World Journal of Trauma and Critical Care Medicine

Review

Open Access

Trauma induced coagulopathy

Naoki Hashimoto

Kindai University, School of Medicine, Ohno-Higashi Osaka-Sayama, Osaka 589-8511 Japan

Abstract

Coagulopathy is frequently present in trauma. Acute coagulopathy associated with trauma (ACoT) has been recognized as a distinct entity associated with increased mortality, morbidity and transfusion requirements. Uncontrolled bleeding is the most frequent preventable cause of death in trauma patients reaching hospital alive. Coagulopathy in trauma has been long thought to develop as a result of hemodilution, acidosis and hypothermia often related to resuscitation practices. The lack of well defined diagnosis criteria for ACoT impedes early identification and treatment. Prolongation of prothrombin time (PT) and activated thromboplastine time (APTT) have been used by most author to diagnosis ACoT. Mechanisms contributing to ACoT include anticoagulation, consumption, platelet dysfunction and hyperfibrinolysis. Early administration of tranexamic acid, recombinant factor VII and aggressive blood product transfusional management for ACoT with a red blood cell: plasma: platelets ratio close to 1:1:1 could result in decreased mortality from uncontrolled bleeding. This article reviews the pathophysiology and management of ACoT.

Key words: Acute coagulopathy associated with trauma (ACoT); tranexamic acid; recombinant factor VII

Introduction

Trauma remains a leading cause of death and disability in adults in spite of advances in resuscitation, surgical management, and critical care [1]. From 25 to 35% of injured civilian trauma patients develop a biochemically evident coagulopathy when they arrived at emergency department, though there are improved efficiency of trauma system and reducing the time interval between acute injury and treatment [2]. Coagulopathy may be the result of physiologic derangements such as acidosis, hypothermia or hemodilution related to fluid or blood administration. The etiology, diagnosis and treatment, the pathophysiology and management of acute coagulopathy of trauma (ACoT) is reviewed in this article.

Correspondence to: Naoki Hashimoto MD, PhD, Kindai University, School of Medicine 377-2 Ohno-Higashi Osaka-Sayama, Osaka 589-8511 Japan.
Email gojigen000@gmail.com

Submitted: Thursday, August 4, 2016; Accepted: Sunday, August 21, 2016; Published: Monday, August 22, 2016

Impact

Injury to brain tissue may predispose to acute traumatic coagulopathy and about one-third of patients with traumatic brain injury (TBI) have

a coagulopathy, although whether TBI-associated coagulopathy is fundamentally different from injury-related coagulopathy is not yet clearly understood [3].

Etiology

The precise physiopathology of acute coagulopathy of trauma (ACoT) is still unclear, but likely multifactorial and related to the severity of trauma and degree of shock, given the higher incidence with increasing injury severity score (ISS). Two main mechanisms have been proposed. The first is the activation of protein C (APC) secondary to hypoperfusion due to massive bleeding. APC inactivates factor VII and V and increases fibrinolysis due to consumption of antifibrinolytics. Increased fibrinolysis is enhanced by the release of tissue plasminogen activator (tPA) secondary to tissue damage. The second mechanism poses that endothelial damage and tissue factor exposure generate disseminated intravascular coagulation (DIC) with subsequent increase in thrombin generation, microthrombosis, and consumption of coagulation factors [4]. Regardless of the initial mechanisms of ACoT, coagulopathy will continue to worsen if hemodilution, acidosis, and hypothermia develop due to an inadequate treatment [5].

Acidosis

Acidosis causes clotting dysfunction in experimental model at pH<7.2 by interfering with the assembly of coagulation factor complexes involving calcium and negatively-charged phospholipids [6]. As an example, the activity of the factor Xa/Va/phospholipid/prothrombin complex is reduced by 50, 70, and 90% at a pH of 7.2, 7.0 and 6.8 respectively. However, correction of acidosis alone does not correct the coagulopathy, because injury causes coagulopathy via additional mechanism [7].

Hypothermia

Hypothermia in injured patients is graded into mild (36 to 34°C, moderate (34 to 32 °C) and sever (<32°C) [8]. Most of trauma patients have a temperature below 36°C on arrival at emergency hospital.9% of trauma patients have a temperature below 33°C [9].

The effect of hypothermia on clotting includes platelet dysfunction and impaired enzymatic function. Overall thrombin generation in activated in vitro clotting systems is generally preserved at a temperature of 33°C; however, impairment of tissue factor activity, platelet aggregation, and platelet adhesion are evident at temperatures between 33 to 37°C [10].

Dilution coagulopathy

A retrospective study of 8724 injured patients from the German Trauma Registry found a positive correlation between pre hospital fluid resuscitation volume and coagulopathy [11]. Frequency of coagulopathy was more than 50% when they are received >3L of intravenous fluid prior to arrival, but that of coagulopathy was also present in 10% of patients administered <500ml. Another factor contributing to coagulopathy is the effect of shelf time on packed red blood cells which undergo progressive functional and structural changes over time. The shelf life includes decreased pH, decreased of calcium, low 2, 3 diphosphoglycerate levels, and decreasing clotting factor concentration.

Diagnosis

Prolongation of prothrombin time (PT) and activated thromboplastin time (APTT) have been used by most authors to diagnose ACoT. Bronhi et al established the presence of ACoT if PT and APTT were 1.5 times over the normal values [2]. The prevalence of prolonged PT is higher, but prolongation of the PTT is more specific.

While these tests are simple and widely available, they have several limitations. PT and APTT reflect hemostasis in plasma during the first 60 seconds of clotting. Moreover, these tests have a turnaround time of 35-45 minutes, are carried out at 37°C and pH 7.5, and do not consider the presence of hypothermia, acidosis, hypocalcium and anemia. Therefore, the use of devices which

we can measure the value of PT and APTT for short time has been proposed.

Decrease platelet count and decreased platelet function also contribute to coagulopathy and poor outcome following trauma, although little information about platelet function is evident from the platelet count alone. Thromboelastography (TEG) and rotation thromboelastometry (ROTEM) to diagnose ACoT has been proposed, since both techniques allow complete evaluation of coagulation (beginning, speed and extent of the clot formation) and fibrinolysis. A positive correlation between TEG, ROTEM and traditional coagulation tests (PT, APTT, and INR) has been reported.

Treatment

Tranexamic acid (TXA)

The most studied antifibrinolytic has been tranexamic acid (TXA). TXA inhibits plasminogen activation, as well as plasmin activity, preventing fibrin clot lysis. The CRASH-2 study [13] evaluated the use of TXA versus placebo in trauma within 8 hours of injury. This was a multicenter RCT that recruited more than 20000 trauma patients with hemodynamic compromise or at risk of significant bleeding. The study showed that the use of TXA was associated with a decrease in mortality and deaths resulting from bleeding, without an increase in thrombotic complications. Based on the key role of hyperfibrinolysis in ACoT pathogenesis and the results of CRASH-2, several authors have proposed that the use of TXA should be a standard in trauma management [14].

Recombinant factor VIIa

Two RCTs have evaluated the use of activated factor VII (rF VIIa) in trauma. This agent was developed for the treatment of hemophilia A or B. Recently, the control study [15], was performed to compare rF VIIa to placebo. This trial found a decrease in transfusion requirement but no mortality difference. Given these results and its elevated cost, rF VIIa is currently recommended only as a final option in controlling massive bleeding in blunt trauma (after surgery, interventional procedures and blood transfusion) [16].

This drug has been used at the R Adams Cowley Shock Trauma Center (STC) in Baltimore since 2001. 2 doses are used at STC. The higher dose (100μg/kg) is suitable for patients in shock with active ongoing hemorrhage. The smaller dose (50μg/kg) is used for patients who are not in shock but still have life-threatening hemorrhage and coagulopathy. The typical patient is elderly, is receiving warfarin therapy, and has intracranial hemorrhage after traumatic brain injury.

Red blood cell: plasma: platelets ratio

Determining an appropriate fluid resuscitation technique during trauma induced coagulopathy in challenging. The addition of crystalloid or nonblood colloids with further exacerbates a tenuous situation [17]. We advocate a balanced administration of RBC, plasma and platelets (1:1:1) for massive resuscitation. This is the closest representation of whole blood administration and provides maximal resuscitation while maintain the ability for clot formation. US military data from operation Iraqi Freedom tend to support this review [18].

Conclusion

Coagulopathy is frequent present in trauma. Acute coagulopathy associated with trauma (ACoT) has been recognized as a distinct entity associated with increased mortality, morbidity and transfusion requirements.

Uncontrolled bleeding is the most frequent preventable cause of death in trauma patients reaching hospital alive. Early correction of ACoT through damage control resuscitation is a promising treatment for preventable trauma death. Early administration of tranexamic acid, recombinant factor VII and aggressive blood product transfusional management for ACoT with a red blood cell: plasma: platelets ratio close to 1:1:1 could result in decreased mortality from uncontrolled bleeding.

Authors' contribution

NH conceived and designed the study prepared the manuscript.

Conflict of Interests

The author declare that there is no conflict of interests

Funding

None declared

References

1. Mathers CD, Loncar D. Projection of global mortality and burden of disease from 2002 to 2030. PLos Med 2006;3:e442 [PubMed]
2. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy.J Trauma. 2003 Jun;54(6):1127-30. [PubMed]
3. Lee TH, Hampton DA, Diggs BS, McCully SP, Kutcher M, Redick BJ, Podbielski J, Cotton BA, Cohen M, Schreiber MA. Traumatic brain injury is not associated with coagulopathy out of proportion to injury in other body regions. J Trauma Acute Care Surg. 2014 Jul;77(1):67-72; discussion 72. doi: 10.1097/TA.0000000000000255 [Pubmed].
4. Cushing M, Shaz BH. Blood transfusion in trauma patients: unresolved questions. Minerva Anestesiol. 2011 Mar;77(3):349-59. [PubMed]
5. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care. 2007 Dec;13(6):680-5. [PubMed]
6. Martini WZ Coagulopathy by hypothermia and acidosis; mechanisms of thrombin generation and fibrinogen availability. J Trauma. 2009 Jul;67(1):202-8; discussion 208-9. doi: 10.1097/TA.0b013e3181a602a7. [PubMed]
7. Martini WZ, Dubick MA, Wade CE et al. Evaluation of tris-hydroxymethylaminomethane on reversing coagulation abnormalities caused by acidosis in pigs. Crit Care Med. 2007 Jun;35(6):1568-74. [PubMed]
8. Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. Injury. 2004 Jan;35(1):7-15. [Pubmed]
9. Wolberg AS, Meng ZH, Monroe DM 3rd, Hoffman M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma. 2004 Jun;56(6):1221-8. [PubMed]
10. Meng ZH, Wolberg AS, Monroe DM 3rd, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma. 2003 Nov;55(5):886-91 [Pubmed].
11. Maegele M1, Lefering R, Yucel N, Tjardes T, Rixen D, Paffrath T, Simanski C, Neugebauer E, Bouillon B; AG Polytrauma of the German Trauma Society (DGU). Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury. 2007 Mar;38(3):298-304. Epub 2007 Jan 9. [Pubmed]
12. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010 Jul 3;376(9734):23-32. doi: 10.1016/S0140-6736(10)60835-5. Epub 2010 Jun 14. [Pubmed]
13. Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH. Tranexamic acid for trauma patients: a critical review of the literature. J Trauma. 2011 Jul;71(1 Suppl):S9-14. doi: 10.1097/TA.0b013e31822114af. [PubMed]
14. Hauser CJ, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, Leppaniemi A, Parr M, Vincent JL, Tortella BJ, Dimsits J, Bouillon B; CONTROL Study Group. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. J Trauma. 2010 Sep;69(3):489-500. doi: 10.1097/TA.0b013e3181edf36e. [Pubmed]
15. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E,

Ozier Y, Riddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR; Task Force for Advanced Bleeding Care in Trauma. Management of bleeding following major trauma: an updated European guideline. Crit Care. 2010;14(2):R52. doi: 10.1186/cc8943. Epub 2010 Apr 6 [Pubmed]
16. Amand R, Hess JR Treating coagulopathy in trauma patients. Transfusion Med Rev 2003;17:223-231 [PubMed]
17. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma. 2007 Oct;63(4):805-13. [Pubmed]

World Journal of Trauma and Critical Care Medicine

Published by Narain Publishers Pvt. Ltd. (NPPL)
The **Open Access** publishers of **peer reviewed** journals. All articles are immediately published online on acceptance.
All articles published by NPPL are available **free** online