

Trauma-associated hyperfibrinolysis

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Keywords

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Summary

Trauma-induced coagulopathy (TIC) has been considered for a long time as being due to depletion of coagulation factors secondary to blood loss, dilution and consumption. Dysfunction of the remaining coagulation factors due to hypothermia and acidosis is assumed to additionally contribute to TIC. Recent data suggest that hyperfibrinolysis (HF) represents an additional important confounder to the disturbed coagulation process. Severe shock and major tissue trauma are the main drivers of this HF. The incidence of HF is still speculative. According to visco-elastic testing of trauma patients upon emergency room admission, HF is present in approximately 2.5–7% of all trauma patients. However, visco-elastic tests provide information on severe forms of HF only. Occult HF seems to be much more common but diagnosis is still challenging. Results from a recent randomized, placebo-controlled trial suggest that the early treatment of trauma patients with tranexamic acid may result in a significant reduction of trauma-associated mortality.

Schlüsselwörter

Hyperfibrinolyse, Trauma, ROTEM®, TEG®, Tranexamsäure

Zusammenfassung

Bislang wurden Trauma-induzierte Gerinnungsstörungen häufig als Kombination aus Verlust und Dysfunktion von Gerinnungsfaktoren verstanden. Azidose und Hypothermie bedingen eine weitere Funktionseinschränkung der verbleibenden Gerinnungsfaktoren. Neue Daten legen nahe, dass Hyperfibrinolyse den Gerinnungsprozess zusätzlich beeinträchtigt. Als wesentliche Ursachen für profibrinolytische Prozesse werden die Kombination aus schockbedingter Hypoperfusion und substanziellem Gewebetrauma vermutet. Die wahre Inzidenz der Hyperfibrinolyse nach Trauma ist nach wie vor unklar. Anhand thromboelastometrischer/thrombelastographischer Befunde bei Aufnahme im Schockraum wird gemutmaßt, dass 2.5–7% der Schwerverletzten betroffen sind. Viskoe-lastische Testverfahren erlauben allerdings nur die Diagnose ausgeprägter HF-Formen. Okkulte Hyperfibrinolyse treten vermutlich wesentlich häufiger auf und sind nach wie vor schwierig zu detektieren. Aktuelle Daten einer großen multizentrischen, multinationalen, randomisierten Doppelbildstudie legen nahe, dass die Mortalität von Traumapatienten durch den frühen Einsatz von Tranexamsäure signifikant gesenkt werden kann.

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Trauma-assozierte Hyperfibrinolyse

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- cardiac surgery and
- vascular surgery.

Recent evidence suggests that severe trauma is also associated with an activation of profibrinolytic pathways (6, 7).

Historically, coagulopathy after trauma has been considered as secondary to depletion of a combination of critical coagulation factors due to blood loss, coagulation factor consumption and haemodilution (8). This coagulopathy is further aggravated by a dysfunction of the remaining coagulation proteases, hypothermia and acidosis (9). However, it has recently been shown that a number of trauma patients develop coagulopathy very early after the initial impact, independently of the reasons noted (10, 11).

This “endogenous” trauma-related coagulopathy is in part linked to profibrinolytic activation.

Currently, the degree to which HF contributes to coagulopathy in trauma is unclear. However, it is an issue which warrants investigation as the presence of HF in trauma has been related to poor patient outcome (12, 13).

HF following major trauma

Pathophysiology

At present, there are two major hypotheses describing how profibrinolytic pathways may be activated following major trauma.

Brohi et al.

The first hypothesis stems from Brohi and co-workers and suggests that a combination of pronounced haemorrhagic shock and tissue trauma is the principle driver of HF (14). According to this hy-

perfibrinolysis (HF) is defined as an enhanced fibrinolytic breakdown of the clot resulting in pronounced coagulopathy and sometimes fatal bleeding (1). In contrast to congenital HF, which is a rare disease, ac-

quired HF is much more common and has been observed in a variety of clinical scenarios (2–5), for example,

- liver transplantation,
- postpartum haemorrhage,

pothesis, shock and hypoperfusion result in the release of significant amounts of tissue plasminogen activator (t-PA) derived from endothelial cells. Furthermore, hypoperfusion results in expression of thrombomodulin (TM) on endothelial surfaces. TM binds thrombin and subsequently activates the protein C pathway. Activated protein C, together with its cofactor protein S, inhibits acceleration of the coagulation process by inactivating activated factor V (FVa) and activated factor VIII (FVIIIa). Moreover, high amounts of protein C lead to consumption of plasminogen activator inhibitor-1 (PAI-1), the major antagonist of t-PA. Consequently, overwhelming amounts of t-PA are available, creating a hyperfibrinolytic state (6). Thus, breakdown of the fibrin network occurs and clot stability decreases (► Fig. 1).

In addition to fibrinolysis, high amounts of plasmin also cause degradation of fibrinogen, contributing to substantial defibrination. The formation of high amounts of fibrin/fibrinogen degradation products inhibits further fibrin polymerisation, resulting in poor clot quality (1). Furthermore, high plasmin levels compromise platelet adhesion and aggregation by degradation of glycoprotein receptor 1b and IIb/IIIa (15).

Gando et al.

The second hypothesis originates from Gando and colleagues (7). These authors considered the early coagulopathy of trauma as disseminated intravascular coagulation (DIC) with a profibrinolytic phenotype, resulting in substantial consumption of coagulation factors, especially fibrinogen. In their study, trauma patients with a fibrinolytic phenotype of DIC presented with high levels of fibrinopeptide B_{β15-42} and D-dimers in the emergency room (ER), suggesting excessive fibrin formation (7). Massive tissue hypoxia also results in an increased t-PA concentration, plasmin-induced activated fibrinolysis, and high levels of plasmin-antiplasmin complexes (16).

Hyakawa et al. observed that both high amounts of t-PA and neutrophil-derived elastase contribute to excessive fibrinolysis and fibrinogenolysis, resulting in life-

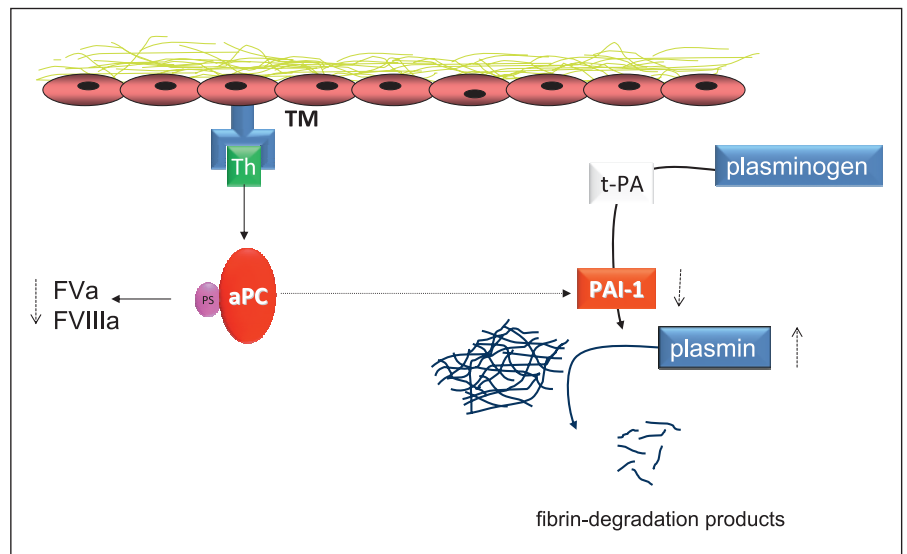


Fig. 1 Pronounced haemorrhagic shock and tissue trauma may induce a hyperfibrinolytic state according to Brohi et al. (6). Shock and hypoperfusion stimulate release of tissue plasminogen activator (t-PA) derived from endothelial cells, and hypoperfusion also results in expression of thrombomodulin (TM) on endothelial surfaces. Subsequent downstream effects inhibit acceleration of coagulation and promote degradation of fibrin, thus decreasing clot stability.

Th: thrombin; aPC: activated protein C; PS: protein S; FVa: activated factor V; FVIIIa: activated factor VIII; PAI-1: plasminogen activator inhibitor-1.

threatening haemorrhage (17). In another study by this group, non-survivors presented with lower fibrinogen levels, prolonged prothrombin times, and higher levels of fibrinogen degradation products and D-dimer, when compared with survivors (16).

Diagnosis in acute trauma care

In general, HF is a life-threatening bleeding disorder in major trauma patients which is clearly under-diagnosed and under-reported in the literature. A variety of assays have been developed to detect HF but most of these tests lack practicability and reliability, making them unsuitable for rapid diagnosis of HF (18). Specific tests determining t-PA activity, plasminogen activator inhibitor-1 (PAI-1) activity, α 2-antiplasmin (α 2-AP) or plasmin-antiplasmin-complexes are time consuming and are not routinely available in most trauma centres. Assays measuring fibrin/fibrinogen degradation products and D-dimers lack sensitivity and specificity, as these markers are elevated in most trauma patients (19). Functional tests like euglobulin lysis time (ELT)

have also been introduced to estimate the fibrinolytic capacity of plasma (20). However, ELT is also labour-intensive, time-consuming and lacks reproducibility (21).

From a practical point of view, viscoelastic tests such as thromboelastometry (ROTEM) or thrombelastography (TEG) are currently considered to be the most appropriate tools to detect HF in surgical settings as these devices allow diagnosis of pronounced HF within a short time-frame (1, 22). The principles of the devices and assays, now in routine use, have been published previously (22, 23). A good correlation between in vivo t-PA activity and maximum lysis (ML) in ROTEM-based assays has been described in human volunteers following endotoxin infusion (24). However, an endotoxin experiment in pigs did not confirm these findings (25). A substantial increase in t-PA following endotoxin infusion was not followed by increased ML in ROTEM-based assays.

It should be emphasised that viscoelastic tests detect and confirm massive HF only (► Fig. 2, ► Fig. 3), and that these tests are not sensitive enough to diagnose low-grade HF. Previous work has demonstrated that platelet-rich plasma is more resistant

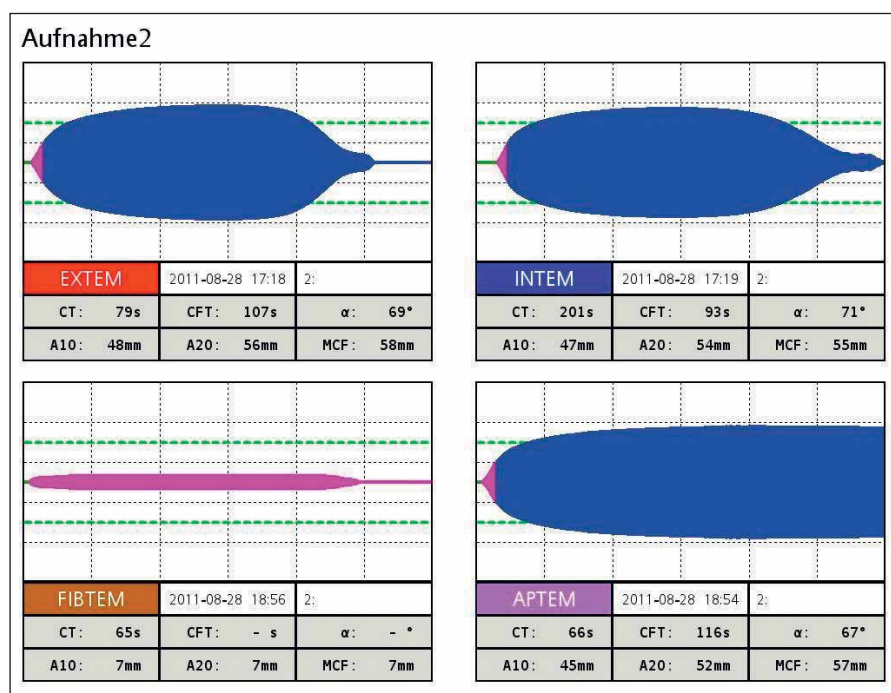


Fig. 2 Hyperfibrinolysis with a breakdown of the clot in the EXTEM, INTEM and FIBTEM test. The APTEM assays reveal stable clot formation.

to artificial lysis with low amounts of t-PA than platelet-poor plasma (26). An explanation for this finding may be that platelets are the source of 90% of the circulating PAI-1 antigen (27). Furthermore, platelets contain high amounts of α 2-AP and factor XIII, resulting in a higher resistance to clot lysis (26). Considering this fact, the FIBTEM assay, in which platelet function is inhibited by cytochalasin D, is potentially more sensitive for detecting lytic breakdown of the clot than the EXTEM assay, in which platelets are still active (► Fig. 4). Our group recently observed a significantly lower lysis index after 60 minutes (LI60) in the FIBTEM assay compared with the EXTEM assay as a result of the combination of

- pronounced shock: base deficit (BD) \geq 6 mmol/l) with
- major tissue trauma: Injury Severity Score (ISS) $>$ 45.

However, further studies are needed to confirm this finding.

Clinical data on HF

To date, there is only limited data on HF in trauma patients. The incidence of HF following massive trauma is still speculative and not substantiated by clinical data. Estimated frequencies of HF range from 3% to 20% in all trauma patients depending on inclusion criteria, magnitude of shock and the extent of tissue trauma. Fibrinolysis detected via viscoelastic testing (ROTEM/TEG) has been reported in seven small studies (12, 13, 28–32).

Levrat and colleagues matched ELT against ROTEM measurements in a cohort of 87 trauma patients (28). HF was defined by $ELT < 90$ min and was compared with the reliability of ROTEM-based assays to diagnose profibrinolytic breakdown of the clot at 30 min (LI30), as well as with thresholds of MCF in EXTEM and APTEM assays. The ELT was determined in a subgroup of just 23 out of 87 patients. However, these were the most severely injured patients. According to the ELT score, five patients (6%) presented with HF. ROTEM analyses revealed 100% specificity for HF. The patients in the HF subgroup suffered from a significantly higher median ISS of

75 (IQR 75–75) compared with the non-HF group, and had no measurable fibrinogen concentration. Unfortunately, haemodynamic variables on ER admission were not reported. All patients with HF died (28).

Carroll and co-workers assessed the incidence of HF in a prospective cohort study enrolling 161 trauma patients (29). Blood samples were drawn on arrival at the scene of trauma and within one hour after admission to the ER. HF, defined as reduction of the maximum amplitude of the clot greater than 15% after 60 min, was observed in three blood samples taken in the field by paramedics. In one of these patients, HF had been reversed before ER admission, followed by a favorable outcome. Another patient developed HF upon arrival and died. All patients that displayed HF were in shock with a systolic blood pressure $<$ 90 mmHg. The incidence of HF in this cohort was 2.5%. However, in patients that died the incidence of HF was 14%. HF detected by TEG[®] resulted in a mortality of 67% compared with 9% in the entire group (29).

In a retrospective study conducted over four years, Schöchl and co-workers identified 33 cases of HF (12). Three patterns of HF were discriminated:

- Group A – fulminant HF – exhibited a complete breakdown of the clot within 30 min.
- Group B – intermediate group – showed clot breakdown within 30–60 min.
- Group C had complete lysis after 60 min.

Notably, all patients in the fulminant group died in the ER or soon upon ICU arrival. Only one patient in the intermediate group survived. The lowest mortality rate was observed in group C. These findings suggest that fulminant HF might be a sign of irreversible processes refractory to immediate therapy with antifibrinolytic agents, even in combination with other therapeutic efforts.

Fulminant HF may therefore be considered as a potential marker of non-survivable injury and a premortem sign.

The observed mortality in all groups was significantly higher compared with the

predicted mortality according to the Trauma and Injury Severity Score (TRISS). This illustrates an independent contribution of HF to the poor outcome of major trauma patients (12).

Recently, Theusinger and colleagues reported 35 patients (13 trauma and 22 non-trauma patients) with established HF diagnosed using ROTEM assays upon ER admission (13). The 30-day mortality rate in the trauma HF group was significantly higher than in the non-trauma HF group ($p = 0.001$). Additionally, trauma patients with HF were matched to a group of trauma patients without signs of HF. In the HF group, significantly lower fibrinogen levels were recorded compared with trauma patients without HF. Furthermore, trauma patients with HF received significantly more red blood cells (RBC), platelet concentrate, tranexamic acid, and prothrombin complex concentrate than did the matched non-HF trauma group. Trauma patients with HF also had a higher mortality rate compared with trauma patients without HF ($p = 0.009$), suggesting an additional effect of HF on mortality. Interestingly, one patient with fulminant HF survived, in contrast to other reports which showed 100% mortality rate for trauma patients with fulminant HF. These findings emphasize the potential importance of early detection and treatment of this life-threatening condition (13).

In a prospective study, Tauber and colleagues presented results of ROTEM investigations in 334 major trauma patients upon admission to the ER. HF was observed in 23 patients, resulting in an incidence of 6.8%. In 14 cases HF was considered fulminant, with a complete breakdown of the clot observed within 60 minutes. A reduction of clot firmness between 16–35% was observed in another 9 patients. The mortality rate in patients with fulminant HF was 85.7%, compared with 11.1% in low-grade fibrinolysis. Patients with HF had sustained more severe injuries, as reflected by higher ISS, lower Glasgow Coma Score (GCS), lower systolic blood pressure upon ER admission, lower pH and base excess (BE), and higher lactate levels, compared with patients without HF (30).

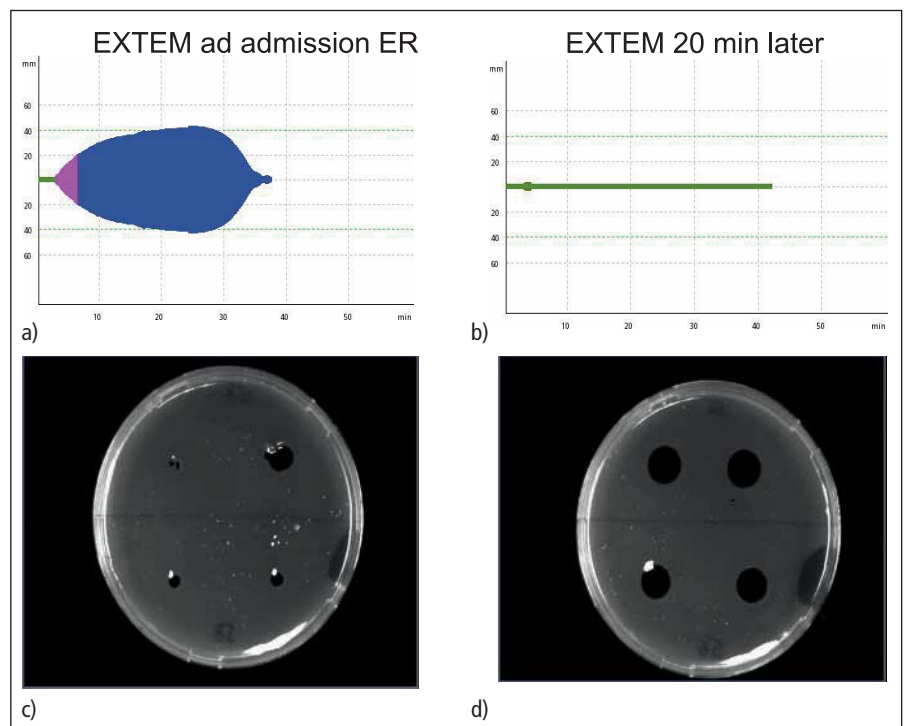


Fig. 3 HF observed by ROTEM (EXTEM)

a) on admission in the emergency room

b) After 20 min no clot formation in the ROTEM analysis could be detected.

c, d) Plasma (200 μ l) collected on admission (c) and after 20 min (d) was spiked on fibrin plates: Substantial increase in the fibrinolytic area after 20 min corresponds to increased lysis observed in EXTEM.

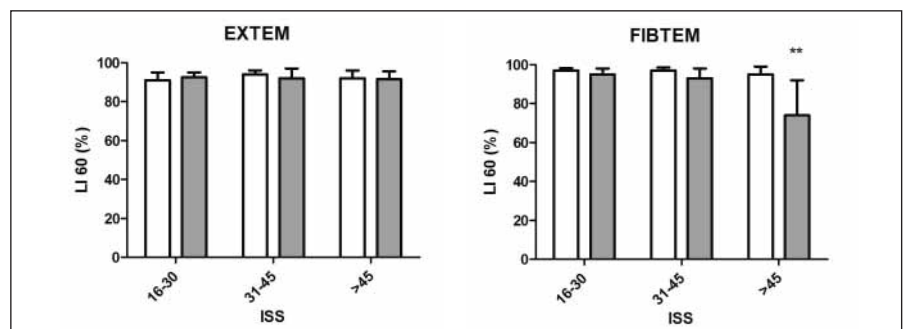


Fig. 4 No difference in LI60 min was observed in the EXTEM assay between the patients with moderate tissue trauma and moderate shock (low ISS and low BD) and severe tissue trauma with increased ISS and shock severity. For FIBTEM, patients with pronounced shock (■ $BD \geq 6$ mmol/l) and high ISS (>45) had lower LI after 60 min. This finding suggests that the FIBTEM assay is more sensitive in diagnosing low-grade fibrinolysis than is the EXTEM assay. □ $BD < 6$ mmol/l; ISS: injury severity score; LI60: lysis index after 60 min; ** $p < 0.01$.

Kashuk and co-workers reported a prospective study on 61 major trauma patients with a median ISS of 32.5 (31). TEG-based assays were performed immediately after ER admission. HF was defined as a reduction in clot maximum amplitude greater than 15% and the authors termed this

phenomenon “primary fibrinolysis” (PF). PF occurred at median 58 minutes after ER arrival. For patients receiving massive transfusion, a PF incidence of 34% was observed. This group of trauma patients also revealed a significantly higher mortality rate compared with patients without PF

($p=0.026$). A reduction in clot strength was associated with massive transfusion and poor outcome (31).

HF in traumatic brain injury

It has been suggested that patients suffering from major traumatic brain injury (TBI) are prone to develop HF (33, 34). Recently, Schöchl and colleagues reported ROTEM® findings from 88 ER patients with substantial isolated brain trauma. LI60 and ML did not differ significantly between survivors and non-survivors. However, HF was observed only in non-survivors ($n=3$; 14% of the non-survivors). The authors concluded that HF in patients with severe brain injury is infrequent but, if present, is associated with high mortality (32). Tauber and co-workers have confirmed this finding. In their study, concomitant brain injury was not associated with the occurrence of HF (30).

Therapeutic options

HF is a life-threatening bleeding disorder requiring immediate therapeutic intervention.

The first-line therapy for HF is the administration of antifibrinolytics, for example tranexamic acid (TXA).

TXA is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis by blocking the lysine binding sites of plasminogen. TXA has been shown to effectively stop even fulminant HF (35). The results from the CRASH-2 trial demonstrated improved survival in patients receiving early antifibrinolytic therapy (36). This finding supports the hypothesis that HF occurs far more frequently in trauma patients than previously assumed or diagnosed. This double-blinded, randomised, controlled study included more than 20 000 trauma patients with substantial blood loss, or at risk for significant bleeding. Patients received either 1 g of TXA over 10 minutes, followed by continuous infusion of another 1 g TXA over 8 h or placebo. The treatment group showed a significantly

higher survival rate (14.5% mortality) compared with the placebo group (16% mortality). There was no apparent increase in fatal or non-fatal vascular occlusive events (36).

Subgroup analyses revealed that TXA should be given as early as possible to trauma patients. If TXA was given > 3 h after the initial trauma the drug was less effective and potentially harmful (37). After blocking fibrinolysis with TXA, normalisation of fibrinogen plasma concentration is necessary by administration of fibrinogen concentrate, cryoprecipitate or adequate amounts of fresh frozen plasma.

Conclusion

Due to insufficient monitoring tools, hyperfibrinolysis still under-diagnosed and under-reported in trauma patients.

Recent data suggest that hyperfibrinolysis occurs predominantly in major trauma with pronounced shock and major tissue trauma.

As most patients are in shock, some may require vasopressors. High catecholamine concentrations result in severe endothelial dysfunction, massive release of t-PA from the endothelium and a profibrinolytic state (38).

HF seems to be an independent predictor of poor outcome and is associated with higher mortality.

Visco-elastic monitoring using techniques such as thromboelastometry or thrombelastography allows rapid, early diagnosis of severe profibrinolytic activation, but not low-grade HF.

Recent data suggest that immediate therapy with TXA may improve survival.

In addition, as fulminant HF degrades both fibrin and fibrinogen, therapeutic intervention to increase plasma fibrinogen concentration is warranted after treatment with antifibrinolytics.

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