Coagulopathy in trauma

Trauma is still a leading cause of morbidity and mortality in the contemporary community, particularly in population younger than 40 years of age. Recent studies have offered new knowledge on the central role of coagulopathy in traumatized people. Massive hemorrhage is a cause of death in severely traumatized people in 40% of cases, and the control of bleeding is a special challenge in the developed and verified coagulopathy. After severe trauma, massive hemorrhage is very often the consequence of associated surgical and coagulopathic bleeding. Massive blood loss diminishes the capacity of coagulation system, resulting in coagulopathy even in patients whose hemostasis before the injury has been within physiological limits.

Key words: Coagulopathy, trauma, mechanism, uncontrolled hemorrhage

INTRODUCTION

In the largest number of cases, multi-system injuries in polytraumatized patients are followed by massive bleeding. The most frequent cause of such massive, uncontrolled bleeding is posttraumatic acquired coagulopathy, which is also the most often cause of lethal outcome. Although there has not been yet a consensus and true definition of massive hemorrhage, the clinicians are guided by the following definitions:

1. massive hemorrhage is a loss of the whole circulatory volume within 24 hours
2. the loss of a half of a total blood volume within 3 hours
3. the loss of blood volume rate of 150 ml/min
4. loss of 1-5 ml/kg/min within 20 minutes

Coagulation system traditionally acts as completely separate system that has been developed to prevent and restrict the loss of blood volume and blood components. Coagulation is an integral part of inflammation and an extensive coagulation activation results in syndrome of systemic inflammatory response and significant susceptibility to sepsis. This is further intensified by immunological effects of transfusion therapy.

Normal hemostasis is a complicated and very complex dynamic equilibrium of pro- and antithrombotic pathways. Coagulation reactions occur on membrane surfaces of the endothelial cells, platelets, monocytes and neutrophils. Any disorder of this complex dynamic balance results in procoagulant state. In these situations (trauma, tissue damage, shock), three major procoagulant pathways are being activated: coagulation cascade, platelets and vasoconstriction. These aforementioned pathways are balanced by the inhibitory systems: TFPI (tissue factor pathway inhibitor), antithrombin (AT), protein C system (PC) and fibrinolytic pathways. Thrombomodulin (TM) on the endothelial cell surface integrates these pathways, binding the prothrombic thrombin to thrombomodulin (TM), resulting in PC activation, and thus increasing the fibrinolysis through the TAFI (thrombin-activatable fibrinolysis inhibitor).

MATERIAL AND METHODS

This review article is the analysis of all relevant aspects related to the problems of early and late posttraumatic coagulopathy, which have been addressed in the available, relevant professional literature.

RESULTS AND DISCUSSION

Coagulopathy in trauma is a multifactorial disorder, encompassing all components of hemostatic system. Activation or dysfunction of fibrin production or both, platelets and endothelium play significant role in development of coagulopathy and resulting uncontrolled hemorrhage, including the subsequent inhibition of production of a stable clot, by activation of anticoagulant and fibrinolytic
pathways. What mechanism will predominate depends on mechanism of origin and severity of injury, degree of circulatory dysfunction and side-effects of the applied therapy.

The majority of studies have been focused on coagulation proteases, which may be consumed or inhibited. The loss of coagulation proteases is direct sequela of their extensive activation or massive consumption, or direct consequence of hemodilution occurring during circulatory volume supplementation for correction of circulatory dysfunction and hemodynamic instability. Inhibition of serum proteases results from the physical factors, such as hypothermia and acidosis or activation of anticoagulant and fibrinolytic pathways.

Based on all recent studies, it may be said that there are several key triggers of coagulopathy in trauma: tissue damage, shock, hemodilution, hypothermia, acidosis, inflammation, anemia and electrolyte imbalance.

Tissue damage is the universal mechanism in trauma. However, an extentiveness of trauma and tissue damage is directly responsible for development of early coagulopathy as well as extent of coagulopathy14-16. In specific, the injuries followed by enormous release of kinetic energy, crush or blast injuries are characterized by extensive tissue damage, in distinction from the lethal penetrating injury, which is featured by lesser tissue damage. Regardless of all these, coagulopathy may develop to have both clinical pictures. Clinically, severity of injury is closely associated with the extent of coagulopathy.12

Trauma-induced tissue damage initiates the coagulation process. Endothelial damage leads to exposure of subendothelial collagen type III and tissue factor (Thromboplastin), which starts the activation of coagulation, which then may upstream the consumption coagulopathy. Tissue factor binds von Willebrand’s factor, platelets and activated factor VIIa. Tissue factor or recombinant VIIa complex activates the plasma coagulation proteases, resulting in production of thrombin and fibrin formation.17 The amount of tissue factor required for initiation of coagulation is minimal. Thereupon, the process is being enhanced by factor FIX, predominantly on the surface of activated platelets.11

Hyperfibrinolysis is usual after trauma. It is a direct consequence of tissue damage and shock.18 Endothelial lesion results in an increase of fibrinolytic activity due to direct release of tissue activator plasminogen (tPA) from endothelial cells, as well as plasminogen activator inhibitor (PAI-1). Endothelial tPA expression also rises in the presence of thrombin.19 Fibrinolysis is enhanced because of combined effects of the endothelial tPA that is released due to ischemia and the initial inhibition in shock within the first hours of trauma. In addition, reduced concentration of thrombin causes an abnormal polymerization of fibrin monomers, which are susceptible to plasmatic degradation.20 The aim of this fibrinolysis is probably to restrict the propagation of clots to the site of vascular lesion.

The injuries of some organs are also associated, in a specific way, with an early posttraumatic coagulopathy. Specifically, severe traumatic lesion of the brain is usually followed by intensified bleeding, what is the result of release of specific cerebral thromboplastins into the circulation with the consequential consumption of coagulation factors6-20. Specific cerebral thromboplastins, tissue factor (TF) and cerebral phospholipids are occasionally released into circulation, however, the majority of recent studies have suggested that hyperfibrinolysis may even be a predominant mechanism and basic cause of intensified bleeding in patients with severe, isolated brain lesion.21-23

Fractures of long bones are also associated with coagulopathy; however, studies and literature data reporting these cases are scarce. The fact is that fat embolism, which is relatively frequent complication of the long bone fracture, may mimic the picture of typical DIC-type syndrome. Nevertheless, it rarely happens in early posttraumatic phases. An explanation for coagulopathy in this orthopedic trauma lies in the fact that multiple fractures of long bones are associated with an impaired coagulation due to massive tissue trauma, shock and inflammation.24

SHOCK

Recently, pathophysiology of the shock posttraumatic condition has been recognized as very significant and complex. Direct tissue damage initiates local response of affected cells that provoke systemic reaction that is significantly enhanced. A system of components that are present in plasma as the consequence of membrane cellular damage is released from the lesioned cells. Among them is a tissue factor (thromboplastin), as a part of adaptive response to injury. Non-lesioned cells in other parts of body react with mediators releasing their own compounds, i.e. adhesive molecules in the lungs during the hemorrhagic shock. The result of all this is a cascade of biochemical changes that synergistically produces the systemic disease, such as the acute lung injury after severe musculoskeletal trauma. Massive hemorrhage, with resulting shock state, is recognized as a trigger of complex multisystem disease and consequential change of dynamic equilibrium of coagulation system. Accordingly, the shock could be a primary initiator of early coagulopathy. There have been descriptions on dose-dependent relation between the degree and severity of tissue hyperfusion and degree of coagulation measured by prothrombin time (PT) and activated partial thromboplastin time (aPTT). Base deficit higher than 6 was associated with coagulopathy in one-quarter of patients in the enlarged study. Contrary to expected, platelet count remained unchanged. On the contrary, patients who do not develop shock state, have normal coagulation parameters (PT, aPTT), in spite of high ISS (Injury Severity Scores). All these disorders are present before fluid administration for volume supplementation and are not the sequela of dilution effects.
Brohi et al.\textsuperscript{28} has proven that tissue damage and consequent shock state give rise to intensification of fibrinolysis by protein C activation. The fact that coagulopathy is an early predictor of the severity of disease and the most frequent cause of lethal outcome from bleeding, significantly contributes to modification and improvement of resuscitation strategy.

In spite of all this knowledge, the true mechanism of origin of shock-induced coagulopathy has remained unclarified. Acidosis as the consequence of the circulatory volume loss and resulting hypoperfusion interferes with the function of coagulation proteases. It seems that the shock state is a sequela of changes in hemostatic system, which is under conditions of tissue damage, tissue perfusion and intravascular volume deficit, anticoagulant and hyperfibrinolytic.\textsuperscript{7} All these disorders are the result of massive endothelial disruption and tissue damage. One study relies on activation of protein C (aPC), which results from the increase of thrombomodulin activity.\textsuperscript{7} Thrombin through thrombomodulin complex results in hyperfibrinolysis either because of aPC consumption by PAI-1\textsuperscript{30} or reduced activity of TAFI (thrombin-activatable fibrinolysis inhibitor) \textsuperscript{30,31}.

In early post-traumatic phase, direct tissue trauma and shock with systemic hypoperfusion and circulatory dysfunction are probably primary factors responsible for the development of early coagulopathy. Early coagulopathy has been present in at least one of four patients with severe trauma and high ISS, so the mortality has been increased fourfold, as reported by several studies \textsuperscript{5,6}. Such form of coagulopathy is intensified by additional physical and physiological impairments associated with imminent hemorrhage, inadequate volume supplementation or transfusion therapy.

**Hemodilution**

Hemodilution is the main cause of clinical coagulopathy in trauma.\textsuperscript{32,33} During shock state, reduction of intravascular hydrostatic pressure results in redistribution of fluids to body compartments, that is, transfer of fluids, deficient in coagulation factors, from the intracellular and interstitial space into plasma. Resulting dilution of coagulation factors also occurs as the effect of fluid administration for correction of intravascular volume. In distinction from crystalloid solutions producing phenomenon of passive hemodilution, the application of colloid solutions significantly interferes with coagulation, both by passive hemodilution and direct modification of the primary clot quality because of reduction of adhesion forces in the primary clot and deficient activation of platelets. In addition, erythrocyte therapy induces dilution of coagulation factors by diminishing coagulation ability and reduced amount of coagulation factors. Erythrocyte and blood derivatives transfusion should be administered in 1:1:1 ratio (erythrocytes, plasma, platelets). Within hemodilution, the fact worth mentioning is that the fibrin clot is more susceptible to t-PA induced hyperfibrinolysis.\textsuperscript{34} Hemodilution reduces the PAI-1 levels, and therefore it insufficiently antagonizes the activity of t-PA. Moreover, the levels of FXIII, a2 antiplasmin and TAFI are decreased due to hemodilution, thus the existing fibrin is more susceptible to fibrinolysis.\textsuperscript{34}

**Hypothermia**

Hypothermia diminishes the synthesis of coagulation factors, inhibits the activity of coagulation proteases and interferes with platelet function.\textsuperscript{34,35} It accelerates fibrinolysis, and decelerates the activity of coagulation cascade, enzymatic processes, metabolism of lactates and citrates, thus advancing the development and deepening already existing metabolic acidosis.\textsuperscript{34} Activity of tissue factor or FVIIa complex declines linearly with temperature, whereby its activity is only 50% at temperature of 28°C\textsuperscript{35-37}. However, hypothermia may also have minimal effect on activated factor VIIa (FVIIa) and other proteases.\textsuperscript{37}

Platelets are probably more sensitive to hypothermia, because low temperature diminishes their activity.\textsuperscript{38} Lowered activity of platelets in hypothermia is the result of reduced and insufficient binding of von Willebrand’s factor to glucoprotein receptors Ib/IX. Activation is completely absent at temperature below 30°C.\textsuperscript{39}

Mild hypothermia is usual in traumatized patients due to reduced thermal production from hyper-perfused and non-perfused muscles and intensive loss of heat from body shivering and evaporation from body cavities during surgical intervention. Hypothermia may also be the consequence of medicament administration and infusion of cold solutions for volume supplementation.\textsuperscript{41}

Clinically significant effects on coagulation system, platelets and clinical bleeding may be seen in moderate hypothermia, at temperature below 34°C.\textsuperscript{35-37,42,43} Mortality rate from traumatic hemorrhage is significantly higher in severe hypothermia when body temperature is lower than 32°C.\textsuperscript{44}

Hypothermia weakens the immune response and reduces the production of cytokines and migration of neutrophils. Although this lowered immune response protects tissue from reperfusion lesion and inflammatory damage, yet hypothermia increases the risk of infection. Duration and degree of hypothermia are critical variables that have effect on the increase of infection incidence. Short-term deep hypothermia is not the same as mild or moderate one. Hypothermia lowers the systemic clearance of drugs cytochrome p450 approximately from 7%\textsuperscript{-22%} below temperature of 37°C. At cellular level, the reduction of adenosine-5-triphosphatase (ATP) plays an important role in development of spontaneous hypothermia.

Hypothermia that develops spontaneously after severe trauma is a marker of the severity of disease and associated with higher demand for transfusion and volume supplementation, therefore, it is a predictor of poor outcome.\textsuperscript{45,46}

In spite of all the aforementioned, fast control of hemorrhage, followed by adequate volume supplementation, keeps on being the baseline of resuscitation of severely traumatized patients. Nevertheless, the control of hemorrhage is not easy to achieve. At cellular level, hemor-
rhage and resuscitation induce changes that are alike ischemia-reperfusion lesion, including the production of reactive oxygen species, inflammatory cascade activation and increase of cellular apoptosis 47-49.

**Acidosis**

Iatrogenic factors (high level of citrates due to massive transfusion and intravenous volume supplementation by large quantities of saline), hypothermia, shock, ischemia-reperfusion phenomenon are the main reasons of acidosis interfering with the hemostatic potential 50. Lethal triad - hypothermia, acidosis, coagulopathy - significantly increases mortality. Degree of acidosis correlates with the severity of coagulopathy and percentage of mortality rate 51,52.

Acidosis changes the function of coagulation proteases. Clinically, it is very difficult to differentiate the effects of acidosis per se from the effects of shock and tissue hypoperfusion. Other than its interference with the activity of coagulation proteases, acidosis also disturbs the fibrin polymerization, and accordingly reduces the stability of blood clot.

Activity of FXa/Va complex is reduced by 50%, 70% and 90% at pH 7.2, pH 7.0 and pH 6.8, respectively 53. In addition, acidosis increases degradation and consumption of fibrinogen 54. Coagulopathy will not be corrected by buffer solution used for correction of metabolic acidosis 53,55, meaning that acidosis is a multi-constituent mechanism and not only the basic reduction of activity of coagulation proteases.

**INFLAMMATION**

Trauma is a potent initiator of inflammation, and the systemic inflammatory response syndrome (SIRS) is a common "companion" of the severe trauma 56. Endothelial activation and tissue damage lead to activation of cellular and humoral elements of the immune system. This simultaneous activation of inflammatory response and coagulation cascade, followed by tissue damage, phylogenetically has been and is an ancient strategy of survival. Activation of coagulation proteases may induce the inflammation through the transmembrane protease receptors that are located on the cellular surface and directly activate the complement 57-60. Degranulating platelets release lysophospholipid mediators that potentiate immune response by activation of neutrophils and endothelium 61,62. Conversely, the initiation of inflammatory response causes the disorder of coagulation. Higher monocye expression of tissue factor (TF) enables platelet adhesion at the site of injury 63-66. Endothelial activation of thrombomodulin-protein C pathway and competitive binding of C4b-binding protein to protein S bring about the alterations in anticoagulant pathways 67.

Initially, traumatized patients are in the state of early coagulopathy with the increased deficits due to massive hemorrhage; however, such state may easily be transferred to hypercoagulable condition, increasing the risk of thrombosis 68. This late prothrombotic state has unusual conspicuous similarity with coagulopathy in severe sepsis and additional protein C consumption 69. The incidence of sepsis is higher in traumatized patients, and in both events - trauma and sepsis - the episode of coagulopathy results in prothrombotic state 69 and propensity towards multiple organ failure (MOF).

**HYPOCALCEMIA**

Ionized calcium acts as a bridge between the negatively charged vitamin K-dependent coagulation factors, phospholipids and endothelium. Calcium is a protector of fibrinogen, because it prevents denaturation and proteolysis, and influences the function of platelets as well. Hemostasis is impaired if calcium levels are below 0.6-0.7 mmol/L. Critical levels are expected after administration of colloid solutions and vast amounts of fresh frozen plasma, especially in patients with the impaired hepatic function. Hypocalcemia potentiates hemorrhagic diathesis 34.

**CONCLUSION**

Etiology of trauma-induced coagulopathy is multifactorial. This condition is associated with massive blood loss, including the consumption of coagulation factors, platelets and hemodilution. Subsequent hyperfibrinolysis, hypothermia, shock, hypoperfusion, metabolic acidosis and electrolyte imbalance additionally interfere with the activity of coagulation system.

**SUMMARY**

KOAGULOPATIJA U TRAUMI

Trauma je i dalje vodeći uzrok morbiditeta i mortaliteta u savremenom svetu, naročito u populaciji mladih od 40 godina. Nedavne studije pružaju nova saznanja o centralnoj ulozi koagulopatije kod traumatizovanih. Masivna hemoragija je u 40% slučajeva uzrok smrti kod teško traumatizovanih i kontrola krvarjenja predstavlja poseban izazov u prisustvu razvijene i utvrđene koagulopatije. Nakon teške traume masivno krvarjenje je vrlo često posledica udruženog hirurškog i koagulopatskog krvarjenja. Masivan gubitak krvi umanjuje kapacitet koagulacionog sistema, te se posledično razvija koagulopatija, ćak i kod pacijenata čija je hemostaza pre povređivanja bila u fiziološkim granicama.

Ključne reči: koagulopatiija, trauma, mehanizam, nekontrolisano krvarjenje

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