Adv Ther (2020) 37:4132–4148
https://doi.org/10.1007/s12325-020-01467-y

REVIEW

Advances in Topical Hemostatic Agent Therapies: A Comprehensive Update

Liang Huang · Geoffrey L. Liu · Alan D. Kaye · Henry Liu

Received: July 9, 2020 / Published online: August 19, 2020

ABSTRACT

Severe hemorrhage causes significant metabolic and cellular dysfunction secondary to deficient tissue perfusion and oxygen delivery. If bleeding continues, hemodynamic destabilization, hypoxemia, multiple organ failure, and death will occur. Techniques employed to promote hemostasis include surgical suture ligatures, cautery, chemical agents, self-assembling nanoparticles, and physical methods, like mechanical pressure. Improved understanding of the natural clotting cascade has allowed newly designed agents to become more targeted for clinical and military use. Topically-applied hemostatic agents have enormous clinical applications in achieving hemostasis. This manuscript describes currently available and developing topical hemostatic materials, including topical active agents, mechanical agents, synthetic/hemisynthetic hemostatic agents, and external hemostatic dressings for clinical practice.

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12767606.

L. Huang
Department of Anesthesiology, Perioperative and Pain Medicine, New York University Langone School of Medicine, New York, USA

G. L. Liu
Department of Radiology, Ochsner Clinic Foundation, New Orleans, LA, USA

A. D. Kaye
Department of Anesthesiology and Pharmacology, LSU Health Shreveport, Shreveport, LA, USA

A. D. Kaye
Department of Toxicology, and Neurosciences, LSU Health Shreveport, Shreveport, LA, USA

H. Liu (✉)
Department of Anesthesiology and Perioperative Medicine, Milton S. Hershey Medical Center, Penn State University School of Medicine, Hershey, PA, USA
e-mail: henryliupa@gmail.com

Keywords: Adhesive; Fibrin; Gelatin; Hemostatic dressings; Hemostats; Sealant; Thrombin; Topical agent

Key Summary Points

Severe hemorrhage causes significant hemodynamic instability, hypoxemia, multiple organ failure, and death.

Perioperative hemostasis techniques include surgical ligatures, cautery, chemical agents, self-assembling nanoparticles, and topical methods.

Topically-applied hemostatic agents include active agents, mechanical agents, synthetic agents, and external dressings.

Topical mechanical agents only work in patients with intact coagulation system.

Appropriate method is determined by the type of bleeding, the specific etiology, the individual coagulation status, and the clinician's experience and preference.

Future hemostatic agents can be engineered towards both primary and secondary hemostasis mechanisms for an enhanced hemostatic response.

INTRODUCTION

Various factors, such as surgery and trauma, can cause hemorrhage in human beings. Severe hemorrhage can potentially induce significant morbidity and mortality. Hemorrhage ensues if the vascular wall integrity gets disrupted [1]. The extent of cellular injury and organ dysfunction secondary to hemorrhage is a complex process dependent upon the duration and severity of bleeding and hypoperfusion [2]. Some of these patients will require allogeneic blood transfusion, which has its own intrinsic risks, such as infectious disease transmission, allergic reactions, hemolytic reaction, and lung injury. There are pharmacological and non-pharmacological strategies to facilitate hemostasis. In this review, we summarize what is new in topical hemostatic agents. When there is a bleeding, surgeons and other health care providers can utilize many techniques to stop bleeding. Intraoperatively, surgeons usually employ direct mechanical pressure or compression, thermoelectric cautery, and surgical ligation to stop bleeding. In emergency rooms, trauma sites or battlefields, tourniquet and anti-shock trousers are commonly used options. Some new intravenously-administered pharmacological agents and topically-applied hemostatic agents have been developed in the last decades aiming to facilitate hemostasis by providing either intravascular coagulation cascade component(s) or extravascular substrate(s). External hemostatic dressings can be used to stop bleeding in emergency situations, such as in combat injury or junctional (groin or axillary) hemorrhage. Topical hemostats are often used as adjunctive measures to improve hemostasis during or after surgery [3]. The aim of this manuscript, therefore, is to help all healthcare providers understand and appropriately use these new hemostatic agents in accordance with clinical settings, patient coagulation status, and surgical scenarios.

METHODS

We searched the PubMed Central with "topical hemostatic agent" in April 2020, when we started working on this manuscript, and found 1859 items. Since we are aiming for perioperative and traumatic hemostasis, we did not include dental literature or veterinary literature. We summarized other pertinent literature and categorized the topical hemostatic agents into four major categories: topical active agents, topical mechanical agents, topical synthetic/hemisynthetic agents, and external hemostatic dressings. We selected more pertinent literature to validate each category based on our classifications. All authors participated in the preparation of this manuscript by searching PubMed and selecting literature, categorizing the topical hemostatic agents, drafting the preliminary version of the manuscript, and revising the manuscript multiple times. This article is based on previously conducted studies and does not involve any studies with human participants or animals performed by any of the authors. None of the authors have any conflicting interest from the commercial products mentioned in this article.

CLASSIFICATIONS OF TOPICAL HEMOSTATIC AGENTS

The topically-applied hemostats are categorized as active or adhesive agents, mechanical hemostats, synthetic/hemisynthetic sealants, and external dressings. Topical active agents are a category which contains fibrinogen and thrombin and works by actively triggering the coagulation cascade and fibrin clot formation [3, 4]. These agents are especially useful in patients with coagulation disorders. They are

usually supplied in flowable liquid formulation (fibrin glues) [5] or in combination with collagen (fibrin patch). These agents are sometimes also called adhesive hemostats due to their hemostatic and adhesive sealing effect [6]. Topical mechanical hemostats contain bovine collagen-oxidized cellulose, porcine gelatin, and plant-derived polysaccharide spheres. These topically-applied products promote platelet activation and aggregation, thus form a clotting matrix at the bleeding site. These hemostatic agents are known as passive hemostats. The action of these hemostats can enhance the functional coagulation system to achieve hemostasis. Topical synthetic/hemisynthetic sealants are usually supplied in low-viscosity liquids, which form a solid film through a process of polymerization to connect tissue surfaces [7]. These sealants can be categorized as synthetic sealants, such as cyanoacrylate and polyethylene glycol sealants [8], and semisynthetic, such as glutaraldehyde albumin-derived sealants [9]. Newly developed hemostats with nanotechnology have also been clinically employed, such as self-assembling peptide nanofibers and chitosan nanofibers.

TOPICAL ACTIVE HEMOSTATS

Fibrin-Based Active Adhesives

Adhesive hemostats participate at late stages of the coagulation cascade to form a fibrin clot. They are usually made of two essential components: human purified fibrinogen and thrombin. Factor XIII, fibronectin, and antifibrinolytic agents, such as aprotinin or tranexamic acid, may be added [8]. Some aprotinin-free and tranexamic acid-free adhesives have been developed, since aprotinin may be associated with hypersensitivity and tranexamic acid with potential neurotoxicity [10, 11]. These newer agents are generally believed to have fewer side effects. Several adhesives come in liquid formulations or as medicated sponges/patches (Tachosil, Evarrest). Adhesives are metabolized by fibrinolysis and phagocytosis, such as endogenous fibrin [1]. Liquid fibrin adhesives supply exogenous fibrinogen and/or thrombin, thus being particularly effective in achieving hemostasis in congenital or acquired bleeding disorders (e.g., hemophilia, and antiplatelet or anticoagulation therapies) [11]. Reports have indicated that fibrin adhesive administration leads to significantly less blood transfusion requirements in hemophiliacs undergoing total knee and total hip replacement, and facilitate hemostasis and less intraoperative blood loss post-cardiopulmonary bypass [10, 11]. The effectiveness of liquid fibrin adhesives in achieving hemostasis in polytetrafluoroethylene arterial anastomosis bleeding has been proved [10, 11]. Fibrin adhesive efficacy as a hemostat has been demonstrated in more than 20 multicenter clinical trials, demonstrating benefits in abdominal [10], cardiac [1], pediatric extracorporeal oxygenation cannulation, liver resection, peripheral vascular, skin graft donor harvest site, and total hip or knee arthroplasty [12].

Liquid fibrin adhesives can be used after surgical hemostasis to manage residual oozing, especially on broad exposed tissue surfaces and vascular anastomoses. Foam fibrin adhesives are better in irregular and deep surfaces. Liquid fibrin adhesives have both fibrinogen and thrombin. High fibrinogen concentration will enhance clot strength, whereas high thrombin concentration will enhance clotting time. Platelet-rich or platelet-poor plasma may be added with calcium, and any one of the three free-standing thrombin to manufacture fibrin sealant. Platelet-rich fibrin sealant has a lower fibrinogen concentration with lower mechanical strength, but the platelet activity offers clinical value [13]. Combinations of separate additional absorbable gelatin sponges with liquid fibrin sealants allow pressure application for several minutes [4].

Any product containing thrombin should never be injected intravascularly because of the risk of thrombosis, hypotension, and death. Gas-driven sprayers at higher pressures (> 20 to 25 psi) or at shorter distances (< 10 to 15 cm) are potentially associated with air embolism [5]. Adhesives containing tranexamic acid must not be used if cerebrospinal fluid leakage or dura mater tear are present because of neurotoxicity. Tranexamic acid-induced hyperexcitability and

convulsions via GABA-mediated inhibition has been reported [14]. While HIV and hepatitis transmission appear unlikely, parvovirus B19 transmission by fibrin sealant has been reported [15]. Poor wound healing and infection may occur with excess use. Hypersensitivity, edema, and coagulopathy are potential adverse effects when using aprotinin (Tisseel), bovine (Vitagel), or equine products (Tachosil).

Application of these liquid fibrin adhesives without a component of an antifibrinolytic, bovine collagen, and thrombin, or an equine collagen patch, may minimize the above-mentioned risks (Evicel). The efficacy of fibrin sealant as a hemostat has been shown by multiple clinical investigations, which demonstrated significant benefits in various surgical procedures [11, 16, 17]. However, a significant impediment to the use of fibrin adhesives has been the challenges of preparing the liquid products. Significant efforts have already been made to simplify liquid formulation preparations. After warming, the liquid must be used within 4 h by either dripping or spraying with and without compressed air propulsion in open as well as laparoscopic and thoracoscopic procedures. If the package is unopened, the pouch may be stored at room temperature for use within 24–48 h. Another brand of liquid fibrin adhesive, such as Evicel by Ethicon/Johnson & Johnson, Somerville, NJ, USA, can be thawed and used in 24 h at room temperature. It can even be stored in a refrigerator for up to 1 month.

Fibrin adhesives in liquid formulation are also effective to improve the watertight closure of the dural suture line for the prevention of cerebrospinal fluid leak [14]. However, cautions are warranted in using fibrin adhesive containing tranexamic acid in a neurosurgical setting because tranexamic acid may cause hyperexcitability and convulsions by blockade of GABA-mediated inhibition [14]. However, evidence regarding the efficacy of liquid fibrin adhesives in preventing pancreatic, biliary, and intestinal and air leakages is still controversial [4, 18]. In thoracic settings, the effect of liquid fibrin adhesive to prevent or treat air leaks is not significant.

Fibrin Patch

Fibrin patch adhesives are usually provided as a patch (TachoSil, PGA-felt, Fibrin Pad). Fibrin patches are effective in ongoing severe hemorrhage as well as preventing oozing or spurting, since they prevent the "streaming effect" of blood, and thus are good for controlling residual bleeding on vascular anastomosis. They are routinely used by some surgeons in preventing pancreatic, biliary, and urinary leakages, although it is not recommended because of the weak evidence [4, 18, 19].

The advantage of a fibrin patch compared with liquid formulations is the mechanical support provided by collagen or oxidized cellulose/polyglactin 910 matrix. This allows better adherence to bleeding tissues/materials, preventing the "streaming effect" observed with fluid adhesives. The sponge formulation additionally allows pressure application at active bleeding sites, which can potentially be more advantageous in certain clinical scenarios. A disadvantage is the high cost of the fibrin patch. The fibrin patch has also been demonstrated efficacious in some clinical trials in cardiac surgical procedures, nephrectomy, and liver resection [10–12].

Some fibrin patches come in a pouch (TachoSil) stored at room temperature and used immediately in the sterile field. TachoSil is an equine collagen patch coated with coagulation factors, human fibrinogen, and human thrombin. Fibrin Pad and PGA-felt are absorbable hemostats made with polyglactin (PG 910), oxidized regenerated cellulose (ORC), thrombin, and fibrinogen [20]. Reports supported its use in bleeding during abdominal, retroperitoneal, and pelvic surgical procedures [11, 12, 20]. TachoSil in preventing air leaks after thoracic surgery and bile leaks after pancreatic procedure are controversial [6, 21].

Thrombin-Based Hemostats

These topical active agents include thrombin derived from different sources: human pooled plasma, bovine thrombin, and recombinant thrombin. Thrombin facilitates the

conversion of fibrinogen to fibrin, leading to a faster thrombus formation [22]. Both recombinant human thrombin and bovine thrombin can be stored at room temperature in powder form; thus, they need to be reconstituted with saline solution before use, with a shelf life of 8–24 h after reconstitution [4]. Human pooled plasma preparation is provided as a frozen liquid which can be kept at room temperature for up to 24 h after thawing. The efficacy of thrombin product can be enhanced by a porcine gelatin sponge which enables direct pressure application [22]. A meta-analysis indicated that thrombin-based hemostatic agent applied before wound closure decreased postoperative blood loss and transfusion rate without elevated risk of infection, deep vein thrombosis, or other complications [4]. Fu et al. revealed that a thrombin-based hemostatic agent is effective in primary total knee arthroplasty [23]. However, the utility of thrombin-based hemostatic agents to reduce transfusions remains controversial [23].

Thrombin collected from pooled human plasma risks transmission of viral disease (e.g., HIV, hepatitis, parvovirus B19) or prion disease (e.g., Creutzfeldt–Jakob). There has not been reported for HIV or hepatitis transmission by sealants derived from pooled human plasma for over 20 years. Recombinant human thrombin solves this safety issue. However, the recombinant product may be theoretically associated with allergic responses to the cell lines (hamster) and proteases (reptile) used in its manufacturing process. Rarer complications can include thrombosis of cardiopulmonary bypass or cell saver circuits resulting from thrombin's competitive inhibition of the heparin used to anticoagulate the system.

Topical Combined Flowable Gelatin and Thrombin-Based Hemostats

Bovine or porcine gelatin matrix may be combined with human pooled plasma thrombin. Their efficacy can be enhanced with combination of a porcine gelatin sponge, which facilitates direct pressure application. Topical gelatin and thrombin-based hemostats include Surgiflo (Johnson & Johnson) and Floseal (Baxter Healthcare). Both Surgiflo and Floseal are absorbable gelatin-based products that form hemostatic matrices. They are indicated as adjuncts to hemostasis when control of bleeding by suture, ligature, or cautery is inadequate or impractical.

The efficacy of these combined agents is among the best of any category of hemostats. Floseal was used locally to reduce blood loss in gynecological, cardiac, knee, and general surgery [4]. Surgiflo use may have some cost savings for flowable products without difference in clinical outcomes when compared with Floseal [24]. A systematic review demonstrated that gelatin–thrombin matrix sealant was associated with a significantly higher rate and shorter time of successful hemostasis in different surgical fields compared with other alternatives [25]. Several multicenter prospective randomized trials documented efficacy across multiple specialties, with some superiority of products containing bovine thrombin over a porcine gelatin sponge [22]. Other recent single-center prospective randomized studies for adenoidectomy, acute anterior epistaxis, adenotonsillectomy, total thyroidectomy, and cardiac procedures have revealed the significant benefits of using bovine gelatin matrix and thrombin in achieving more rapid hemostasis [26].

Cost savings may be achieved by combining the porcine gelatin matrix with any of the freestanding thrombin products. To obtain the best hemostatic effect, it is important to reproducibly create this material by adding the appropriate volume of the liquid thrombin (usually 3–5 mL) to the porcine gelatin matrix so that the final material is neither too diluted nor too thick. Related to swelling and following potential induction of a compression of other nearby anatomic structures, the minimal amount of gelatin agent should be used to achieve hemostasis. Risks for this gelatin and thrombin combined product are matrix swelling and potential subsequent infection. Other risks are similar with those of both the mechanical and active hemostat agents discussed above.

TOPICAL MECHANICAL HEMOSTATS

The topical mechanical products contain oxidized regenrated cellulose (ORC)-based, gelatins, collagen-based agents, and polysaccharides. Mechanical hemostats are only appropriate for patients with a functioning coagulation system to improve control of residual oozing [27]. Mechanical hemostats absorb fluid several times of their own weight. They also promote platelet activation and aggregation, produce a matrix at the site of bleeding, and activate the extrinsic clotting pathway. These agents can be used as first-line agents because of their immediate availability and cost-effectiveness [27]. In the absence of plasma constituents, especially factors VIII and XII, they usually fail to induce adequate hemostasis [27].

The mechanical materials are easy to use and storable at room temperature. The porcine gelatin and bovine collagen classes are manufactured in sponges, sheets, and powders. The ORC-based material is provided in single or multiple woven sheets, or fibrillar with cotton puff-like consistency. The polysaccharide spheres are usually supplied in two different product volumes in blunt tip or bellows applicators. All mechanical agents perform best when placed with manual pressure.

Oxidized Cellulose

Cellulose is a homopolysaccharide produced by polymerization of glucopyranose through β-glucosidic bonds. Oxidized cellulose can be either regenerated (ORC, organized fibers are formed before oxidation) or non-regenerated (ONRC, with unorganized fibers prior to oxidation). Oxidized cellulose is known for its ease of use, favorable biocompatibility, and bactericidal properties. Direct pressure applied at the hemorrhage site is required to optimize efficacy, and oxidized cellulose may be used as an adjunct to gauze packing [28].

ONRC-based topical hemostats are seemingly more effective, but unhandy compared with ORC-based topical hemostats. Hemostasis at 90-s post-application was 97.5% for ONRC and 70% for ORC. Oxidized cellulose-based topical hemostats are unable to control biliary, urinary, pancreatic, and air leakage. As an adjunct to packing to control bleeding from parenchymal injuries, these topical hemostats carry the risk of ischemia due to compression or local inflammatory reaction. They should not be left in place in proximity to nerves, ureters, or intestinal and vascular structures. The additional benefit of ORC (Surgicel, Surgicel Fibrillar, Nu-Knit) may be its bactericidal effect by creating an acidic environment [29]. If possible, mechanical agents should be removed to reduce the risk of infection. Although oxidized cellulose can be absorbed in 2–5 weeks, excess material may cause granulation formation without bio-degradation, complicating radiological and clinical diagnosis of abscess, residual/recurrent tumors, and granuloma. Poor adhesion to tissue in wet environments may potentially complicate deployment. When oxidized cellulose is used in proximity to nerve structure in areas of bony confinement (e.g., foramina, spinal cord, optic chiasm), it may lead to nerve damage [30]. Surgicel Fibrillar applied to epidural venous plexus led to swelling and significant mass effect causing rapid neurological deterioration. Moreover, when ORC has been applied as a wrap during vascular or urologic procedures, a stenotic effect was reported [30]. Thus, it is important to be cautious when applying it tightly as a wrapping material.

Gelatin-Based Mechanical Hemostats

Gelatin-based agents are mechanical hemostats prepared from porcine or bovine skin-derived gelatin, acting at the end stage of the coagulation cascade by facilitating fibrin formation [4]. They provide a mechanical matrix for clot to adhere and are reabsorbable within 4–6 weeks. Caution should be used because gelatin swelling could result in compression and necrosis of surrounding structures, especially within bony spaces [4]. Gelfoam paste is associated with less inhibition of bone healing and less infection than bone wax. Gelfoam swells more than

collagen or cellulose products, increasing compressive complications. Penetrating trauma through solid organs (e.g., hepatic gunshot wounds) can be treated with a hemostatic plug composed of gelatin foam wrapped in oxidized cellulose inserted into the traumatic cavity. Recent novel hemostatic agents induce in situ gel formation via microbial transglutaminase to cross-link gelatin, which showed similar hemostatic effect with stronger adhesion and elasticity in rat liver models compared to Surgiflo [31].

Bovine Collagen Based Mechanical Hemostats

Bovine collagen-based products provide a physical matrix that stimulates clot formation by promoting platelet aggregation and clotting factor release. Microfibrillar collagen is derived from bovine corium and supplied in powder, nonwoven sheet, sponge, and pad forms (e.g., Avitene Ultrafoam, EndoAvitene, Avitene UltraWrap, Helitene, Helistat). Collagen provides a large surface area to allow platelets to activate, aggregate, and adhere to wide-area parenchymal hemorrhage. Thus, it is less effective in patients with severe thrombocytopenia but successfully achieves hemostasis even in the setting of heparinization. Its use was reported to have improved blood loss and postoperative drainage volume compared with gelatin-based products during spinal fusion surgery [32].

It usually does not swell significantly and gets absorbed in less than 8 weeks. Caution should be used during blood-saving device use because bovine collagen-based agents can normally pass through their filters; thus, blood collected from operative sites where collagen was used should not be given back to the patient [3, 32].

Polysaccharide-Based Mechanical Hemostats

Microporous polysaccharide hemospheres enhance endogenous clotting processes by absorbing water and concentrating platelets and clotting proteins [7]. Their application leads to reduction in hemostasis time, postoperative chest drain output, and transfusion requirements during cardiothoracic surgery [7]. They are completely re-absorbable, thus limiting infection or granuloma formation [7]. Limited neurotoxicity compared to ORC improves safety and efficacy in the brain hemorrhage model. Polysaccharide spheres also demonstrate superiority over ORC in animal models of partial nephrectomy. They may be equally effective as flowable hemostats in endoscopic sinus surgery. There is embolic risk if accidentally injected into blood vessels. No more than 50 g of this product should be used in diabetic patients due to the product's glucose load [7].

TOPICAL SYNTHETIC HEMOSTATIC AGENTS

Cyanoacrylates

Cyanoacrylates form polymers from liquid monomers in the presence of water to glue adjacent surfaces together. Octyl-2-cyanoacrylate (such as Dermabond) was initially developed to repair combat wounds, and the embolization of portosystemic venous shunts, pseudoaneurysm anastomoses, arteriovenous fistulas, vascular reconstructions, and cardiac surgery [33–35]. Butyl-2-cyanoacrylate was developed in Asia for the embolization of gastric and esophageal varices by direct injection into the bleeding vessels. Cyanoacrylates need no follow-up visit for suture removal and provide a waterproof barrier. Octyl-2-cyanoacrylate does not show any difference in the incidence of infection, dehiscence, or cosmetic appearance when repairing lacerations as compared to standard sutures, staples, or adhesive strips [34, 35]. It is safe to use cyanoacrylates for wounds, lacerations, and minimal incisions (e.g., laparoscopy).

Antibiotic ointment or petroleum jelly should not be concomitantly applied for 7 days to avoid polymer breakdown. It cannot be used on avulsed tissues, joints, hands, feet, or mucosal surfaces. Use around vascular anastomoses is not recommended due to lack of large clinical trials. There is embolic risk if accidentally injected into blood vessels. There is

toxicity evident from cyanoacrylates degradation products, namely formaldehyde and cyanoacetate.

Polyethylene Glycol Hydrogel

Polyethylene glycol polymer (such as CoSeal) can be sprayed on tissue to form a hydrogel matrix with contacting tissue. CoSeal was reported to be noninferior to Gelfoam/thrombin during aortic aneurysm grafting, infra-inguinal revascularization, and dialysis shunt creation. This cross-linked network functions as a sealant as well as a barrier to adhesion formation. The reaction is not exothermic and is not prone to inflammation or infection. It has been shown to decrease pericardial adhesion from multiple sternotomies in children with congenital heart defects [36].

CoSeal continues to swell the first day after application, and should be avoided when compressing surrounding structures is an anticipated potential harm. CoSeal has been reported to adhere poorly to renal parenchyma [36].

Glutaraldehyde Cross-Linked Albumin

Glutaraldehyde covalently cross-links lysine residues of albumin to form a tough scaffold. BioGlue is a 10% glutaraldehyde and 45% bovine serum albumin loaded into a single-nozzle dispenser that mixes components at application. BioGlue can adhere to synthetic graft materials. Thus, it has increased roles in cardiac graft and vascular anastomotic surgery [37, 38]. BioGlue and bovine pericardium with a polytetrafluoroethylene patch have been used to repair atrioventricular disruption and splenic lacerations [38, 39]. Glutaraldehyde is a toxic fixative, and its cross-linking proteins kills cells in the application field and should be used with caution. It is often avoided in young patients for fear of compromising tissue growth. BioGlue can react with tissue to contribute to stenosis [37].

Synthetic Topical Hemostatic Nanomolecules

A model of self-assembling fibers comprised of nanofabricated chitosan fibers shows hemostatic action possibly due to the cation properties of chitosan and nonspecific cell membrane binding to improve platelet aggregation over traditional chitosan sponge. Mesh structures have achieved hemostasis in a rabbit liver model [39, 40]. Another topical hemostatic employed narrow-sized, rapid-swelling cationic hydrogel particlea based on N-(3-aminopropyl) methacrylamide with significant blood loss reduction in a rat liver and tail amputation model [40, 41].

EXTERNAL HEMOSTATIC DRESSINGS

External hemostatic dressings were invented to stop severe hemorrhage in the battlefield due to lack of surgical care in an urgent scenario. Severe hemorrhage causes a high mortality rate in potentially survivable casualties in today's battlefields. Hemostatic dressings are used for external hemorrhage at junctional sites (e.g., axilla, groin) when tourniquets have failed to achieve hemostasis. They are grouped as factor concentrators (zeolite) [41], procoagulants (kaolin), and mucoadhesive (chitin) [41, 42]. These products come as granules, powders, or bandages, and the dressings are commonly used to increase local concentrations of platelets, clotting factors, and erythrocytes at the wound. Military and civilian groups recommend external hemostatic agents for prehospital control of severe hemorrhage uncontrollable with a tourniquet. Significant improvements in hemostatic dressings for prehospital care have been introduced, and many tactical and conventional care guidelines have been upgraded.

Fibrinogen-Based Hemostatic Dressing

These are attractive alternatives to current agents because of their ability to form clots in the absence of host coagulation proteins or in

the presence of factors such as hypothermia that contribute to a coagulopathic state [43]. An example of fibrinogen-based dressing is Salmon Thrombin-Fibrinogen, which can be used for open wounds, and the clot formation effect is not hindered by hypothermia.

Zeolites-Based hemostatic dressing

Zeolites are microporous crystalline aluminosilicate minerals found in nature. Their structure is based on tetrahedral units of $[SiO_4]^{4-}$and $[AlO_4]^{5-}$ which are coordinated through shared oxygen atoms. Zeolites have cage-like cavities which accommodate both water molecules and positively charged ions such as Ca^{2+} and Na^{+}. The cations can exchange with other cations in physiological solutions [44]. Zeolites contain a 3D structure which helps the movement of water molecules in and out while remaining rigid. Zeolite is marketed as QuikClot granular powder (QuikClot; Z-Medica, Wallingford, CT, USA) and Advanced Clotting Sponge (ACS; Z-Medica). Case studies reported QuikClot utilization to achieve hemostasis in trauma victim and patient with uncontrollable pelvic bleeding [45].

QuikClot increases the temperature at both the wound surface and the surrounding tissue causing potential thermal injury and necrosis. Difficulty in removing QuikClot once at the site of bleeding is an additional concern. QuikClot was removed from the military inventory in 2008, but a newer generation of zeolite hemostats, such as ACS and ACS Plus (ACS+), were approved by FDA for external use. ACS+ produced minimum exothermic reaction and was easy to use and remove. The product is ineffective against arterial bleeding, and was replaced by second-generation dressings (e.g., clay materials) [46].

Clay-Based Hemostatic Agents

Clay minerals consist of tetrahedral silicate and octahedral aluminate sheets. Based on the ratio of tetrahedral to octahedral sheets, these clays can be classified into two groups, 1:1 and 2:1 [47]. Clay 1:1 is comprised of one silica tetrahedral layer to one aluminum octahedral layer (e.g., kaolin). Clay 2:1 consists of one octahedral sheet between two tetrahedral sheets (e.g., smectite). Clays possess thermal stability, small particle size, large surface area, significant surface charge, and ion exchange capability. Zeolites are similar to clay minerals (both are aluminosilicates), but they are structurally different. Clay minerals have a layered crystalline structure that can shrink and swell when water is eliminated and absorbed between the layers [47].

Kaolin Group

Kaolin is a 1:1 clay made of the mineral kaolinite. Its absorption property and surface charge are low. It is associated with low surface area and substitution of other elements (e.g., ferric iron and titanium for aluminum and silicon) [48]. Kaolin in contact with plasma can lead to intrinsic coagulation cascade activation. The polar aluminosilicate framework of kaolin provides a surface for contact activation of the intrinsic pathway. Kaolin's net negative surface charge is also involved in triggering the intrinsic pathway by auto-catalytic activation of coagulation factors XII and XI, prekallikrein, and cofactor HWK–kininogen. Kaolin has been marketed under various names including QuikClot Combat Gauze, QuikClot Combat Gauze XL, QuikClot Combat Gauze Trauma Pad and QuikClot Interventional. The materials reportedly expedite hemostasis without the complications related to previously mentioned QuikClot products. Kaolin-impregnated gauze continues to be used as the primary hemostatic dressing by the US military force [43]. QuikClot Combat Gauze may be justified as the optimal agent due to the volume of clinical data on prehospital care of severe hemorrhage [48].

Smectite Group

Smectite clays are 2:1 phyllosilicates consisting of one octahedral sheet between two tetrahedral sheets. Smectite product displays a large surface area, a large cation exchange capacity, and a high viscosity. Smectite can also absorb large amounts of water. In comparison to kaolin,

smectite demonstrates higher plasticity, absorption, swelling, and viscosity. Smectite also has a negative surface charge that activates the intrinsic coagulation pathway. Although WoundStat was reported as an effective hemostatic offering improved survival, it can cause significant inflammatory response, neurovascular changes, and necrosis. WoundStat removal also requires extensive and meticulous debridement. WoundStat utilization was halted in 2009 by the U.S. Army while the FDA recommended removal from the United States market [49].

Polysaccharide and Polyelectrolyte

Some third-generation chitosan-based dressings have recently been introduced. Both chitin and its deacetylated form, chitosan, have hemostatic properties. For chitin dressings, these properties are believed to result from vasoconstriction and mobilization of erythrocytes, clotting factors, and platelets to the site of the injury. These induce hemostasis through direct interaction with erythrocytes, and are therefore ideal dressings to stop bleeding in coagulopathic patients because their hemostasis mechanism is not dependent on host coagulation pathways. Chitin dressings, such as the rapid deployment hemostat, are effective in treating minor wounds and have shown efficacy in swine models of splenic lacerations, being faster than with fibrin glue [50]. Although the first generation of rapid deployment hemostats was ineffective in controlling severe bleeding, newer modified formulations are effective in controlling both venous and arterial bleedings, even in patients with coagulopathy. These dressings are believed to be the most expensive among the hemostatic agents currently available on the market [51]

Chitosan dressing (as HemCon) contains chitosan from shellfish, so it is contra-indicated in patients with shellfish allergy. However, testing showed no adverse reaction during bandage challenges in shellfish-allergic patients [50]. As a popular biopolymer for the development of drug delivery systems, chitosan is a unique positively charged polysaccharide. It possesses excellent biocompatibility, high biodegradability, little toxicity, and low production cost. Its acidic pH allows it to disrupt the membranes of Gram-negative bacteria, resulting in its natural highly microbicidal properties [50].

Delivery systems are fabricated from natural biopolymer-based polyelectrolyte complexes (PEC), formed by electrostatic interactions between two oppositely charged biopolymers. These PECs using carboxymethyl starch and chitosan oligosaccharide were evaluated in rabbit hepatic hemorrhage models. The complexes could significantly activate and accelerate the coagulation cascade and showed some antimicrobial activity against *S. aureus*. Moreover, the PEC displayed good tissue compatibility in a rabbit liver model [52]. Various chitosan-based PEC drug delivery systems have been developed for different specific applications, such as nanoparticles, microparticles, beads, tablets, gels, films, and membranes. Chitosan dressings appear to function through mechanically sealing wounds and adhering to surrounding tissue. HemCon is currently used by the US forces and achieved successful hemostasis in military and civilian settings [53]. HemCon needs hands-on training. The efficacy of HemCon depends on the bandage, adhering well. This may prove difficult in emergencies and requires training and experience.

Applications of hemostatic agents can potentially significantly reduce morbidity and mortality from hemorrhage. A variety of topical agents and external dressings are available for clinical and military use. All currently available topical hemostatic agents are summarized in Table 1. The effects of topical hemostatic agents on coagulation cascade was depicted in Fig. 1. The type of bleeding, the specific mechanism of etiology, the patient's individual coagulation status, and the clinician's preference and experience may determine which agent or a combination of techniques to be used. Current methods of resolving perioperative bleeding or after trauma include topical hemostats and transfusion of blood products or recombinant clotting factors to restore hemostatic function, in addition to surgical hemostasis.

Table 1 Topical hemostatic agents: classification, mechanisms, products, and clinical features

Category	Class	Mechanism(s) of action	Brand names	Clinical feature
Topical active agent	Fibrin-based active adhesives and fibrin patch	Contains fibrinogen and/or thrombin, fibrin	Tiesseel, Evicel, Tachosil	Congenital or acquired bleeding disorders; coagulation disorders
	Thrombin-based topical hemostats	Trigger the coagulation cascade and fibrin clot formation actively	Thrombin JMI, Evithrom	Not good for preventing pancreatic, biliary, urinary, and intestinal leakages
	Combined flowable gelatin and thrombin or collagen-based topical hemostats	Removal: metabolized by fibrinolysis and phagocytosis	Surgiflo, Floseal, Vitagel, Tachosil	
Topical mechanical hemostats	Oxidized cellulose	Contain bovine collagen, oxidized cellulose, or gelatin, plant-derived polysaccharide spheres	Surgicel, Nu-Knit, Surgicel Fibrillar	Only indicated for patients with a functioning coagulation system
	Gelatin-based mechanical hemostats	Provide a clotting matrix	Gelfilm, surgifoam,Gelfoam	Less effective in patient with thrombocytopenia;
	Bovine collagen-based mechanical hemostats	Promote platelet activation and aggregation	Avitene, Avitene, Ultrafoam, UltraWrap, Instat, Helitene, Helistat	
	Polysaccharide-based mechanical hemostats	Removal: absorbable by human body	Arista, Hemostase, Vitasure	
Topical synthetic/ hemisynthetic hemostatic agents	Cyanoacrylates	Form a solid film polymerization to connect tissue surfaces	Dermabond	Dermabond for open wound bonding
				Butyl-2-cyanoacrylate for intravenous embolization;
	Polyethylene glycol hydrogel	Sprayed on tissue to form a hydrogel matrix	CoSeal	Vascular anastomosis bleeding
	Glutaraldehyde cross-linked albumin	Chemical reaction between aldehydes and amines, provided by the ε-amino groups of lysine residues in albumin and extracellular matrix in the tissues	BioGlue	Tissue laceration or vascular graft bleeding
	Synthetic topical hemostatic nanomolecules	Self-assembling peptide or chitosan nanofibers facilitating coagulation	CaMXS	Especially suitable for bleeding in bone defect

Table 1 continued

Category	Class		Mechanism(s) of action	Brand names	Clinical feature
External hemostatic dressings	Fibrinogen-based hemostatic dressings		External mechanical pressure Increase local concentrations of platelets, clotting factors, and erythrocytes at the wound	Salmon thrombin-fibrinogen (STF)	Clot formation not hindered by hypothermia
	Zeolites		Acts as a molecular sieve and rapidly adsorbs water Zeolite reaction with blood is exothermic	QuikClot, Advanced Clotting Sponge	Trauma-induced severe bleeding, removed from market in 2008
	Clay-based hemostatic agents	Kaolin group	Kaolin activates factor XII Absorb water	QuikClot Combat Gauze, TraumaPad,	Traumatic open wound
		Smectite group		WoundStat Celox Gauze (CEG)	WoundStat utilization was halted in 2009
	Polysaccharide and Polyelectrolyte		3rd generation chitosan-based dressings mechanically sealing wounds	HemCon	Trauma bleeding

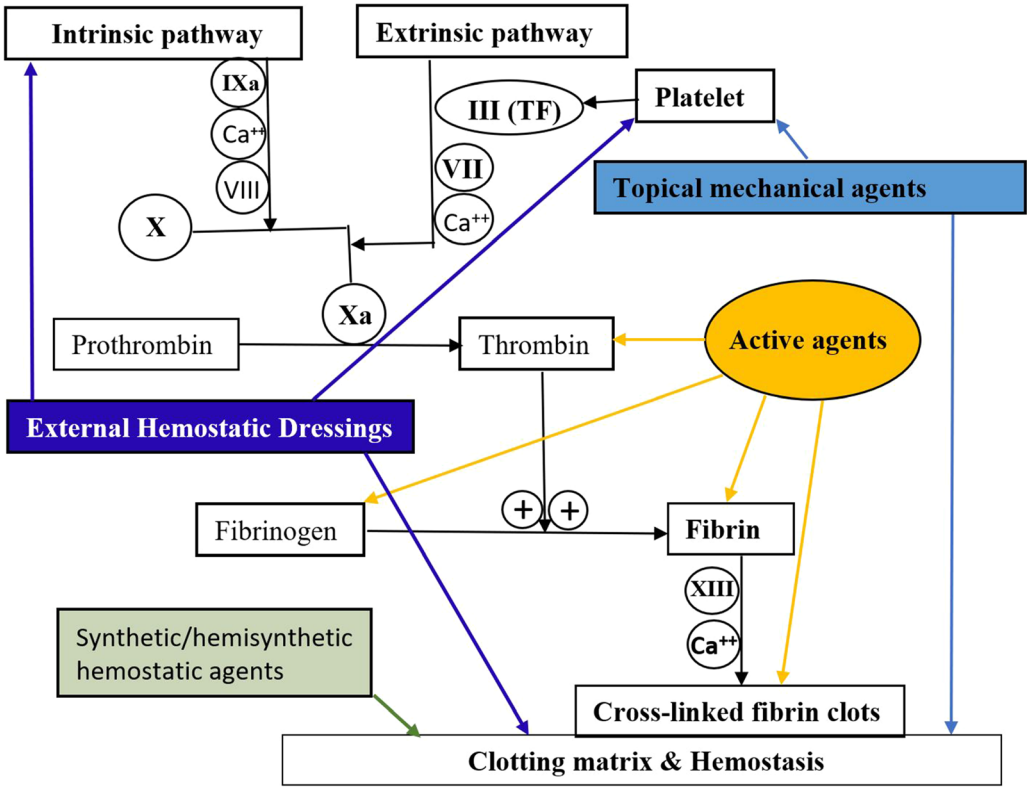

Fig. 1 Effects of topical hemostatic agents on coagulation cascade

SUMMARY

Topically-applied hemostatic agents are usually applied as a supplemental strategy for surgical hemostasis and/or pharmacological hemostatic medications. Their utilization is often limited to treating accessible locations in the body. Topical active agents contain fibrinogen and/or thrombin and fibrin, which actively trigger the coagulation cascade and fibrin clot formation; thus, they are good for congenital or acquired bleeding disorders and coagulation abnormalities. Topical mechanical hemostats contain oxidized cellulose, or collagen, gelatin, or plant-derived polysaccharide spheres, which provide a clotting matrix, and potentially promote platelet activation and aggregation. However, topical mechanical hemostats may not be suitable for pancreatic, biliary, urinary, and intestinal leakages. Topical synthetic/hemisynthetic hemostatic agents usually form, either forming a polymerized solid film or a matrix to block bleeding. External hemostatic dressings work by external mechanical pressure and/or increased local concentrations of local platelet, clotting factor, or absorbing water. These agents are indicated for severe traumatic hemorrhage, or locations not easy for surgical hemostasis. Biologically-derived products can be effective but have many limitations, such as short shelf life, risk of disease transmission, involved manufacturing processes, and protentional compression of surrounding tissues. Tranexamic acid-containing hemostatic agents may have neurotoxicity, so should be avoided for application close to nerve tissue. Glutaraldehyde is a toxic fixative which may cross-link proteins and kill the cells in the neighboring tissue, and thus should be used with caution. Hemostatic external dressings, such as minerals and polysaccharides together with mechanical compression, are effective in controlling severe bleeding. In the future, hemostatic agents can be engineered towards involving both primary and secondary hemostasis mechanisms for enhanced hemostatic responses.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for the publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Liang Huang, Geoffrey Liu, Alan Kaye and Henry Liu have no conflict of personal, financial, commercial and academic interests.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Lowe J, Luber J, Levitsky S, Hantak E, Montgomery J, Schiestl N, et al. Evaluation of the topical hemostatic efficacy and safety of TISSEEL VH S/D fibrin sealant compared with currently licensed TISSEEL VH in patients undergoing cardiac surgery: a phase 3, randomized, double-blind clinical study. J Cardiovasc Surg (Torino). 2007;48(3):323–31.

2. Oklu R, Albadawi H, Jones JE, Yoo HJ, Watkins MT. Reduced hind limb ischemia-reperfusion injury in toll-like receptor-4 mutant mice is associated with decreased neutrophil extracellular traps. J Vasc Surg. 2013;58(6):1627–36. https://doi.org/10.1016/j.jvs.2013.02.241.

3. Chiara O, Cimbanassi S, Bellanova G, Chiarugi M, Mingoli A, Olivero G, et al. A systematic review on the use of topical hemostats in trauma and emergency surgery. BMC Surg. 2018;18(1):68. https://doi.org/10.1186/s12893-018-0398-z.

4. Echave M, Oyagüez I, Casado MA. Use of Floseal®, a human gelatine-thrombin matrix sealant, in surgery: a systematic review. BMC Surg. 2014;14:111. https://doi.org/10.1186/1471-2482-14-111.

5. Rojas S, Arias B, Miquel I, Sánchez P, Ureta C, Rincón E, López R, Murat J. Experimental evaluation of a new tissue factor-based topical hemostat (TT-173) for treatment of hepatic bleeding. J Invest Surg. 2018;31:1–11. https://doi.org/10.1080/08941939.2018.1517840.

6. Cheng Y, Ye M, Xiong X, Peng S, Wu HM, Cheng N, et al. Fibrin sealants for the prevention of postoperative pancreatic fistula following pancreatic surgery. Cochrane Database Syst Rev. 2016;2:CD009621. https://doi.org/10.1002/14651858.CD009621.pub2**(Review. Update in: Cochrane Database Syst Rev. 2018 6:CD009621)**.

7. Bruckner BA, Blau LN, Rodriguez L, Suarez EE, Ngo UQ, Reardon MJ, et al. Microporous polysaccharide hemosphere absorbable hemostat use in cardiothoracic surgical procedures. J Cardiothorac Surg. 2014;9:134. https://doi.org/10.1186/s13019-014-0134-4.

8. Wright NM, Park J, Tew JM, Kim KD, Shaffrey ME, Cheng J, et al. Spinal sealant system provides better intraoperative watertight closure than standard of care during spinal surgery: a prospective, multicenter, randomized controlled study. Spine (Phila Pa 1976). 2015;40(8):505–13. https://doi.org/10.1097/BRS.0000000000000810.

9. Miscusi M, Polli FM, Forcato S, Coman MA, Ricciardi L, Ramieri A, et al. The use of surgical sealants in the repair of dural tears during non-

instrumented spinal surgery. Eur Spine J. 2014;23(8):1761–6. https://doi.org/10.1007/s00586-013-3138-1.

10. Fischer CP, Wood CG, Shen J, Batiller J, Hart JC, Patel B, et al. A randomized trial of aprotinin-free fibrin sealant versus absorbable hemostat. Clin Appl Thromb Hemost. 2011;17(6):572–7. https://doi.org/10.1177/1076029611404212.

11. Chalmers RT, Darling Iii RC, Wingard JT, Chetter I, Cutler B, Kern JA, et al. Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. Br J Surg. 2010;97(12):1784–9. https://doi.org/10.1002/bjs.7235.

12. Wang GJ, Goldthwaite CA Jr, Burks SG, Spotnitz WD, Orthopaedic Research Group. Experience improves successful use of fibrin sealant in total knee arthroplasty: implications for surgical education. J Long Term Eff Med Implants. 2003;13(5):389–97. https://doi.org/10.1615/jlongtermeffmedimplants.v13.i5.40.

13. Prakash S, Thakur A. Platelet concentrates: past, present and future. J Maxillofac Oral Surg. 2011;10(1):45–9. https://doi.org/10.1007/s12663-011-0182-4.

14. Esposito F, Angileri FF, Kruse P, Cavallo LM, Solari D, Esposito V, Tomasello F, Cappabianca P. Fibrin sealants in dura sealing: a systematic literature review. PLoS ONE. 2016;11(4):e0151533. https://doi.org/10.1371/journal.pone.0151533.

15. Montana M, Tabélé C, Curti C, Terme T, Rathelot P, Gensollen S, Vanelle P. Organic glues or fibrin glues from pooled plasma: efficacy, safety and potential as scaffold delivery systems. J Pharm Pharm Sci. 2012;15(1):124–40. https://doi.org/10.18433/j39k5h.

16. Taylor LM Jr, Mueller-Velten G, Koslow A, Hunter G, Naslund T, Kline R, et al. Prospective randomized multicenter trial of fibrin sealant versus thrombin-soaked gelatin sponge for suture- or needle-hole bleeding from polytetrafluoroethylene femoral artery grafts. J Vasc Surg. 2003;38(4):766–71. https://doi.org/10.1016/s0741-5214(03)00474-9.

17. Zhang WH, Bai YY, Guo W, Li M, Chang GX, Liu W, Mao Y. Application of intrapulmonary wire combined with intrapleural fibrin glue in preoperative localization of small pulmonary nodules. Medicine (Baltimore). 2019;98(4):e14029. https://doi.org/10.1097/MD.0000000000014029.

18. Vakalopoulos KA, Daams F, Wu Z, Timmermans L, Jeekel JJ, Kleinrensink GJ, et al. Tissue adhesives in gastrointestinal anastomosis: a systematic review. J Surg Res. 2013;180(2):290–300. https://doi.org/10.1016/j.jss.2012.12.043.

19. Greenberg JA, Robinson JN, Carabuena JM, Farber MK, Carusi DA. Use of a fibrin sealant patch at cesarean for conservative management of morbidly adherent placenta. AJP Rep. 2018;8(4):e325–e327327. https://doi.org/10.1055/s-0038-1675848.

20. Fischer CP, Bochicchio G, Shen J, Patel B, Batiller J, Hart JC. A prospective, randomized, controlled trial of the efficacy and safety of fibrin pad as an adjunct to control soft tissue bleeding during abdominal, retroperitoneal, pelvic, and thoracic surgery. J Am Coll Surg. 2013;217(3):385–93. https://doi.org/10.1016/j.jamcollsurg.2013.02.036.

21. Simo KA, Hanna EM, Imagawa DK, Iannitti DA. Hemostatic agents in hepatobiliary and pancreas surgery: a review of the literature and critical evaluation of a novel carrier-bound fibrin sealant (TachoSil). ISRN Surg. 2012;2012:729086. https://doi.org/10.5402/2012/729086.

22. Spotnitz WD. Hemostats, sealants, and adhesives: a practical guide for the surgeon. Am Surg. 2012;78(12):1305–21.

23. Fu X, Tian P, Xu GJ, Sun XL, Ma XL. Thrombin-based hemostatic agent in primary total knee arthroplasty. J Knee Surg. 2017;30(2):121–7. https://doi.org/10.1055/s-0036-1582137.

24. Comadoll JL, Comadoll S, Hutchcraft A, Krishnan S, Farrell K, Kreuwel HT, Bechter M. Comparison of hemostatic matrix and standard hemostasis in patients undergoing primary TKA. Orthopedics. 2012;35(6):e785–e793793. https://doi.org/10.3928/01477447-20120525-14.

25. David G, Lim S, Gunnarsson C, Kocharian R, Roy S. Similar patient outcomes yet different hospital costs between flowable hemostatic agents. J Med Econ. 2015;18(9):735–45. https://doi.org/10.3111/13696998.2015.1044994.

26. Nasso G, Piancone F, Bonifazi R, Romano V, Visicchio G, De Filippo CM, et al. Prospective, randomized clinical trial of the FloSeal matrix sealant in cardiac surgery. Ann Thorac Surg. 2009;88(5):1520–6. https://doi.org/10.1016/j.athoracsur.2009.07.014.

27. Wagenhäuser MU, Mulorz J, Ibing W, Simon F, Spin JM, Schelzig H, et al. Oxidized (non)-regenerated cellulose affects fundamental cellular processes of wound healing. Sci Rep. 2016;2016(6):32238. https://doi.org/10.1038/srep32238.

28. Brodbelt AR, Miles JB, Foy PM, Broome JC. Intraspinal oxidised cellulose (Surgicel) causing delayed paraplegia after thoracotomy—a report of three cases. Ann R Coll Surg Engl. 2002;84(2):97–9.

29. Cheng F, Wu Y, Li H, Yan T, Wei X, Wu G, et al. Biodegradable *N*, *O*-carboxymethyl chitosan/oxidized regenerated cellulose composite gauze as a barrier for preventing postoperative adhesion. Carbohydr Polym. 2019;207:180–90. https://doi.org/10.1016/j.carbpol.2018.10.077.

30. Menovsky T, Plazier M, Rasschaert R, Maas AI, Parizel PM, Verbeke S. Massive swelling of Surgicel® Fibrillar™ hemostat after spinal surgery. Case report and a review of the literature. Minim Invasive Neurosurg. 2011;54(5–6):257–9. https://doi.org/10.1055/s-0031-1284394.

31. Lv F, Cong X, Tang W, Han Y, Tang Y, Liu Y, et al. Novel hemostatic agents based on gelatin-microbial transglutaminase mix. Sci China Life Sci. 2017;60(4):397–403. https://doi.org/10.1007/s11427-015-9019-x.

32. Abbott WM, Austen WG. The effectiveness and mechanism of collagen induced topical hemostasis. J Cardiovasc Surg (Torino). 1976;17(1):95–6.

33. Yamagami T, Kanda K, Kato T, Hirota T, Nishida K, Yoshimatsu R, et al. Embolisation of proximal anastomotic pseudoaneurysm developing after surgical repair of abdominal aortic aneurysm with a bifurcated graft with n-butyl cyanoacrylate. Br J Radiol. 2006;79(948):e193–e195195. https://doi.org/10.1259/bjr/97367208.

34. Coulthard P, Worthington H, Esposito M, Elst M, Waes OJ. Tissue adhesives for closure of surgical incisions. Cochrane Database Syst Rev. 2004;(2):CD004287. https://doi.org/10.1002/14651858.CD004287.pub3.

35. Jeanmonod D, Rammohan G, Jeanmonod R. Thrombostatic agents and tissue adhesives in the emergency department: stopping the bleeding, closing the wound, and novel applications. In: Firstenberg MSS, Stawicki SP, editors. Biosurgicals—the next frontier in operative approaches. 2020. https://doi.org/10.5772/intechopen.91470. https://www.intechopen.com/online-first/thrombostatic-agents-and-tissue-adhesives-in-the-emergency-department-stopping-the-bleeding-closing-.

36. Pace Napoleone C, Oppido G, Angeli E, Gargiulo G. Resternotomy in pediatric cardiac surgery: CoSeal initial experience. Interact Cardiovasc Thorac Surg. 2007;6(1):21–3. https://doi.org/10.1510/icvts.2006.141531.

37. Bhamidipati CM, Coselli JS, LeMaire SA. BioGlue in 2011: what is its role in cardiac surgery? J Extra Corpor Technol. 2012;44(1):P6–12.

38. Gurusamy KS, Li J, Vaughan J, Sharma D, Davidson BR. Cardiopulmonary interventions to decrease blood loss and blood transfusion requirements for liver resection. Cochrane Database Syst Rev. 2012;(5):CD007338. https://doi.org/10.1002/14651858.CD007338.pub3.

39. Luo Z, Wang S, Zhang S. Fabrication of self-assembling D-form peptide nanofiber scaffold d-EAK16 for rapid hemostasis. Biomaterials. 2011;32(8):2013–20. https://doi.org/10.1016/j.biomaterials.2010.11.049.

40. Sun H, Lv L, Bai Y, et al. Nanotechnology-enabled materials for hemostatic and anti-infection treatments in orthopedic surgery. Int J Nanomed. 2018;13:8325–38. https://doi.org/10.2147/IJN.S173063.

41. Te Grotenhuis R, van Grunsven PM, Heutz WM, Tan EC. Prehospital use of hemostatic dressings in emergency medical services in the Netherlands: a prospective study of 66 cases. Injury. 2016;47(5):1007–111. https://doi.org/10.1016/j.injury.2016.01.005.

42. Shina A, Lipsky AM, Nadler R, Levi M, Benov A, Ran Y, et al. Prehospital use of hemostatic dressings by the Israel Defense Forces Medical Corps: a case series of 122 patients. J Trauma Acute Care Surg. 2015;79(4 Suppl 2):S204–S209209. https://doi.org/10.1097/TA.0000000000000720.

43. Grissom TE, Fang R. Topical hemostatic agents and dressings in the prehospital setting. Curr Opin Anaesthesiol. 2015;28(2):210–6. https://doi.org/10.1097/ACO.0000000000000166.

44. Mortazavi SM, Atefi A, Roshan-Shomal P, Raadpey N, Mortazavi G. Development of a novel mineral based haemostatic agent consisting of a combination of bentonite and zeolite minerals. J Ayub Med Coll Abbottabad. 2009;21(1):3–7.

45. Shanmugam V, Robinson MH. Case report of uncontrollable pelvic bleeding–managed by a previously unreported method (QuikClot). Colorectal Dis. 2009;11(2):221–2. https://doi.org/10.1111/j.1463-1318.2008.01550.x.

46. Arnaud F, Tomori T, Carr W, McKeague A, Teranishi K, Prusaczyk K, et al. Exothermic reaction in zeolite hemostatic dressings: QuikClot ACS and ACS+®. Ann Biomed Eng. 2008;36:1708. https://doi.org/10.1007/s10439-008-9543-7.

47. Williams LB, Haydel SE. Evaluation of the medicinal use of clay minerals as antibacterial agents. Int Geol Rev. 2010;52(7/8):745–70. https://doi.org/10.1080/00206811003679737.

48. Boulton AJ, Lewis CT, Naumann DN, Midwinter MJ. Prehospital haemostatic dressings for trauma: a systematic review. Emerg Med J. 2018;35(7):449–57. https://doi.org/10.1136/emermed-2018-207523.

49. Kheirabadi BS, Mace JE, Terrazas IB, Fedyk CG, Estep JS, Dubick MA, et al. Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine. J Trauma. 2010;68(2):269–78. https://doi.org/10.1097/TA.0b013e3181c97ef1.

50. Khan MA, Mujahid M. A review on recent advances in chitosan based composite for hemostatic dressings. Int J Biol Macromol. 2019;124:138–47. https://doi.org/10.1016/j.ijbiomac.2018.11.045.

51. Khoshmohabat H, Paydar S, Kazemi HM, Dalfardi B. Overview of agents used for emergency hemostasis. Trauma Mon. 2016;21(1):e26023. https://doi.org/10.5812/traumamon.26023.

52. Chen X, Yan Y, Li H, Wang X, Tang S, Li Q, et al. Evaluation of absorbable hemostatic agents of polyelectrolyte complexes using carboxymethyl starch and chitosan oligosaccharide both in vitro and in vivo. Biomater Sci. 2018;6(12):3332–44. https://doi.org/10.1039/c8bm00628h.

53. Brown MA, Daya MR, Worley JA. Experience with chitosan dressings in a civilian EMS system. J Emerg Med. 2009;37(1):1–7. https://doi.org/10.1016/j.jemermed.2007.05.043.