Efectividad del concentrado de fibrinógeno en pacientes traumáticos con hemorragia crítica

Celia González Guerrero

42   EUR J CLIN PHARM
VOL 18 NUM 1 JAN-FEB 2016
     Abrogoua DP, Doffou E, Akroman M, Soro L, Amonkou A

13. Bond CA, Raehl CL, Franke T. Clinical pharmacy services, hospital pharmacy staffing, andmedication errors in United States Hospitals. Pharmacother 2002; 22: 134-47.

14. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics 1987; 79: 718-22.

15. Bjornson DC, Hiner WO, Potyk RP, Nelson BA, Lombardo FA, Morton TA, et al. Effect of pharmacists on health care outcomes in hospitalized patients. Am J Hosp Pharm 1993; 50: 1875-84.

16. McMullin ST, Hennefent DJ, Ritchie DJ, Huey WY, Lonergan TP, Schaiff RA, et al. A prospective, randomized trial to assess the cost impact of pharmacists initiated interventions. Arch Intern Med 1999; 159: 2306-9.

17. Bond CA, Raehl CL, Franke T. Clinical pharmacy services, pharmacy staffing, and the total cost of care in United States hospitals. Pharmacother 2000; 20: 609-21.

18. Pitterle ME, Bond CA, Raehl CL, Franke T. Hospital and pharmacy characteristics associated with mortality rates in United States hospitals. Pharmacother 1994; 14: 620-30.

19. Bond CA, Raehl CL. Clinical pharmacy services, pharmacy staffing, and hospital mortality rates. Pharmacother 2007; 27: 481-93.

20. MacLaren R, Devlin JW, Martin SJ, Dasta JF, Rudis MI, Bond CA. Critical care pharmacy services in United States hospitals. Ann Pharmacother 2006; 40: 612-8.

21. Jiang SP, Zhu ZY, Wu XL, Lu XY, Zhang XG, Wu BH. Effectiveness of pharmacist dosing adjustment for critically ill patients receiving continuous renal replacement therapy: a comparative study. Ther Clin Risk Manag 2014; 10: 405-12.

22. Ernst AA, Weiss SJ, Sullivan A, Sarangarm D, Rankin S, Fees M, et al. On-site pharmacists in the ED improvemedicalerrors. Am J Emerg Med 2012; 30: 717-25.

23. Klopotowska JE, Kuiper R, van Kan HJ, de Pont AC, Dijkgraaf MG, Lie-A-Huen L, et al. On-ward participation of a hospital pharmacist in a Dutch intensive care unit reduces prescribing errors and related patient harm: an intervention study. Crit Care 2010; 14: R174.

24. MacLaren R, Bond CA, Martin SJ, Fike D. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. Crit Care Med 2008; 36: 3184-9.

25. Bedouch P, Charpiat B, Roubille R, Juste M, Rose FX, Escofier L, et al. Site Internet de la Société française de pharmacie clinique pour l'analyse des interventions pharmaceutiques: finalités, mode d'emploi et perspectives. J Pharm Clin 2007; 26: 40-4.

26. Dorosz Ph, Vital-Durand. D, Le Jeune C. Dorosz 2014-guide pratique des médicaments. Maloine 33ème édition. Edition Maloine.

27. Vidal 2013. Date de parution 15/02/2013. Editeur: VIDAL ISBN: 978-2-85091-203-0.

28. ANSM. Thésaurus des interactions médicamenteuses. Available at: <www.ansm.sante.fr> [Consulted: 13th September 2013].

29. Raynard B, Bernard B, Bleichner G, Fagon J.Y. Prévention des hémorragies digestives hautes de stress en réanimation. Réanim Urgences 2000; 9: 555-60.

30. Chedru V, Juste M. Evaluation médicale de l'impact clinique des interventions pharmaceutiques. J Pharm Clin 1997; 16: 254-8.

31. Guignon AM, Grain F, Allenet B, Brudieu E, Barjhoux C, Bosson JL, et al. Evaluation de l'impact clinique des opinions pharmaceutiques dans un service de médecine spécialisée. J Pharm Clin 2001; 20: 118-23.

32. Bayliff CD, Einarson TR. Physician assessment of pharmacists' interventions: a method of estimating cost avoidance and determining quality assurance. Can J Hosp Pharm 1990; 43: 167-71.

33. Leape LL, Cullen DJ, Clapp MD, Burdick E, Demonaco HJ, Erickson JI, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. JAMA 1999; 282: 267-70.

34. Bedouch P, Allenet B, Labarere J, Brudieu E, Chen C, Chevrot D, et al. Diffusion des opinions pharmaceutiques dans le cadre d'une activité de pharmacie clinique en unité de soins. Thérapie 2005; 60: 115-22.

35. Brudieu E, Grain F, Guimier C, Calop J. Analyse des erreurs de prescription et de l'activité de pharmacie clinique dans une unité de soins informatisée. J Pharm Clin 1999; 18: 56-7.

36. Yapi AD, Polneau S, Kouakou SG, Kouakou L, Kacou A, Amonkou A, et al. Profil pharmaco-thérapeutique des médicaments utilisés au service de réanimation du centre hospitalier universitaire de Yopougon (Abidjan-Côte d'Ivoire). J Sci Pharm Biol 2009; 10: 31-40.

37. Gaillard K, Bohand X, Beranger C, Boulliat C, Guevel C. Evaluation of pharmaceutical interventions at Sainte-Anne militaryhospital as part of a unit dose drugdaily distribution system. J Pharm Clin 2006; 25: 39-47.

38. Grangeasse L, Fagnoni-Legat C, Chaigneau L, Medjoub M, Larosa F, Bracconolin C, et al. Computerized prescribing of standardized chemotherapy schedules: residual medication errors and pharmaceutical interventions. J Pharm Clin 2006; 25: 33-8.

39. Vandel P. Bizouard P. Effets indésirables médicamenteux: Etude épidemiologique dans un service de psychiatrie hospital universitaire. Thérapie 1995; 50: 67-72.

40. Demange C. Analyse pharmaceutique des prescriptions en unité de soins à l'aide de la fiche d'intervention de la Société française de pharmacie clinique. J Pharm Clin 2007; 26: 45-52.

41. Bedouch P, Charpiat B, Conort O, et al. Assessment of Clinical Pharmacists' Interventions in French Hospitals: Results of a Multicenter Study. Ann Pharmacother 2008; 42: 1095-103.

42. Jiang SP, Chen J, Zhang XG. Implementation of pharmacists' interventions and assessment of medication errors in an intensive care unit of a Chinese tertiary hospital. Ther Clin Risk Manag 2014; 10: 861-6.

43. Dumont-Perlade C, Lefort I, Frimat B, Carpentier I, Biet R. Non conformités de prescriptions et interventions pharmaceutiques dans le cadre d'une dispensation journalière individuelle nominative. J Pharm Clin 2002; 21: 56-63.

44. Zamparutti P, Nicolle I, Polard E, Le Duff M. Analyse de prescription: 2. Résultats obtenus dans un service de gériatrie. Pharm Hosp Fr 1997; 119: 12-6.

45. Maugin D, Josse AM, Stam B, Chapaux B. Les avis pharmaceutiques au centre Hospitalier Général de Saint-Nazaire. Pharm Hosp Fr 1995; 114: 229-32.

46. Krupicka MI, Bratton SL, Sonnenthal K, Goldstein B. Impact of a pediatric clinical pharmacist in the pediatric intensive care unit. Crit Care Med 2002; 30: 919-21.

47. Brudieu E, Grain F, Bosson JL, Bontemps H, Guimier C, Sang B, et al. Analyse pharmaceutique dans le cadre de la prescription informatisée. J Pharm Clin 1999; 18: 227-32.

48. Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother 1992; 26: 1580-4.

REVIEW

FIBRINOGEN REPLACEMENT IN TRAUMA UNCONTROLLED BLEEDING: A REVIEW OF THE LITERATURE

González Guerrero Celia, Montoro Ronsano José Bruno

ABSTRACT

There are many theoretical reasons to consider the fibrinogen replacement in the patient with Trauma-Induced Coagulopathy (TIC), but not many conclusive high-quality prospective studies have been carried out to determine its optimal efficacy and safety. The fibrinogen use is based on scarce observational data and empiric experience; while uncontrolled post-traumatic bleeding is still the leading cause of potentially preventable death among trauma patients.

This review aims to collect the data available in PubMed about the use of fibrinogen replacement in patients with TIC.

TREATMENT FOR CRITICAL BLEEDING – TRAUMA-INDUCED COAGULOPATHY – FIBRINOGEN – BLOOD DERIVATES

RESUMEN

La teoría apoya el uso del concentrado de fibrinógeno en la coagulopatía asociada al traumatismo; sin embargo, no se dispone de resultados concluyentes obtenidos de ensayos clínicos prospectivos de alta calidad para determinar qué circunstancias son óptimas para su uso y para estudiar su seguridad. A pesar de que la hemorragia crítica asociada al traumatismo es la principal causa de muerte evitable entre los pacientes traumáticos, el uso del concentrado de fibrinógeno, hasta el momento, se ha basado en datos observacionales y en experiencia empírica.

Esta revisión pretende recoger la evidencia disponible en la base de datos PubMed sobre el tratamiento de la hemorragia crítica asociada al traumatismo.

TRATAMIENTO DE LA HEMORRAGIA CRÍTICA – COAGULOPATÍA ASOCIADA AL TRAUMATISMO – FIBRINÓGENO – HEMODERIVADOS

González Guerrero C.
Montoro Ronsano JB.

Pharmacy Service. Vall d'Hebron Hospital. Barcelona. Spain.

Both authors are currently doing some research on fibrinogen, and CSL Behring has contributed economically to the research project.

INTRODUCTION

Uncontrolled post-traumatic bleeding is the leading cause of potentially preventable death among trauma patients. Excessive and uncontrolled bleeding, commonly referred to as Trauma-Induced Coagulopathy (TIC), affects a quarter of all trauma patients and it is associated with substantial injuries, increased transfusion requirements, and poor outcomes.[1-7]

Despite the limitation of a clear definition of TIC, evidence supports a role for platelet dysfunction, endothelial activation, endogenous anticoagulation, oxidative modification of proteins involved in the coagulation process, protein C activation and low fibrinogen levels. A variety of causes for fibrinogen depletion in major trauma have been identified, such as blood loss or dilution, consumption, hyperfibrinolysis, hypothermia and acidosis.[8-25]

Normal hemostasis is critically dependent on fibrinogen as a substrate for clot formation. Fibrinogen is usually the most vulnerable coagulation factor, reaching lower critical levels during the course of a severe injury. Fibrinogen is a plasma glycoprotein synthesized solely in the liver, and it plays a key role for both platelet aggregation and fibrin formation and stabilization. It has been described that low fibrinogen concentrations are associated with an increased risk of bleeding and a higher mortality.[1-7]

The plasma concentration of fibrinogen in healthy subjects ranges from 2-4.5 g/L; nevertheless, in patients with various congenital or acquired conditions, fibrinogen is markedly reduced and sometimes even undetectable with current methods of determination. The techniques for the fibrinogen measurement are also controversial.

44 **EUR J CLIN PHARM**
VOL 18 NUM 1 JAN-FEB 2016

González Guerrero C, Montoro Ronsano JB

Fibrinogen replacement in trauma uncontrolled bleeding: a review of the literature **EUR J CLIN PHARM**
VOL 18 NUM 1 JAN-FEB 2016 45

While laboratory measurement of fibrinogen, classically by Clauss, is time consuming and prone to errors at the extremes of values; point-of-care tests consisting on functional measurements of fibrin polymerization (for example, thromboelastometry or thromboelastography) are increasingly being used.

The fibrinogen level at which treatment is required is open to debate. According to some recent reviews,[1,2] there is no universally accepted critical fibrinogen concentration in trauma patients, although the key role of fibrinogen in the control of life-threatening hemorrhages is widely accepted. British [29, 31, 32] and American [30] guidelines are the most restrictive, recommending the fibrinogen replacement if the concentration falls below 1 g/L. Meanwhile, the current European Trauma Guidelines,[26, 27] the ones from the European Society of Anaesthesiology[28] and the Canadian National Advisory Committee on Blood and Blood Products[33] recommend a plasma fibrinogen concentration in trauma patients not lower than 1.5-2 g/L. However, these recommendations are not definitive as they are based on scarce observational data.

LITERATURE REVIEW

Ozier et Hunt[34] back in 2010 wrote an article in order to deplore the indiscriminate use of fibrinogen supplementation. On one hand, they claimed that there are many reasons to consider fibrinogen supplementation in the patient with a coagulopathy caused by excessive bleeding as fibrinogen is the first haemostatic factor to decrease critically. They even took into consideration the fibrinogen prophylactic administration to prevent the postpartum and cardiac surgery hemorrhage, based on the pre-procedure critical fibrinogen plasma concentrations which are considered to be independent predictors of excessive bleeding. On the other hand, unfortunately, no randomized or blinded study has been carried out to support this prophylactic administration. In this article, the authors claim that large, well-conducted clinical trials are required to measure clinically significant outcomes such as transfusion requirements. Moreover, the possible negative effects of using fibrinogen (for example, increased rate of postoperative venous thromboembolism) should be studied in order to obtain a full-risk-benefit analysis.

Hayakawa et associates[35] have recently published a retrospective observational study which aimed to elucidate the time-dependent changes in platelet count and coagulation variables, including fibrinogen levels, during the early phase of severe trauma. Eighty trauma patients were enrolled; and 35 were diagnosed with Disseminated Intravascular Coagulation (DIC). The results of laboratory tests on arrival at the emergency department show some remarkably elevated Fibrin/fibrinogen Degradation Products (FDP) and D-dimer levels, whereas fibrinogen levels are consequently lower among these patients. It demonstrates that fibrinogen reaches its critical level before the other routine coagulation parameters in trauma patients. A clear consumption of platelets and coagulation factors is also observed during the early phase of DIC.

Deras et al.[36] retrospectively reviewed 663 trauma patients. At admission, 105 patients (20%) had severe coagulopathy, 215 (33%) had moderate coagulopathy, and 313 (47%) had no coagulopathy. The number of patients with a fibrinogen level of less than 1.5 g/L at admission increased with the severity of the coagulopathy: 87% (severe), 29% (moderate) and 1% (without coagulopathy), p <0.001. It concluded that the severity of coagulopathy at admission was an independent risk factor of the occurrence of fibrinogen deficit within the first 24 hours (p <0.001).

Several studies have established a relationship between plasma fibrinogen levels and survival in acquired fibrinogen deficiency. Kenji et al.[37] retrospectively reviewed a cohort of massively transfused trauma patients. They carried out a 12-year study period in which 758 patients required a massive transfusion. Only in 260 patients a fibrinogen level was obtained on admission. 92 patients had normal admission fibrinogen levels (≥180 mg/dL); 114 had abnormal admission fibrinogen levels (≥101 to ≤180 mg/dL), and 54 patients had critical levels (≤100 mg/dL). Patients with a critical fibrinogen level had significantly higher mortality at 24 hours compared with patients with abnormal (31.5% vs 5.3%; p <0.001) and normal fibrinogen levels (31.5% vs 4.3%; p <0.001). A critical fibrinogen level was the most important independent predictor of mortality (p = 0.012).

Rourke et al.[38] carried out a prospective cohort study that included 517 patients. Fibrinogen levels were determined with the Clauss method, and global hemostatic competence was assessed with thromboelastometry. Low admission fibrinogen level was independently associated with injury severity score (p <0.01), shock (p <0.001), and prehospital fluid volume (p <0.001). It is to highlight that fibrinogen level was an independent predictor of mortality at 24 hours and 28 days (p <0.001).

A unique analysis among injured soldiers on army combat was performed by Stinger and associates.[39] It supports the importance of fibrinogen replacement in the early phase of the trauma-induced coagulopathy. The typical amount of fibrinogen within each blood product was used to calculate a fibrinogen-to-Red Blood Cells (RBC) ratio. Patients were divided depending on the transfusions received and such ratio: low (<0.2 g fibrinogen/RBC Unit) or high (≥0.2 g fibrinogen/RBC Unit). A strong association between increasing fibrinogen-to-RBC ratios and survival was observed.

Schöchl et al.[40] investigated administration of fibrinogen concentrate as first-line of haemostatic therapy in trauma patients with severe bleeding; additional PCC therapy was administered if recent coumarin intake or prolonged clotting time. These treatments were guided by thromboelastometry which is claimed to be a huge improvement in the coagulopathy diagnose as it precisely tells which coagulation factors are missing. The observed mortality (24.4%) was compared with the theoretical mortality calculated by the TRISS (Trauma Injury Severity Score) mortality (33.7%, p = 0.032) and the RISC (Revised Injury Severity Classification) score of 28.7% (p >0.05). As

TABLE 1.

Authors	Contents	Fibrinogen measurement method	Conclusion
Ozier et Hunt[34]	Reasons to consider fibrinogen supplementation in the patient with a coagulopathy.		Well-conducted clinical trials are required to obtain a full-risk-benefit analysis.
Hayakawa et associates[35]	Observational retrospective study. 80 trauma patients enrolled to elucidate the time-dependent changes in platelet count and coagulation variables, including fibrinogen levels, during the early phase of severe trauma.	Standard laboratory tests, any available fibrinogen level value on admission was used.	Fibrinogen reaches its critical level before the other routine coagulation parameters in trauma patients. A clear consumption of platelets and coagulation factors is also observed during the early phase of DIC.
Deras et al.[36]	Observational retrospective study. 663 trauma patients included. The results of coagulation tests and plasma fibrinogen levels at admission were studied.	Plasma fibrinogen levels were measured by the Clauss method, using the same analyser.	The severity of coagulopathy at admission was an independent risk factor of the occurrence of fibrinogen deficit within the first 24 hours (p <0.001).
Kenji et al.[37]	Observational retrospective study. 758 patients required a massive transfusion. Fibrinogen levels at admission and survival were studied.	Standard laboratory tests, any available fibrinogen level value on admission was used.	A critical fibrinogen level (<100 mg/dL) was the most important independent predictor of mortality (p = 0.012).
Rourke et al.[38]	Prospective cohort study. 517 trauma patients included. The overall objective was to characterize the changes and role of fibrinogen in major trauma patients.	Fibrinogen levels determined by the Clauss method. Global haemostatic competence assessed with thromboelastometry.	Low admission fibrinogen level was independently associated with injury severity score (p <0.01), shock (p <0.001), and blood loss (p <0.001). Fibrinogen level was an independent predictor of mortality at 24 hours and 28 days (p <0.001).
Stinger and associates[39]	Observational retrospective study. 252 patients at a U.S. Army combat support hospital who received a massive transfusion were divided depending on the transfusions received and such ratio: low (<0.2 g fibrinogen/RBC Unit) or high (≥0.2 g fibrinogen/RBC Unit).	Fibrinogen levels on hospital admission were not available.	A strong association between increasing fibrinogen-to-RBC ratios and survival was observed.
Schöchl et al.[40]	Observational retrospective study. 131 major trauma patients included. Fibrinogen concentrate was administered as first-line haemostatic therapy, guided by thromboelastometry.	Coagulation management was guided by thromboelastometry (ROTEM).	The observed mortality (24.4%) was compared with the theoretical mortality calculated by the TRISS (Trauma Injury Severity Score) mortality (33.7%, p = 0.032) and the RISC (Revised Injury Severity Classification) score of 28.7% (p >0.05).
Farriols et al.[41]	Observational retrospective study. 69 patients suffering from various forms of acquired severe hyperfibrinogenemia with life-threatening consumptive thrombo-haemorrhagic disorders (surgery, trauma and digestive haemorrhage), or underlying disease states that limit fibrinogen synthesis (hepatic dysfunction, haematological malignancies) were included. The aim of the study was to assess the efficacy and safety of the fibrinogen administration.	Standard laboratory tests.	A direct relationship between plasma fibrinogen levels and survival in acquired fibrinogen deficiency. After a median dose of 4 g, a mean absolute increase of 1.09 g/L in plasma fibrinogen was measured and coagulation parameters were significantly improved (p <0.001).

46 EUR J CLIN PHARM
VOL 18 NUM 1 JAN-FEB 2016

González Guerrero C, Montoro Ronsano JB

Fibrinogen replacement in trauma uncontrolled bleeding: a review of the literature

EUR J CLIN PHARM
VOL 18 NUM 1 JAN-FEB 2016 47

a consequence, it can be concluded that an early normalization of the fibrinogen levels improves the expected survival.

Farriols et al.[41] carried out a study including all forms of acquired severe hyperfibrinogenemia not only trauma patients. 69 patients were included, and the 62% corresponded to consumptive hyperfibrinogenemia. The mean initial fibrinogen plasma level was 0.76 g/L. After a median dose of 4 g, a mean absolute increase of 1.09 g/L in plasma fibrinogen was measured and coagulation parameters were significantly improved (p <0.001). These data indicate a direct relationship between plasma fibrinogen levels and survival in acquired fibrinogen deficiency (Table 1).

Finally, the epidemiology and overall effect of hyperfibrinolysis were recently described by Raza et al.,[25] showing that the vast majority of patients exhibit some degree of fibrinolysis, and that 5% of patients develop severe hyperfibrinolysis. This was not due to hypothermia or iatrogenic complications, suggesting that this condition is a distinct disease entity and contributor to TIC. Fibrinolysis is controlled by plasmin that is generated following activation of plasminogen by tPA and uPA. Plasmin degrades fibrin clots by cleaving cross-linked fibrin, a process that is inhibited by PAI-1, as PAI-1 inactivates tPA and uPA. The protein C activation, for instance, inhibits PAI-1 so it does not inhibit the fibrinolysis performed by plasmin, and contributing to the endogenous anticoagulation.

CONCLUSION

After reviewing the recent literature on PubMed, there are many reasons to consider fibrinogen supplementation in the patient with trauma-induced coagulopathy. The studies have supported that fibrinogen is the first haemostatic factor to decrease critically, as it reaches its critical level before the other routine coagulation parameters.

It has also been observed that a critical fibrinogen level on admission is an independent predictor of mortality, and the direct relationship between the severity of the coagulopathy on admission and the fibrinogen deficit. As a consequence, it seems logical to assume that the early normalization of the critical fibrinogen levels would improve the expected survival.

However, there is no consensus about where to establish the critical threshold for the fibrinogen supplementation. Globally, supplementing when fibrinogen plasma levels are above 2 g/L would be groundless; and, on the contrary, the replacement is of highly urgency when they are below 1 g/L. The clinical situation of the patient should have the last word for administering or not fibrinogen when its plasma levels values are among 1 g/L and 2 g/L.

Moreover, the fibrinogen supplementation has to be prescribed in such rational background. The risk-benefit analysis of the fibrinogen replacement when fibrinogen plasma levels are correct is not favourable. It should not be forgotten that fibrinogen is a blood product with its associated difficulties (high cost, purification and sterility of the product, limited supply and increased risk of venous thromboembolism). CP

REFERENCES

1. Levy JH, et al. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy. Transfusion 2014; 54: 1389-405.

2. Schlimp CJ, Schöhl H. The role of fibrinogen in trauma-induced coagulopathy. Hämostaseologie 2014; 34.

3. Franchini M, Lippi G. Fibrinogen replacement therapy: a critical review of the literature. Blood Transfus 2012; 10: 23-7.

4. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost 2005; 3: 1894-904.

5. Rahe-Meyer N, Sørensen B. Fibrinogen concentrate for management of bleeding. J Thromb Haemost 2011; 9: 1-5.

6. Aubron C, Reade MC, et al. Efficacy and safety of fibrinogen concentrate in trauma patients —a systematic review. J Crit Care 2014; 29: 471 e11-17.

7. Leal Noval SR, Muñoz M, Asuero M, et al. Spanish Consensus Statement on alternatives to allogeneic blood transfusion: the 2013 update of the «Seville Document». Blood Transfus 2013; 11: 585-610.

8. Cardenas JC, Wade CE, Holcomb JB. Mechanisms of trauma-induced coagulopathy. Curr Opin Hematol 2014; 21: 404-9.

9. Brohi K, Singh J, Heron M, Coats C. Acute traumatic coagulopathy. J Trauma 2003; 54: 1127-30.

10. MackLeod JBA, Lynn M, Mckenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma 2003; 55: 39-44.

11. Oshiro A, Yanagida Y, et al. Hemostasis during the early stages of trauma: comparison with disseminated intravascular coagulation. Critical Care 2014; 18: R61.

12. Smith SA. The cell-based model of coagulation. Vet Emerg Crit Care 2009; 19: 3-10.

13. Hoffman M, Monroe DM. A cell-based model of Hemostasis. Thromb Haemost 2001; 85: 958-65.

14. Ross Davenport. Coagulopathy following major trauma hemorrhage: lytic, lethal and a lack of fibrinogen. Critical Care 2014; 18: 151.

15. Brown LM, Call MS, Margaret Knudson M, et al. A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. J Trauma 2011; 71 (Supl 3): S337-42.

16. Wohlauer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg 2012; 214: 739-46.

17. Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg 2012; 73: 13-9.

18. Sillesen M., Rasmussen LS, Jin G, et al. Assessment of coagulopathy, endothelial injury, and inflammation after traumatic brain injury and hemorrhage in a porcine model. J Trauma Acute Care Surg 2014; 76: 12-9.

19. Ostrowski SR, Johansson PI. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. J Trauma Acute Care Surg 2012; 73: 60-6.

20. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg 2012; 255: 379-85.

21. Chesebro BB, Rahn P, Carles M, et al. Increase in activated protein C mediates acute traumatic coagulopathy in mice. Shock 2009; 32: 659-65.

22. Closa D, Folch Puy E. Oxygen free radicals and the systematic inflammatory response. IUBMB Life 2004; 56: 185-91.

23. Wood MJ, Helena Prieto J, Komives EA. Structural and functional consequences of methionine oxidation in thrombomodulin. Biochim Biophys Acta 2005; 1703: 141-7.

24. Burney PR, White N, Pfaendtner J (2014). Structural Effects of Methionine Oxidation on Isolated Subdomains of Human Fibrin D and aC Regions. PLoS ONE 9: e86981.

25. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost 2013; 11: 307-14.

26. Rossaint et al. Management of bleeding following major trauma: an updated European guideline. Crit Care 2010; 14: R52.

27. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013; 17: R76.

28. Kozek-Langenecker SA, Afshari A, Albaladejo P, et al. Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2013; 30: 270-382.

29. Stainsby D, MacLennan S, Thomas D, et al. Guidelines on the management of massive blood loss. Br J Haematol 2006; 135: 634-41.

30. American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. Practice guidelines for perioperative blood transfusion and adjuvant therapies: an updated report. Anesthesiology 2006; 105: 198-208.

31. Association of Anaesthetists of Great Britain and Ireland, Thomas D, Wee M, Clyburn P, et al. Blood transfusion and the anaesthetist: management of massive haemorrhage. Anaesthesia 2010; 65: 1153-61.

32. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee. Handbook of Transfusion Medicine. 2014, 5th edition. Available at: <http://www.transfusionguidelines.org.uk/transfusion-handbook> [Consulted: June 2015].

33. Dzik WH, et al. Clinical review: Canadian National Advisory Committee on Blood and Blood Products – Massive Transfusion Consensus Conference 2011: report of the panel. Crit Care 2011; 15: 242.

34. Ozier Y, Hunt BJ. Fibrinogen concentrate for management of bleeding: against indiscriminate use. J Thromb Haemost 2011; 9: 6-8.

35. Hayakawa M, Gando S, et al. Fibrinogen Level Deteriorates before Other Routine Coagulation Parameters and Massive Transfusion in the Early Phase of Severe Trauma: A Retrospective Observational Study. Semin Thromb Hemost 2015; 41: 35-42.

36. Deras P, Villiet M, et al. Early coagulopathy at hospital admission predicts initial or delayed fibrinogen deficit in severe trauma patients. J Trauma Acute Care Surg Volume 2014; 77: 433-40.

37. Kenji I, Efstathios K, et al. Impact of Fibrinogen Levels on Outcomes after Acute Injury in Patients Requiring a Massive Transfusion. J Am Coll Surg 2013; 216: 290-7.

38. Rourke C, Curry N, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. Journal of Thrombosis and Hemostasis 2012; 10: 1342-51.

39. Stinger HK, Spinella PC, et al. 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: S79-85.

40. Schochl, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEMR)-guided administration of fibrinogen concentrate and prothrombin complex Concentrate. Crit Care 2010; 14: R55.

41. Farriols Danés A, et al. Efficacy and tolerability of human fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high-risk severe bleeding. Vox Sang 2008; 94: 221-6.