Chapter

Biosurgicals and Trauma

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Abstract

Hemorrhage plays a prominent role in the outcome of trauma patients, from initial injury, through resuscitation, and stabilization. Biosurgicals have recently drawn attention to both the control of bleeding and chronic wound management. However, their role will be examined here in the context of adjuncts to control preoperative, intraoperative, and postoperative bleeding in trauma. A review of the scientific literature relevant to the use of passive and active topical hemostatic devices, as well as systemic pharmacologic agents, for control of hemorrhage is provided, in both military and civilian contexts. Bibliometric publication patterns and published guidelines are examined to identify the range of individual products available and the degree of attention they receive in the management of acute traumatic injuries. It is imperative that the evidentiary basis for the use of these agents be weighed against their cost and potential risks.

Keywords: biologic glues, fibrin patches, thrombin gels, topical agents, bleeding, coagulopathy, hemostasis

1. Introduction

Injuries occur in remote and sometimes austere environments compared to the controlled environment of elective surgical procedures. The time from injury to definitive control of hemorrhage can vary dramatically according to circumstances. Although differences in prehospital transport times has little effect on mortality in hemodynamically stable patients, both military and civilian analyses indicate prehospital transport times are associated with an increased risk of mortality in patients with signs of active bleeding [1, 2].

The natural response to injury leads to the activated coagulation process through the intrinsic pathway and extrinsic pathway, which converge on the final common pathway, converting prothrombin to thrombin and subsequently fibrinogen to fibrin. Excessive bleeding can overcome coagulation reserve through exhaustive consumption of coagulation factors and activation of molecular inflammatory processes. Resuscitative efforts may result in hemodilution, combined with physiology that is dramatically altered due to hypothermia and acidosis. This can be associated with overactive fibrinolysis, which heightens the need for local hemorrhage control.

The state of coagulation function must often be assessed clinically. Traditional coagulation tests like the PT and PTT are not available in the immediate post injury phase and can have limited correlation with bleeding. Contemporary coagulation monitoring focuses on the use of functional point-of-care whole blood coagulation test such as the activated clotting time (ACT) [3] or thromboelastography (TEG) [4] to detect traumatic coagulopathy. The need to control traumatic bleeding at the earliest feasible moment, for both the coagulation competent and coagulopathic

patient has driven recent interest in the development of adjuncts to hemostasis for the management of military and civilian injuries. Mechanical and biosurgical adjuncts for hemorrhage control have been designed and tested in prehospital, emergency facility, and intraoperative contexts. In addition to applicability for extremity injuries, some of these adjuncts are designed with the advantage of feasible application to torso and junctional injuries, which are less accessible for mechanical control of bleeding.

This chapter will deal mainly with commercially available gauze, absorbable matrix, liquid, and foam products, with and without procoagulant activators used for the control of bleeding in the context of managing acute trauma.

2. Background on biosurgicals for trauma

2.1 Literature considerations

The term "biosurgical" does not have a reserved place in the National Library of Medicine (NLM) medical subject heading (MeSH) tree. Most of the relevant literature can be identified using the disjunctive combination of terms: "Hemorrhage/*therapy" OR "fibrin glue" OR "tissue adhesives," subsequently conjoined by AND to "wounds and injuries." A recent Medline search with that strategy yielded 748 articles between 1952 and 2019 (searched 10/1/2019). **Figure 1** shows the 5 year period publication pattern of this strategy from 1960 to present. Excluding three articles before 1960, it can be seen that modern era of biologic-based adjuncts to hemostasis began in the late 1960s, when fractionated blood products began to be generally available. However, consideration of the Final Common Pathway factors, thrombin (Factor II) and fibrin (Factor I), as adjuncts for surgical bleeding goes back as far as World War II [5].

Thrombin was likely the first biologic agent used to stop bleeding. Barber's and boxers were reported to use it to stop bleeding from shaving cuts and fight wounds as early as 1892 [6]. Human thrombin has partially replaced the use of bovine thrombin to avoid bovine antibodies that disrupt various components of the coagulation system, leading to hemorrhagic and thrombotic complications [6]. However, both bovine thrombin and human thrombin remain in current usage. Salmon Thrombin-Fibrin in a lyophilized form is an inexpensive, readily available alternative which has supportive data in an animal model [7]. The problem of potential disease

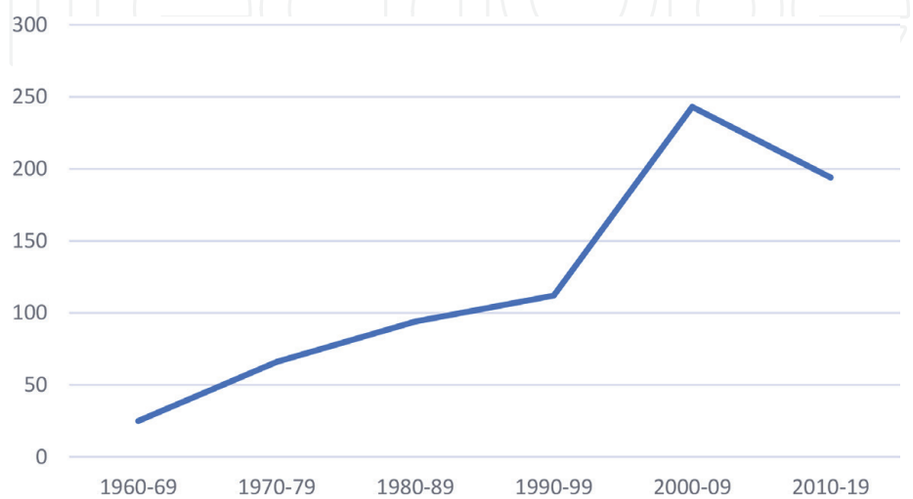

Figure 1.
*Number of Medline publications each 5 year period 1960 to 2019. Medline search results for: "Hemorrhage/*therapy" OR "fibrin glue" OR "tissue adhesives," AND "wounds and injuries."*

transmission from human thrombin was resolved with the subsequent development of recombinant thrombin. Although thrombin can be used alone, it is commonly applied with a carrier such as Gelfoam, made from processed and purified porcine skin. Thrombin combined with fibrinogen is the component of fibrin glue, which is packaged under various brand names, further elaborated below.

Sources used for this chapter include articles identified by the above search, their bibliographic references, and focused Medline searches for specific products. The literature dealing with biologic surgical products for hemorrhage control can be generally divided into three areas: (1) biochemical property assessment (2) comparison of efficacy in standardized animal injury models, and (3) series descriptions of clinical use. Animal experiments can be further categorized as using models for arterial, venous, or mixed hemorrhage. These usually involve creation of standardized injuries. However, different investigators use various injury mechanisms, making direct comparison of results difficult. Among animal trials, there are comparisons of single agents to controls and comparisons of multiple agents with or without controls.

There are numerous considerations in comparing the results between various animal model experiments for control of bleeding. These include differences in the rate of bleeding at the time of dressing application; attempts at simulating a realistic field-use scenario versus an isolated dressing challenge; consideration of the vessel type lacerated and the type and size of laceration; consideration of the duration of hemorrhage before application and arterial pressure level at the time of dressing application; differences in resuscitation regimens after dressing application, and; consideration of whether dressing application is performed with or without prior vascular control [8]. Additional problems with many of the animal studies concerns the large variance in blood loss volumes within groups, such that the standard deviation is often several times the mean blood loss [9]. This makes the detection of statistical superiority for any particular hemorrhage control strategy problematic.

Most of the clinical literature related to biosurgical adjuncts for hemorrhage control in trauma exists in small series, where a topical agent was applied in prehospital or emergency facility settings. The outcome measures are usually described as the subjective assessment of bleeding control and qualitative evaluation of user satisfaction with the products. In most clinical series, there is no opportunity to measure blood loss or specify time between application and control of bleeding.

2.2 Adjunctive methods for hemorrhage control

There are a number of standard and adjunctive methods for hemorrhage control. These include (1) direct, local wound pressure with standard gauze, (2) proximal tourniquets to limit extremity bleeding, (3) gauze pads impregnated with procoagulant activators, (4) powdered procoagulant activator agents, (5) absorbable matrix agents with or without an added procoagulant, and (6) liquid or foam products with reconstituted coagulation factors.

Currently there are a large number of products utilized as adjuncts for hemorrhage control. These are grouped by mechanism of action in **Tables 1**–**3**, described further below. Direct, local wound pressure with gauze, supplemented by the use of tourniquets remains the baseline standards to which topical hemostatic agents have been compared. A common pitfall of gauze dressings, particularly in the hands of the inexperienced, lies in the wide distribution of pressure beneath a bulky dressing, when focal pressure at the specific bleeding site is more effective. This may lead to inefficient control of hemorrhage and unnecessary blood loss. This can also prompt the more aggressive use of limb tourniquets, which promote ischemia of a larger downstream soft tissue mass, when local pressure may have

Type of agent	Main products	Components/mechanism of action	Uses
Zeolite based	QuikClot Combat Gauze(CG) Combat GauzeXL(CGX) Woundstat	Kaolin -impregnated rolled gauze Activates the intrinsic coagulation pathway	Traumatic wound treatment for high-volume blood loss and hemostasis in large wounds
	Woundstat	Smectite + polyacrylic polymer	Traumatic wound treatment for high-volume blood loss and hemostasis in large wounds
Chitosan-based: (Chitosan-polysaccharide derived from crustacean exoskeleton)	Chito Gauze (HCG) Chitoflex (HCF) (single sided), Hem Con (HC) (double sided) Omni Stat (OS) Rapidly Deployable Hemostat (RDH) & Modified Rapidly Deployable Hemostat (mRDH) Celox-A, Celox(CE) Granules, Celox Gauge(CEG) &Celox Rapid (CR)	Chitosan/large surface area, hemostatic pressure & hemostatic agent Chitosan/cross links RBC's to form a mucoadhesive barrier and activates platelets	Traumatic wound treatment for high-volume blood loss and hemostasis in large wounds

Table 1.
Biologically active inorganic stimulants of coagulation for topical application.

been effective. Tourniquets are limited to use in mid and distal extremity wounds. There use is controversial due to a high rate of ineffective application and concerns for complications. Improper tourniquet placement, such that constriction is applied above venous pressure, but not tight enough to occlude arterial inflow, can promote venous bleeding. When properly applied, extended ischemic insult may contribute to subsequent compartment syndromes or systemic metabolic stress when the tourniquet is removed, and resuscitative efforts ensue. In a 2011 report, Kragh, et al., reviewed tourniquet use in 499 soldiers with application of 862 tourniquets to 651 limbs. Complications of tourniquet use noted in that review, in order of decreasing frequency, included amputation, fasciotomy, clotting complications, myonecrosis, palsy at the tourniquet site, acute renal failure, significant pain, and rigor [10]. However, this was in observational cohort study, without the ability to compare potential outcomes with any alternate approach. Tourniquet use was supported based on the perception of minor morbidity and infrequent major complications. In cases where arterial extremity hemorrhage is difficult to control with point pressure, tourniquet use can be lifesaving.

Much of the early interest and experience with biological adjuncts for hemorrhage control comes from the military starting with World War II. The immediate

Type of agent	Main products	Components/mechanism of action	Uses
Gelatin-based	Gelfoam Surgifoam Floseal Surgiflo	Porcine gelatin Bovine gelatin + Human thrombin Porcine gelatin +/− Bovine thrombin	Mechanical barrier to bleeding-provides matrix for clot formation. Adjunct to hemostasis on wet, actively bleeding tissue
Collagen-based	Avitene, Ultrafoam Instat, Instat MCH Helistat, Helitene D-Stat	Bovine collagen Bovine collagen + Bovine thrombin	Mechanical barrier to bleeding, provide matrix for clot formation Compression pad or flowable solution
Cellulose-based	Surgicel, Surgicel Nu-knit Surgicel Snow Oxycel	Oxidized regenerated cellulose Oxidized non-regenerated cellulose	Mechanical barrier to bleeding, denatures blood proteins

Table 2.
Scaffold-based absorbable matrix adjuncts for surface bleeding.

Type of agent	Main products	Components/mechanism of action	Uses
Albumin-based	Bioglue	Bovine serum albumin + Glutaraldehyde	Tissue adhesive-seals leaks around sutures/ staples in large blood vessels
Polyethylene-glycol-based (PEG-based)	Coseal Duraseal	2 PEG polymers PEG ester + trilysine amine + blue dye	Mechanically sealing leaks in peripheral vascular reconstructions Dural sealing
Fibrin-based	Tisseel Quixil, Evicel Vivostat Cryoseal Tachocomb H, Tachosil Vitagel Tachocomb Salmon Thrombin-Fibrin Dry Fibrin Sealant Dressing (DFSD)	Human fibrinogen + Human thrombin Autologous Human fibrinogen + Human thrombin Bovine collagen + Bovine thrombin + Autologous plasma Human fibrinogen + Bovine thrombin Lyophilized salmon + human thrombin and human fibrinogen Human fibrinogen + Human thrombin + calcium chloride	Adjunct to surgical hemostasis, seals tissue and stops diffuse bleeding Forms a collagen/fibrin platelet scaffold Mechanical barrier to bleeding and also provides fibrinogen Mechanical barrier/ fibrin clot to stop bleeding by packing

Table 3.
Fibrin-based hemostatic tissue sealants.

attention available from combat medics, combined with the staged treatment and evacuation model of care created incentives to identify portable products and reducing the risk of exsanguination between injury and definitive care. Seven Criteria for the optimal field dressing has been described by the US military [8]:

1. It should have the ability to stop large vessel bleeding within 2 minutes, even If applied to active bleeding or pooled blood;

2. It should be ready for use without premixing or special preparation;

3. It should be simple to apply with minimal training;

4. It should be lightweight and durable;

5. It should be stable and functional at room temperature, plus functional at temperature extremes (between –10° Centigrade and 55° Centigrade);

6. It should safe to use, without risk of tissue damage or disease transmission, and;

7. It should be inexpensive

The introduction of gauze pads impregnated with procoagulant activators has raised hopes that a more efficient means of local hemorrhage control, particularly in the prehospital setting, could be achieved. There are a variety of such products, with various activators, described further below. **Table 1** contains a listing of the most commonly available products with biologically active inorganic stimulants of coagulation for topical application, showing common trade names. Hemostatic agents also come in granular form. These provide the opportunity to fill deep wound tracks, where direct local pressure is less efficient, and tourniquets are not practical. One of the most powerful, kaolin (Zeolite) granules, serves to activate the intrinsic pathway through factor XII and rapidly absorbs water in an exothermic reaction. It has not found common clinical usage, given its strong associated exothermic, hydrophilic reaction, which can cause local tissue damage [11].

As an alternative to gauze, there are a variety of absorbable matrix agents, which can be used as temporary topical dressings or left within body cavities for absorption. These are available with and without the addition of coagulation activators. **Table 2** shows commonly available products based on a scaffold mechanism.

One of the most common used biosurgical approaches for intraoperative hemorrhage control is the direct application of thrombin mixed with fibrinogen in the form of a liquid, spray, or foam. This is intended to create a sealant barrier that promotes coagulation on bleeding surfaces. There a various products based on a similar barrier layer/sealant approach and are also known as tissue adhesives. These are usually applied by mixing a primary component with an activator through a dual chamber syringe at the moment of application. These products are represented in **Table 3**.

2.3 Topical wound dressings for hemorrhage control

Fibrinogen and thrombin were the first two components of the coagulation cascade that were isolated, thus they are referred to Factor I and Factor II, respectively. There was extensive early testing of topically applied dried human fibrin and thrombin in controlled animal models of liver, spleen and brain injuries. Additionally, it was used in a series of human neurosurgical cases, which identified advantages, included better hemostasis than alternative methods, shortening of operative time, ability to leave the absorbable products behind with minimal tissue reaction, and producing no impairment of the effects of local antibiotics [12]. Subsequent case reports of clinical applications suggested topical biologic procoagulants were well tolerated but led to a consensus that they had only transient effects in the control of bleeding. These findings were mostly documented in administrative

meeting minutes of the Subcommittee on Blood Substitutes, of the Army's Division of Medical Sciences [5]. Thus, fibrin and thrombin held limited particularly in the ensuing years. The combination of thrombin with Gelfoam served as the mainstay for bothersome, but limited, intraoperative bleeding from raw surfaces.

Subsequently, there was a resurgence of interest in biologically assisted topical hemostatics at the end of the 20th Century, again driven by military relevance. A modern version of the dry fibrin sealant dressing (DFSD) was compared to a standard dry gauze dressing. When applied with direct pressure for 2 minutes DFSD was shown to significantly reduce both total blood loss (124 ml ±64 vs. 377 ± 64, $P = 0.01$) and blood loss per kilogram of body weight (1.3 ml/kg ±0.6 vs. 3.8 ml/kg ±0.6, $P = 0.02$) in a ballistically injured goat model. The animal's mean arterial pressure was also preserved with the reduced blood loss [13]. Similar hemorrhage reduction was noted when dry fibrin sealant dressing was used in a swine model for packing controlled liver injuries in normothermic conditions [14] and hypothermic, hemodiluted conditions [15] aimed at simulating the clinical coagulopathy of trauma. The product, which has not yet received FDA approval, has been utilized in Afghanistan and Iraq under an Investigational New Drug (IND) protocol, with strong military proponents. However, clinical data to confirm its effectiveness is elusive.

The Rapid Deployment Hemostat (RDH) ™ (Marine Polymer Technologies, Danvers, MA) and modified Rapid Deployment Hemostat (mRDH) have been a key component of frontline military hemorrhage control efforts. This dressing is made with Poly-N-acetyl glucosamine (pGlcNAc) which is a substance isolated from cultures of a marine micro Algae and is FDA approved to treat bleeding in trauma patients. The mechanism of action is to induce hemostasis by vasoconstriction, erythrocyte agglutination, and RBC and platelet activation. RDH was compared to standard linen dressings in a swine model with a standardized 4 mm aortic punch wound. Outcome measures were blood loss and survival after removal of the dressing and at 2 hours following removal. RDH treated animals had an average blood loss of 234 ml, compared to 1071 ml in the control animals ($p < 0.001$). These animals also had an 80% survival on release of compression and 2 hours later, compared to 40% survival on compression release and 0% survival 2 hours later for the controls [16].

Another topical dressing which consists of gauze combined with a coagulation activator is marketed as QuikClot Combat Gauze ®. The activator, Kaolin, is hydrated aluminum silicate, also known as Porcelain or China clay. It belongs to a broader category of Zeolite substances and forms a microgranular white powder which is biologically inert except as a binder. However, when ingested orally it is known to activate coagulation Factor XII thereby stimulating the intrinsic clotting cascade. It is commonly used as an activator for the Activated Clotting Time (ACT) and in Thromboelastography (TEG). QuikClot was introduced in 2002 as a gauze bandage substitute for actively bleeding wounds. However, it entered mainstream military use in 2008. In 2013 it gained FDA approval and has gained increasing support for civilian management of surgical bleeding and traumatic wounds. It is commonly available in various configurations of pads and rolls for prehospital, emergency room, and operating room application. It carries a low risk of allogenic reactions due to a lack of shellfish, human, or animal proteins. Both military and civilian case series report successful prehospital control of bleeding in 70–90% of applications of QuikClot [17, 18], however, most of the reported support is based on survey data [18], due to the difficulty of obtaining objective clinical data.

QuikClot was evaluated against standard gauze for the control of hemorrhage in a 2012 porcine groin injury model. Blood loss and stability of hemorrhage control when stressed by limb motion were the primary outcomes. It was found to significantly reduce blood loss and produce a stable clot which resisted recurrent bleeding

with movement in the injured groin. Bleeding in the experimental group ranged from 0 to 514 ml (mean = 50, SD ± 154 ml) and the control group ranged from 0 to 1002 ml (mean = 351, SD ± 354 ml). The number of movements tolerated before rebleeding in the experimental group ranged from 3 to 40 (mean = 36.6 ± 11) and for control group ranged from 0 to 9 (mean = 0.9 ± 2.7). Both outcomes showed statistically significant difference by Multivariate Analysis of Variance, although specific tests designed for high Variance and non-normal data distributions were not described [19].

There are several case series reporting the use of QuikClot to stop bleeding in the field and emergency rooms. In a multi-institutional clinical series reported in 2008, QuikClot combat gauze was applied in 103 cases, including 83 cases involving external use and 20 cases of intracorporeal use by civilian and military personnel. The overall success rate for control of bleeding was 92%. The reported failures were attributed to coagulopathy or inability to apply the product directly to the source of hemorrhage [20]. This study used self-reported survey data to assess effectiveness, illustrating again the difficulty in obtaining objective clinical data.

Zeolite impregnated gauze in the form of Combat Gauze ™ and Trauma Pads ™ have also been used for temporary intra-abdominal packing during damage control laparotomy. Choron, in a 2017 retrospective review, compared 28 patients packed with QuikClot plus laparotomy pads to 40 patients that underwent standard laparotomy pad packing as part of damage control maneuvers. There were no distinguishing clinical characteristics between the two groups, except that the patient's packed with QuikClot gauze plus laparotomy packs received approximately twice the number of packed red cells and fresh frozen plasma (10 vs. 5 and 8 vs. 4, respectively) at the time of initial operation. This suggests they may have had more serious and hemorrhage prone injuries. Blood products transfused after the initial operation were similar. There were no significant differences noted in multiple outcome variables, including: number of subsequent operations, days until abdominal closure, total fluid requirements, infectious complications, bowel complications, and length of stay. Hospital mortality was 29% in those who received QuikClot packing and 28% in those who did not. While the study did not show superiority of Zeolite product, it was interpreted to indicate safety in the context of damage control and supported further clinical studies in that setting [21].

Zeolite has been studied in the form of granules directly applied to bleeding wounds and within a containment bag, which simultaneously absorbs water from blood, activates platelets and the clotting cascade, plus applies local pressure as process progresses. However, the hydrophilic process is associated with an exothermic reaction severe enough to produce local burns [22]. A modified formulation of granules (QuikClot Advanced Clotting Sponge+ ®, Z-Medica Corp., Wallingford, CT) has been developed which reduces the exothermic risk by partial prehydration. This product reduced bleeding in a porcine femoral artery injury model as effectively as the unhydrated product, with minimal measured temperature elevation and without exothermic injury to the tissues [23].

An alternate procoagulant incorporated into topical dressings to promote hemostasis is Chitosan. It consists of a linear, positively charged polysaccharide derived from chitin, a compound of natural origin obtained from the shell of crabs and shellfish. There are numerous chemical variations based on cross-linking the Chitosan backbone to inert or biologically active agents, including antimicrobials. It has been studied for several biomedical uses including tissue engineering scaffolds, drug/gene delivery systems, hemostasis materials, antibacterial materials, and wound dressing. It promotes hemostasis by various mechanisms, not all of which

are fully understood [23]. It is reported to form a mucoadhesive barrier in wounds by cross-linking red blood cells.

There are numerous Chitosan based products (see **Table 1**) with availability varying by market. Chitosan based products have been compared to each other and to Zeolite based products in various animal experiments. In a 2018 controlled rat model, Stricker-Krongrad, et al. showed that Opticell ™ (Medline Industries, Chicago, Ill) dressing could effectively reduce blood loss from excisional dermal wounds, even in the presence of heparin [24]. De Castro et al. compared a modi-fied preparation of Chitosan, created by adding a polymerized hydrophobic side chain to the naturally hydrophilic Chitosan backbone, to standard Chitosan, and to standard dressing in a swine model. Hemodynamic stability after splenectomy was required to avoid autotransfusion from the animal's contractile spleen. A 4.4 mm diameter arteriotomy using a vascular punch was then performed to create a standardized injury in the exposed femoral artery. After 30 seconds of free bleeding, one of the two test dressings or the standard dressing was applied, and post treatment blood loss was measured. Eight animals subjected to standard gauze as the means for hemostasis all exsanguinated. Six of eight animals managed with a typical Chitosan dressing achieved hemostasis. Eight of eight animals treated with the Chitosan dressing modified by adding a hydrophobic component achieved hemostasis with survival to the endpoint. Hemorrhage control with both of the Chitosan based dressings was statistically superior to standard gauze. The Chitosan variants were not statistically different compared to each other, but the authors support the use of the hydrophilic modification as superior [25].

A similarly structured study using 36 swine randomized to three groups compared the efficacy of standard gauze to Celox Rapid ™ (Medtrade, Crewe, UK) gauze and QuikClot Combat Gauze ™ (Z-Medica, Wallingford, CT). This study use a 6 mm lateral femoral arteriotomy and allowed 60 seconds of free hemorrhage prior to wound packing with one of the three study materials. Each animal received a 500 cc bolus resuscitation consisting of a solution hetastarch solution at the time of wound packing. The animals in each group had similar pretreatment characteristics. All 12 animals in each group survived to the study endpoint. Dressing failure, defined as blood spilling beyond the confines of the wound and dressing was assessed at 120 minutes and recurrent bleeding was assessed as a secondary outcome. There were two dressing failures in the standard gauze group and two in the Zeolite based QuikClot group, but none in the Chitosan based Celox group. This did not reach statistical significance [26].

Clinical Experience with HemCon ™, a topical gauze dressing impregnated with freeze-dried Chitosan was described in 2006. Effective hemostasis was achieved with HemCon in 97% of 68 wounded soldiers, with wounds involving the head and neck, torso, and extremities [27]. A 2017 study utilizing the Department of Defense Trauma Registry identified 28,222 soldiers injured in the Iraq and Afghanistan conflict with and Abbreviated Injury Score (AIS) of three or greater. Specialized hemostatic gauze products were used in only 259 (0.9%) of cases. Although the brand of product was not always identified in the registry, the type of product was identified. Of the 259 patients, 58 patients received chitosan-based dressings (HemCon ™ Gauze, or Celox ™ Gauze) and 201 patients received kaolin-based dressings (QuikClot ™ Combat Gauze). In an extensive comparison of the cohorts, those who were managed with a hemostatic adjunct were noted have higher Injury Severity Scores (ISS) and received greater amounts of blood component therapy but had no statically significant difference in mortality [28].

3. Biosurgical agents for operative hemorrhage control

3.1 General considerations for operative hemorrhage control

Control of cavitary hemorrhage can be one of the most challenging aspects of trauma surgery. Mechanical control of large vessel bleeding by suture ligation, mechanical clips, arteriography or venography, primary anastomosis, or interposition grafts are the mainstays of hemostasis. In addition to vascular bleeding, rapid, reliable control of solid organ bleeding is one of the top imperatives in trauma care. The highly vascularized hepatic parenchyma and those of spleen and kidneys are subject to persistent bleeding when injured. In this setting, clotting factor consumption combined with dilution by crystalloid resuscitation or massive blood component transfusion induce patients to develop coagulopathy. Damage control techniques involve the immediate control of life-threatening hemorrhage, followed by an extended period of resuscitation and stabilization, with the aim of restoring normal physiology, prior to staged definitive repair of injuries [29]. It is in the interest of the trauma surgeon to control organ surface bleeding as soon and as effectively as possible at the initial operative episode.

Adjunctive agents for the control of bleeding have found role in both damage control and definitive repair contexts. In damage control procedures, recurrent bleeding stimulated by removal of packing agents is an additional risk. Surgeons are faced with the consideration of using non-adhesive materials, which only provide mechanical compression, but do not debride clots on removal, versus adherent, procoagulant materials, which must either be absorbable or risk clot debridement upon removal. Potential roles for these agents include reduction of vascular suture line bleeding, control of parenchymal bleeding from liver injury, splenic salvage, or reduction of splenic bed bleeding after splenectomy.

3.2 Specific product adjuncts for intraoperative hemorrhage control

Biosurgical products that have found a role for intraoperative control of bleeding include collagen-based, gelatin-based, cellulose-based, albumin-based, polyethylene glycol-based (PEG)-based, and polysaccharide-based hemostatic adjuncts to standard mechanical techniques. These commonly work through distinct, but similar mechanisms that produce mechanical barriers to bleeding. Collagen and cellulose based products form a scaffold matrix promoting adherence of red cells, platelets, and clotting factors onto the bleeding surface. They are generally absorbable and can be left in the operative wound with limited risk. The remaining products are dual component fluids that when mixed, form biocompatible chemically bonded hydrogels, which create an adherent layer bound to tissues, and may achieve hemostasis when suturing, ligation, or cautery have failed. These agents are associated with extensive clinical publications, although most available data is in the form of case reports or case series. These establish feasibility and safety, but there is little comparative data in a controlled clinical setting.

The Surgicel ™ (Johnson & Johnson, New Brunswick, NJ) line of products is made of oxidized regenerated cellulose available in the form of loosely knitted sheets, microfibrillar sheets, or powder. Oxycel ™, (BD, Franklin Lakes, NJ) is a similar oxidized, non- regenerated cellulose product. These can be applied to bleeding surfaces but are less effective in coaguloapthic models [30]. Oxycel, sutured into a polyglycolic acid mesh has been described to promote splenic salvage after injury [31]. This product has also been placed laparoscopically to control bleeding from a penetrating wound of the liver [32]. Oxidized cellulose products are commonly placed intraoperatively and left in place, since they slowly absorb. The products are

bacteriostatic, but not bactericidal. Bacteriologic seeding is uncommon, but abscess formation has been reported. Additionally, the material can trap gas bubbles and have a radiologic appearance very similar to abscess on postoperative CT scans. In a blinded evaluation of 18 cases, radiologists misinterpreted the appearance of these products as abscess or other pathology 90% of the time [33]. Performance improved to 80% accuracy when they were informed of the presence of Surgicel prior to CT scan interpretation. A rare but dramatic complication, spinal cord compression, has been reported with the use of Surgicel in proximity to the spine after elective and trauma related procedures [34, 35].

Agents considered mechanical hemostats including cellulose, collagen, polysaccharides, and gelatins are generally only effective for minor surface bleeding and in patients with an intact coagulation system. Agents which produce an adhesive barrier and those which are based on fibrin plus thrombin are considered preferred when there is a derangement of the coagulation system. There are several commercially available products based on fibrin plus thrombin generally known as fibrin glue (see **Table 3**). These are usually applied as a liquid with a double barrel syringe. As soon as the two components are mixed, they begin to form a substitute for natural clot. Low pressure gas-powered spray applicators are also available for covering broader surfaces. Injection of these materials into the wound tracks, either by hand or spray, is considered dangerous, due to the potential for air or thrombus embolization. There is extensive cased based literature describing the use of fibrin glue in the context of trauma and in elective surgery, across several subspecialties. However, there is no high-level evidence that it reduces blood component usage or improves outcomes.

4. Conclusion

The role of biosurgical products in trauma care is not yet fully defined. There is a widely held belief that modified field dressings that incorporate procoagulants, whether organic or inorganic, are more efficient for stopping wound bleeding in accessible wounds. There is ongoing interest in testing similar agents for torso injuries and deep wounds. There is some supportive, but not conclusive evidence from animal studies that these agents can control arterial bleeding, including large vessel injuries, at least as temporizing maneuvers, until definitive surgical repair can be performed. Data from controlled animal models indicate that these agents are effective, but the results of comparative trials are mixed.

This is partly due to inherent difficulties in standardizing the injury model and a physiologic response to injury. Adhesive barrier products also have an evolving role in the control of small vessel and organ surface bleeding, although controlled comparative trials are missing. Coagulation system derangements commonly encountered in trauma patients adds an additional level of complexity to interpreting the data. The use of modified gauze packing during damage control laparotomy remains of great interest, but the use of common cotton laparotomy pads remains the standard approach. Numerous subspecialty applications have been described for management of urologic, gynecologic, and facial injuries. The supportive data is similarly structured.

Clinical support for the use of modified dressings, adhesive barrier agents, and fibrin glue remains largely anecdotal and relies heavily on satisfaction and subjective assessment of effectiveness. It is unlikely that rigorous research protocols are feasible in the clinical context of acute trauma. This is partly due to the inherent difficulties in trauma research. Patient consent to participate in research protocols is impractical to obtain and waived consent protocols are difficult to design and

conduct. Meanwhile, sporadic reports continued to emerge of complications associated with various specific products that rely on either mechanical properties or coagulation system effects to promote hemostasis. The risk to benefit ratio of biosurgical products used in a trauma context remains essentially unknown. The potential remains for extensive future research on the use of these products as adjuncts for trauma care in both civilian in military contexts.

Conflict of Interest

The authors declare no conflict of interest.

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