Nonsurgical Techniques to Control Massive Bleeding

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KEYWORDS

• Trauma • Shock • Traumatic hemorrhage • Embolization • Angiography • Hemostatic therapy • Coagulation factors

KEY POINTS

- Despite new therapeutic approaches to prevent and overcome trauma-associated coagulopathy, morbidity and mortality remain unacceptably high.
- Studies from recent years have shown that coagulation factors and factor concentrates may be useful for reducing the need for fresh frozen plasma, platelet, and red blood cell transfusions.
- It is necessary to identify the cause of the coagulation deficiency to tailor the therapy for terminating coagulopathy using coagulation factor concentrates to each patient's specific needs. Further research and randomized controlled trials are urgently needed to better understand and develop clear strategies to overcome coagulopathy.

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INTRODUCTION

Trauma is responsible for most deaths worldwide and is the leading cause of death before the age of 45 years in the United States.[1] Uncontrolled bleeding still poses a major challenge and is second in the list of early overall causes of trauma-related death,[2] accounting for almost half of all trauma deaths within the first 24 hours.[3]

In recent years, significant improvements in the nonsurgical and surgical treatment of trauma patients have been made. For example, damage control surgery is aimed at increasing the survival of severely injured patients and stopping life-threatening hemorrhage. The principles of damage control surgery incorporate the choice of the appropriate type and timing of surgical procedures. The repair of minor injuries is deferred because prolonged surgical treatment might initiate or exacerbate a preexisting coagulopathy. Coagulopathy occurs early after injury,[4] is associated with a 4-fold to 5-fold increased mortality,[5–7] and is present in approximately one-fourth to one-third of trauma patients at admission to a hospital.[5,6,8] Thus, the management of bleeding in the first hours after trauma is crucial to prevent death from hemorrhage. The combination of surgery, principles of damage control, external fixation, and angiographic embolization may sufficiently arrest bleeding from vascular damage in some cases of traumatic injury. Nonsurgical approaches are urgently required to successfully manage diffuse bleeding in the presence of coagulopathy or to prevent the fortification of coagulopathy. The overarching goals are to reverse the existing coagulopathy and to regain physiologic conditions to facilitate hemostasis, and these goals require more specific treatment in most cases. The directed use of coagulation factors and factor concentrates can support the correction of coagulopathy associated with massive blood loss in severely injured patients. Trauma-induced coagulopathy is complex and therefore requires a wide-ranging approach to therapy. However, the best treatment options and their timing are still under debate. Therefore, this article considers new developments in the contemporary, nonsurgical management of critical trauma bleeding.

TOURNIQUET AND PELVIC BINDER

Studies from military settings have shown that the use of tourniquets is highly effective for controlling life-threatening arterial bleeding from mangled extremities.[9–14] Overall, the studies show a low rate of complications after the use of tourniquets.[15] To reduce the potential side effects of tourniquets, such as limb ischemia and nerve paralysis, it is advised to keep the time of tourniquet application to a minimum.[16,17] Lacking published evidence, the role of the prehospital use of tourniquets remains unclear, although positive results have been reported for certain indications, such as severe trauma from firearms and industrial machinery as well as in cases of multiple casualties with limited resources.[18]

Several circumferential pelvic binders have been introduced in recent years. Their application is fast and simple and allows a temporary and quick pelvic closure. The stabilization of pelvic fractures in the emergency department with commercial compression devices or simple bed sheets in hemodynamically unstable patients is also advised according to the advanced trauma life support guidelines.[19] Although the prehospital application of a pelvic binder as initial treatment of a diagnosed or suspected unstable pelvis (for example, after high-energy trauma) might be advantageous, few studies have shown a benefit to clinically relevant end points.[20]

ANGIOGRAPHY AND EMBOLIZATION

In addition to surgery as the cornerstone of bleeding control, transcatheter angiographic embolization (TAE) is an established, minimally invasive technique used to control arterial bleeding from solid organ injury or pelvic fracture.[21–25]

This continuously evolving technique is used to arrest posttraumatic hemorrhage from solitary organs such as the spleen[26–28] and liver.[29–33] However, the main indication for the use of embolization is the control of bleeding resulting from pelvic fractures. This technique is regarded as part of the multidisciplinary treatment of severely injured patients, and success rates of more than 90%[25,34–37] have been reported. For instance, Fangio and colleagues[38] reported a radiologic success rate of 96% in a series of 25 patients with pelvic injuries. Using this technique, hemodynamic stabilization was achieved in 84% of patients. Hagiwara and colleagues[39] documented a successful outcome after TAE in 19 patients with blunt multiple trauma who showed only a transient response to fluid resuscitation.

Hemodynamically unstable patients with pelvic fractures should be considered for pelvic angiography/embolization if nonpelvic sources of bleeding have been excluded.[40]

The Technique and its Safety

The widespread use of multidetector computed tomography scanners within the initial diagnostic testing of trauma patients can provide early evidence for arterial contrast extravasation. This finding supports the identification of injuries that require embolization regardless of the hemodynamic status of the patient. To perform angiography, arterial access has to be gained first. An abdominal flush can then be used to assess abdominal sites. This procedure is followed by a pelvic flush and more selective evaluations in the internal and external iliac arteries.[41] Using angiography, the signs of vascular injuries in need of embolization include the extravasation of injected contrast, false aneurysm, vasospasm, and arteriovenous fistula.[42,43] The embolization of large vessels (main arteries and branches) is achieved using gelatin sponges or steel coils. Smaller vessels can be embolized with particles, gelatin sponges, or microcoils. Temporary agents such as a gelatin sponge suspension can also be used for multiple arterial injuries to allow subsequent recanalization.[42] After the initial treatment, angiography should then be repeated to ensure successful occlusion and exclude new sites of bleeding or ongoing bleeding fed by collateral pathways.

In general, pelvic embolization is associated with low morbidity.[24,25,44,45] However, serious complications have been reported, including necrosis of the distal colon and ureter, uterine and bladder necrosis, perineal wound sepsis,[46] ischemic damage to the gluteal muscle,[47] and paresis.[48] Risks should be considered if angiographic embolization is an option for the treatment of the patient, and the likelihood of nontarget embolization has to be minimized by assiduously performing the procedure and using (super-) selective techniques whenever feasible. The success of angiographic embolization highly depends on the experience with this technique. Furthermore, not all trauma centers can provide emergency angiographic diagnostic and treatment facilities that operate day and night.

Timing and Management

Delayed intervention (>3 hours) increases mortality from 14% to 75%.[34] Angiography and embolization should be conducted early after admission in hemodynamically unstable patients with ongoing or suspected bleeding.[41] However, the most beneficial sequence of angiographic embolization for controlling bleeding relative to surgical

interventions is controversial.[49,50] For the early detection of the main source of hemorrhage, the best sequence is dependent on the individual patient. Whereas bleeding from veins, smaller arteries, and cancellous bone may be effectively controlled by external fixation, arterial bleeding may be successfully treated using surgery or angiographic embolization. Each of these therapeutic options is primarily concerned with a different site of bleeding. At best, the initial treatment should address the predominant source of bleeding and determine whether it is arterial or venous. In several studies, angiography detected arterial lesions in 44% to 76% of patients.[24,25,34,49–53] A retrospective case series of bleeding pelvic fractures identified positive angiographic findings in 73% of patients who remained hypotensive despite resuscitation.[49] The investigators concluded that an adequate response to resuscitation makes arterial bleeding unlikely. Furthermore, the investigators found arterial bleeding amenable to embolization in 7 of 16 patients (44%) who underwent external fixation before angiography. In these cases, treatment might have been delayed.[49] A retrospective multicenter study including 217 patients showed the need for TAE in 23 of 24 patients (96%) with severe injuries that could not be controlled by various surgical interventions.[50] The investigators concluded that nontherapeutic laparotomy should be avoided.

To determine the best sequence of management, several investigators have studied the underlying pattern of pelvic fractures according to the Young-Burgess classification to predict the potential requirement for acute embolization.[52,54,55] Eastridge and colleagues[52] retrospectively analyzed 86 patients with pelvic fractures (40 stable, 46 unstable) who presented in shock with an ongoing resuscitative requirement. Patients with unstable fractures undergoing laparotomy before angiography had a higher mortality (60% vs 25%). These findings suggest that angiography should be considered before laparotomy in patients with unstable fracture patterns.[52] In contrast, a study performed by Sarin and colleagues[54] including 283 patients with pelvic fracture and a systolic blood pressure 90 mm Hg or less at admission did not show a correlation between the fracture pattern, the order of embolization, external fixation, or laparotomy and the outcome. Accordingly, no correlation was found between specific fracture classes, outcome variables, and the need for early angiography.[55] A more recent prospective observational study identified the presence of sacroiliac joint disruption, female gender, and the duration of hypotension as reliable and simple risk factors to predict the need for therapeutic TAE.[56]

Typically, angiographic embolization is performed in a specialized angiography suite. The spatial distance between the emergency department, the angiography suite, and the operation theater requires the transport of a potentially hemodynamically unstable patient. To address this problem, an intra-aortic balloon occlusion procedure for hemodynamically unstable patients has been described.[57] Morozumi and colleagues[58] reported the use of mobile angiography and embolization in the emergency department to improve resuscitation intervals. C-arm digital subtraction angiography may also be used to perform emergency angiographic embolization in the operating theater.[45] This procedure enables the simultaneous surgical treatment of extrapelvic injuries if the institutional concepts are defined and logistical problems are solved.

Therefore, in most institutions, it is necessary to determine which treatment should be performed first. Nonetheless, it is generally agreed that the optimal resuscitation of these severely injured patients requires a multidisciplinary approach. Further clinical studies are needed to aid clinical decision making and refine the optimal timing of embolization relative to surgical bleeding control.

COAGULOPATHY AFTER TRAUMA

Life-threatening bleeding in polytraumatized patients is typically caused by a combination of traumatic injury and coagulopathy. Several mechanisms contributing to trauma-induced coagulopathy have been described (**Box 1**).[59] Immediately after trauma, shock and tissue hypoperfusion can cause metabolic changes affecting the initiation of coagulation.[60] Tissue hypoperfusion also leads to increased concentrations of activated protein C and thrombomodulin. The activation of this pathway overstimulates anticoagulation with a downregulation of thrombin generation.[4] Coagulopathy is further aggravated by hypothermia, anemia, low concentrations of calcium, acidosis, and the dilution and loss of coagulation factors.[61] To restore the coagulation system, fresh frozen plasma (FFP), cryoprecipitate, platelets, and coagulation factor concentrates are used. There are well-known drawbacks to the use of FFP,[62] including the induction of transfusion-related acute lung injury, transfusion-associated circulatory overload, and multiorgan failure.[63] In recent years, there has been a shift from empiric coagulation therapy toward an early targeted therapy using thromboelastometry and a more intense replacement of coagulation factors using recombinant and lyophilized coagulation factors. The application of recombinant and plasma-derived coagulation factor concentrates is argued by their immediate availability, decreased volume, rapid administration, and good viral safety.

BLOOD COMPONENT REPLACEMENT THERAPY

Antifibrinolytics

Antifibrinolytic agents include the serine protease inhibitor aprotinin, the synthetic lysine analogue e-aminocaproic acid and tranexamic acid.[64] The antifibrinolytic mechanism of the lysine analogues is mediated by competitive binding to the lysine binding site of the fibrin clot. Thereby, they block the binding of plasminogen to tissue plasminogen activator. This process hampers the conversion of plasminogen to plasmin and the subsequent plasmin-mediated fibrinolysis. In a large randomized study, the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) trial investigated the impact of tranexamic acid in 20,211 patients (admitted to 274 hospitals in 40 different countries) with major trauma who had or were at risk of severe hemorrhage.[65] Within 8 hours of injury, patients were treated with either tranexamic acid (1 g over 10 minutes followed by an additional 1 g over 8 hours) or with placebo. Overall, treatment with tranexamic acid decreased the rate of mortality and the risk of death as a result of hemorrhage. In addition, it was shown that early tranexamic acid treatment (within 1 hour) reduced the rate of death as a result of

Box 1
The factors contributing to trauma-induced coagulopathy are multifactorial and interrelated

- Loss and consumption of coagulation factors
- Shock-induced activation of the protein-C pathway
- Hyperfibrinolysis
- Dilution of coagulation factors
- Anemia and low platelet counts
- Metabolic changes (acidosis)
- Hypothermia
- Hypocalcemia

bleeding compared with its late application (1–3 hours).[66] A nested control study also showed that patients with traumatic brain injury showed a decrease in the mean intracranial size of hemorrhage.[67] Overall, treatment with tranexamic acid did not result in major adverse or thrombotic complications. Even before the results of these studies were published, the European guidelines for the management of bleeding recommended considering the use of tranexamic acid in bleeding trauma patients.[68] Based on the findings of the CRASH-2 trial, it is likely that the early administration of antifibrinolytic treatment using tranexamic acid will be recommended as a first-line treatment of established or suspected hyperfibrinolysis in patients presenting with major blood loss after trauma.

Fibrinogen

In normal plasma, fibrinogen is one of the most abundant coagulation factors with a concentration of 150 to 400 mg/dL. On dilution, fibrinogen is the first factor to reach critically low concentrations, as shown by Hiippala and colleagues.[69] Similarly, in severely injured patients with massive bleeding, fibrinogen typically reaches critical concentrations at an early stage. Next to the loss and consumption of fibrinogen after trauma, hyperfibrinolysis, hypothermia, and acidosis may further compromise the fibrinogen concentration.[70] Experimental data from animal studies and in vitro studies have shown that the application of exogenous fibrinogen increases clot firmness and reduces blood loss after blunt liver injury.[71–74] Several retrospective and prospective clinical studies performed in an array of clinical areas have shown that fibrinogen levels less than 150 to 200 mg/dL enhance the risk of perioperative and postoperative hemorrhage tendency.[75,76] In patients with postpartum hemorrhage, the fibrinogen level has also been shown to predict the severity of hemorrhage.[77] Evidence supporting the administration of fibrinogen to traumatized patients is derived from a retrospective study including 252 seriously injured soldiers and civilians who received a massive transfusion (defined as >10 units of red blood cells [RBC] in 24 hours).[78] The analysis of these data showed that the strategy of increasing the fibrinogen/RBC ratio was independently associated with improved survival to hospital discharge, primarily by decreasing death from hemorrhage. Despite the current evidence showing that the early use of fibrinogen concentrate exerts a protective effect against blood loss in severely bleeding patients, no prospective confirmatory data in traumatized patients are available. In addition, the critical threshold value is a matter of debate. Recent international recommendations suggest that the trigger of 100 mg/dL may be too low and that fibrinogen concentrations of 150 to 200 mg/dL may be appropriate.[68]

FFP, cryoprecipitate, and fibrinogen may be used to restore low concentrations of fibrinogen. However, large volumes of FFP are needed to efficiently resolve low levels of fibrinogen. Compared with FFP, the concentration of fibrinogen in fibrinogen concentrates is approximately 10-fold higher. As an alternative, cryoprecipitate containing factor VIII, fibrinogen, fibronectin, Von Willebrand factor, and factor XIII may be used.[79] A dose of approximately 10 single bags of cryoprecipitate derived from units of whole blood typically increases the plasma fibrinogen level by up to 60 to 100 mg/dL. However, because of the risk of blood-borne pathogen transmission, the use of cryoprecipitate for this indication should be considered with caution. Compared with FFP and cryoprecipitate, pasteurized fibrinogen is virus inactivated and has had a good overall safety profile.

Prothrombin Complex Concentrate

Prothrombin complex concentrates (PCCs) are concentrates of the vitamin K-dependent clotting factors (II, VII, IX, and X). Although PCCs with low amounts of factor VII

are available (3-factor PCCs), PCCs containing higher concentrations of factor VII (4-factor PCCs) are more commonly used in Europe for the acute reversal of vitamin K antagonists. PCCs may also contain heparin, proteins C, S, and Z, and antithrombin, and the levels of these constituents differ markedly between PCCs.[80] The indications for the use of PCC are a fast reversal of oral anticoagulation with warfarin or a known deficiency of the vitamin K-dependent factors in potentially life-threatening bleeding.[81] The substitution should be supplemented by intravenous vitamin K to induce the endogenous synthesis of vitamin K-dependent factors. Because PCCs are highly efficacious thrombin generators, there is a growing interest in their use in trauma-related coagulopathy with multifactor deficiencies. Nevertheless, no prospective studies have investigated the use of PCC as a first-line monosubstance therapy for trauma-related coagulopathy. All evidence supporting the use of PCCs in trauma-related coagulopathy has been provided by observational and animal studies.[82–88] The results of these animal studies show that the application of PCC reduces blood loss, shortens bleeding time, and enhances thrombin generation. However, one animal study also showed that high concentrations of PCC increased the risk of thrombosis and disseminated intravascular coagulation.[83] This finding was attributed to an imbalance of procoagulatory and anticoagulatory proteins.

In addition to these experimental studies, three observational studies investigated the use of PCC as part of coagulation therapy in different surgical areas. Although the results also imply that PCC may effectively terminate severe bleeding, the evidence is limited by the retrospective design of the studies and the small number of patients.

For instance, a retrospective analysis investigated the efficacy of PCC in patients with severe bleeding not related to coumadin.[87] The data were mainly obtained from patients undergoing different surgical interventions, and PCC was administered at a median dose of 2000 IU. A coagulation analysis revealed a significant reduction in international normalized ratio after PCC infusion that was associated with bleeding termination in 36% of patients with surgical bleeding and in 96% of patients with signs of diffuse bleeding. However, 32% of patients received FFP before PCC was administered, and 29% of patients received FFP after PCC. Another observational trial investigated the effects of fibrinogen and PCC in trauma patients using a thromboelastometry-guided algorithm[88]; 77% of patients received fibrinogen followed by PCC infusion. PCC was administered at a median dose of 1800 IU to patients with prolonged clot initiation. This therapeutic approach significantly decreased mortality compared with that predicted by the trauma injury severity score. PCC may be useful for correcting trauma-induced coagulopathy, but given the lack of clinical safety data for PCCs for trauma-associated coagulopathy, clinical studies, particularly in patients with comorbidities, are needed to optimize dosing and ascertain the safety of PCCs for the treatment of severely injured patients.

Activated Recombinant Factor VII

The current understanding of hemostasis according to the cell-based model attributes a pivotal role of factor VII to coagulation. Eptacog alfa (activated recombinant factor VII [rFVIIa]) is structurally almost identical to endogenous FVIIa and is produced through recombination by baby hamster kidney cell lines. rFVIIa binds to thrombin-activated platelets in supraphysiologic doses, leading to the activation of factor X and prothrombin (thrombin burst).[89] Through enhanced thrombin generation, platelet activation and platelet adhesion are greatly increased.[90] Therapy with rFVIIa is licensed for the treatment of patients with hemophilia, inhibitory antibodies, and Glanzmann thrombasthenia.[91] rFVIIa has gained popularity as an adjunct for the treatment of coagulopathy in a wide array of clinical conditions with serious or life-threatening bleeding. The

number of case reports and case series documenting the successful off-label use of rFVIIa as a last resort to terminate uncontrollable bleeding has steadily grown.[92] The results from a multicenter phase II randomized controlled trial (RCT), stratifying for severe blunt and penetrating trauma, showed a significant reduction in the primary end points (ie, RBC units transfused and the need for massive transfusion) in patients with blunt trauma who survived for more than 48 hours after rFVIIa treatment.[93] The need for massive transfusion was reduced by nearly 20%. Another multicenter phase III trial (CONTROL) was stopped after an analysis predicted the low likelihood of reaching a successful outcome in the primary end points (mortality and morbidity).[94] Because rFVIIa is a potent hemostatic agent, there is concern that its use may increase the risk for adverse events, particularly in patients with known risk factors for thromboembolic disease or a history of thrombosis. According to a report from the US Food and Drug Administration, 168 of 431 reports of approved and off-label uses of rFVIIa described 185 thromboembolic events between 1999 and 2004; 90% of the reports accounted for the off-label use of rFVIIa, and in part, these adverse events resulted in serious morbidity and mortality.[95] However, in 38% of these reports, a concomitant hemostatic medication was documented. A large and comprehensive study systematically analyzed data from 35 RCTs including 4468 subjects.[96] rFVIIa was administered to treat or prevent bleeding. The investigators found increased rates of arterial thromboembolic events among those who were treated with rFVIIa compared with placebo (5.5% vs 3.2%, respectively; $P = .003$), particularly in the elderly population. In contrast, Dutton and colleagues[97] did not find an association between the administration of rFVIIa to trauma patients for active hemorrhagic shock and thromboembolic events. However, the European Medicines Agency (EMEA) has advised that rFVIIa should not be administered outside the approved indications. Therefore, rFVIIa should be considered as a final rescue therapy attempt if first-line treatment with a combination of surgical approaches and best-practice use of blood products fails to control bleeding. To enhance rFVIIa efficacy, normothermia, hematocrit level greater than 24%, platelet count greater than 50,000/μL, pH 7.2 or greater, and fibrinogen 150 to 200 mg/dL or greater should be targeted.[68]

SUMMARY

Despite new therapeutic approaches to prevent and overcome trauma-associated coagulopathy, morbidity and mortality remain unacceptably high. However, the use of new nonsurgical techniques in addition to traditional surgical procedures may help rapidly stop hemorrhage and exsanguination. Studies from recent years have shown that coagulation factors and factor concentrates may be useful for reducing the need for FFP, platelet, and RBC transfusions. It is necessary to identify the cause of the coagulation deficiency to tailor the therapy for terminating coagulopathy using coagulation factor concentrates to each patient's specific needs. Further research and RCTs are urgently needed to better understand and develop clear strategies to overcome coagulopathy.

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