Management of uncontrolled hemorrhagic trauma: state of the art

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Uncontrolled hemorrhagic trauma represents a challenge to the intensivist as it is a leading cause of potentially preventable death in trauma patients. Recently, damage control resuscitation and hemostatic resuscitation has become the standard of care for the management of these patients. The aim of this review is to highlight the pathophysiology of acute traumatic coagulopathy and the management of these challenging patients.

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Epidemiology

Trauma is a leading cause of death in children and adults, 1–44 years of age, in the USA. It is the third common cause of death across all ages, after cardiovascular disease and malignancy [1]. Uncontrolled hemorrhagic trauma represents 30% of trauma-related deaths. It is second only to traumatic brain injury as a cause of death. However, it is a leading cause of potentially preventable early in-hospital death. In other words, better resuscitation may lead to a better outcome in these patients [2].

Acute traumatic coagulopathy

Acute traumatic coagulopathy is often perceived as uncontrolled hemorrhagic trauma. Hess *et al.* [3] identified six key initiators for acute traumatic coagulopathy:

(1) Tissue trauma initiates the coagulation cascade through exposure of subendothelial collagen and tissue factor, which bind to the von Willebrand factor, platelets, and activated factor VII, resulting in thrombin and fibrin formation. Tissue trauma also initiates fibrinolysis through the release of tissue plasminogen activator from endothelium [4].
(2) Shock and hypoperfusion induce systemic anticoagulation and hyperfibrinolysis. During shock and hypoperfusion, there is increased endothelial thrombomodulin expression, which has high affinity of binding to thrombin. The subsequent binding of thrombin to thrombomodulin leads to activation of the protein C pathway. Activated protein C exerts an anticoagulant effect through irreversible inactivation of factors Va and VIIIa, and a fibrinolytic effect through inhibition of plasminogen activator inhibitor 1 [5].
(3) Hemodilution results from a shift of extracellular fluid into the vascular space because of a reduced intravascular hydrostatic pressure. In addition, hemodilution is further aggravated by intravenous fluid resuscitation through the administration of crystalloids and colloids [6].
(4) Hypothermia inhibits coagulation cascade enzyme reactions and induces platelet dysfunction. At body temperatures less than 33°C, there is reduced thrombin generation by 25%, reduced platelet adhesion by 33%, and decreased size of platelets aggregate by 40% [6].
(5) Acidemia impairs the activity of the extrinsic and intrinsic coagulation pathways, and also reduces platelet function. It has been shown that at pH 7.2, activity of the factor Xa/Va complex is reduced by 50%, whereas at pH 7.0, it is reduced by 70% [6].
(6) Inflammation: trauma and tissue injury lead to activation of cellular and humoral responses. Cellular response occurs through endothelial activation, platelet activation, endotoxin release, and an inflammatory adhesion molecule cascade, stimulating neutrophil activation and release of proteolytic and vasoactive substances. Humoral response occurs through activation of proinflammatory cytokines, and complement, kallikrein, eicosainoid, and fibrinolytic cascades [7].

The interplay between hypothermia, acidosis, and progressive coagulopathy is often referred to as the 'lethal triad', and often results in a vicious circle of uncontrolled hemorrhage.

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Damage control resuscitation

Following the wars in Iraq and Afghanistan, a new approach has been developed for the management of patients with uncontrolled hemorrhagic trauma, called damage control resuscitation. In fact, damage control is a naval term, used during maritime disaster, when military sailors have to save their ship, limit its damage, carry out emergency repair, and finish their mission.

In medical terms, damage control resuscitation is defined as 'Systematic approach to major trauma combining the catastrophic bleeding, airway, breathing and circulation paradigm with a series of clinical techniques from point of wounding till definitive treatment in order to minimize blood loss, maximize tissue oxygenation and optimize outcome' [8].

The armamentarium of damage control resuscitation includes permissive hypotension, early prevention of hypothermia and acidosis, rapid control of bleeding, and hemostatic resuscitation.

Permissive hypotension

Aggressive fluid resuscitation for uncontrolled hemorrhagic trauma patients is detrimental. Aggressive fluid may cause clot disruption, dilution of clotting factors, and reversal of vasoconstrictive reflex. The concept behind permissive hypotension involves keeping the blood pressure low enough to avoid exsanguination while maintaining perfusion of end organs. However, this concept represents a double-edged sword as a prolonged duration of shock may further aggravate acute traumatic coagulopathy. The target for permissive hypotension includes a systolic blood pressure of 80 mmHg and the presence of radial pulse. There is increasing evidence that hypotensive resuscitation exerts a beneficial effect on survival rates in penetrating trauma patients [9,10].

Early prevention of hypothermia and acidosis

Both hypothermia and acidosis have been associated with an increased risk of uncontrolled hemorrhage and death in hemorrhagic trauma patients. As stated before, hypothermia and acidosis slow down the activity of the coagulation cascade, reduce the synthesis of coagulation factors, increase fibrinolysis, and affect platelet function. Early prevention of hypothermia and acidosis is crucial for the successful management of hemorrhagic coagulopathy [6].

Rapid control of bleeding

Damage control surgery has emerged as an acceptable surgical technique in the management of uncontrolled hemorrhagic trauma patients. Damage control surgery involves two-stage surgery. The first-stage surgery is a limited surgical procedure that is performed for rapid control of hemorrhage. Following a period of intensive care management for correction of hypothermia, acidosis, and coagulopathy, the second-stage surgery is performed for definitive surgical repair [11].

Hemostatic resuscitation

Massive transfusion protocol

Development of the massive transfusion protocol for patients with uncontrolled hemorrhagic trauma is essential to standardize the blood transfusion approach in such a chaotic situation. The blood bank should be alerted immediately to incidents of uncontrolled hemorrhagic trauma to facilitate the preparation of various blood components at the appropriate time. Recently published studies have shown that the use of massive transfusion protocols decreased the overall consumption of blood products and reduced morbidity and mortality in uncontrolled hemorrhagic trauma patients [12–14].

Fresh whole-blood transfusion

Patients with uncontrolled hemorrhagic trauma lose whole blood, and hemodilution is inevitable with conventional blood component therapy, even with administration of the optimum ratio of blood component therapy. There has been renewed interest in fresh whole-blood transfusion, especially in the military setting. The use of fresh whole-blood transfusion has been shown to improve the survival rate in hemorrhagic trauma patients [15,16].

Optimum ratio of blood products

There is increasing evidence suggesting that blood component therapy in a ratio of 1 U packed red blood cells: 1 U plasma: 1 U platelet is the best possible alternative to fresh whole-blood transfusion when fresh whole blood is not available in our civilian setting. It has been shown that blood component therapy in such a ratio significantly increased the survival rate in hemorrhagic trauma patients [17,18].

Point-of-care coagulation assays

Coagulopathy is often monitored through conventional coagulation tests including prothrombin time and activated partial thromboplastin time. However, these tests have not been validated for the prediction

of hemorrhage in a clinical setting. Moreover, recent literature has shown that these tests are inappropriate for monitoring coagulopathy or to guide blood transfusion therapy. The advantages of thrombelastography have been reported in hemorrhagic trauma patients as thrombelastography is a rapid, simple test that can broadly determine coagulation abnormalities. Thrombelastography has been used to evaluate acute traumatic coagulopathy and has been shown to correlate with blood transfusion requirements and mortality rate [19,20].

Antifibrinolytic therapy (tranexamic acid)

There is increasing use of tranexamic acid during the management of uncontrolled hemorrhagic trauma patients. Tranexamic acid acts through a competitive inhibition of plasminogen activation. At higher doses, it also directly inhibits plasmin activity. There is evidence that early administration of tranexamic acid within first 8 h after trauma in patients with, or at risk of, significant hemorrhage, at a loading dose of 1 g over 10 min, followed by an infusion of 1 g over 8 h could reduce the risk of death from hemorrhage without an apparent increase in thromboembolic complications [21,22].

Recombinant factor VIIa

Coagulation factor VIIa plays an important role in the initiation, amplification, and propagation phases of the new cell-based model of hemostasis as it binds to tissue factor at the site of injury, initiates coagulation, and potentiates thrombin burst on the surface of activated platelets. Recombinant factor VIIa (rFVIIa) was initially developed for use in hemophilic patients with inhibitors to factors VIII and IX. However, it has been off-label used with a variety of other hemorrhagic conditions, including trauma and surgery. Recently, there has been increasing evidence that rFVIIa reduces red blood cell requirements in patients with blunt traumatic hemorrhage [23,24].

In fact, rFVIIa acts on the patient's own clotting system. Thus, administration of rFVIIa should only be considered after the following preconditions are achieved: fibrinogen levels more than 50 mg/dl and platelets count more than 50 000×10^9/l, and pH of more than 7.2. Thereafter, the recommended initial dose of rFVIIa is 120 μg/kg, administered intravenously over 5 min. If uncontrolled hemorrhage persists beyond 20 min, a second dose of 100 μg/kg should be considered. However, if uncontrolled hemorrhage still persists, preconditions for the administration of rFVIIa should be rechecked and corrected before a third dose is considered [25].

Vasopressin

Vasopressin is an important neuroendocrine mediator released from the posterior pituitary in response to increased plasma osmolarity and severe hypovolemia. A deficiency in vasopressin secretion contributes toward catecholamine-refractory shock after uncontrolled hemorrhagic trauma. An infusion of low-dose vasopressin 4 IU bolus, followed by 2.4 IU/h has been shown to maintain increased serum vasopressin concentrations and decrease fluid requirements during resuscitation, and was associated with increased survival. This beneficial effect was hypothesized to be mediated through diversion of blood flow from the periphery to vital organs. In fact, this low-dose vasopressin infusion is believed to be a hormone-replacement therapy rather than vasopressor therapy [26–28].

Summary

The concept of damage control resuscitation and hemostatic resuscitation should be used in the management of uncontrolled hemorrhagic trauma as all other efforts would fail to stop such hemorrhage.

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Conflicts of interest

None declared.

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