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Trauma-Induced Coagulopathy

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1. Abstract

Trauma continues to be the leading cause of death in people less than 40 years old worldwide. Appropriate management and resuscitation decrease mortality significantly. The underlying mechanism of trauma-induced coagulopathy is discussed in this article. Latest investigations and management protocols were reviewed.

2. Introduction

Trauma continues to be the leading cause of death in people less than 40 years old worldwide [1], and accounts for almost 10% of death in general [2].

Studies have shown that among trauma patients, post-traumatic uncontrolled hemorrhage is the main cause of potentially preventable death [3]. Despite the significant development in acute trauma care, uncontrolled hemorrhage remains to be responsible for 40% of trauma-related deaths [4].

It was found that among severely injured patients presenting to the Emergency Department, one in four present with hemodynamic depletion and trauma induced coagulopathy [5].

Trauma induced coagulopathy (TIC) is a clinical, physiological & molecular disorder that results from hemostatic failure due to tissue injury and shock [6]. It is associated with higher rate of transfusion, more incidence of organ failure, and longer in-hospital stay. Contrarily, it has been found that earlier diagnosis of TIC, adequate and aggressive management results in a better control of bleeding, reversal of coagulopathy, reduction in the frequency of transfusion and improvement in the outcome in these patients [5].

Appropriate management and control of severely injured patients decrease the mortality rate significantly. Damage control resuscitation is a modified approach for the management of the severely injured trauma patients. The earlier approach, damage control surgery, aimed to manage coagulopathy in trauma patients with the following three steps; abbreviated surgical control of hemorrhage and contamination, intensive care unit (ICU) resuscitation and re-operation for definitive management. However, this approach did not improve coagulopathy. Recently, after better understanding of trauma induced coagulopathy, damage control resuscitation has been implemented. Damage control resuscitation aims for a balanced, hemostatic resuscitation and prevention of acidosis, hypothermia, and hypocalcemia [7].

3. Incidence of Coagulopathy of Trauma

In 2017, a study looked into the presence of coagulopathy in emergency admission in 61,212 trauma patients derived from the Trauma Register DGU® [8]. The cutoff value was platelets <100,000/µl and/or Quick's value <70%. Results showed that coagulopathy was present in 24.5% of all trauma patients [8].

Trauma induced coagulopathy can happen as early as on-scene or later in the hospital. A study was done for 45 patients demonstrated that on-scene coagulation was abnormal in 56% of the patients. On hospital admission, coagulation was abnormal in 60% of patients [9].

4.Trauma Triade of death

Trauma triad of death: hypothermia, acidosis & coagulopathy is

recognized as a significant cause of death in trauma patients.

4.1. Hypothermia

Around two-thirds of all bleeding trauma patients arrive to the hospital with core temperature below 36 Celsius [10], with increased risk in extremes of age. Measures that should be taken to correct the hypothermia include covering patients or using warming machine, warming all the blood and fluids before infusing them, increasing the temperature in the ambulance and treatment area and controlling the hemorrhage to reverse shock as quickly as possible [10].

4.2. Acidosis

trauma patients are at risk of developing acidosis due to increased level of lactic acid. This happens because a bleeding patient will have vasoconstriction and hypovolemia which in turn impairs oxygen delivery to tissues, that will result in a change in the cellular metabolism from aerobic to anerobic with the resulting production of lactic acid [10]. acidosis manifests as altered level of consciousness and decrease cardiac function [10]. Studies showed that improving tissue oxygenation as well as treating hypothermia play major role in reversing acidosis [10].

4.3. Coagulopathy

Trauma patients are at risk of developing coagulopathy. There are several mechanisms of trauma induced coagulopathy including: activation of protein C, endothelial injury, factors deficiency, hyper fibrinolysis, platelet dysfunction and many others [5]. Death can occur due to bleeding from wounds or secondary coagulopathy [10]. Patient with coagulopathy can present with intracranial hemorrhage, bleeding from gastrointestinal tract or bladder, mucus or cutaneous bleed and petechia and bruising [10].

5. Mechanisms of Trauma Induced Coagulopathy

There are several mechanisms that are found to be the principal drivers of coagulopathy of trauma [5].

Coagulopathy of trauma is caused by both endogenous and exogenous mechanisms.

The endogenous mechanisms happen immediately after the occurrence of the injury, and they include:

5.1. Activation of the C Protein Pathway

The protein C pathway is an important factor contributing to coagulopathy in trauma, it occurs when there is tissue injury with tissue hypo perfusion [11].

Protein C, also known as Auto prothrombin AII, is a vitamin K-dependent anticoagulant glycoprotein in the plasma which gets activated on the surface of the endothelial cell when thrombin & transmembrane glycoprotein thrombomodulin (TM) bind to its receptor, the endothelial protein C receptor (EPCR), forming thrombin-TM complex [11]. Studies demonstrated that the tissue hypo perfusion in shock status leads to over expression of (TM) and (EPCR) on the endothelial cell surface, then the EPCR binds to protein C and leads to 5-20 fold increase in the rate of protein C activation by thrombin-TM complex [12] (Figure 1-4).

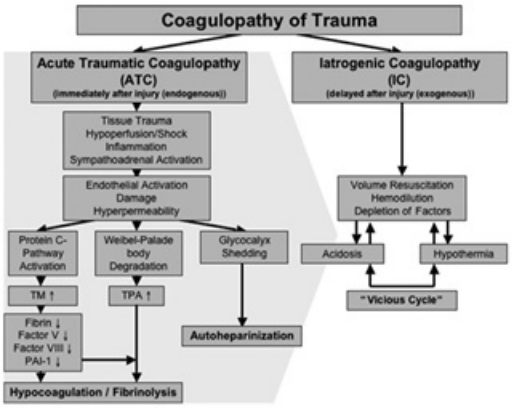

Figure 1: The mechanisms of coagulopathy of Trauma (5)

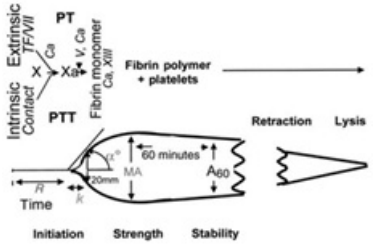

Figure 2: Graphic demonstration of TEG

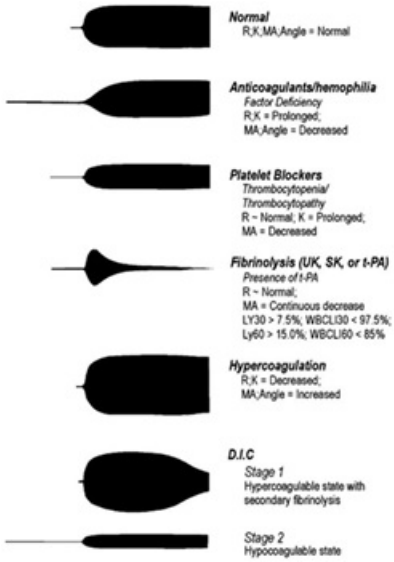

Figure 3: TEG outcomes

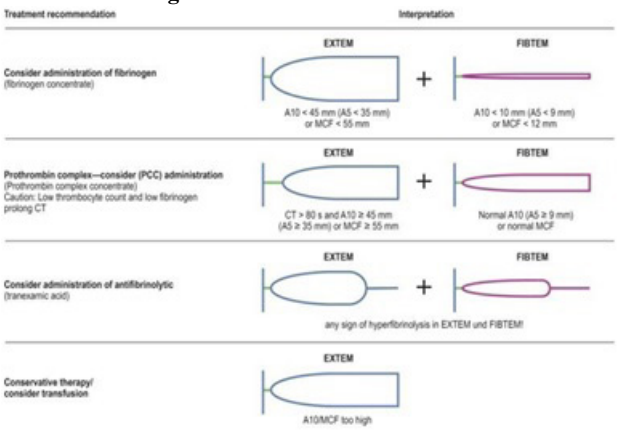

Figure 4: TEG based management

Activated protein C has two main anticoagulating effects, prompting coagulopathy in trauma. First, it cleaves the peptide bond in the coagulation factor V and VIII which are essential for activating factor X and

II. Second, it inhibits plasminogen activator inhibitor 1 (PAI-1) therefore enhancing fibrinolysis [5].

5.2. Endothelial Injury

Disruption of the vascular endothelial cells is also linked to developing coagulopathy of trauma. The endothelial surface is covered by glycocalyx, which forms a negatively charged antiadhesive and anticoagulant layer that protects the endothelium and the vascular barrier [13] The catecholamines surge in trauma patients is associated with glycocalyx degradation [6]. Moreover, endothelial injury itself triggers the release of syndecan1 that also causes glycocalyx degradation [14]. Glycocalyx contains significant amount of heparin like substance, when degraded this results in auto-heparinization [14].

In addition, endothelial injury promotes the release of tissue plasminogen activator (TPA) and angioprotein 2, both of which cause vascular endothelial growth factor (VEGF) and Weibel-Palade body degranulation hence losing vWF and causing vWF deficiency [15].

5.3. Coagulation Factors Deficiency

More recent evidence reveals that coagulation abnormalities appear to happen more in more severe injuries with acidosis & higher transfusion rate [5].

One of the causes of coagulopathy of trauma is clotting factors deficiency which has been found to happen immediately after injury and is linked to worse prognosis [16]. Lucy Z. Kornblith and colleagues showed that although coagulation factors are reproducible, in trauma setting their level declines to 20-30%, which impairs the coagulation process at the site of injury (6). In addition, a prospective cohort study done in UK proposed that fibrinogen level also declines in trauma setting, reaching the critical levels of less than 1.5g/L in 14% of trauma patients more than 16 years old[17]. Fibrinogen is the last product in the clotting formation process, lower level or quality of fibrinogen will result in more bleeding and hence higher mortality [19].

5.4. Hyper Fibrinolysis

Fibrinolysis is a normal process that is activated by local hypercoagulability in order to prevent clot formation in non-injured tissues [20] Hyper fibrinolysis occurs in less than 1 hour after injury and is associated with increased incidence of hemorrhage-related death in trauma [21]. It is diagnosed by thromboelastography and was found to be present in 7% to 20% of trauma patients [21]. A prospective observational study conducted in USA on 163 trauma patients looked into the role of tissue plasminogen activator(tPA) system in hyper fibrinolysis. It found that lasmin-a2 antiplasmin was directly related to tPA and inversely related to plasminogen activator inhibitor (PAI-1).

Therefore, patients with increased tPA and decreased PAI-1 are more likely to have fibrinolysis, and consequently have more transfusion requirements and longer in-hospital stay [22].

5.5. Platelet Dysfunction

The mechanism of platelet dysfunction is not yet very clear. However, it is thought to be related to decreased platelet stimulation by adenosine diphosphate (ADP) agonism [5]. Wohlauer and colleagues studied the platelet function in stabilizing the thrombus and compared this between trauma patients and healthy volunteers using thrombelastography-based platelet functional analysis [23]. The results identified significant impairment of platelet aggregation in trauma patients. The mean of ADP inhibition in trauma patients was 86.1% compared with 4.2% in the healthy individuals [23]. These results suggest the possible role of platelet transfusion in severe trauma patients.

5.6. Hypothermia

Hypothermia in trauma patients happens because of environmental exposure to cold temperature, decrease muscle heat production, administration of cold intravenous fluids, and evaporation from body cavities during surgeries which cause heat loss [24]. Studies have demonstrated that hypothermia has a major inhibitory effect on platelet function and to a lesser extent on coagulation protease [24]. The mechanism in which hypothermia affects the platelet function is by diminishing the effect of von Willebrand factor on glycoprotein Ib/IX, which is essential for transducing signals from adhesion to activation of the platelets [25].

Moreover, hypothermia decreases the activity of the coagulation factor VIIa, as it was found that at a temperature of 28°C, its activity is reduced by 50%[27, 28]. Previous studies showed increased mortality with severe hypothermia less than 32°C [29].

5.7. Acidosis

Acidosis affects the coagulation by lowering the pace of plasma biochemical reaction needed to achieve coagulation [5]. In addition, a review of the literature on this topic have found that acidosis affects both thrombin and fibrinogen; it inhibits the propagation phase of thrombin generation, and increases the degradation of fibrinogen leading to reduced level of fibrinogen [30]. Moreover, J C Kermode studies the effect of acidosis on the coagulation factor complex activity and found that in a pH of 7.2, the activity of coagulation factor complex is reduced by 50%. [30] Similarly, coagulation factor complex activity is diminished to 20% of normal activity in pH of 6.8 [30].

5.8. Hemodilution

In trauma setting, dilution of coagulation factors is one of the factors leading to coagulopathy [31]. It has now been demonstrated that reduced intravascular hydrostatic pressure in shock causes flu-

id that is deficient in coagulation factors to be shifted from cells and interstitial space into the plasma [32]. This dilution of coagulation factors is further worsened by unguided and over administration of fluid in acute setting of trauma [5]. Packed red blood cells also causes dilution of coagulation factors as well as weakening the clotting ability [33].

6. Investigations

Trauma induced coagulopathy should be expected in patients with severe mechanism of injury or in the presence of signs suggestive of massive bleeding like tachycardia, hypotension, decreased level of consciousness, hypo perfusion, base deficit more than 6 mmol/L, high lactate and decreased urine output [35]. The following are the tests used to diagnose trauma induced coagulopathy.

7. Coagulation studies

7.1. Hemoglobin

It is recommended in the fifth edition of the European guideline on management of major bleeding and coagulopathy following trauma, that the initial hemoglobin level should be considered as an initial indicator of coagulopathy in a traumatic patient [34]. Hemoglobin level value in traumatic patients is not that specific and its value has been doubtful as the decrease in hemoglobin level takes time and the resuscitative measures might mask a low hemoglobin [36]. However, Knottenbelt et al. evaluated 1000 trauma patients with moderate tosevere hemorrhagic shock and found a low initial hemoglobin level [37].

7.2. Conventional Coagulation Assay

Prothrombin level (PT) is more sensitive while activated partial thrombin level (aPTT) is more specific for coagulopathy in trauma. These values are considered deranged if the results are 1.5 times more than the upper laboratory limit.

It was noted that the initial PT value can be used to estimate the degree of shock as well as to determine the outcome of patients with traumatic hemorrhage [34]. Peltan et al, found that 50% of patients with traumatic bleeding develop trauma induced coagulopathy defined as PT: INR ratio greater than1.2. It also found that 21% of patients have coagulopathy if defined as INR more than 1.5. However, the second definition was associated with higher morbidity and mortality rates. Thus, a ratio PT: INR > 1.2 was used to assess the presence of coagulopathy in trauma [38].

8. Viscoelastic Methods (VEMs)

The principle of these methods is to measure the whole blood viscoelastic properties during clot formation. They provide information about clot initiation, strength and fibrinolysis. Based on these values, a goal-oriented management of coagulopathy can be achieved. VEMs have reduced blood products transfusion and improved clinical outcomes [39]. There are two evident devices available for VEM: Thromboelastography (TEG), Rotational thromboelastometry (RoTEM).TEG was first described by Hertert in 1948 and RoTEM is the new modification of TEG. Compared to the conventional coagulation assays which gives information about clot initiation only, TEG and RoTEM gives a graphic demonstration of clot initiation, strength and lysis as demonstrated in Figure [2]. This visual demonstration makes it easy to make the diagnosis and treat accordingly as will be described later in the management section.

There are differences in the operating system of TEG and RoTEM, but that is beyond the scope of this article. Figure [3] compares normal TEG output to many different coagulation disorders

These new devices provide fast bedside results within 10 minutes compared to 45 minutes with the conventional test [39]. Few limitations have been noted in the use of VEMs which include: high coast, limited availability, training requirements and lack of cut off points for the definite diagnosis of trauma induced coagulopathy [35].

9. Fibrinogen level

Low fibrinogen levels are noted in trauma patients. Rourke et al. stated that the consumption of fibrinogen in trauma occurs much faster than consumption of other coagulation factors [40]. The benefit of antifibrinolytic agents noted in CRASH-2 trial supports that the onset of fibrinolysis occurs early in trauma. Hyper fibrinolysis and fast consumption of fibrinogen are the reasons behind hypofibrinogenemia in trauma. 3% fibrinolysis within 30 minutes, noted in TEG results, is associated with higher transfusion need and higher mortality as well [41].

10. D-dimer

D-dimer is a degradation product of fibrinogen. Higher levels of d-dimer are associated with higher transfusion requirements and higher mortality. D- dimer level was 7-fold higher in a group of critically injured patients who died compared to those who survived [43].

11. Management

In severely Injured patients, death cannot be prevented unless the lethal triad of coagulopathy, hypothermia and acidosis is prevented. This is addressed in the new strategy of dealing with severely injured patients which is damage control resuscitation. Damage control resuscitation aims to reduce the incidence of trauma induced coagulopathy by balanced resuscitation, hemostatic resuscitation and prevention of acidosis, hypothermia and hypocalcemia. [7].

It is recommended, in the European guideline, to allow for permissive hypotension 80-90 mmHg systolic in severely injured patient without traumatic brain injury instead of massive crystalloid administration. This action reduces the risk of dilutional coagulopathy related to massive crystalloid administration. [34].

11.1. Hypothermia

It is recommended to target normothermia in trauma between 36

and 37 °C. This can be achieved by different rewarming strategies: removing wet cloths, covering the patient to avoid heat loss, using warm IV fluids, forced air warming and using rewarming kit. Re-warming kit is a cheap and light device that can provide a continuous dry heat.

11.2. Acidosis

Treatment of acidosis starts with limiting tissue hypoperfusion and restoration of the circulation. It is important to treat acidosis as it can cause death specially in patients who receive massive transfusion products as they will be at risk of coagulopathy. Buffering can be achieved by using sodium bicarbonate or trihydroxymethylaminomethane (THAM). THAM is found to be better than sodium bicarbonate as it does not inhibit thrombin formation [44, 45].

11.3. Empiric Transfusion Strategies

The current practice for the initial management of severely bleeding patients is transfusion protocol at a ratio 1:1:1 of Fresh Frozen Plasma, Platelets and PRBC. However, the European guideline recently advised for either of the following strategies for the initial management of bleeding patient: FFP and PRBC at a ratio of 1:2 or fibrinogen concentrate with PRBC according to the hemoglobin level [34].

11.4. VEMs based transfusion

A goal-oriented transfusion using TEG and RoTEM is recommended and has shown an improved survival and decreased mortality. A randomized controlled trial which included one hundred eleven patients assigned to be treated either by TEG-guided or CCA- guided transfusion protocol. Survival was higher in the TEG-group than the CCA-group with 20 deaths in CCA-group and 11 in TEG group [46]. Diagnosis and treatment guidance is summarized in figure [4].

11.5. Management of Fibrinolysis, Tranexamic Acid (TXA)

It is recommended in CRASH-2 trial to use antifibrinolytic tranexamic acid in a bleeding trauma patient as soon as on-scene assessment is made. It should be given as a bolus of 1 g over 10 minutes followed by infusion of 1g over 8 hours [34]. Tranexamic acid action is preventing fibrin clot lysis by inhibiting plasminogen activation and plasmin activity.

12. Monitoring

Patients who are severely bleeding and being resuscitated are considered critical and need to be monitored frequently. If available, monitoring with VEMs is recommended as it can guide the approach and management. If VEMs are not available, serial monitoring with conventional coagulation assays can be used. ABG should also be sent serially to assess the progress of acidosis and base deficit.

13. Conclusion

Trauma-induced coagulopathy is a serious and preventable cause of mortality in trauma patients. Prevention is important and starts at trauma scene until the patient is discharged. Early diagnosis and management improve the mortality in bleeding trauma patients significantly.

References

1. Krug EG, Sharma GK, Lozano R. The global burden of injuries. Am J Public Health. 2000; 90:523-6.
2. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world. Global Burden of Disease Study. Lancet. 1997; 349: 1269-76
3. JD. Gates SA, M. Hirsch PC, CC. Cothren EEM, RA. Davenport MG, K. Brohi JS, D. Frith JCG, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition [Internet]. Critical Care. BioMed Central; 1970.
4. Armand R, Hess JR.Treating coagulopathy in trauma patients.Transfus Med Rev. 2003; 17: 223-31.
5. Maegele, M., Schöchl, H. and Cohen, M.J. An Update on the Coagulopathy of Trauma: Shock. 2014; 41 :21-5.
6. Kornblith LZ, Moore HB, Cohen MJ. Trauma- induced coagulopathy: The past, present, and future. J Thromb Haemost.2019; 17: 852-62.
7. Mizobata Y. Damage control resuscitation: a p ractical approach for severely hemorrhagic patients and its effects on trauma surger.BMC. 2021.
8. JA. Evans KJW, A. Sauaia FAM, JB. Holcomb NRMM, K. Brohi JS, B. Floccard LR, M. Maegele RL, et al. Trauma-induced coagulopathy upon emergency room arrival: still a significant problem despite increased awareness and management? [Internet]. European Journal of Trauma and Emergency Surgery. Springer Berlin Heidelberg; 1970 [cited 2021Feb7].
9. Floccard B, Rugeri L, Faure A. Denis SM, Boyle ME,Penguet O, et al. Early coagulopathy in trauma patients: An on-scene and hospital admission study. Injury. 2012; 43: 26-32.
10. Lewis AM. Trauma triad of death emergency.ProQuest Central.2000; 10: 85-94.
11. Brohi K; Cohen MJ; Ganter MT; Matthay MA; Mackersie RC; Pittet JF; Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway?. Ann Surg. 2007; 245: 812-8.
12. Esmon CT. The role of protein C and thrombomodulin in the regulation of blood coagulation. J Biol Chem. 2010;264:4743-6.
13. Nieuwdorp M, Meuwese MC, Vink H, Hoekstra J, Kastelein J, Stroes E. [PDF] The endothelial glycocalyx: a potential barrier between health and vascular disease.Curr Opin Lipidol. 2005; 16: 507-11.
14. Johansson IP, Stenssballe J, Rasmussen SR, Ostrowski RS A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients.Ann Surg. 2011; 254: 194-200.
15. Rehm M, Bruegger D, Christ F, Conzen P, Thiel M, Jacob M, et al. Shedding of the endothelial glycocalyx in patients undergoing ma-

jor vascular surgery with global and regional ischemia. 2007; 116: 1896-906.

16. Lowenstein JC, Morell NC, Yamakuchi M. Regulation of Weibel-Palade body exocytosis. Trends Cardiovasc Med.2005; 15: 302-8.
17. Rizoli SB, Scarpelini S, Callum J, Nascimento B, Mann GK, Pinto R, et al. Clotting factor deficiency in early trauma-associated coagulopathy.J Trauma.2011; 17: 427-34.
18. Kornblith LZ; Kutcher ME; Redick BJ; Calfee CS; Vilardi RF; Cohen MJ; Fibrinogen and platelet contributions to clot formation: implications for trauma resuscitation and thromboprophylaxis.J Trauma Acute Care Surg.2014; 76: 255-6.
19. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost.2012; 10: 1342-51.
20. Innes D, Sevitt S. Coagulation and Fibrinolysis in Injured Patients. J Clin Pathol. 1964; 17: 1-13
21. Schöchl, H., Frietsch, T., Pavelka, M. and Jámbor, C. Hyperfibrinolysis After Major Trauma: Differential. J Trauma. 2008 ;16: 125-13
22. Cardenas J, Matijevic N, Bare La, Holcomb Jb, Cotton Ba, Wade Ce. Elevated tissue plasminogen activator and reduced plasminogen activator inhibitor promote hyperfibrinolysis in trauma patients. Shock (Augusta, Ga.). 2014; 41: 514-521
23. Wohlauer M, Moore E, Thomas S, Sauaia A, Evans ED , Harr J, et al.Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg. 2012; 214: 739-46.
24. Farkash U, Lynn M, Scope A, Maor R, Turchin N,Sverdlik B, et al. Does prehospital fluid administration impact core body temperature and coagulation functions in combat casualties?. Injury. 2002; 33: 103-10.
25. Reed RL,Bracey AW,Hudson JD,Miller TA,Fischer RP. Hypothermia and blood coagulation: dissociation between enzyme activity and clotting factor levels.Circ Shock. 1990; 32: 141-52.
26. Valeri CR,Feingold H,Cassidy G,Ragno G,Khuri S,Altschule MD. Hypothermia-induced reversible platelet dysfunction. Ann Surg. 1987; 205: 175-81.
27. Wolberg AS, Meng ZH,Monroe DM, Hoffmann M. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma. 2004; 56: 1221-8.
28. Meng, Z., Wolberg, A., Monroe, D. and 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; 55: 886-91.
29. Gentilello LM, Jurkovich GJ,Stark MS,Hassantash SA,O'Keefe GE.Is hypothermia in the victim of major trauma protective or harmful? Ann Surg . Annals of surgery. 1997; 226: 439-47.
30. Martini JW. Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. J Trauma. 2009; 67: 202-8.
31. Kermode JC, Zheng Q,Milner E P. Marked temperature dependence of the platelet calcium signal induced by human von Willebrand factor. Blood. U.S. National Library of Medicine. 1999; 94: 199-207.
32. Brummel-Ziedins, K., Whelihan, M., Ziedins, E. and Mann, K. The resuscitative fluid you choose may potentiate bleeding J Trauma. 2006;61:1350-8.
33. Hess J, Brohi K, Dutton R, Hauser C, Holcomb J, Kluger Y, et la. The Coagulopathy of Trauma: A Review of Mechanisms. J Trauma. 2008; 65(4): 748-54.
34. Ho A, Karmakar M and Dion PPW. HAMKMKD. Are we giving enough coagulation factors during major trauma resuscitation?. Ame j surg. 2005; 190(3): 479-84.
35. Ruiz C, Andresen M. Treatment of Acute Coagulopathy Associated with Trauma. Hindawi. 2013.
36. Spahn DR, Bouillon B, Cerny V. et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. Crit Care 23, 98 (2019).
37. Paradis NA, Balter S, Davison CM, Simon G, Rose M. Hematocrit as a predictor of significant injury after penetrating trauma. Am J Emerg Med. 1997 May; 15(3): 224-8.
38. JD Knottenbelt. Low initial hemoglobin levels in trauma patients: an important indicator of ongoing hemorrhage. J Trauma. 1991; 31(10): 1396-9.
39. Peltan ID, Vande Vusse LK, Maier RV, Watkins TR. An International Normalized Ratio-Based Definition of Acute Traumatic Coagulopathy Is Associated With Mortality, Venous Thromboembolism, and Multiple Organ Failure After Injury. Crit Care Med. 2015 Jul; 43(7): 1429-38.
40. Benes J, Zatloukal J, Kletecka J. Viscoelastic methods of blood clotting assessment – a multidisciplinary review. Frontiers in Medicine. Front Med (Lausanne). 2015 Sep 14; 2: 62.
41. Rizoli S, Scarpelini S, Callum J. Clotting Factor Deficiency in Early Trauma-Associated Coagulopathy. Wolters Kluwer J Trauma. 2011; 71(5 Suppl 1): S427-34
42. Chapman MP, Moore EE, Ramos CR, Ghasabyan A, Harr JN, Chin TL, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. J Trauma Acute Care Surg. 2013; 75(6): 961-7.
43. Gall L, Vulliamy P, Gillespie S. The S100A10 Pathway Mediates an Occult Hyperfibrinolytic Subtype in Trauma Patients. 2019; 269(6): 1184-1191
44. El Sayad M, Noureddine H. Recent Advances of Hemorrhage Management in Severe Trauma. Hindawi. 2014; 2014: 638956.
45. Cripps MW, Kutcher M, Izenberg R, et al. Aggressive Correction of Severe Acidosis with Tris-Hydroxy Amino Methane (THAM) IN Severely Injured Trauma Patients. 2012.
46. Gonzalez E, Moore EE, Moore HB, Chapman MP, Chin TL, Ghasabyan A, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Ann Surg. 2016; 263(6): 1051-9.