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Updates in the management of severe coagulopathy in trauma patients

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Abstract Coagulopathy is the major cause of bleeding-related mortality in patients who survive the operating room. Its association with hypothermia and metabolic acidosis is common and constitutes a vicious cycle. Usually, post-traumatic coagulopathy is an early event and may be present during surgery. The pathogenesis of severe post-traumatic coagulopathy is complex and multifactorial. Virtually every aspect of the normal coagulation cascade is affected in the cold, acidotic, exsanguinating trauma patient. In the last decade many surgeons have emphasized the role of prevention or early treatment of this vicious cycle. Damage control surgery with planned re-operations has demonstrated superiority over the traditional approach in cases where the patient's condition is deteriorating. Early control of surgical bleeding and

significant contamination, together with vigorous correction of hypothermia and continuous resuscitation, has improved the survival of these patients. Recently, a new adjunct to the treatment of coagulopathy in trauma patients has been reported and is undergoing controlled animal trials. Recombinant activated factor VII (rFVIIa) was originally developed as a pro-hemostatic agent for the treatment of bleeding episodes in hemophilia patients. rFVIIa has been successfully used in moribund trauma patients in whom standard procedures had failed to correct bleeding. Preliminary preclinical and clinical studies are under way.

Keywords Coagulopathy · Hypothermia · Hemorrhage · Recombinant activated factor VII (rFVIIa)

Introduction

Massive hemorrhage is a major cause of trauma-related mortality and is the second most common cause of death after central nervous system injuries in the pre-hospital setting [1]. Moreover, uncontrolled bleeding is the most common cause of early in-hospital mortality (first 48 h) due to major trauma [2].

Coagulopathy, when presenting with hypothermia and metabolic acidosis, is associated with high mortality and is the most common cause of bleeding-related mortality in the early postoperative period [3]. Severe injury itself, or together with multiple subsequent pathophysiologic

events leading to severe post-traumatic coagulopathy, is the cause of hemostatic failure in these patients. Virtually every aspect of the normal coagulation cascade is affected in the cold and acidotic trauma patient [4]. In the past decades many surgeons have emphasized the role of prevention or early treatment of this deadly triad and damage control surgery together with planned re-operations has been advocated. Indeed, immediate control of surgical bleeding, aggressive resuscitation and vigorous early correction of hypothermia improves survival in these patients [5]. Nevertheless, ongoing diffuse bleeding in this environment continues to be an ominous sign and a predictor of early trauma-related mortality [3, 6, 7].

Overview of the physiology of hemostasis

Hemostasis is achieved, under normal physiological conditions, through the interaction of blood vessels, formed elements of the blood and enzymatic reactions, which act in concert to produce a platelet plug within minutes of vessel injury. The exposure of subendothelial tissues and collagen after vessel injury allows platelet adhesion and aggregation. Moreover, production of thromboxane A₂ at the site of injury causes potent local vasoconstriction and further stimulation of platelet aggregation. The subsequent release of platelet granule contents (platelet factor 4, thromboglobulin, thrombospondin, platelet-derived growth factor, fibrinogen, von Willebrand factor, ADP and serotonin), particularly ADP, allows further platelet aggregation to occur at the site of the lesion. Platelet activation also leads to procoagulant activity through surface coagulation factors (factor Va), which ultimately lead to the production of a stable fibrin clot through a series of enzymatic reactions.

An effective fibrinolytic system is vital to maintain the fluid characteristics of blood in the intravascular space and to oppose the tendency toward blood coagulation. The principal reaction that takes place in this system is the activation of plasminogen to plasmin through the actions of plasminogen activators such as tissue plasminogen activator and urokinase. The system is regulated by the inhibitory actions of plasminogen activator inhibitor-1, which usually has low plasma levels but increases after trauma, and 2-antiplasmin which normally circulates at relatively high levels in the plasma. Small changes in the production or elimination of plasminogen activators and inhibitors can significantly change the balance of their activities in the plasma and thus have considerable effects on hemostasis.

Pathogenesis of coagulopathy in trauma patients

The multifactorial nature of post-traumatic coagulopathy involves hemodilution, hypothermia, consumption of clotting factors and metabolic derangements [8]. The constituents of the complex coagulopathy affecting trauma patients are discussed below.

Hemodilution

Dilutional thrombocytopenia represents the most common of the coagulation abnormalities occurring in trauma patients, and is particularly common in patients who receive transfusion volumes in excess of 1.5 times their blood volume. After replacement of one blood volume, only about 35–40% of platelets remain in circulation. Moreover, dilution of procoagulant factors is an acknowledged feature of fluid resuscitation, occurring as a

result of transfusion of packed red blood cells or crystalloid solutions. In a study involving 61 patients with major blood loss, the dilution of platelets and factors after administration of packed cells and colloid plasma substitutes was monitored [9]. Of the factors measured, fibrinogen was the most sensitive to dilution and levels reduced to 1.0 g/L (normal being 1.5–3.5 g/L) after the replacement of 142% of the calculated blood volume with packed red blood cells. Critical levels of prothrombin, platelets and coagulation factors V and VII were reached at 201–236% blood loss.

Other factors are also subject to dilution after massive transfusion, the ultimate result of which is a significant coagulopathy. These include the principal anticoagulant factors antithrombin III, protein C and protein S [10]. Levels of these anticoagulant factors probably decrease in a manner similar to the dilution of procoagulant factors, as described by Hiippala et al. [9].

Hypothermia

The severely bleeding patient has a high risk of developing hypothermia, and this condition has a tremendous adverse effect on normal coagulation mechanisms. Hypothermia can affect hemostasis at various levels including quantitative or qualitative platelet dysfunction, alteration of coagulation enzyme kinetics and disruption of the fibrinolytic equilibrium.

Effects on platelets

The occurrence of thrombocytopenia during hypothermic bleeding has been known for many years. In early canine studies, platelet sequestration in the liver and spleen was found to contribute to hypothermia-induced bleeding [11, 12]. Rewarming quickly reversed sequestration. Although these models highlighted quantitative platelet defects as an important cause of bleeding in hypothermia, studies in other species found that the effects on platelet function are also involved in the pathology [13, 14].

It has been reported that production of thromboxane B₂ was reduced during experimental hypothermia in baboons and human volunteers, and the effects were correlated with increased bleeding time [13, 14]. In both species, rewarming reversed the inhibitory effects on thromboxane B₂ levels. Additionally, platelet aggregation and the expression of platelet-surface molecules have been reported to be altered in hypothermic conditions in human volunteers [13]. Hypothermia at 22°C abolished the time-dependent upregulation of surface GMP-140 expression (a marker of granule secretion) and expression of the GPIb-IX complex (von Willebrand factor receptor) was almost eliminated. Moreover, platelet aggrega-

tion in shed blood from a standardized bleeding time wound was markedly reduced. All these effects were reversible on rewarming to 37°C.

Effects on coagulation factors and fibrinolysis

Although previous studies have attributed the bleeding abnormality in trauma patients to thrombocytopenia, platelet dysfunction or dilutional effects, recent investigations have focused on the role of the coagulation cascade.

Temperature is an important factor determining the results of clotting studies: as the assaying temperature is decreased from 37° to 25°C, clotting times are prolonged significantly [15, 16, 17, 18]. Prothrombin time (PT) appears to be the index most sensitive to a reduction in assay temperature, being significantly increased at all temperatures below 35°C. The activated partial thromboplastin time (aPTT) was significantly prolonged at temperatures below 33°C [15]. The disparity between hypothermic coagulopathy and results from clotting studies has been further illustrated in an animal study [18]. When clotting studies were performed at incrementally lower temperatures (from 37 to 25°C) in blood obtained from normothermic rats, the PT, aPTT and thrombin time were all significantly prolonged. In contrast, performance of clotting tests at 37°C in blood obtained from hypothermic rats revealed no significant abnormalities. These findings highlight the disparity between the clinically evident hypothermic coagulopathy and near normal clotting studies, and suggest that altered enzyme kinetics in the coagulation cascade are a major effect of hypothermia.

Alterations in clotting factor enzymatic activities are functionally important and the changes in coagulopathy have been compared with specific clotting factor deficiencies. At temperatures below 33°C, hypothermia is equivalent to significant factor deficiency states under normothermic conditions, despite the presence of normal clotting factor levels [19]. At a temperature of 33°C, the impairment in coagulation processes is equivalent to a factor IX deficiency of 33% of its normal level. Just as hypothermia has an impact on platelet function and the coagulation cascade, it also exerts an effect on the fibrinolytic system. In the hypothermic state, fibrinolysis is increased in an animal model [20]. Moreover a greater degree of clot lysis, attributed to the impairment of intrinsic inhibitors of fibrinolysis such as plasminogen activator inhibitor or 2-antiplasmin, occurs at lower temperatures [21].

Clotting factor depletion

Systemic clotting factor depletion and diffuse coagulopathy may also develop in patients with massive injuries due to the body's continuous attempts to form clots at

multiple injury sites. Fibrinolysis, which teleologically serves to clear thrombi from the microvasculature and to limit the formation of thrombus, is activated by clotting. Hence massive clotting factor activation resulting from multiple injuries may lead to uncontrolled activation of the fibrinolytic system and a cycle of clotting factor activation with further production of antithrombins [22].

A number of specific injuries may lead to the rapid development of a state of coagulopathy. Severe pulmonary contusions or breakdown of the blood-brain barrier after brain injury may result in the release of tissue thromboplastin from the damaged tissue into systemic circulation [23]. Regardless of its source, the release of thromboplastin causes intravascular activation of coagulation and formation of thrombin and subsequent fibrin clots. Vigorous fibrinolysis, manifest as an elevation in D-dimer levels, renders the clots soluble again. Consequently, coagulation factors and fibrinogen are depleted and a profile of disseminated intravascular coagulation (DIC) develops. Coagulopathy may also result from severe liver injury via several different mechanisms. The injury may be severe enough to reduce coagulation factor production [24]. Alternatively, resuscitation of a patient with severe liver injury may involve administration of a large amount of crystalloids, leading to hemodilution and a consequential dilutional coagulopathy.

Metabolic derangements

Hemorrhagic shock eventually results in intracellular derangements in oxygen and substrate utilization that lead to metabolic acidosis. Correction of acidosis can significantly reduce organ failure rates and mortality, compared with those in patients with persistently elevated lactate levels and reduced oxygen consumption [25]. Studies demonstrate a strong correlation between the development of coagulation abnormalities and the hypotension duration. There are also studies demonstrating that hypoperfusion is associated with consumptive coagulopathy and microvascular bleeding occurring independently of the amount of blood loss [26]. In one study, shock-induced acidosis lasting in excess of 150 min independently resulted in significant prolongation of the aPTT and decreases in factor V activity [27].

Diagnosis

Coagulopathy is usually easy to recognize in a trauma patient by the clinical assessment of ongoing bleeding, physical examination and observation of oozing from cut surfaces, intravascular catheter sites or mucus membranes. The laboratory studies performed most commonly in these patients include platelet count, PT, aPTT and fibrinogen level.

As hypothermia is a significant independent contributor to coagulopathy, care should be taken when interpreting laboratory coagulation studies in the hypothermic patient. The standard assays used to assess clotting function are all performed at a temperature of 37°C and, although they provide useful quantitative information regarding clotting factors, qualitative dysfunctions due to hypothermia are not taken into account. Indeed, the contribution of hypothermia to a bleeding diathesis might potentially be overlooked on the basis of testing at standardized temperatures [16]. Additionally, there is often a considerable time interval before completion of the main coagulation tests, with PT and aPTT often taking up to 1 h to obtain [22].

Thromboelastography (TEG) is a promising new method for predicting hemorrhage and can be performed at the bedside. This technology measures the viscoelastic properties of blood [28] using a warm cup containing a fixed piston that does not touch the side walls, into which approximately 0.4 mL of blood is added. The cup rotates around the piston until a bridging clot has formed and the amount of power required to maintain the rotational movement of the cup is measured. TEG examines whole blood coagulation, providing information on how fast the clot forms, the speed of clot growth and whether clot strength is maintained or breaks down early. These are key elements in determining the likelihood of platelet and clotting factor deficiencies, and fibrinolysis [29]. The technique of TEG has influenced both blood utilization and re-operation rates in cardiac surgery, and its successful use is being increasingly reported in the trauma literature [30, 31].

Treatment

Therapy of patients with coagulopathy after major trauma should be rapidly initiated and aggressively pursued throughout all steps of resuscitation and treatment. Management begins with ensuring that adequate help and equipment (e.g., fluid warmers, blood filters, pressure gauges) are available for the rapid administration of fluid, blood and blood products, and the blood bank should be informed of large transfusion requirements as early as possible. Dependable, large-bore venous access must also be established.

Staged laparotomy

Prolonged operative times in patients with multiple injuries increase the likelihood of progressive physiological decline into hypothermia, coagulopathy and acidosis. When exsanguinating trauma patients undergo surgery, attempts should be directed towards rapid cessation of surgical bleeding and control of contamination rather

than attempts to repair all the injuries definitively. Using the technique of staged laparotomy, a minimal operation is performed to stop surgical bleeding and contamination, and diffusely bleeding surfaces can be packed with multiple laparotomy pads allowing temporary abdominal closure followed by rapid transfer of the patient to an intensive care unit (ICU) for resuscitation. Priorities in the ICU focus on restoring the global physiological function of the patient before return to the operating room for definitive repair and reconstruction [32].

Management in the ICU

The major goal of treatment in the ICU is to arrest the bloody vicious circle of hypothermia, coagulopathy and acidosis to minimize blood loss. Hypothermia is ideally treated by prevention, and routine use of environment and fluid warmers will help to decrease the progressive decline in body temperature. Despite attempts to minimize ongoing heat loss and passively rewarm the patient, hypothermia may develop and in some cases invasive procedures such as body-cavity lavage or extracorporeal circulatory rewarming may be required to raise body temperature [33].

Recognition and prompt treatment of hypoperfusion is also vital to minimize and reverse cellular shock and correct metabolic acidosis. Blood and blood product therapy is essential to these patients. Although optimal therapy should be directed by abnormalities in coagulation laboratory tests, when massive exsanguination occurs and large volumes of packed red blood cells are required, both clinical and laboratory coagulopathy is usually noted. In this situation, delay in the initiation of blood component therapy for confirmation of coagulopathy by laboratory studies is detrimental to the outcome, and the essential first step is transfusion of clotting factors and platelets until the consumptive process resolves. The time-consuming nature of current coagulation monitoring tests (40–60 min) compromises the optimal treatment of bleeding. Moreover, if clotting factors are needed, an additional 30–40 min is added for thawing and transport. During this time the entire blood volume of the bleeding trauma patient may have been exchanged, making the results of the laboratory tests obsolete. Also, the significance of coagulopathy in the hypothermic patient is often underestimated [15, 16, 17] by standard coagulation tests performed at 37°C and a state of abnormality may not be revealed.

The practice of damage control surgery requires recognition and treatment of coagulopathy even faster than immediate laboratory turnaround time permits [8]. Accordingly, the diagnosis of coagulopathy should be based on clinical grounds if laboratory studies are not available. Specifically, if patients show oozing from cut surfaces, intravenous lines or other visible signs of overt coagulopa-

thy, platelets and fresh frozen plasma should be transfused while awaiting the results of laboratory investigations.

Recombinant activated factor VII for adjunctive hemorrhage control

Recently, a new adjunct to the treatment of coagulopathy in trauma patients has been reported [34, 35] and is undergoing controlled animal trials. Recombinant activated factor VII (rFVIIa) was developed as a pro-hemostatic agent for the treatment of bleeding episodes in patients with hemophilia A or B with inhibitors to factors VIII or IX, respectively. rFVIIa is almost identical in structure and activity to human factor VII [36] and its mode of action highlights it as a promising agent for treating acquired coagulopathy. rFVIIa becomes active after forming a complex with tissue factor, which is located in the subendothelial media and thus is only exposed to circulating blood after vessel injury [37]. Formation of the tissue factor-rFVIIa complex initiates activation of factors IX and X, inducing a thrombin burst and faster formation of the fibrin clots at the site of vascular injury.

A case report described the first successful use of rFVIIa in an exsanguinating trauma patient [34]. A 19-year-old soldier with a high-velocity rifle injury to the

inferior vena cava continued to bleed despite conventional surgical and medical attempts to restore hemostasis. Administration of rFVIIa 60 µg/kg corrected the coagulopathy and a further dose 1 h later resulted in immediate cessation of bleeding. Subsequently, the compassionate use of rFVIIa for patients suffering massive life-threatening bleeding as a result of surgery or trauma was approved by the Ethical Committee of the Israeli Ministry of Health. A series of seven critically ill coagulopathic multitransfused trauma patients, in whom conventional medical and surgical hemostatic techniques had failed, were treated with rFVIIa 40–120 µg/kg [35]. The diffuse bleeding decreased within 5 min of the administration of 1–3 doses (median 2) of rFVIIa, allowing identification of the vessels requiring surgical intervention (e.g., cauterization, ligation, argon beam). Blood requirements, PT and aPTT were all significantly decreased compared with pretreatment values after rFVIIa administration (Table 1). Three of the seven patients died from causes other than bleeding or thrombotic events and no thromboembolic complications were reported in any patient.

Since the first reports of the use of rFVIIa in trauma patients, controlled animal studies have been undertaken to evaluate this agent systematically and to establish “proof of concept” in trauma models. The use of rFVIIa as an adjunctive measure for hemorrhage control has been evaluated in hypothermic coagulopathic swine with grade V liver injury [38]. Anesthetized swine underwent an isovolemic hypothermic exchange transfusion (60% of estimated blood volume) with 6% hydroxyethyl starch cooled to 33°C, before creation of the liver injury (large parenchymal defect and laceration of 1–3 major central hepatic veins). All animals were gauze packed, received resuscitation fluids to return the mean arterial pressure to pre-injury levels and were randomized to receive rFVIIa 180 µg/kg or placebo. Post-treatment blood loss was 46% ($p<0.05$) lower in animals receiving rFVIIa compared with those in the control group (Table 2), although

Table 1 Effect of 1–3 doses of recombinant activated factor VII (rFVIIa) 40–120 µg/kg on blood requirements and coagulation parameters in patients with blunt or penetrating traumatic injury in whom conventional hemostatic measures had failed. Median values (range) are presented. Data from Martinowitz et al. [35]

Parameter	Baseline	After rFVIIa
Packed cell units	36.5 (25–30)	2 (1–2)*
Prothrombin time (s)	24 (20–31.8)	10.1 (8–12)*
Activated partial thromboplastin time (s)	79 (46–110)	41 (28–46)*

* $p<0.05$ versus baseline

Table 2 Effect of recombinant activated factor VII (rFVIIa) or placebo on hemostatic parameters in swine models of hypothermic coagulopathy [38] and hemorrhagic shock [39] after liver trauma. Data presented are mean ± SD in [38] and mean ± SEM in [39]

Parameter	Grade V liver injury in hypothermic coagulopathy Martinowitz et al. 2001 [38]		Grade IV liver injury in hemorrhagic shock Lynn et al. 2002 [39]	
	Control (n=5)	rFVIIa (n=5)	Control (n=7)	rFVIIa (n=6)
60-min mortality (%)	0	0	43	0
Resuscitation volume (mL)	2792±2463	2070±1217	–	–
Blood loss	976±573 mL	527±323 mL ^a	33.3±3.4 mL/kg	27.6±2.1 mL/kg
Prothrombin time (s) ^c				
Baseline	18±1.6	18±0.9	11.6±0.3	10.8±0.2
5 min	20±0.7	11±1.1 ^a	10.8±0.3	6.2±0.2 ^b
15 min	19±0.8	11±0.5 ^a	11.4±0.3	6.1±0.1 ^b
60 min	21±3.3	12±1.0 ^a	10.4±0.4	6.4±0.1 ^b

^a $p<0.05$ versus baseline; ^b $p<0.05$ versus placebo and baseline; ^c Measured at 33°C in [38]

the resuscitation volume did not differ between the groups. Administration of rFVIIa also produced a significant reduction in PT compared with baseline values, whereas there was no shortening of this parameter in the control group (Table 2). Systemic activation of the coagulation system was not observed. These results indicate the ability of rFVIIa to reduce blood loss and resolve abnormal coagulation when used in conjunction with liver packing in hypothermic animals.

Another pilot study has evaluated the efficacy of rFVIIa in reducing bleeding when administered early after injury in a pre-hospital model of hemorrhagic shock [39]. A reproducible grade IV liver injury was created in anesthetized swine by crushing and avulsion of the left median lobe and major vessels of the left lateral lobe. After a decrease in mean arterial pressure of 10% from baseline (indicative of major bleeding) animals were randomized to receive rFVIIa 180 µg/kg ($n=6$) or placebo ($n=7$). The PT was significantly shorter in the rFVIIa-treated group compared with baseline and placebo after 5 min (Table 2). Moreover, the mean arterial pressure was significantly reduced in the placebo group ($p<0.05$) compared with baseline and the rFVIIa group after 5 (30±6.1 vs 59±8.7 mmHg), 15 (35.6±4 vs 58.3±7.2 mmHg) and 60 min (33.5±8.8 vs 65.6±5 mmHg). Although mor-

tality and calculated blood loss during the first 15 min were lower in animals receiving rFVIIa than in the placebo group, the small sample size did not allow demonstration of statistical significance. The results of this study indicate that administration of rFVIIa early after induction of injury shortens the PT and improves mean arterial pressure in a non-resuscitated model of severe liver injury.

Conclusion

Refractory coagulopathy in trauma patients is a common event and is associated with high mortality when combined with hypothermia and acidosis. The diagnosis of coagulopathy is made on a clinical basis and TEG may be a new aid allowing fast diagnosis of coagulation abnormalities. The mainstay of treatment for refractory coagulopathy is immediate control of bleeding, rapid termination of surgery and early and aggressive correction of hypothermia and metabolic derangements. rFVIIa, a potential new therapy for hemorrhage control early after injury, and as an adjunctive measure in situations of hypothermic coagulopathy, is being evaluated in controlled animal studies and in randomized, double-blind clinical trials.

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