

# Local and systemic hemostatics in trauma: a review

## Travmada lokal ve sistemik hemostatik ajanlar: Derleme yazısı

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Hemorrhage is the leading cause of trauma-related deaths. The early identification and surgical control of this hemorrhage is the crucial first step in the management of the injured patient; however, this objective remains challenging in the most critically ill trauma patients. As an adjunct to traditional methods of surgical hemorrhage control, several advanced hemostatic agents are currently available. Oxidized cellulose, fibrin glue and synthetic adhesives constitute the first-line of local hemostatic agents. Materials such as Zeolite and Chitosan comprise the newest generation of local hemostatics and the efficacy and safety of these agents are currently under investigation. Recombinant factor VIIa has emerged recently as a promising systemic hemostatic adjunct for the treatment of intractable surgical bleeding; however, until completion of the ongoing multinational randomized control trial, the indications for its use in trauma patients and its safety profile are unclear. This article reviews the role of commercially available local and systemic hemostatic products in the trauma patient population; it also addresses the unique set of characteristics, indications, limitations and rationale for their use.

**Key Words:** Coagulopathy; hemorrhage; hemostatics; trauma.

Kanama, travma ile ilişkili ölümlerin başta gelen nedenidir. Kanamanın erken tanısı ve cerrahi kontrolü, travmalı hastanın tedavisinin düzenlenmesinde kritik ilk adımdır; ne var ki bu amaca ulaşmak, ileri derecede kritik travma hastalarında hala ciddi bir sorun olagelmektedir. Geleneksel cerrahi kanama kontrolü yöntemlerine ek olarak, günümüzde bazı ileri hemostatik ajanlar da kullanılmaktadır. Oksidize selüloz, fibrin yapıştırıcı ile sentetik yapıştırıcılar, lokal hemostatik ajanların öncelikli grubunu oluşturmaktadır. *Zeolite* ve *Chitosan*, lokal hemostatiklerin en yeni jenerasyonunu oluşturur ve bu ajanların etkinliği ve güvenilirliği halen araştırma aşamasındadır. Rekombinant faktör VIIa yakın zamanda, kontrol altına alınmayan cerrahi kanamanın tedavisine yardımcı, ümit verici bir sistemik hemostatik ajan olarak ortaya çıkmıştır; ancak devam eden çok uluslu randomize kontrollü çalışma tamamlanıncaya kadar rekombinant faktör VIIa'nın travma hastalarındaki kullanımını ile ilgili endikasyonlar ve güvenilirlik profili belirsizdir. Bu yazıda, ticari olarak mevcut bulunan lokal ve sistemik hemostatik ürünlerin travma hastalarındaki rolü gözden geçirildi; aynı zamanda bunların akılcı kullanımıyla ilgili benzersiz özelliklerle endikasyon ve kısıtlamalar değerlendirildi.

**Anahtar Sözcükler:** Hemostatik; kanama; koagülopati; travma.

### Introduction

Hemorrhage is the leading cause of preventable mortality after injury.<sup>[1]</sup> Coagulopathy, commonly associated with trauma, contributes significantly to hemorrhagic blood loss and is the sum result of a number of contributing mechanisms. These include hemodilution of factors and platelets during resuscitation, coagulation factor consumption and

hypothermia-induced platelet dysfunction.<sup>[2]</sup> The prevention of coagulopathy after trauma requires both prompt surgical control of hemorrhage and the maintenance of an appropriate homeostatic milieu for effective functioning of the coagulation system. A variety of local and systemic adjuncts can be utilized to support these efforts, including several advanced pharmacological hemostatic treatments.

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## Local hemostatics

As an adjunct to traditional methods of surgical hemorrhage control, a wide spectrum of hemostatic agents is currently available. Each of the commercially available products has its own unique characteristics, and it is essential that surgeons employing such materials be familiar with their benefits and limitations. Traditionally employed local hemostatic agents include cellulose-based products, fibrin and synthetic glues. More recently, the effectiveness of newer products, such as Chitosan and Zeolite, are being investigated in ongoing trials to examine the utility of this newer generation of local hemostatic agents.

### Cellulose-based hemostatics

Some of the most widely available and commonly utilized hemostatic agents are derived from oxidized cellulose, commercially available in the US as Surgicel© and Nu-Knit© (Ethicon, Inc., Cincinnati, OH). This class of agent is intended for use as an adjunct to gauze packing, with their hemostatic properties primarily based on their ability to locally activate the coagulation cascade. While they do not contain any intrinsic coagulation components, they are designed to stimulate clot formation and to provide a favorable three-dimensional structure for clot organization. In order for these products to function, therefore, a functional coagulation system must be present. In a study by Krizova and colleagues, the investigators demonstrated that a local hemostatic comprised of oxidized cellulose failed to induce platelet activation in the absence of plasma constituents, especially factors VIII and XII.<sup>[3]</sup>

These cellulose-based products have distinctive potential limitations that should be considered prior to their use. Their effective deployment may prove difficult in wet environments, due to their poor adhesion to tissue in this setting. Frequently, the application of adequate pressure at the site of hemorrhage is also required to provide the tamponade necessary to facilitate their effectiveness. Given the fact that this range of products relies on an intact coagulation mechanism, their utility in coagulopathic patients is also limited. For these reasons, cellulose-based products should be utilized only to assist in the local control of mild hemorrhage.

Potential local complications associated with the

use of these local hemostatics also warrant careful consideration. Injury to nerves, ureters and other specialized structures due to local desiccation, ischemia due to compression, or local inflammatory reaction may be under-appreciated. Brodbelt et al. have reported three cases of local neurological sequelae after the use of oxidized cellulose in thoracic surgery.<sup>[4]</sup> It is therefore advisable that caution be taken when applying these adjuncts in proximity to such structures, and excess material not contributing to hemostasis should be removed, if possible, at subsequent re-operation following damage control procedures.

Another frequently discussed potential complication of local hemostatic use is that of infection. It has been theorized that these substances may serve as a nidus for bacterial adherence and promote infection and abscess formation, particularly in the heme-rich environment in which they are employed. Despite these concerns, it has actually been observed that oxidized regenerated cellulose may confer some protective bacterial resistance against a wide variety of pathogenic organisms.<sup>[5,6]</sup> This effect has been attributed to the decrease in pH associated with the use of this agent, a change in the local milieu that hinders bacterial proliferation.

### Fibrin adhesives

Fibrin adhesives are a group of biological tissue adhesives composed of thrombin and purified human or bovine fibrinogen that mimic the final step of the physiologic coagulation cascade, depositing a fibrin-rich clot at the site of application. The use of fibrin-based adhesives has been well examined in both animal and human studies. Commercially available in many forms (Tisseel™, Floseal™, Baxter Inc., Deerfield, IL), differing in their source components and physical characteristics, these products have been proposed for use in a wide variety of surgical subspecialty settings, as well as in humans with hemophilia and other bleeding disorders.<sup>[7-13]</sup> Various animal models have also shown successful control of bleeding in the presence of coagulopathy. Holcomb et al. found that, after creating a grade V liver injury in a hemodiluted, hypothermic coagulopathic swine model, the use of fibrin-based sealants provided rapid hemorrhage control, decreased fluid requirements and improved survival.<sup>[11]</sup> In another animal model of liver injury, Feinstein and colleagues concluded

that the use of fibrin adhesives in heparinized swine rapidly controlled hemorrhage and eliminated the need for packing.<sup>[12]</sup>

Several human studies have also provided evidence for the efficacy of fibrin-based adhesives. In a review by Matthew and colleagues, the investigators reported that in a series of 689 cases, the use of these products resulted in a 94% success rate in controlling blood loss and an 88% reduction of air leakage when utilized for various cardiovascular procedures.<sup>[14]</sup> In another prospective, randomized, open-label controlled study in coagulopathic pediatric patients, Codispoti et al. showed that topical application of fibrin adhesives to multiple sites, including suture lines and vascular anastomosis sites, resulted in a significant decrease in microvascular oozing and general bleeding. These investigators found that this resulted in a reduction of the amount of intraoperative blood loss (26 ml/kg vs. 65 ml/kg,  $p < 0.01$ ) and blood products required (11.3 ml/kg vs. 24.8 ml/kg,  $p < 0.05$ ).<sup>[15]</sup>

The clinical utility of fibrin-based adhesives in trauma patients with coagulation disorders secondary to massive transfusions, disseminated intravascular coagulation and chronic disease was first described by Kram in 1989, who utilized fibrin glue to achieve liver and spleen hemostasis following traumatic injury. Findings from this study suggested that these types of hemostatic adjuncts were useful in patients with coagulation disorders and solid organ injuries.<sup>[16]</sup> In a separate study, Chen et al. demonstrated that in six patients with blunt hepatic trauma who had failed initial nonoperative management, the use of adjunctive fibrin glue sprayed over the wound surface laparoscopically dropped the laparotomy rate to zero (0 of 6).<sup>[17]</sup> While further investigation is needed to more precisely define the role of fibrin-based adhesives, these studies have demonstrated that fibrin-based adhesives may serve as a valuable hemostatic adjunct in specific situations.

### **Zeolite**

Commercially available in the US as QuikClot® (Z-Medica LLC, Wallingford, CT), zeolite is a naturally occurring mineral, which works by absorbing water from the injury site in an exothermic reaction that promotes the concentration of coagulation factors and platelets to augment

clot formation. This material is, however, only Food and Drug Administration (FDA)-approved for external use at the present time.

In animal models of external bleeding, QuikClot® (QC) has been demonstrated to result in decreased blood loss and mortality.<sup>[18-20]</sup> In a swine study, Alam et al. found that, following complex groin injuries with complete division of the femoral artery and vein, the application of QC® was associated with a significant decrease in mortality (0% vs. 83%) and improved hemodynamic response to injury.<sup>[18]</sup> Pusateri et al. have also examined the internal applications of QC® following solid organ injury. In a swine model with grade V liver injuries, these investigators found that the application of 50 grams of QC® followed by 60-second compression intervals was associated with a significant decrease in the amount of post-treatment blood loss, resuscitation fluids utilized and an improved survival rate (12% vs. 88%).<sup>[20]</sup>

Concerns about thermal injuries following the application of QC®, however, have been raised. Various investigators have demonstrated that significant heat production occurs when QC® is combined with blood or other physiologic fluids.<sup>[19-23]</sup> Local temperatures between 93 to 95.4 degrees Celsius at the tissue surface have been reported.<sup>[20,21]</sup> Although this risk of localized exothermic injury may prove relatively minor compared to that of life-threatening hemorrhage, this potential adverse effect should be considered when utilizing QC®.

Despite the potential impact of zeolite and promising performance in animal models, relatively few authors have described its use in coagulopathic human patients. Case reports, however, have suggested the therapeutic potential of this hemostatic adjunct. In a report by Wright and colleagues, the investigators presented the description of the successful management of a posterior chest wall gunshot injury using QC®.<sup>[24]</sup> However, further investigation particularly for intra-corporeal use is warranted.

### **Chitosan**

Chitosan is a novel local hemostatic that is produced commercially by the deacetylation of Chitin (Poly-N-acetyl glucosamine), a structural element in the exoskeleton of crustaceans. It is commercially available in the US as CELOX™ (Medtrade,

Newport, OR) or HemCon® (HemCon Medical Technologies, Inc., Portland, OR). At this time, they are only approved by the FDA for external usage. While the hemostatic mechanism of this agent has not yet been fully elucidated, it has been proposed that its primary activity occurs via the promotion of both platelet activation<sup>[25,26]</sup> and electrophysiologic interactions between red blood cells (RBCs) and the tissue surface.<sup>[27]</sup> Schwaitzberg et al. have found, in multiple animal protocols, that Chitosan may be beneficial in achieving hemostasis even in the presence of acquired or congenital coagulopathic disorders.<sup>[28]</sup> Klokkevold and colleagues have, likewise, demonstrated its effectiveness in a heparinized rabbit model. In that study, the investigators found that, after application of Chitosan to a lingual laceration, the use of this agent resulted in 43% less blood loss when compared to controls ( $p=0.001$ ). The authors hypothesized that these results were facilitated through an interaction between the erythrocytes and Chitosan that resulted in a cellular hemostatic plug.<sup>[29]</sup> Despite the promising results of these initial studies, further investigations are needed to define the role of this agent under coagulopathic conditions, especially for internal usage.

### Synthetic adhesives

Commercially available as Coseal™ (Baxter Inc., Deerfield, IL) or BioGlue® (Cryolife Inc., Kennesaw, GA), synthetic adhesives constitute an alternative to fibrin-based glue that can be stored at room temperature and do not require complicated preparation. Most of the available clinical experience, however, is derived from the use of Bioglue®, which is a synthetic two-component surgical adhesive composed of purified bovine serum albumin (45%) and glutaraldehyde (10%). Its mechanism of action involves the formation of covalent bonds with albumin and tissue surface proteins to form a mechanical seal at the site of hemorrhage. These products, however, are relatively expensive compared to fibrin-based hemostatics.

The use of this sealant has been well studied for use in cardiothoracic surgery. In a study by Chao et al., the investigators found that Bioglue® had a significant impact on decreasing complications following the repair of acute aortic dissection, decreasing both the amount of blood loss in the first 24 hours and the amount of packed RBCs required

(3.4 vs. 7.6 units,  $p=0.02$ ) when compared to historic controls.<sup>[30]</sup> In a prospective randomized, multicenter, controlled clinical trial, Coselli and colleagues were able to demonstrate that Bioglue®, as an adjunct to conventional repair methods, significantly reduced the occurrence of anastomotic bleeding in patients undergoing various types of cardiovascular repair (18.8% vs. 42.9%,  $p<0.001$ ).<sup>[31]</sup>

The clinical use of Bioglue® has been associated with specific complications. Gundry et al. were among the first to note that the application of Bioglue® around an aortic anastomosis in animal models produced anastomotic stenosis and impeded normal growth.<sup>[32]</sup> For this reason, circumferential application of Bioglue® to a vascular anastomosis, particularly in pediatric patients, should be avoided.<sup>[32,33]</sup> Other reported adverse effects of Bioglue® have included nerve and tissue toxicity from glutaraldehyde<sup>[34]</sup> and development of secondary coagulopathy due to the development of inhibitors to human factor V.<sup>[35-39]</sup> In other regions, it may be less effective. In a retrospective study conducted by Fisher and colleagues, the investigators found no advantage to the use of Bioglue® for preventing pancreatic fistula following pancreatic resection.<sup>[40]</sup> Although there is no literature to support its use in the bleeding trauma patient, its positive properties warrant further investigation into its potential use for this indication.

### Systemic hemostatics

Compared to local hemostatics, there are limited systemic hemostatic agents available for use in coagulopathic trauma patients. Recently, however, recombinant factor VIIa (rFVIIa) has emerged as a promising potential adjunct to conventional hemostatic techniques for treatment of intractable bleeding. Initially utilized in the treatment of hemophiliac patients with inhibitory allo-antibodies, several case series have recently examined the use of rFVIIa as a hemostatic agent in a broader variety of patients.<sup>[41-45]</sup> Kenet and colleagues were among the first to describe the successful management of coagulopathy using rFVIIa in a 19-year-old soldier with an inferior vena cava and paravertebral muscle injury.<sup>[43]</sup> Subsequently, several case series and a single randomized clinical trial have reported the use of rFVIIa in trauma patients.<sup>[46-49]</sup> In a double blind, randomized, placebo-controlled trial,

Boffard and colleagues found that the administration of rFVIIa in patients with severe blunt trauma was associated with a significant reduction in the amount of RBC transfusions required (reduction of 2.6 RBC units,  $p=0.02$ ) and a reduction in the need for massive transfusions (14% vs. 33%;  $p=0.03$ ). Among patients with penetrating trauma, however, the investigators were only able to demonstrate a non-significant trend towards reduced RBC requirements (reduction of 1.0 RBC unit,  $p=0.10$ ). No significant differences in mortality or overall adverse events were observed.<sup>[50]</sup> In a subgroup analysis from the same study, Rizoli et al. found that the use of rFVIIa in coagulopathic patients resulted in a significant reduction in both the utilization of blood products (reduction of 2.6 units,  $p=0.02$ ) and the incidence of acute respiratory distress syndrome (ARDS) when compared to placebo (2% vs. 12%,  $p=0.04$ ).<sup>[51]</sup> Currently, the safety and efficacy of rFVIIa are being investigated in a multinational, phase III clinical trial. Until these results are available, the appropriate prophylactic or therapeutic applications of this promising agent remain undefined.

### Summary

Hemorrhage constitutes the leading cause of preventable morbidity and mortality. Prompt control of surgical sources of hemorrhage is essential. A wide variety of hemostatic adjuncts are available, each with its own unique set of characteristics, and it is essential that surgeons employing such materials be familiar with the benefits and limitations of these adjuncts.

Oxidized cellulose, fibrin glue and synthetic adhesives constitute a first line of local agents, all of which have been proven effective and safe in the appropriate setting and when used as indicated. Zeolite and Chitosan comprise the newest generation of local hemostatics, currently approved by the FDA for external use only. Their role in several animal models and case series has shown promising results for achieving hemostasis when compared to conventional methods. Concerns have been raised due to the risk of localized exothermic injury; however, further investigation, particularly for intracorporeal use, is warranted.

Limited systemic hemostatic agents are available for use in trauma patients. Recently, rFVIIa has emerged as a promising adjunct for the treatment of

intractable bleeding; however, its safety and efficacy are currently under investigation, and until these results are available, the applications of this promising agent in trauma patients remain undefined.

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