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REVIEW

# A review of the application of cellulose hemostatic agent on trauma injuries

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**Introduction:** Planning for management of bleeding in trauma injuries is very important. The initial purpose in emergency situations should be immediate establishment of an efficient hemostasis, principally in its topical application. In this study, we aimed to review the major relevant articles in the case of application of cellulose hemostatic agent on trauma injuries.

**Methods:** We searched the online databases such as PubMed, MEDLINE, Wiley, EMBASE, ISI Web of Knowledge, and Scopus. Two reviewers independently searched and assessed the titles and abstracts of all articles.

**Results:** Upon screening the titles and abstracts, 24 studies were identified for full-text review. The oxidized cellulose had the best clotting times, while it demonstrated low absorption ability. Surgical and thermosensitive chitosan hemostatic could be valuable for managing hemorrhage from liver injuries in trauma patients.

**Conclusion:** Recently, the application of cellulose hemostatic agents has been one of the main improvements obtained for controlling bleeding in trauma injuries. However, generally according to the literature review, the decision about using each agent should be made on a case-by-case basis. However, it can be mentioned that the perfect hemostatic agent has not been still identified.

**Keywords:** cellulose hemostatic agent, trauma, injury

## Introduction

Bleeding has been known as the most common preventable reason for mortality in traumatic patients.[1–3] Because of direct tissue injury in these patients, trauma-induced coagulopathy also represented an important function in mortality.[4] Therefore, planning for the management of bleeding in trauma injuries is very important.[1,2] In situations where a patient has undergone trauma and its resulting hemorrhage, the initial purpose in emergency situations should be immediate establishment of an efficient hemostasis, principally in its topical application.[5,6]

The most prevalent places of intra-abdominal bleeding following penetrating or blunt abdominal injury due to intra-abdominal organs injuries are particularly the liver and spleen including problems that should be given preference in the research of traumatic injuries.[6–8]

Management of complex injuries, particularly its deep lacerations, is still a controversial subject. There are some advantages in utilizing cellulose hemostatic agents, but some studies have reported some complications such as sepsis.[9–11]

Several topical cellulose and other novel hemostatic agents, which use their outcomes by various mechanisms, have been applied efficiently to manage bleeding.

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Oxidized cellulose (Surgicel©; Ethicon, Inc., Cincinnati, OH, USA) 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. Zeolite (QuikClot®; Z-Medica LLC, Wallingford, CT, USA) works by absorbing water from the injury site that promotes the concentration of coagulation factors and platelets to augment. Chitosan (HemCon®; HemCon Medical Technologies, Inc., Portland, OR, USA); it is a novel local hemostatic agent that is produced by the Poly-N-acetyl glucosamine, a structural element in the exoskeleton of crustaceans.[12]

Recently, novel hemostatic materials have been developed, e.g., nano-/micro-fibers and High-performance cellulose–halloysite hemostatic nanocomposite fibers (CHNFs), and are gaining more and more interest in biomedical research due to the fact that they can incorporate pro-coagulative substances or drugs that can decrease the bleeding duration and can be made with cellulose.[13,14]

Research in these fields is increasing with objects to obtain new approaches to control bleeding because of trauma injury.[11,15] Hemostatic properties of cellulose-based hemostatics agents are based on their ability to locally activate the coagulation cascade, and this product is deliberately used as an adjunct to gauze packing.[12]

In this study, we proposed to review the major relevant articles in the case of application of cellulose hemostatic agent on trauma injuries in order to help clinicians to have better knowledge of these technologies and reach a better therapeutic decision.

## Methods

The online databases such as PubMed, MEDLINE, Wiley, EMBASE, ISI Web of Knowledge and Scopus and the Cochrane Database of Systematic Review were systematically searched by two independent reviewers, using the following medical subject headings: hemorrhage, hemostasis, cellulose, wounds, injuries, damage, etc. Additionally, all articles included in the analysis underwent reference review for other potential articles. The inclusion criteria for eligibility consisted of: 1) articles comparing the mechanism of hemostatic agents; 2) studies that reported outcomes of the application of hemostatic agents (especially cellulose hemostatic agent), and 3) studies that showed complication of hemostatic agents like incidence of infection, nerve injury, abscess formation, etc. Articles not reported in English were excluded.

## Results

Our search initially retrieved 200 studies published until July 2019. However, 144 papers were excluded because of the duplication between databases. Then, 44 studies were included for primary screening. Upon screening of titles and abstracts, 24 studies were identified for full-text review.

## Animal model

Khoshmohabat et al (2019) evaluated a Surgicel employing a partial hepatic incision hemorrhage model in the experimental rat models. In their study, 20 male Wistar albino rats were divided into two groups. Within each treatment group, gauze packing or Surgicel was applied to the liver laceration site in the large lobe of the liver. They concluded that Surgicel could be valuable to manage hemorrhage from liver injuries in trauma patients.[15]

In a study conducted by Fontes et al (2018) on the Wistar rats, the results showed that the use of regenerated cellulose and collagen presented higher amounts of collagen in the injured area, showing a greater stimulus in the tissue repair in comparison to the gelatin sponge (GS) in liver injury. The regenerated cellulose sponge stimulated the production of type I collagen more than that of gelatin and collagen did.[16]

Karahaliloglu et al (2017) evaluated the effectiveness of a fabricated nano/microbilayer hemostatic dressing for blood conservation in the diabetic rat. They set a nano/microbilayer hemostatic dressing that contains effective properties. They determined the coagulative performances through the calculation of blood loss, bleeding time, and mortality rate in the diabetic rat femoral artery injury model. They proposed that the high positive charge and porosity provide the ability of rapid control of bleeding by electrostatic interactions between components of coagulation in this fabricated nano/microbilayer homeostatic dressing.[17]

Dorterler et al (2016) evaluated and compared the histopathological and homeostatic properties of oxidized cellulose, Ankaferd Blood Stopper (ABS; Ankaferd Medical Products Inc, Istanbul, Turkey), and calcium alginate (CA) in an experimental liver injury. They randomly divided 40 Wistar albino rats into 4 groups of 10 animals each, getting 0.9% CA NaCl, ABS, and OC, subsequent to liver injury. They did the histopathological assessment after 5 days. They evaluated hematocrit (Htc) level and histopathological examination for estimation of the efficacy of the agents. The lowest quantity of bleeding was shown significantly in the ABS-treated rats. Also, they illustrated less necrosis in the ABS-treated rats than those receiving OC. They concluded that the ABS decreased the quantity of hemorrhage in liver surgery and partial liver injury; however, the hemostatic outcome of CA was restricted.[18]

Sener et al (2015) investigated the impacts of hemostatic agents and tissue adhesive on the injured nerve tissues in 42 rats that were randomly divided into 7 groups including control, gelatine sponge (GS), oxidized regenerated cellulose (ORC), Glutaraldehyde Surgical Adhesive (BioGlue®), ABS, bovine collagen, and N-butyl-2 cyanoacrylate (Glubran®2), and follow up for 12 weeks. They showed, according to previous studies, that ABS agent is the most proper hemostatic agent for tissue adhesive on the injured nerve tissues, and its constructive result on the healing of injured tissues. Also, they reported that the BioGlue was an appropriate surgical agent with no unfavorable outcome.[19]

Lewis et al (2015) evaluated microporous polysaccharide hemospheres (MPH) as a replacement for flowable hemostatic agents because of similar application techniques and handling, especially Hemostatic matrix. They demonstrated that hemostatic matrix provided better hemostatic achievement than MPH and control at 5 and 10 mins. They concluded that these results confirmed other MPH researches regarding its low efficiency and proposed that MPH was not a suitable replacement for hemostatic matrix; however, there are similar techniques. They reported that the reason for the lower efficiency of MPH could be lack of a procoagulant.[20]

Greenawalt et al (2012) showed a sodium hyaluronate/carboxymethylcellulose barrier used for hemostatic agents at the time of surgery presented effects on after surgery adhesions in these preclinical models.[21] They hypothesized that a resorbable barrier would effectively reduce the adhesions to hemostatic agents and that hemostatic agents would be a significant nidus for adhesion formation.

Yin et al (2013) showed that the thermosensitive chitosan hemostatic film had a positive hemostasis impact on the liver laceration in rat models.[22] Cellulose hemostatic cotton, chitosan hemostatic film, thermosensitive chitosan hemostatic film and GS were applied in 50 adult Sprague Dawley rat's liver injury model. Gross observation showed better hemostatic effect and faster hemostatic time in chitosan hemostatic film and cellulose hemostatic cotton, thermosensitive chitosan hemostatic film; GS had weaker hemostatic effect and slower hemostatic time.

The chitosan, as a polysaccharide that belongs to the group of biopolymers, is not accurately recognized. It may provoke vasoconstriction; consequently, it induces local accumulation of clotting factors and the blood cells. Furthermore, the chitosan increases thrombocyte adhesion and accumulation at the damaged tissue.[23] Also, numerous investigations demonstrated a considerable decrease in bleeding and mortality.[24,25] The chitosan indicates superior outcomes in dry weight and absorption ability as physical factors, but its absorption speed is relatively slow. The clotting time of chitosan is six-fold faster than alginate and even dominates the collagen Lyostypt®.

Satar et al (2013) investigated the hemostatic and histopathological effects and intra-abdominal adhesion scores of ABS in an experimental liver injury model and compared it with regenerated oxidized cellulose. They recommended that ABS is more efficient than Surgicel in obtaining the hemostasis and decreasing the bleeding. They reported that ABS made more supportive histopathological varieties and better intra-abdominal adhesion amounts in rat liver trauma model.[26]

In Valentine et al's study (2011), Floseal, ORC, chitosan gel, muscle patch, or the U-Clip anastomotic device were used in the sheep model of endoscopic internal carotid artery (ICA) injury and showed that the muscle application and U-Clip anastomotic device significantly enhanced the survival, decreased the bleeding, and reached the initial hemostasis while controlling vascular patency.[27]

Also, Karakaya et al (2009) showed ABS on liver injury is as efficient as Surgicel in achieving hemostasis after incomplete liver laceration in an animal rat model.[28]

Ereth et al (2008) created experimental rat models by Arista, Surgicel, Avitene (microfibrillar collagen; Alcon, Inc., Humacao, PR, USA), FloSeal (gelatin matrix thrombin sealant; Baxter Healthcare Corp., Deerfield, IL, USA), or kaolin (positive control). Time to hemostasis was documented. They showed these hemostatic agents were efficient in the management of bleeding in the majority of regulated neurosurgical injuries. Arista degrades more quickly than Surgicel, Avitene, and FloSeal and does not affect any foreign body response.[29]

## Clinical, in vitro and in vivo models

Udangawa et al (2019) evaluated CHNFs for human plasma coagulation by activated partial thromboplastin time and showed that CHNFs exhibited 2.4 times faster plasma coagulation time compared with the industry gold standard QuikClot Combat Gauze (QCG). The CHNFs also coagulated the whole blood 1.3 times faster than the QCG and retained the clotting performance twice after washing. CHNFs showed a 7-fold greater clay loading than QCG. The drastic reduction in coagulation time makes this novel nanocomposite a potential lifesaving material for patients undergoing major surgical procedures.[14]

Nakielski and Pierini (2018) in a review article demonstrated that electrospun nano- and micro-fibers, as novel materials, offered many opportunities for material development and were therefore attractive for multiple applications.[13] The impact of the diameter and orientation of the nano- and micro-fibers on the platelet aggregation, although inconclusive in several publications, can influence the coagulation cascade and platelet adhesion.[30] Despite little clinical and commercial success, nano-fibers have a strong potential for application as hemostatic agents.

The results of a retrospective cohort study conducted by Masci et al (2018) showed that applicant of ORC on the liver bed after laparoscopic cholecystectomy in patients with bleeding not responding to conventional techniques provided adequate hemostasis and effectively controlled bleeding.[31]

Yang et al (2016) developed a choline phosphate modified cellulose membrane which ensured bleeding control and wound healing. They functionalized the cellulose membrane with choline phosphate. They reported strong interactions among the red blood cells and the choline phosphate-doped cellulose membrane. Ultimately, they reported that this modified cellulose membrane can present a talented approach to bleeding control and trauma management.[32]

Chen et al (2015) evaluated the replacement of bioactive glass/chitosan/carboxymethyl cellulose (BG/CS/CMC) composite scaffold with conventional wax. They reported that biocompatibility of the BG/CS/CMC composite was excellent without any cytotoxicity. Also, they demonstrated that the BG/CS/CMC composite had an essential function in the hemostasis and bone regeneration. Subsequently, they indicated that these scaffolds were able to serve as a latent matter for hemostasis and bone repair in the crucial-sized bone defects.[33]

Rembe et al (2015) assessed the hemostatic prospective and physical factors of various types of superficial wound dressings in vitro including two alginates, standard wound pad, collagen, oxidized cellulose, chitosan, and QuikClot®. They reported the fastest coagulation for oxidized cellulose and the lowest coagulation for collagen Lyostypt®. However, QuikClot® demonstrated the lowest absorption ability and speed regarding physical parameters although chitosan and both alginates showed the highest ability. The oxidized cellulose had the best clotting times, while it demonstrated low absorption ability. They concluded that all of the agents provoked clotting and provided the possibility to neglect the disadvantage in clotting times arising from anticoagulation on a local basis.[34]

In a study conducted by Chung et al (2011) on the patients with intraoperative splenic injury during laparoscopic urological surgery, the results demonstrated that the use of Surgicel® on the injured area can provide hemostasis without any postop complication.[35]

Thomas et al (2008) showed the topical hemostatic agent could be reflected for use either during or following sinus operation to decrease bleeding.[36] Because of its local pH-lowering effect, ORC has bactericidal effects against a wide spectrum of pathogens, including methicillin-resistant *Staphylococcus aureus*.[37]

In a study by Krizova et al (2007), it was demonstrated that hemostatic agents comprised of oxidized cellulose-induced platelet activation in the presence of plasma constituents, mainly factors XII and VIII.[38]

Brodbelt et al's (2002) study reported three patients with local neurological sequelae after the use of oxidized cellulose in thoracic surgery.[39]

Cellulose-based hemostatics products have some limitations that should be considered prior to their use; due to their poor adhesion to the tissues in wet environments, their effective deployment may prove difficult in this setting. The application of adequate pressure at the site of hemorrhage is needed to provide the tamponade necessary to improve their effectiveness. The effect of these products depends on an intact coagulation mechanism, and their use in patients with coagulopathy is limited. Some of the complications associated with the use of local cellulose-based hemostatics products consist of local inflammatory reaction, ischemia due to compression, injury to the ureters, nerves and other specialized structures because of local desiccation and promotion of infection and abscess formation.[12]

## Discussion

Two basic methods were used for the control of bleeding in all parenchymal organs including inhibiting bleeding from injured vessels by decreasing the quantity of blood getting the parenchyma.[40] The second method is using current hemostatic agents. Many studies have been done associated with ABS, CA, and oxidized cellulose (OC) for the control of bleeding. Therefore, the knowledge about these agents for the control of bleeding is adequate. The functional mechanisms of these agents are distinct, so that the CA is converted into a humid gel, and it acts as transferring sodium and calcium ions from the alginate to the tissue.[41] The OC has hydrophobic properties and through this feature, it activates a cascade caused by protein agglutination. Also, 5 plants extract in the ABS acted as an activator of protein agglutination cascade. Many studies have been done, associated to the efficiency of these agents; for example, Henderson et al[42] reported that CA did not have benefits over the standard sterile gauze for management of bleeding after tooth removal in the children.

Henderson et al[42] and Ingram et al[43] reported and concluded that CA could not be an effective agent for the control of bleeding in clinical studies.

Dorterler et al[18] reported that the quantity of hemorrhage in the CA group was less than the control group; this result was explained by Dorterler et al indicating that the Htc levels in the rats are high; therefore, the early termination of bleeding is the reason of lower bleeding in the studies. However, the CA is more useful than saline for controlling bleeding.

In another study, Davidson et al[44] reported that OC significantly reduced bleeding in comparison with the control group. Karakaya et al[28] also assessed the hepatic laceration model to evaluate the hemostatic effects of OC and ABS; they concluded that ABS was as useful as OC in providing hemostasis.

Aysan et al[45] reported that ABS notably decreased bleeding compared to 9% NaCl solution in the rat hepatic resection. Dorterler et al demonstrated that the ABS was more efficient than OC and CA in halting bleeding. Also, the OC and CA are valuable compared to saline although they are not as efficient as ABS either in the quantity of preoperative bleeding or alteration in Htc. The 5 special plant extracts in ABS could lead to a better inflammatory reaction in the hepatic parenchyma. The histopathological studies demonstrated that ABS relatively indicated the lower severity of inflammation, fibrosis, and adhesions compared to the OC treated rats.[44]

Several accessible contemporary agents include silicates, fibrin sealants, and others advance local hemostasis.[46–48] Most of the studies have focused on major bleeding in combat with zone injuries or surgical interference of severe trauma. Injury pads with hemostatic skin are well acknowledged by the urgent situation and military medicine with QuikClot® Combat Gauze, Lyostypt®, Celox ®, WoundStat® and a dry fibrin sealant dressing as universal representatives. All pads, excluding the fibrin sealant, according to the FDA categorization, are class II products; thus, they have not released substances. The QuikClot® indicated quick coagulation, but it demonstrated reduced absorption aptitudes and it cannot take up the essential blood volume of bleeding of external wounds. The possibility of the reopening of the injury is increased in QuikClot® because QuikClot® indicated the following maximum adhesive strength. In addition, the before created QuikClot®, consequent from the volcanic rock was substituted by the company in 2010 because of unfavorable effects including (micro-)embolism and tissue injury due to an exothermic response.[49,50] Oxidized cellulose consists of a polyanhydroglucuronic acid and is manufactured from wood pulp, and the precise mechanism of its hemostatic response is unidentified. It is mostly applied in the surgical setting because it is absorbable and is able to leave in the body cavities. Rembe et al[34] reported that oxidized cellulose is as good as QuikClot® considering the hemostatic abilities, and it is better thanLyostypt® regarding blood absorption ability. Also, the oxidized cellulose is significantly superior to QuikClot®; therefore, it can be used as a superficial wound dressing as an advantage. In contrast, its facet to dissolve and its physically powerful adhesion may be harmful in treating superficial wounds.

## Conclusion

According to this review, hemostatic agents containing ORC are easy to use and effective in ensuring adequate hemostasis. They stimulate clot formation and are designed to provide a favorable three-dimensional structure for clot organization. They have limited side effects and have bactericidal effect. All exterior wound dressings decrease the coagulation time. Therefore, the physical interactions such as pH, temperature determine the hemostatic effect. The spectrophotometry method is a procedure that can be recognized as a gold standard technique for selected research of clotting in solid organs.

In some studies, results demonstrated that the dressings can be ranked as followed: oxidized cellulose ≥ alginate-L > QuikClot® > chitosan > Lyostypt® > alginate-D > standard wound pad.

The oxidized cellulose had the best clotting times, while it demonstrated low absorption ability. The ABS decreases the quantity of hemorrhage in liver surgery and partial liver injury, however, the hemostatic outcome of

CA is restricted. The alginate-L has requirements of a superficial wound dressing because of its quick coagulation and subsequently; it induces physical properties such as low tissue adhesion, and high absorption ability.

Recently, new agents such as CHNFs and electrospun nano- and micro-fibers have offered many opportunities for hemostatic agent development, but further experimental and clinical studies are recommended to confirm the results of this study. However, generally according to the literature review, the decision about using each agent should be determined on a case-by-case basis.

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## Disclosure

The authors declare that they have no conflicts of interest in this work.

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