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Review Article

TRANEXAMIC ACID, FIBRINOGEN CONCENTRATE, AND PROTHROMBIN COMPLEX CONCENTRATE: DATA TO SUPPORT PREHOSPITAL USE?

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ABSTRACT—Trauma-induced coagulopathy (TIC) occurs early after severe injury. TIC is associated with a substantial increase in bleeding rate, transfusion requirements, and a 4-fold higher mortality. Rapid surgical control of blood loss and early aggressive hemostatic therapy are essential steps in improving survival. Since the publication of the CRASH-2 study, early administration of tranexamic acid is considered as an integral step in trauma resuscitation protocols of severely injured patients in many trauma centers. However, the advantage of en route administration of tranexamic acid is not proven in prospective studies. Fibrinogen depletes early after severe trauma; therefore, it seems to be reasonable to maintain plasma fibrinogen as early as possible. The effect of prehospital fibrinogen concentrate administration on outcome in major trauma patients is the subject of an ongoing prospective investigation. The use of prothrombin complex concentrate is potentially helpful in patients anticoagulated with vitamin K antagonists who experience substantial trauma or traumatic brain injury. Beyond emergency reversal of vitamin K antagonists, safety data on prothrombin complex concentrate use in trauma are lacking.

KEYWORDS—Trauma-induced coagulopathy, massive blood loss, tranexamic acid, coagulation factor concentrate fibrinogen concentrate, prothrombin complex concentrate

INTRODUCTION

It has been recognized that trauma-induced coagulopathy (TIC) occurs early after severe injury. Trauma-induced coagulopathy is associated with a substantial increase in bleeding rate, transfusion requirements, and a 4-fold higher mortality (1). Exsanguination is potentially avoidable by rapid surgical control of blood loss and early aggressive hemostatic therapy (2). It is of upmost interest to achieve hemostasis as soon as possible to reduce blood loss, minimize allogeneic blood transfusion, and improve survival. Thus, it seems reasonable to start hemostatic therapy early—potentially in the prehospital setting.

RATIONALE FOR PREHOSPITAL HEMOSTATIC THERAPY

Fibrinolysis is integral in major trauma

Hyperfibrinolysis has been identified as a significant contributor of mortality in major trauma patients (3). Cotton et al. (4) investigated almost 2,000 trauma patients on emergency department admission by thrombelastography and found primary fibrinolysis in approximately 2%. However, the real incidence of (hyper)fibrinolysis is still speculative and depends mainly on the patients included in the studies and the devices or assays that were used. For example, Raza et al. (5) reported that in only 5% of patients was fibrinolysis detected by ROTEM, but 57% had evidence of moderate fibrinolysis indicated by plasmin - antiplasmin (PAP) levels elevated more than twice as normal (>1,500 μg/L) but without any fibrinolysis in viscoelastic testing.

Tranexamic acid (TXA) blocks the lysine binding sites on plasminogen. Therefore, it prevents plasminogen from binding to fibrin and inhibits the conversion of plasminogen to plasmin (6). Data from the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) study revealed that early administration of TXA reduced the risk of death in trauma patients compared with that after placebo (4.9% vs. 5.7%, respectively; $P = 0.0077$) (7). Importantly, a *post hoc* analysis found that TXA administered beyond 3 h after injury increased mortality (8). The Military Application of TXA in Trauma Emergency Resuscitation (MATTERs) study (9) investigated severely traumatized combat casualties treated with either TXA or placebo, along with standard care. Overall mortality rates were 6.5% lower in the TXA group compared with those in the placebo group ($P = 0.03$). These studies advocate the use of TXA as an integral part of coagulation management of major trauma patients who are in pronounced shock or at risk of severe bleeding. As the effect of TXA is time dependent, it is reasonable to initiate antifibrinolytic therapy as soon as possible, potentially in the field. The most recent European Trauma Bleeding Guidelines recommend using TXA en route to the hospital (grade 1B) (10). However, safety aspects are still not fully addressed.

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The MATTERs study reported that pulmonary embolism and deep vein thrombosis occurred nine and 12 times more often among patients receiving TXA compared with those who did not. (9). Safety and efficacy of prehospital TXA administration will be investigated in the PATCH study (Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage study), which intends to recruit 1,200 injured patients across Australia and New Zealand (11).

Fibrinogen: the first coagulation factor reaching critical low levels

In severe trauma-related blood loss, coagulation factors do not decrease in a uniform manner. Plasma fibrinogen (FIB) reaches critical low levels earlier than any other coagulation proteins and has been identified as the primary coagulation factor deficiency during major bleeding (12). Low FIB has been associated with increased blood loss and/or transfusion requirements in trauma (13, 14). Floccard et al. (15) collected blood samples of trauma patients during initial care in the field and found a median FIB of 1.2 g/L in patients with an Injury Severity Score higher than 40. A further significant drop of FIB was observed until emergency department admission. Recently, Schlimp et al. (16) analyzed data from 675 trauma patients on emergency department admission and observed that FIB strongly correlated with the Injury Severity Score, blood loss, dilution, and shock.

Fibrinogen supplementation—Current European Trauma Guidelines recommend treatment with fibrinogen concentrate (FC) or cryoprecipitate if significant bleeding is accompanied by thromboelastometric signs of functional fibrinogen deficit or an FIB of less than 1.5 to 2 g/L (grade 1C) (10). In combat casualties, improved outcome rates were reported in patients receiving more than 0.2 g fibrinogen for every unit of red blood cells (RBCs) as compared with lower doses of fibrinogen (17).

For logistic reasons, neither cryoprecipitate nor fresh-frozen plasma as a source of fibrinogen are useful for prehospital supplementation of FIB. Both hemostatic agents have to be thawed before transfusion, and the content of FIB is variable. Furthermore, because FFP contains fibrinogen at concentrations of approximately 2.5 g/L only, high volumes are necessary to maintain FIB in a bleeding patient (18).

In many European countries, FCs have a broad label for congenital and acquired bleeding (CSL Behring and LFB BIOMEDICAMENTS). This is in contrast to the United States, where FC is licensed for bleeding episodes in patients with congenital fibrinogen deficiency only. Fibrinogen concentrate does not require thawing or cross matching and allows rapid administration (19). High and consistent doses of fibrinogen can be delivered in small volumes and in the emergency setting of major bleeding, and delivery of 6 g in 1 to 2 min has been reported (19). An ongoing study investigates the effect of prehospital FC administration on outcome in major trauma patients (20).

Potential compensatory effect of fibrinogen on low platelet count—Severe ongoing blood loss results not only in depletion of coagulation proteins but also in a critical drop of platelets. The availability of platelet concentrate (PC) in remote areas is limited because of a short storage life (5 days). Data from animal studies revealed that high fibrinogen levels may potentially compensate for low platelet counts by increasing overall clot firmness (21). Velik-Salchner et al. (21) investigated the effect of FC transfusion on blood loss in a thrombocytopenic swine model (target platelet count, <30,000/μL). Transfusion of FC (250 mg/kg body weight) resulted in lower blood loss and improved survival rate compared with the transfusion of 2 U of PC. In situations where platelet count is low and PCs are not available, high fibrinogen supplementation might be considered as a treatment option.

Fibrinogen supplementation—Data showing that fibrinogen supplementation improves survival in trauma patients are still limited (17, 22). Stinger et al. (17) found an association between the fibrinogen:RBC ratio and survival. Patients receiving 0.48 g fibrinogen per unit of RBC had improved survival compared with patients treated with 0.1 g fibrinogen per unit of RBC. In a retrospective study, the administration of FC along with prothrombin complex concentrate (PCC) (four-factor concentrate) resulted in favorable survival rates as compared with those predicted by both the Trauma Injury Severity Score and the Revised Injury Severity Classification score (22).

THROMBIN GENERATION IS INITIALLY NOT DEFICIENT IN MAJOR TRAUMA

Diminished thrombin generation does not seem to be an essential deficit in the early stages of TIC (23, 24). Therefore, thrombin-generating substances such as PCC or activated recombinant factor VII are not advocated as first-line therapy in trauma. Prothrombin complex concentrate preparations can be formulated with either three factors (FII, FIX, FX) or four factors (FII, FVII, FIX, FX) (25). Beyond emergency reversal of vitamin K antagonists, data are limited on PCC use in trauma and prospective trials have not yet been performed (22, 26–32). Until now, only a single case report is published on the prehospital use of PCC in a patient on a vitamin K antagonist who had a major traumatic brain injury (33). One study compared a ROTEM-guided coagulation therapy based on coagulation factor concentrates (FC and PCC) with controls from the German Trauma Registry treated with FFP. Red blood cell and PC transfusions were avoided in significantly higher proportions of patients in the coagulation factor concentrate group. However, no difference in mortality could be observed (28). Joseph et al. (27, 32) reported that PCC application resulted in a rapid correction in international normalized ratio in trauma patients and a reduction in blood product transfusion. Prothrombin complex concentrates are potent procoagulants and, as such, the possibility of associated thromboembolic complications should be carefully considered. Robust safety data relating to PCC use in TIC are still lacking. Therefore, the actual European Trauma Bleeding Guidelines recommend PCC primarily for emergency reversal of vitamin K antagonists (grade 1B) (10).

CONCLUSIONS

Results from large, randomized, controlled trials revealed that administration of TXA should be an integral step in all

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trauma resuscitation protocols and initiated as soon as possible. Safety and efficacy of prehospital TXA administration will be investigated in a prospective study (PATCH). Administration of FC in cases of TIC effectively treats early and critical fibrinogen depletion. The effect of prehospital FC administration on outcome in major trauma patients is subject of an ongoing prospective investigation (FIinTIC). The use of PCC could be helpful in patients anticoagulated with vitamin K antagonists who experience substantial trauma or traumatic brain injury. Beyond emergency reversal of vitamin K antagonists, safety data on PCC use trauma are still lacking.

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