separate set-up [7**,11*], but thrombocytopenia per se can be assessed by EXTEM-A$_{10}$ (<40 mm) [7**], EXTEM-A$_{15}$ (<48 mm) [42], or TEG-maximum amplitude (maximum amplitude<50 mm) in the presence of normal fibrin polymerization (or fibrinogen level) [31,55]. Enzymatic defects of coagulation can be estimated by viscoelastic testing in the case of bleeding and hemodilution. EXTEM-CT (normal 42–74 s) is prolonged to more than 80 s on the ROTEM in the presence of vitamin K-dependent enzymatic deficiency. Prolonged (kaolin) reaction time (R-time>10 min) is used as a cut-off for hemostatic intervention on the TEG [31,55]. Prolonged CT and R-time have been traditionally addressed by the administration of plasma, but relatively large amounts of plasma (10–30 ml/kg) are required to correct enzymatic defects [31,56]. In a prospective randomized study of POC testing vs. central laboratory testing (control) for hemostatic management involving 100 cardiac surgical patients, Weber et al. [7**] described the use of prothrombin complex concentrate (PCC, 25 IU/kg) according to EXTEM-CT over 80 s after restoring fibrin polymerization. In the control group, plasma transfusion was allowed if INR was more than 1.4 or after 4 units of erythrocytes were transfused (if INR value was unavailable). The frequency of plasma transfusion was reduced by half (40 vs. 80% with laboratory testing; $P<0.001$), whereas the frequency of PCC infusion was similar between two groups (44 vs. 52% with laboratory testing; $P=0.433$). The overall rate of adverse events (acute renal failure, sepsis, thrombotic complications, and allergic reactions) was also reduced in the POC group (8 vs. 38%; $P<0.001$). In their study, 4-factor PCC was used in the transfusion protocol, but similar findings have been reported with the post-CPB use of 3-factor PCC [57]. The main difference between 4-factor and 3-factor PCCs concerns the amount of FVII, which is considered to be therapeutic in 4-factor PCCs (Table 3).

One 4-factor product (Kcentra; CSL Behring, Marburg, Germany) has been recently approved by the Food and Drug Administration for the urgent reversal of vitamin K antagonists (e.g., warfarin) in adult patients with acute major bleeding [58,59]. Another 4-factor PCC (Octaplex; Octapharma, Lachen, Switzerland) has been available in Canada since 2006, and this product is expected to be available in the USA pending approval from the FDA. In patients receiving vitamin K antagonists, 4-factor PCC is preferably used according to the pretreatment INR (Table 4) [59]. The half-life of FVII is relatively short (4–6 h), and vitamin K (phytonadione, 5–10 mg slow i.v.) is usually administered before PCC to prevent a rebound increase in PT/INR [58].

#### Table 3. Commercial 3-factor and 4-factor prothrombin complex concentrate products

<table>
<thead>
<tr>
<th>Product name</th>
<th>FII</th>
<th>FVII</th>
<th>FIX</th>
<th>FX</th>
<th>Protein C/S</th>
<th>Additive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bebulin</td>
<td>120</td>
<td>13</td>
<td>100</td>
<td>139</td>
<td>N.R.</td>
<td>Heparin</td>
</tr>
<tr>
<td>Profilnine</td>
<td>148</td>
<td>11</td>
<td>100</td>
<td>139</td>
<td>N.R.</td>
<td>No heparin</td>
</tr>
<tr>
<td>Kcentra (Beriplex)</td>
<td>111</td>
<td>57</td>
<td>100</td>
<td>150</td>
<td>Yes</td>
<td>Heparin, AT</td>
</tr>
<tr>
<td>Octaplex</td>
<td>98</td>
<td>66</td>
<td>100</td>
<td>96</td>
<td>Yes</td>
<td>Heparin</td>
</tr>
</tbody>
</table>

Note: Other PCC products are also available in different countries. AT, antithrombin; N.R., not reported; Protein C/S, protein C/protein S; Yes, contains therapeutic amounts. Relative contents of vitamin K-dependent factors for different PCCs. The percentage (%) activity of each factor is shown relative to FIX activity (based on the prescribing information for each product; actual factor contents may vary for each vial). PCC, prothrombin complex concentrate.

#### Table 4. Treatment for acute warfarin reversal

<table>
<thead>
<tr>
<th>INR</th>
<th>Treatment (i.v.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0–3.9</td>
<td>PCC 25 IU/kg + vit K 5–10 mg</td>
</tr>
<tr>
<td>4.0–5.9</td>
<td>PCC 35 IU/kg + vit K 5–10 mg</td>
</tr>
<tr>
<td>&gt;6.0</td>
<td>PCC 50 IU/kg + vit K 5–10 mg</td>
</tr>
</tbody>
</table>

Note: Dosing of 4-factor PCC based on the clinical trial of Kcentra (CSL Behring, Marburg, Germany) [59], and recommended dosing for other 4-factor and 3-factor PCC may be different (refer to the prescribing information for each PCC product). INR, international normalized ratio; PCC, prothrombin complex concentrate.
Thromboembolic complication is a possible risk of the administration of PCCs. The reported incidence of thrombotic complications after 4-factor PCCs is about 0.7–2% in the patients receiving vitamin K antagonists [60]. As previously mentioned, thromboelastometry-guided administration of PCC after normalizing fibrinogen level in post-cardiac surgical bleeding is effective, and it does not appear to increase thromboembolic complications [7**]. The use of PCCs in patients with DIC unless anticoagulant reserve (e.g., antithrombin) is sufficiently restored before PCC administration [5]. Most PCCs (except for Profilnine and Cofact) contain trace amounts of heparin, and they should be avoided in patients with heparin-induced thrombocytopenia [5,59].

RECENT UPDATES ON TRANEXAMIC ACID

Antifibrinolytic therapy is routinely used for blood conservation in cardiac surgery (Society of Thoracic Surgeons guideline). Aprotinin is seldom used in current practice because of the concerns for higher risk of death indicated in the Blood Conservation Using Antifibrinolytics in a Randomized Trial [61]. Although the European Medicines Agency lifted the suspension of aprotinin in February 2012, N-aminocaproic acid (EACA) and tranexamic acid are the mainstay antifibrinolytic therapy. Both EACA and tranexamic acid are lysine analogues, and are available in oral (tablet) and intravenous formulations. The numerous clinical uses of lysine analogues have been reported in the literature including bleeding treatment for congenital α2-antiplasmin deficiency [62], hemophilia [63], and menorrhagia [63] as well as perioperative blood conservation (cardiac, liver, spinal/orthopedic, postpartum hemorrhage, and trauma) [64]. Clinical effectiveness of tranexamic acid was highlighted in a recent prospective randomized, placebo-controlled trial (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2) involving 20211 trauma patients [65]. The administered dose of tranexamic acid is lower (1 g loading followed by 1 g over 8 h i.v.) in trauma than in cardiac surgical setting (typically, 2 g bolus followed by 0.5 g/h i.v.) [66]. Their study demonstrated significant reductions in all-cause mortality [14.5 vs. 16.0%; relative risk (RR) 0.91; P < 0.0035], and deaths due to bleeding (4.9 vs. 5.7%; RR 0.85; P < 0.0077) [65]. Furthermore, no increase in vascular occlusive events was associated with tranexamic acid compared with the placebo. Thromboembolic complications seem to be rare with EACA and tranexamic acid in bleeding patients, but higher thrombotic risks are expected with DIC, pre-existing thrombophilia, oral contraceptive use, and postoperative hypercoagulability [67]. After hip and knee arthroplasties in elderly patients, there are substantial risks for deep vein thrombosis and pulmonary embolism without a proper thromboprophylaxis regimen (intermittent pneumatic compression, low-dose heparin, etc.) [68]. Blood loss and the need for blood transfusion could be reduced by antifibrinolytic therapy, but there is a remaining concern for thromboembolic events. Wong et al. [69**] recently conducted a prospective randomized study comparing the topical application of tranexamic acid (1.5 or 3 g) vs. placebo in primary knee arthroplasties. One of two doses of tranexamic acid or placebo (in 100 ml physiological saline) was directly applied to the wound 5 min before closure. Both topical doses were shown to reduce postoperative bleeding by 20–25%, and 16–17% higher hemoglobin levels were maintained compared with the placebo. After topical application, mean plasma levels of tranexamic acid were 4.5 and 8.5 µg/ml (up to 120 µg/ml in cardiac surgery) [70,71] at which tranexamic acid is unlikely to exert systemic antifibrinolytic activity. This approach may be preferred in situations in which the wound is accessible, and any interference with venous thromboprophylaxis is undesirable. One precaution about this approach is that direct application of tranexamic acid to spinal cord (by accidental intrathecal injection) elicits an epileptogenic effect [72–74]. This effect is presumably triggered by competitive inhibition of glycine receptors and γ-amino butyric acid receptors by tranexamic acid [75,76].

CONCLUSION

Our understanding of perioperative coagulopathy, diagnostic tools, and therapeutic approaches has evolved in the recent years. It is pivotal to ascertain timely diagnosis and therapeutic intervention(s) for coagulopathy resulting from major surgery, trauma, and postpartum bleeding [4,17,77,78]. It is highly recommended to implement suitable laboratory tests and transfusion protocols at each institution because laboratory test guided, protocol-driven transfusion approach reduces blood component utilization, and possibly leads to improved outcomes [5,6,7**]. Perioperative coagulopathy is often multifactorial, and it can be rarely corrected with a single ‘magic bullet’. Different blood components and pharmacological agents are often combined to achieve hemostasis. However, additional multidisciplinary efforts are required to understand the optimal combinations, cost-effectiveness, and safety profiles.
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Although accessible hemostatic components and factor concentrates vary among different countries [7**,44,79]. Tranexamic acid is a universally available, effective blood conservation measure with a good safety profile [65]. More information on the indication, dosing, and safety profiles of tranexamic acid should be available from several ongoing, large-scale trials in traumatic brain injury (Clinical Randomization of an Antifibrinolytic in Significant Head Injury-3 trial; ISRCTN15088122) [80], and postpartum hemorrhage (World Maternal Antifibrinolytic Trial trial; ISRCTN76912190) [81].

Acknowledgements None.

Conflicts of interest K.A.T. has served as a consultant for Tem International (Munich, Germany), Grifols Biologicals (Barcelona, Spain), and Octapharma (Vienna, Austria), and has previously received research support from CSL Behring (Marburg, Germany); none of the companies were involved in the article preparation. S.O.B. has served as a consultant for Grifols Biologicals. K.G. received honoraria for scientific lectures from CSL Behring and Octapharma; he is the Medical Director of TEM international since July 2012.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
** of outstanding interest


Clinical efficacies of laboratory coagulation testing vs. POC thromboelastometry/impedance platelet aggreometry were prospectively compared in moderate-to-high-risk cardiac surgical patients (n = 50 for each group). Fibrinogen and FPRC were more effectively utilized in the POC group, resulting in reduced postoperative blood loss and clinical outcomes.


The authors demonstrate that clopidogrel-induced platelet inhibition can be highly variable among preoperative cardiovascular patients, and platelet function testing can be utilized to shorten the waiting time by about 50% before coronary bypass grafting surgery.


The authors confirmed the previous finding by Schoch et al. [36] that hyperfibrinolysis on thromboelastography/metry on trauma admission (2% of 1966 cases) underscores the severity of injury, and is associated with high mortality (76%).

Efficacy of antifibrinolytic therapy in this high-risk population is unknown.


Hemostatic efficacy of fibrinogen concentrate (2 g vs. placebo (n = 32) was prospectively evaluated in the patients undergoing major aortic replacement surgery. The median fibrinogen dose of 8 g resulted in higher fibrinogen levels (285 vs. 181 μg/mL, P < 0.001), and clinically significant reductions of erythrocytes, plasma, and platelet transfusions (P < 0.001). The incidence of reexploration for bleeding, and adverse events during 45-day follow-up were not statistically different between the two groups.


