The early use of fibrinogen, prothrombin complex concentrate, and recombinant-activated factor VIIa in massive bleeding

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BACKGROUND: Coagulopathy related to massive bleeding has a multifactorial aetiology. Coagulopathy is related to shock and blood loss including consumption of clotting factors and platelets and hemodilution. Additionally hyperfibrinolysis, hypothermia, acidosis, and metabolic changes affect the coagulation system. The aim of any hemostatic therapy is to control bleeding and minimize blood loss and transfusion requirements. Transfusion of allogeneic blood products as well as the presence of coagulopathy cause increased morbidity and mortality.

STUDY DESIGN AND METHODS: This paper presents a short review on new treatment strategies of coagulopathy, related to massive blood loss.

RESULTS: Paradigms are actively changing and there is still shortage of data. However, there is increasing experience and evidence that "target controlled algorithms" using point-of-care monitoring devices and coagulation factor concentrates are more effective compared to transfusion of fresh frozen plasma, independently of the individual clinical situation.

CONCLUSION: Future treatment of coagulopathy associated with massive bleeding can be based on an individualized point-of-care guided rational use of coagulation factor concentrates such as fibrinogen, prothrombin complex concentrate, and recombinant factor VIIa. The timely and rational use of coagulation factor concentrates may be more efficacious and safer than ratio-driven use of transfusion packages of allogeneic blood products.

INTRODUCTION

Coagulopathy kills trauma patients! In patients with identical Injury Severity Scores, mortality is virtually doubled if patients suffer from coagulopathy. The main goal of any hemostatic intervention is to promptly secure hemostasis, minimize blood loss, and avoid unnecessary transfusion of allogeneic blood products.[1]

Massive bleeding treatment protocols include packages of allogeneic blood products. However, transfusion of allogeneic blood products is known to increase morbidity and mortality.[2] In a recently published study, application of massive transfusion protocol was not able to protect patients from trauma-induced coagulopathy.[3]

FRESH FROZEN PLASMA (FFP)—THE GOLDEN STANDARD?

The transfusion of FFP remains the standard therapy for the prevention and treatment of plasmatic coagulation disorders in case of massive bleeding. Compared with coagulation factor concentrates, FFP is available nearly all over the world and combines the effect of coagulation therapy and volume substitution.

Several side effects related to the administration of FFP have to be considered: It is obvious that the administration of FFP is unavoidably associated with volume expansion (FFP corresponds to an 8.5% protein solution) and that large quantities of FFP are needed (>30 mL FFP/kg) to achieve a clinically meaningful rise in coagulation factor concentrations in the presence of a deficit and ongoing loss. In a coagulopathic but normovolemic

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patient, the resulting volume overload can lead to the clinical situation of transfusion-associated cardiac overload (TACO), particularly in patients with cardiac failure, renal impairment, and liver disorders. Furthermore, a series of retrospective studies showed that the rate of severe infections and respiratory complications was distinctly increased in patients who received FFP.[4-6] This effect was also proven to be dose dependent in a prospective cohort analysis.[7] If administered in large quantities, FFP causes citrate overload (coagulopathy, decreased ejection fraction, arrhythmias, and increased neuromuscular excitability). Another concern with FFP transfusion is the risk of transfusion-related acute lung injury (TRALI), which is now one of the most common fatal side effects of blood transfusion. Because of the logistics involved, there is also a delay of about 45 minutes until requested units of FFP are obtained. With regard to the quantity or the ratio of red blood cell concentrate and/or FFP transfused, the literature contains a highly diverse array of recommendations that describe institution-related algorithms but do not refer to prospectively collected data.

COAGULATION FACTOR CONCENTRATES

Compared with FFP, coagulation factor concentrates are immediately available, contain a defined concentration of the relevant factors, can be administered without volume overload, and may be regarded safe in relation to the transmission of viral diseases and induction of TRALI and TACO. Nevertheless, large prospective randomized controlled trials are still missing to prove their efficacy.

FIBRINOGEN CONCENTRATE

In severe traumatized and massively bleeding patients, fibrinogen usually reaches critical levels at an early stage. Clinical data from gynecology,[8] neurology,[9] and cardiac surgery[10] show that the perioperative and postoperative hemorrhagic tendency is increased when fibrinogen levels are below 150-200 mg/dL. Data on the efficacy of fibrinogen concentrates in acquired fibrinogen deficiency are limited. In vitro studies and experimental investigations, as well as reports from postmarketing surveillance and retrospective data analyses,[11-17] have shown consistently that fibrinogen can increase clot firmness and improves survival of severely injured massively bleeding patients or soldiers.[18] Four small prospective clinical studies examined the use of fibrinogen concentrate (thrombelastometry [ROTEM, TEM Innovation, Munich, Germany], assisted in two studies). In all four studies, coagulation was optimized, perioperative bleeding was reduced by 32%, and transfusion requirement was significantly reduced.[19-22]

PROTHROMBIN COMPLEX CONCENTRATE (PCC)

PCC has been used for many years for the treatment of congenital coagulation disorders and is recommended for reversing oral anticoagulation. PCCs contain coagulation factors II, VII, IX, and X. There are differences among products in the concentrations of these factors and other constituents including heparin, protein C, and protein S. Reduced thrombin formation and an associated need for PCC must be expected if the activity of the procoagulants, and prothrombin especially, is <30%. This generally only occurs with blood losses >150%-200% of the estimated blood volume. Critical levels can be detected with the use of standard coagulation tests (prothrombin time < 30%) or thrombelastography and/or ROTEM.[23,24] A liberal administration practice of PCC might be associated with an increased risk for thromboembolic complications as shown in two animal trials.[25,26] Until now, the efficacy of PCC in massive bleeding has not been proven in any prospective controlled study. The author wants to caution an uncritical application of PCC in clinical practice.

RECOMBINANT-ACTIVATED FACTOR VIIa (NovoSeven)

Recombinant-activated factor VIIa (rFVIIa, NovoSeven, Novo Nordisk, Copenhagen, Denmark) is licensed as a bypassing agent for treatment of patients with hemophilia and inhibitory antibodies. In controlled randomized clinical trials including trauma,[27,28] surgery, garointestinal bleeding, etc., rFVIIa failed to improve outcome. However, througout the past decade, rFVIIa has been successfully used off label in numerous cases of trauma- and surgery-related bleeding.[29-31] Patients with intracerebral hematoma following a traumatic craniocerebral injury showed a statistically nonsignificant trend toward reduced posttraumatic hematoma increase after administration of rFVIIa.[32] To achieve succesful effect from rFVIIa, the product should be administered as early as possible, i.e., at a time when the patient's own hemostasis is not yet severely compromised.[33] Existing hypofibrinogenemia and thrombocytopenia should, as far as possible, be corrected before administration, as thrombin formation alone is not enough to produce a stable hemostatic plug. Hypothermia and acidosis decrease the efficacy of rFVIIa and should likewise be optimized if possible; acidosis in particular should be avoided. If the pH is <7.2, therefore, buffer therapy should be administered. If hyperfibrinolysis is present or the accompanying clinical circumstances suggest this (e.g., postpartum bleeding, after weaning from cardiopulmonary bypass pump, or after administration of protamine), the patient should be treated with antifibrinolytics and fibrinogen before rFVIIa is used.[34]

FUTURE PERSPECTIVES

Besides application of tourniquets, local hemostatic dressings, and administration of systemic antifibrinolytics, future treatment of trauma-induced coagulopathy can be based on an individualized point-of-care guided rational use of coagulation factor concentrates such as fibrinogen concentrate. The "timely and targeted" administration of coagulation factor concentrates might be more effective than ratio-driven use of transfusion packages of allogeneic blood products.[35,36]

Nienaber and colleagues compared the datasets from severely injured and bleeding patients from the German Trauma Data Registry and the Innsbruck Trauma Databank (Austria) in a matched pair analysis. The German patients received FFP without coagulation factor concentrates, while the patients from Innsbruck received solely coagulation factor concentrates (fibrinogen and/or PCCs) guided by thrombelastometry without transfusion of any FFP. The patients from Innsbruck had received substantially less red blood cells as compared with the German patients ($p < 0.005$). The frequency for multiorgan failure was significantly lower within the group that had received exclusively coagulation factor concentrates ($p = 0.015$).[24] The same results were found in a retrospective analysis comparing retrospective data from the Salzburg Trauma Center, Austria with data from the German Trauma Register. A thrombelastometry-guided coagulation management with the use of clotting factor concentrates depending on the individual needs resulted in a decreased rate of allogeneic transfusion.[23,37]

In summary, massive transfusion protocols are unlikely to be suitable for all kinds of bleeding. Nevertheless, prospective randomized controlled trials are necessary to prove this hypothesis and to confirm the currently available data. Right now, one prospective randomized controlled double blinded study investigates the efficacy of early administration of fibrinogen concentrate in severe traumatized patients on the scene, while another prospective randomized controlled trial compares the use of FFP with coagulation factor concentrates in severly injured patients in the emergency room (for further information: http://www.clotwork.at).

CONFLICT OF INTEREST

None.

REFERENCES

1. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127-30.
2. Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM, Napolitano LM. Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. J Trauma 2003;54:898-905; discussion 905-7.
3. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost 2012;10:1342-51.
4. Dara SI, Rana R, Afessa B, Moore SB, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Crit Care Med 2005;33:2667-71.
5. Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, Hubmayr RD, Gajic O. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 2007;131:1308-14.
6. Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med 2008;36:1114-8.
7. Watson G, Sperry J, Rosengart M, Minei J, Harbrecht BG, Moore E, Cuschieri J, Maier R, Billiar T, Peitzman A; Inflammation and Host Response to Injury Investigators. Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma 2009;67:221-7.
8. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, Sibony O, Mahieu-Caputo D, Hurtaud-Roux MF, Huisse MG, Denninger MH, de Prost D, PPH Study Group. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007;5:266-73.
9. Gerlach R, Tolle F, Raabe A, Zimmermann M, Siegemund A, Seifert V. Increased risk for postoperative hemorrhage after intracranial surgery in patients with decreased factor XIII activity: implications of a prospective study. Stroke 2002;33:1618-23.
10. Blome M, Isgro F, Kiessling AH, Skuras J, Haubelt H, Hellstern P, Saggau W. Relationship between factor XIII activity, fibrinogen, haemostasis screening tests and postoperative bleeding in cardiopulmonary bypass surgery. Thromb Haemost 2005;93:1101-7.
11. Fries D, Innerhofer P, Reif C, Streif W, Klingler A, Schobersberger W, Velik-Salchner C, Friesenecker B. The effect of fibrinogen substitution on reversal of dilutional coagulopathy: an in vitro model. Anesth Analg 2006;102:347-51.
12. Fries D, Krismer A, Klingler A, Streif W, Klima G, Wenzel V, Haas T, Innerhofer P. Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. Br J Anaesth 2005;95:172-7.
13. Fenger-Eriksen C, Anker-Moller E, Heslop J, Ingerslev J, Sorensen B. Thrombelastographic whole blood clot formation after ex vivo addition of plasma substitutes: improvements of the induced coagulopathy with fibrinogen concentrate. Br J Anaesth 2005;94:324-9.
14. Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sorensen B. Fibrinogen concentrate substitu-

tion therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth 2008; 101:769-73.
15. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion 2010;50:2571-6.
16. Fenger-Eriksen C, Tonnesen E, Ingerslev J, Sorensen B. Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. J Thromb Haemost 2009;7:1099-105.
17. Gollop ND, Chilcott J, Benton A, Rayment R, Jones J, Collins PW. National audit of the use of fibrinogen concentrate to correct hypofibrinogenaemia. Transfus Med 2012; 22:350-5.
18. Stinger HK, Spinella PC, Perkins JG, Grathwohl KW, Salinas J, Martini WZ, Hess JR, Dubick MA, Simon CD, Beekley AC, Wolf SE, Wade CE, Holcomb JB. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma 2008;64(2 Suppl):S79-85; discussion S85.
19. Fenger-Eriksen C, Jensen TM, Kristensen BS, Jensen KM, Tonnesen E, Ingerslev J, Sørensen B. Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J Thromb Haemost 2009;7: 795-802.
20. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 2009;102:137-44.
21. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, Tanaka KA. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth 2009;102:785-92.
22. Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, Pichlmaier M. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg 2009;138:694-702.
23. Schochl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010;14:R55.
24. Nienaber U, Innerhofer P, Westermann I, Schochl H, Attal R, Breitkopf R, Maegele M. The impact of fresh frozen plasma vs. coagulation factor concentrates on morbidity and mortality in trauma-associated haemorrhage and massive transfusion. Injury [Multicenter Study] 2011;42: 697-701.
25. Mitterlechner T, Innerhofer P, Streif W, Lödl M, Danninger T, Klima G, Hansson K, Fries D. Prothrombin complex concentrate and recombinant prothrombin alone or in combination with recombinant F X and FVIIa in dilutional coagulopathy: a porcine model. J Thromb Haemost 2011;9: 729-37.
26. Grottke O, Braunschweig T, Spronk H, Esch S, Rieg A, van Oerle R, ten Cate H, Fitzner C, Tolba R, Rossaint R. Increasing concentrations of prothrombin complex concentrate induce disseminated intravascular coagulation in a pig model of coagulopathy with blunt liver injury. Blood 2011; 118:1943-51.
27. Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y; NovoSeven Trauma Study Group. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma 2005;59:8-15; discussion 15-8.
28. Dutton R, Parr M, Tortella B, Champion H, Bernard G, Boffard K, Bouillon B, Croce MA, Dimsits J, Holcomb JB, Leppaniemi A, Vincent JL, Hauser CJ; CONTROL Study Group. Recombinant activated factor VII safety in trauma patients: results from the CONTROL trial. J Trauma 2011; 71:12-9.
29. Hsia CC, Chin-Yee IH, McAlister VC. Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized control trials. Ann Surg 2008; 248:61-8.
30. Lynn M, Jeroukhimov I, Klein Y, Martinowitz U. Updates in the management of severe coagulopathy in trauma patients. Intensive Care Med 2002;28 Suppl 2:S241-7.
31. Martinowitz U, Kenet G, Segal E, Luboshitz J, Lubetsky A, Ingerslev J, Lynn M. Recombinant activated factor VII for adjunctive hemorrhage control in trauma. J Trauma 2001; 51:431-8; discussion 8-9.
32. Narayan RK, Maas AI, Marshall LF, Servadei F, Skolnick BE, Tillinger MN. Recombinant factor VIIa in traumatic intracerebral hemorrhage: results of a dose-escalation clinical trial. Neurosurgery 2008;62:776-86; discussion 86-8.
33. Perkins JG, Schreiber MA, Wade CE, Holcomb JB. Early versus late recombinant factor VIIa in combat trauma patients requiring massive transfusion. J Trauma 2007;62: 1095-9; discussion 1099-101.
34. Martinowitz U, Michaelson M. Guidelines for the use of recombinant activated factor VII (rFVIIa) in uncontrolled bleeding: a report by the Israeli Multidisciplinary rFVIIa Task Force. J Thromb Haemost 2005;3:640-8.
35. Fries D, Innerhofer P, Perger P, Gutl M, Heil S, Hofmann N, Kneifel W, Neuner L, Pernerstorfer T, Pfanner G, Schöchl H, Ziegler B, Kölblinger C, Kozek-Langenecker S. [Coagulation management in trauma-related massive

bleeding.—Recommendations of the Task Force for Coagulation (AGPG) of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine (OGARI)]. Anasthesiol Intensivmed Notfallmed Schmerzther 2010;45:552-61.

36. Gorlinger K, Fries D, Dirkmann D, Weber CF, Hanke AA, Schochl H. Reduction of fresh frozen plasma requirements by perioperative point-of-care coagulation management with early calculated goal-directed therapy. Transfus Med Hemother 2012;39:104-13.
37. Schöchl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steits B, Arndt C, Hanke A, Voelckel W, Solomon C. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care 2011;15:R83.