Chapter

Hemostasis and Biosurgicals in Trauma and Orthopedic Surgery

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Abstract

Trauma and orthopedics is a specialty in which significant blood loss can be incurred both in terms of traumatic injuries and operative management. This chapter starts with a brief review of the biology of hemostasis followed by the importance of hemostasis in surgery. This is followed by a discussion on the ideal hemostatic agent. Various strategies of achieving hemostasis will be discussed including mechanical, thermal, pharmacological and topical agents in both elective orthopedic and spine surgery as well as in trauma. Specifically, we will look at synthetic agents such as cyanoacrylate, polyethylene glycol hydrogel and glutaraldehyde cross-linked albumin and absorbable agents such as gelatin foams and oxidized cellulose. We will also look at biological agents such as topical thrombin, sealants and platelet gels. Hemostatic dressings will be discussed in detail.

Keywords: hemostasis, coagulation, trauma

1. Introduction

There are a number of factors that influence patient outcome in trauma and orthopedic surgery in relation to hemorrhage. These can include patient factors, for example anticoagulant and antiplatelet medications, coagulopathies and other conditions, as well as surgical factors such as bony bleeding, large surgical incisions, diffuse venous bleeding and unseen sources of bleeding [1, 2].

Trauma still remains a leading worldwide cause of morbidity and mortality [3] and despite various developments over the years, hemorrhagic shock from trauma continues to form one part of the terrible triad contributing to mortality in both the military and civilian settings [4].

Effective hemostasis during surgery is advantageous to the surgeon as it prevents diffuse bleeding from capillaries and venules obscuring the surgical field and adding to operation time and infection risk [5, 6].

Significant blood loss has been associated with increased need for allogeneic and autologous blood transfusion [2, 7, 8]. These are associated with attendant risks including nosocomial infections [9], transfusion-related injury and fluid overload [10, 11]. In fact blood transfusion is an independent risk factor for infection, respiratory complications and the need for critical care support in traumatic injuries and resulted in a twofold increase in complications and critical care admissions, with more than two units of blood transfusion [7]. The risk of major perioperative complications is also increased with high intraoperative blood loss [2, 12, 13].

Therefore, patient outcome is optimal when the balance between bleeding and clotting is maintained during surgery such that tissue perfusion is adequate without excessive blood loss [5, 6].

2. The biology of hemostasis

Hemostasis in regard to trauma and surgery is a highly regulated process, maintaining flow through vessels at the same time as the thrombotic response to tissue damage is occurring [14], thereby ensuring tissue perfusion and limiting blood loss. The process is a complex interaction between vascular endothelium, platelets, the coagulation and fibrinolytic systems [15, 16].

Following injury, a temporary vascular smooth muscle contraction occurs in an attempt to stem blood flow. Endothelial disruption exposes the subendothelial layer and circulating Von Willebrand factor attaches to the site of injury. Surface glycoproteins also adhere to platelet surfaces. The subendothelial collagen activates adhering platelets and their surface receptors then bind circulating fibrinogen, forming a soft platelet plug comprising aggregated platelets and fibrinogen [14]. The adhering platelets secrete humoral factors including serotonin, prostaglandins and thromboxane that maintain a reduced blood flow, creating an environment that is conducive to clot formation at the site of bleeding. At the same time, circulating coagulating factors produced by the liver are activated in a series of precisely controlled sequential and dependant reactions [14, 17].

The final common pathway is the activation of thrombin that leads to conversion of soluble plasma fibrinogen to insoluble fibrin. The complex of activated factor XIII and fibrin results in cross-linking of fibrin monomers to form a stable clot [17].

3. Techniques for hemostasis in trauma and orthopedic surgery

Broadly speaking, there are mechanical, thermal, pharmacological and topical methods of hemorrhage control [2, 6, 8, 17–20].

Mechanical methods include direct pressure, ligating clips and staples, sutures, fabric pads and gauze while hemostatic scalpels and lasers also reduce bleeding during surgery [6, 7, 17]. However, these methods have their drawbacks with respect to certain situations. The location of bleeding is particularly important with respect to orthopedics and in particular trauma. Bony surface bleeding and bleeding from the intramedullary canals are almost impossible to control with mechanical methods. Inflamed or friable tissues may contain a dense network of friable capillaries may prove a challenge [1, 2, 7]. Junctional bleeding in trauma may be potentially catastrophic and its control may not be amenable to the above methods.

The use of pharmacological methods can be a useful adjunct to other methods in these circumstances [7]. These may include epinephrine, desmopressin, tranexamic acid, vitamin K, aminocaproic acid and others.

In some situations though, even the above methods are ineffective or impractical [15] and hence the development of topical hemostatic agents. These are a diverse group of agents of varying composition and mechanisms of action. They can be versatile in the sense that when blood loss is minimal, they can be used sparingly and when there is severe blood loss then more liberal application could be an option [2]. They may be applied directly to the bleeding site and prevent or reduce continuous and unrelenting bleeding intraoperatively and postoperatively [2] and their topical nature broadly avoids the systemic adverse effects associated with systemic hemostatic medications including thrombosis [8].

4. Topical hemostasis

4.1 Concept of passive and active hemostasis

Topical hemostasis is defined as a process that acts locally to stop bleeding from damaged vessels [21]. Recent and continuing developments have focused on agents that can be used as adjuncts to control bleeding during surgical procedures and control residual problematic bleeding if conventional methods fail. Broadly speaking, topical hemostats can be divided into three types [17, 20].

1. Passive—where the mechanism of action is to provide a physical scaffold around which platelets can aggregate. These act through contact activation and promote platelet aggregation so a clot can form. Examples include collagen, cellulose and gelatins.

2. Active—these have biological activity and their mechanism of action is actively influencing the clotting cascade to promote clot formation [17, 20]. These usually contain thrombin in one form or another [14].

3. Combined—combination of passive product with thrombin.

4.2 Passive hemostasis

4.2.1 Collagen-based products

Contact activation occurs between receptors on platelets and collagen, promoting platelet aggregation [15, 17]. Preparation includes collagen sponges, pastes and powders [15, 17] and is obtained mainly from bovine sources [15], making it potentially immunogenic. In fact a 2–4% allergy in the total population to bovine collagen has been reported in the literature [22] (**Table 1**).

4.2.2 Cellulose-based products

The active ingredient in this product is oxidized regenerated cellulose (ORC). Its exact mechanism of action is poorly understood but contact activation is thought to play a part [15]. Often at reoperation, previously used ORC is visible, indicating reduced absorption and poor biodegradability, although this may be related to the amount used and the site of implantation [8]. For this reason, only the minimum

Hemostatic agent	Examples	Manufacturer
Collagen-based products	Avitene	Davol/BD BARD
	Helistat/Helitene	Integra Lifesciences
	Instat/Ultrafoam	Ethicon, Johnson & Johnson
Oxidized cellulose	Surgicel Fibrillar	Ethicon, Johnson & Johnson
	Surgicel Nu-Knit	Ethicon, Johnson & Johnson
Gelatin-based products	Gelfoam	Pharmacia Corp, Pfizer
	Surgifoam	Johnson & Johnson
Polysaccharide spheres	Arista AH	BD BARD

Table 1.
Passive hemostats.

possible amount to be used is indicated and it is recommended that the product be removed once hemostasis is achieved and before definitive closure [6, 8].

4.2.3 Gelatin-based products

Their mechanism of action involves swelling while in contact with blood, providing a tamponade effect in confined spaces and restoring blood flow, and thereby producing a stable scaffold around which clots can form [17]. This does make it suitable for irregular wounds [6] and confined spaces [17]. However, it tends to stick to instruments when soaked with blood, making it difficult to handle and does not form a tight bond with the bleeding surface and can hence easily be dislodged [17].

4.3 Active hemostasis

Active agents have biological activity and actively participate in the coagulation cascade to induce clot formation at the site of bleeding [20]. They include thrombin, which comes into play in the last stages of the clotting cascade, converting circulating fibrinogen to a fibrin clot [17, 23]. Hence a significant advantage of thrombin is that its action is less susceptible to coagulopathies caused by clotting factor or platelet dysfunction [17]. Its activity constitutes the final steps in the clotting cascade and therefore it bypasses the initial steps in the cascade. Therefore, other aspects of the clotting cascade can be dysfunctional without significantly impairing the local hemostatic activity of thrombin [20].

Thrombin-based products are therefore excellent adjuncts in the presence of congenital and acquired coagulation and platelet disorders and in the presence of pharmacological and antiplatelet agents that are increasingly being used in the general population [5, 17]. Circulating fibrinogen is necessary for hemostasis to occur by active agents as thrombin converts it into insoluble fibrin that forms part of the clot. Therefore in rare cases of fibrinogen deficiency, clotting by thrombin-based products is impaired [17, 23].

5. Combination agents

5.1 Fibrin sealants

These accomplish their action by bypassing the coagulation cascade to the final steps and converting fibrinogen to fibrin [24]. A fibrin precursor and thrombin stored in two separate adjacent syringes (dual syringe kit) with a single lumen enables delivery and mixing of these agents in the lumen and onto the surgical site, causing thrombin to cleave the fibrin precursor, resulting in fibrin monomers that polymerize at the site into a soluble mesh stabilized into a stable clot by factor XIII at the tissue surface [25]. Previously, bovine thrombin was used, which has recently been replaced by human thrombin [26] and more recently autologous human thrombin. Autologous fibrin sealants overcome the risk of allogeneic blood products, for example one is a patient-derived fibrin sealant utilizing the patient's own blood as a source of fibrinogen and prothrombin and mixing it with an alkaline buffer solution to lower the pH, activating endogenous prothrombin [24] (**Table 2**).

5.2 Platelet gels

These are a combination of thrombin, calcium and platelet-rich plasma, usually obtained from autologous sources using centrifugation systems that produce

Biosurgical	Examples	Manufacturer
Liquid fibrin adhesives	Tiseel	Baxter
	Evicel	Ethicon, Johnson & Johnson
	Crosseal	Ethicon, Johnson & Johnson
	Floseal	Baxter
Fibrin patches	Tachosil	Takeda
Platelet gels	Vitagel	Orthovita
Glutaraldehyde cross-linked albumin	BioGlue	Cryolife

Table 2.
Sealants and adhesives.

platelet-rich plasma. Platelets provide growth factors to stimulate wound healing and contribute to the strength of the clot [27].

These systems however rely on an intact coagulation system and may not be as effective in patients on antiplatelet or anticoagulant medications [27]. Also the extraction systems are expensive and there is a risk of contamination.

5.3 Advantages of active and combined products over passive hemostats

In addition to not requiring normal clotting mechanisms to work as mentioned before, active hemostats may offer other advantages. With many passive hemostatic agents, degeneration and reabsorption are a problem. This necessitates their removal from the surgical site prior to closure. With thrombin, this is not the case as degeneration and resorption of the resulting fibrin clot is achieved as part of wound healing [1, 8]. Thrombin and combination products also have a rapid onset of action with hemostasis being achieved within 10 min in most patients [7, 17, 28, 29]. Studies have shown that combining an active hemostat within a hemostatic product accelerates clotting. In a comparison of collagen-based products at different bleeding sites after surgical tumor resection, the combination of a collagen-thrombin product ($n = 23$) achieved complete hemostasis three times faster than the collagen sponge alone ($n = 30$). The median time to hemostasis was 78 seconds versus 243 seconds respectively ($p < 0.001$) [30]. Furthermore, approximately 80% achieved complete hemostasis within 2 min with an active topical hemostatic agent compared with only one-third of patients receiving a passive topical hemostatic agent [31]. Active hemostats are also very versatile and can come in various forms. These include sprays that can be advantageous in covering large bleeding surfaces quickly without the need for tamponade [31], and the concentration of thrombin in the formulation can also be varied depending on the severity and type of bleeding. Surgeons can use them in multiple ways during a single procedure due to their flexibility and range of delivery options [20]. Although bovine sources of thrombin may induce antibodies in hosts, this has not manifest itself as a major problem in the clinical setting [1, 32].

5.4 Hemostasis in the trauma setting

It has been shown that the terrible triad of hypothermia, coagulopathy and acidosis are associated with increased mortality in multiple trauma patients and that infection and multiple organ failure are other potential complications arising from severe blood loss [33, 34]. About a quarter of patients presenting to trauma centers have an established coagulopathy secondary to hemorrhage [35] with attendant risks of significant complications. Multiple defects in hemostasis can occur in

combat injuries and as such, conventional methods of hemostasis may not be possible. Time is of the essence in these situations and non-transfusional approaches to hemostasis and the use of biosurgicals may be indicated [36–39].

The combat setting has proved a challenging environment in many different ways in terms of management of hemorrhage. The tissue available for controlling life-threatening hemorrhage may be limited, the wound severity and the possibility of multiple injuries make the situation uniquely challenging [40]. Most combat injuries are penetrating in nature and a large proportion are limb wounds. Mortality from hemorrhage from these kinds of wounds is potentially preventable [36, 41, 42].

In the combat setting, the three principal sites of lethal hemorrhage are truncal (67%), junctional (19%) and extremity (14%). A report from the National Trauma Database suggests that the mortality from isolated lower limb extremity trauma with arterial injury is 2.8% with a 6.6% amputation rate [38]. Tourniquets can be used for these isolated injuries and their use in the military and civilian setting is supported by the Hartford consensus [39] and by the American College of Surgeons Committee on Trauma [38].

Junctional injuries (neck, axilla, groin and perineum) form a significant proportion of trauma in a combat setting and may damage the large vascular structures. These types of injuries are difficult to compress and are not amenable to tourniquet control [43, 44]. Topical hemostatic agents that have been developed in the last two decades [36, 45] can play a vital role in controlling severe bleeding in these situations and increase survival [33, 46] and have thus been listed as optional basic equipment for ambulances [39]. In addition, in a combat setting, more complex types of wound patterns are encountered than in a civilian setting, including blast injuries, which may be more amenable to topical hemostasis.

5.5 Characteristics of the ideal trauma hemostatic agent

In 2003, USAIR [47] introduced guidelines of what should constitute the perfect hemostatic agent for use in the prehospital and battlefield settings [33, 41, 47–49] that included the following: being able to stop large vessel and arterial bleeding within 2 min of application, ability to be delivered through a pool of blood when applied, ready to use with no need for on-site preparation, simple enough to use by the wounded victim or a paramedic with minimal training, light weight and durable with a minimum 2-year shelf life in extreme environmental conditions, safe to use with no risk of injury to tissues or transmission of infection and inexpensive [41, 45, 50, 51]. In addition, hemostatic dressings need to be conformable and flexible enough due to the irregular shape, depth and wound configurations caused by modern explosive devices [40, 48].

6. Types of hemostatic agents

6.1 Mechanical hemostats

These include gelatin [52], oxidized cellulose [53] and collagen and plant-derived polysaccharide spheres [54]. These agents are not biologically active and rely on the patients' endogenous fibrin production for hemostasis. They provide a scaffold for platelet activation and aggregation, absorbing fluid several times their own weight to form a matrix at the site of hemorrhage, activating the extrinsic coagulation pathway and allowing clotting to occur. This makes them suitable only for patients in whom the coagulation system is intact [55, 56]. In fact in the absence of some coagulation factors, these agents may not be effective [53, 56]. They can be used as first line due

to their ready availability and favorable cost-effectiveness, mostly as adjuncts with direct pressure at bleeding sites to control minimal residual hemorrhage [56].

6.1.1 Bovine collagen

These agents act by forming a physical matrix that stimulates platelet aggregation and degranulation to release factors that encourage clot formation [55].

6.1.2 Oxidized cellulose

Cellulose is a homopolysaccharide made by polymerization of glucopyranose molecules through glucosidic bonds. Surgical oxidized cellulose is either regenerated where organized fibers are formed prior to oxidation (regenerated ORC), or non-regenerated, with unorganized fibers prior to oxidation [55]. ORC conforms more rapidly to the surrounding environment. Surgical oxidized cellulose offers several favorable properties in hemostasis including bactericidal activity, good biocompatibility and ease of use [55]. It is usually resorbed but can take anywhere between 2 and 6 weeks depending on the amount used, the degree of saturation with blood and the tissue bed. The excess material may also cause foreign body reactions and granuloma formation without biodegradation and complicate radiological and clinical diagnoses of abscess, residual or recurrent tumor and granuloma [55, 57, 58]. For this reason, the minimal effective amount should be used and excess material removed prior to definitive closure. In addition, these products should not be used or left in place close to nerves, ureters, intestinal and vascular structures due to the risk of local inflammatory reactions and ischemia [55].

6.1.3 Gelatin-based products

These can be used in combination with active agents such as thrombin in adhesives, or in a stand-alone manner. They are usually of bovine or porcine origin and act at the terminal stages of clotting to facilitate fibrin clot formation and are highly absorptive, forming a mechanical matrix for the clot to adhere to [55, 59]. They are quite versatile and available as sponges, powders or granules and are usually completely resorbed in 4–6 weeks [59]. It is important to use the minimum amount necessary to achieve hemostasis and to remove excess because part of the mechanism of action is swelling to cause a tamponade effect and this could potentially cause compression and necrosis in surrounding tissues if packed in tight spaces. This is particularly important around neural tissue and in bony spaces [59]. They are also useful in irregular wounds and surgical cavities as they can expand and fill these irregular spaces.

6.1.4 Plant-based hemostatic agents

Mucoporous polysaccharide hemispheres are among a relatively new class of hemostatic agents derived from plant starch. Their mechanism of action includes absorbing water and the low-molecular weight components of blood, hence concentrating platelets and clotting factors in the vicinity, thereby enhancing local clotting processes [58, 60]. They have been used safely in cardiothoracic and neurospinal surgery.

6.2 Fibrin sealants/adhesives

These are active formulations containing mostly two agents—human purified fibrinogen and thrombin. They may also have added other compounds such as

factor XIII, fibronectin and antifibrinolytics such as aprotinin used previously and tranexamic acid currently [61]. However, formulations without tranexamic acid or aprotinin are available to avoid hypersensitivity associated with aprotinin and neurotoxicity associated with tranexamic acid [62, 63] (**Table 2**).

These products are available in liquid or low-viscosity forms (fibrin glues) or as part of stiff collagen fleece (fibrin patches) [55]. Once applied, their mechanism of action is cleavage of fibrinogen to fibrin monomers by thrombin, which also activates factor XIII and the complex fibrin matrix forms the clot [55]. Calcium is required in both these steps and then the clot is eventually resorbed via the fibrinolytic pathway [25]. Generally, they connect atraumatically to tissues and form a barrier to leakage and bleeding through covalent polymerization between themselves and adjacent tissue [55]. Chiara et al. set out the properties of an sealant as being strong, rapid to adhere, flexible, sterile, without toxicity, biologically inert, biocompatible and able to be used in relatively wet environments with low thrombogenicity [55].

7. True sealants and bioglues

True sealants are of two types: synthetic (PEG-based or cyanoacrylates) [53, 60, 64–67] or semisynthetic glutaraldehyde [68] (**Table 2**).

True sealants are cross-linking sealants that polymerize through nonenzymatic reactions, free of the need for the presence of blood or coagulation factors although some do have some coagulation factors within them. Both can be used to control residual ooze [53, 67].

PEG sealants are composed of polyethylene glycol and come in both flowing form as well as pads or fleeces. They should be avoided in kidney disease due to the renal clearance of polyethylene glycol and may contain allergenic components such as human albumin that can also lead to the theoretical risk of disease transmission [55].

Cyanoacrylates are products generally used for skin closure or lacerations in areas of low skin tension, for example scalp wounds. They are synthetic sealants that rapidly polymerize with water acting as the catalyst. There are two formulations: octyl-2-cyanocrylate and N-Butyl-2-cyanoacrylate. In a systematic review looking at octyl-2-cyanoacrylate, there were no differences in infections, wound dehiscence or cosmetic appearance when compared with other methods of closure [65]. Polymerization generates heat and therefore the amount used should be just enough and should certainly be avoided in delicate areas such as the spinal canal and neural tissue [55, 65]. Below the skin, a foreign body reaction may occur [65] and intravascular use is contraindicated due to the risk of systemic embolization [55].

Semisynthetic sealants otherwise known as bioglues are compounds of semisynthetic glutaraldehyde—bovine albumin-based sealant. Proteins on the surface of bleeding human tissue link with those of bovine albumin in the bioglue, causing a sealant effect [55]. Within synthetic graft materials, bioglue permeates interstices within the graft matrix [69], making it suitable for sealing anastomotic sites and decreasing postop bleeding [70].

7.1 Liquid fibrin adhesives

These can be used as an adjunct to surgical hemostasis to improve residual moderate bleeding [55]. They are usually applied by double syringe systems. Each component is located in a separate section of the syringe, which then combine in a single lumen. They subsequently are applied using a blunt needle or spray tips in cases of large bleeding surface areas to the bleeding surgical site [25, 61]. Since the components bypass the initial steps in the extrinsic coagulation pathway, they can

be used in achieving hemostasis in patients with congenital or acquired bleeding disorders such as hemophilia and patients on anticoagulants or antiplatelet medications [25, 62, 71] (**Table 2**).

They do have some drawbacks including the risk of thrombosis if injected intravascularly, hypotension and death and the risk of air embolization with the use of gas-driven sprayers [55]. In addition, the cost of sealants is significant and hence they are not recommended for use except in particular situations where indicated, for example in those with coagulation disorders [61]. One cost-effectiveness analysis done in the United Kingdom in patients undergoing total knee replacement on Quixil, one of the commercial brands, in addition to conventional hemostatic agents estimated that the use of a 5-ml dose of Quixil in addition to conventional hemostatic methods was cost saving in comparison to conventional methods alone. But the use of a 10-ml dose increased the cost substantially and they recommended that liquid fibrin adhesives only be used in selected cases [25]. They have however been found to be effective. Echave et al. [59] carried out a systematic review of 27 studies on the effectiveness of human gelatin-thrombin matrix sealant in different surgical fields including orthopedics. All 27 studies demonstrated that this sealant was associated with a significantly higher rate of successful hemostasis, and a shorter time to achieve it ($p < 0.001$) in comparison to other alternatives when conventional methods failed.

7.2 Fibrin patches

These products are also available as patches, for example Tachosil. They may have slightly different components but all of them have essentially the same mechanism of action, offering mechanical support with either collagen, oxidized cellulose/polyglactin 910 matrix, binding coagulation factors, allowing better adherence to bleeding tissue even in the presence of brisk bleeding, preventing the so-called "streaming effect" observed with fluid adhesives [72–74]. Tachosil is a ready-to-use fixed combination of equine collagen patch on one side and coated with coagulation factors, human fibrinogen and human thrombin on the other side [55]. Fibrin-pad and PGA-felt are absorbable hemostats composed of polyglactin 910, oxidized regenerated cellulose, thrombin and fibrinogen shown to be effective in a variety of tissue types [25, 72] and can rapidly achieve hemostasis in brisk bleeding in the retroperitoneum and pelvis, compared with the standard of care [72, 73] (**Table 2**).

8. Hemostasis in major trauma

8.1 Hemostatic dressings

Junctional hemorrhage is a significant problem in major trauma especially on the battlefield and often conventional methods such as tourniquets are ineffective [55]. In this respect, science has led to the development of products that are effective options in these circumstances and they can be divided into factor concentrators [75], procoagulants [76] and mucoadhesives [77] (**Table 3**).

8.1.1 Factor concentrators

These are compounds of either zeolite (microporous crystalline aluminum silicate) or smectite (a nonmetallic clay mineral sodium, calcium and aluminum silicate). Examples include QuikClot (Z-Medica LLC, CT,USA) and QuikClot ACS (advanced clotting sponge), Traumadex (Medafor Inc., MN, USA) and self-expanding hemostatic polymer (SEHP) [35]. As the group name suggests these

Biosurgical	Examples	Manufacturer
Zeolite dressings	QuikClot & QuikClot ACS	Z-Medica
Smectite dressings	WoundStat	TraumaCure Inc.
Kaolin dressings	QuikClot Combat Gauze	Z-Medica
	Rapid Deployment Hemostat	Marine Polymer Technologies
	Celox	Med Trade Products, UK
	Trauma Stat	OreMedix
Fibrin dressings	Dry fibrin sealant dressing (DFSD)	American Red Cross

Table 3.
Hemostatic dressings.

agents rapidly absorb the fluid content of blood. The resulting effect is an increase in relative concentration of its cellular and protein content and therefore clot formation. Water molecules are held in its pores by hydrogen bonds and this results in a relative local increase in concentration of platelets and clotting factors [35]. The first generation of QuikClot was designed as granules that were poured onto the bleeding wound. A high efficiency rate of 92% was demonstrated in a series of 103 patients in the military and civilian setting. There were eight patients in which hemorrhage was not effectively controlled with QC in coagulopathic patients where it was used as a last resort [75]. There were also some side effects of QC including intense exothermic reaction and scar formation from foreign body reaction [75]. Animal and early human studies on QC revealed thermal injury, poor biodegradability and foreign body reactions as the main drawbacks of QC [78–80]. In fact temperature generated by QuikClot in contact with aqueous components of blood at bleeding wounds has been measured to reach and average of 61°C with a potential rise to 76°C [78].

QuikClot has been compared to other hemostatic agents including HemCon (HemCon Medical Technologies Inc., OR, USA) in a military setting in multiple patients injured after explosions and gunshot wounds [81]. In this study, QC was effective but thermal injury was an issue. This has also been investigated in other studies by McMannus et al. [82] in the combat setting and evidence suggests that the greater the amount of blood and the more the QC applied, the greater is the risk of thermal injury. Thus currently it is only recommended for external use and the minimum amount required to achieve effective hemostasis is recommended.

QuikClot ACS is a newer generation of product made by larger zeolite beads packaged into mesh bags. This makes it easier to pack into cavities and irregular wounds often found on the battlefield and at junctional sites of hemorrhage and in cavities [55] and is claimed to produce much less of an exothermic reaction [75, 78] although there is a lack of studies with sufficient numbers to confirm this unequivocally [41].

Self-expanding hemostatic polymer (SEHP) is a dual action factor concentrator. Its mechanism of action results from its extremely potent absorptive capacity following absorption of the fluid component of blood and its ability to expand to conform to large irregular cavities and spaces, exerting a tamponade effect [35]. The other action is the effect of the polymer absorbing the liquid phase of blood into its matrix, thereby leading to a relative increase in concentration of platelets and coagulation factors at the site of bleeding, thereby promoting clotting [83, 84].

Woundstat is a compound of smectite granules that come in granular form. Its mechanism of action is absorption of the aqueous phase of blood, forming a clay substance that adheres to bleeding tissue and acts as a sealant and also concentrates clotting factors and blood cells locally, contributing to hemostasis. Granules are negatively charged and activate the intrinsic pathway as well [85–87].

8.1.2 Mucoadhesive agents

These are products where the basic component is chitosan, which is a polymer derived from crustacean chitin. It is a complex biodegradable carbohydrate [55]. The mechanism of action appears to be related to highly positively charged chitosan interacting electronically with negatively charged cell membranes of erythrocytes. The product adheres strongly to tissues and seals bleeding wounds [77, 88, 89]. Examples include HemCon (HemCon Med Tech, Portland, OR) and Celox (Med. Trade Products, UK).

Celox is a chitosan-based adhesive, which is biodegradable and causes absorption of the aqueous phase and the advancement of red blood cell bonding. The positively charged Celox binds negatively charged red blood cells independently of the body's clotting system, resulting in clot formation without the exothermic reaction associated with certain factor concentrators like QuikClot [35]. Its action is independent of the body's clotting system, a property that makes it useful in patients requiring antiplatelet or anticoagulant medications or in the presence of coagulopathy and its local action means that it is not associated with distant clot formation. It is also reported to be very versatile, being available in granular and bandage forms and easy to remove from the wound after its clot formation activity is complete [49, 90–92]. HemCon, however, does have a hard consistency and is made in a square shape. Therefore, it works best on flat bleeding surfaces rather than deep irregular wounds [79, 83]. Wedmore et al. [77] looked at a series of patients with prehospital combative injuries where chitosan-based products had been used externally in chest, groin, buttock and abdominal wounds in 25 patients, 35 extremity wounds and neck and facial wounds in 4 cases. In about two-thirds of cases, the chitosan dressings were used following failure of hemostasis using only gauze with 100% success. In 97% of cases, bleeding stopped or hemostasis was improved, with failure only occurring in two cases attributed to blind stuffing of bandages into large cavitational injuries [77].

Trauma Stat is another chitosan-based derivative that was developed in collaboration with the United States Army, in which the mechanism of action involves positive charges in the amine groups on the chitosan molecule interacting with negative charges on the red blood cell membranes and in addition the adsorption of chitosan for fibrinogen and plasma proteins [79, 93].

Te Grotenhuis carried out a study of 66 patients in which conventional treatment with gauze and compression failed to control excessive bleeding or where conventional treatment was unlikely to achieve hemostasis. Complete cessation of hemorrhage including arterial hemorrhage occurred in 70% using the HemCon ChitoGauze, and reduction in hemorrhage occurred in 20% of patients despite 21 patients being on anticoagulants or having a clotting disorder and no adverse events occurred [88].

Due to the fact that chitosan is derived from crustaceans, there is a theoretical risk of allergenic reactions in patients allergic to shellfish. However in a study of 19 patients who had a positive IgE test to shellfish, none of the patients demonstrated a positive skin prick test to chitosan powder or expressed a reaction to HemCon bandage during serial bandage challenges, indicating favorable but not completely risk-free use of these products [94].

Chitosan-based dressings are also easy to remove after hemostasis has been achieved [41] and are known to have some antimicrobial properties [41, 95].

8.1.3 Procoagulants

Their mechanism of action is mainly to deliver factors that promote coagulation into the bleeding wound. Examples are dry fibrin sealant dressing (DFSD) and

QuikClot Combat Gauze (QCG) [70, 96, 97]. QCG is a surgical gauze coated with kaolin. On contact with injured endothelium, kaolin activates the extrinsic pathway, enhancing coagulation and promoting hemostasis. It is not degradable and needs to be removed from the wound following achievement of hemostasis [76].

Kaolin-based products have been used in a military setting and have demonstrated good results in both junctional and non-junctional hemorrhage [76]. In the above study, Shina et al. retrospectively reviewed 133 kaolin-based dressings applied to 122 military patients. 27% were for junctional hemorrhage with a success rate of 88% while the rest were extremity trauma where the success rate was 92%.

8.2 Problems with hemostatic agents

In addition to problems specific to certain types of hemostatic agents, there are also general drawbacks.

The hemostats that contain biological agents, usually the active hemostats, can be associated with the risk of disease transmission. For example, DFSD has the theoretical risk of viral disease transmission and hence has not achieved FDA approval.

Some agents have handling characteristics that are beneficial in certain situations. For example agents that have a granular nature can be used for complex irregular wounds with multiple bleeding points. However, the handling characteristics are difficult and they are difficult to apply in combat situations [89]. In addition, many agents are nonabsorbable and need to be removed after hemostasis is achieved. This may be difficult with some agents and require multiple washouts. Granular agents also have the potential to enter the vascular system and occlude the distal parts of vessels, causing endothelial injury and intravascular coagulation [41]. This has been demonstrated by Kheirabadi et al. [89] in their study, and for these reasons a bandage/gauze form of hemostatic agent is preferable as being safer for hemorrhage control, avoiding intravascular complications [38].

8.3 Tranexamic acid in trauma

Any chapter on hemostasis in trauma and orthopedics is incomplete without the mention of tranexamic acid. This drug has been shown to be effective in reducing mortality due to bleeding in both the military and civilian setting.

The CRASH-2 (Clinical Randomization of an Antibrinolytic in Severe Hemorrhage-2) trial was a multicenter trial involving 40 centers looking at 20,211 adult trauma patients with significant bleeding who were randomized to two arms. One arm received TA within the first 3 hours of trauma and the other received placebo. The study demonstrated a reduction in mortality risk due to any cause from 14.5% compared with 16% in the placebo group ($p < 0.001$), with no increase in vasoocclusive events such as pulmonary embolism or myocardial infarction (0.3% versus 0.5% p-0.096) [98].

The MATTER (Military Application of Tranexamic Acid in Trauma) study looked at 896 patients with severe combat injuries and demonstrated a 6.5% absolute risk reduction in mortality in these patients with the use of tranexamic acid [99].

Both these studies have recommended incorporation of intravenous tranexamic acid into clinical practice [24].

8.4 Hemostasis in arthroplasty surgery

Joint replacements are major procedures in elective orthopedics and can be associated with significant blood loss and increased transfusion requirements if appropriate steps are not taken to mitigate against this. In addition to the conventional

methods of blood management including preoperative optimization, tourniquets if appropriate, intraoperative techniques such as cell saver and cauterization, topical and pharmacological hemostats and biosurgicals may offer some excellent solutions to reduce the transfusion requirements and achieve hemostasis.

A few studies have looked at human-derived fibrin sealants in total knee replacement [100–102]. A multicenter randomized control trial looking at 58 patients who underwent total knee replacement demonstrated a reduced postoperative blood loss, reduced postoperative decrease in hemoglobin and calculated blood loss in patients in whom fibrin sealant was used compared with that in the standard group (20% compared with the standard 83% $p = 0.004$) [100]. Another study that showed benefit was done by Dhillon et al. [25]. Results from other studies have been equivocal and have not demonstrated any clear difference.

In total hip arthroplasty, the use of fibrin sealants has been associated with reducing blood loss but inconsistent results have been demonstrated with regard to reduction in postoperative transfusion requirements [24, 103–105].

Multiple studies have looked at platelet gels in arthroplasty surgery. The evidence has been inconsistent in many. One randomized control trial looking at 100 total knee replacements did demonstrate significantly lower transfusion requirements in patients in whom platelet gels were used [106].

Desmopressin is a synthetic analog of anti-diuretic hormone. Its mechanism of action is to increase the levels of factor VIII and Von Willebrand factor, thereby enhancing primary hemostasis and platelet aggregation and adherence. This makes it suitable as a blood management strategy in patients with platelet dysfunction or other clotting disorders such as Von Willebrand's disease and hemophilia A [107, 108]. It has also been used in healthy individuals for reducing postoperative bleeding in total hip and knee replacement surgery [109]. Six randomized placebo-controlled trials addressing the use of desmopressin in total hip and knee arthroplasty have been undertaken [110–115]; however, evidence suggests that desmopressin is not significantly effective in reducing blood loss or transfusion requirements in these patients [24].

There are a number of good-quality randomized control trials that support the use of tranexamic acid in reducing blood loss and transfusion requirements in both knee and hip arthroplasty surgery [24]. There is however considerable amount of heterogeneity between the trials with regard to methods of delivery including single intravenous bolus dose, repeated boluses, prolonged infusion or intraarticular injection [116], and also differing dosing regimes [117]. In total knee arthroplasty, it has been shown that one intraoperative dose is sufficiently effective in reducing transfusion requirements and postoperative bleeding [118]. With the theoretical risk of intravascular thrombosis, intraarticular injection of tranexamic acid was investigated and compared to placebo and the studies showed reduction in blood loss but no reduction in transfusion rates [101, 119, 120]. Only one RCT by Seo et al. [121] showed a reduction in transfusion requirements with intraarticular (20%) rather than intravenous (34%) or placebo (94%). The evidence in total hip replacement with regard to intraarticular tranexamic acid is less convincing than in knee arthroplasty and more studies are needed.

With regard to aminocaproic acid, three RCTs did demonstrate benefit in hip and knee replacement surgery in terms of reducing blood loss in comparison with placebo. However, with regard to reducing transfusion requirements the evidence is much less convincing [24, 122–124].

8.5 Hemostasis and biosurgicals in spine surgery

Spine surgery presents a few unique challenges that limit the products that can be used for hemostasis in these situations. One of them is the friability of neural

tissue and secondly the fact that the spinal cord and nerve roots are enclosed in rigid bony spaces that limit the kinds of hemostats that can be used due to the potential of swelling and compression of neural tissue in a rigid space. In addition, there is the potential for neurotoxicity with certain agents.

Cerebrospinal fluid leaks are a common source of postoperative morbidity in patients who have undergone spinal surgery. The morbidity burden includes severe postural headaches, vomiting, dizziness, photophobia, tinnitus, pseudomeningoceles and the risk of meningitis. It is therefore important that when dural tears occur or when an iatrogenic durotomy is created a water tight repair is essential. PEG hydrogel sealant has been found to be a safe effective way to augment dural closure and prevent these complications. A prospective study by Kim et al. [66] demonstrated that augmentation of standard dural closure techniques with this sealant in patients had significantly higher rates of watertight closure than with controls (100% and 64.3% respectively), without statistical differences in cerebrospinal fluid leaks, infections or wound healing. Complications due to swelling of polyethylene glycol and nerve compression were not demonstrated in this study but this remains a possibility. This led to the development of low-swell PEG hydrogel sealant (Duraseal) [55] and has been found to be safe and effective in a 3-to-1 randomized single-blind multicenter trial in which 100% of patients who had this low-swell formulation achieved watertight dural closure. Another study has also shown that BioGlue (semisynthetic glutaraldehyde-bovine albumin sealant) is safe and cost-effective in proximity to neurological structures despite previous concerns. Miscusi et al. [125] demonstrated a watertight dural closure in 23 patients requiring dural repair, with no incidence of neurological or infection related complications.

Collagen and gelatin-based products can be used to achieve hemostasis in spinal surgery. Xu et al. [64] carried out a study on 92 patients undergoing spinal fusion surgery and concluded that collagen-based products are superior to gelatin-based products in achieving hemostasis in spine surgery, with lower blood loss and postoperative drain volume.

Oxidized regenerated cellulose has been used for hemostasis in spine surgery. However when used around or in foramina with rigid bony walls, the swelling of small portions of the cellulose material may lead to significant mass effect and neural compression 1 day after surgery as demonstrated by Menovsky et al. [126] and may lead to rapid neurological deterioration. Therefore this material should be removed after hemostasis has been achieved prior to closure.

As mentioned before, liquid fibrin sealants can be used in spine surgery for hemostasis, but those containing tranexamic acid may be associated with neurotoxicity and should not be used if CSF leak or dural tear is present [55].

9. Conclusions and future perspectives

Topical hemostats and biosurgicals are a diverse group of compounds that have been developed and can be used in different situations as part of a comprehensive blood management program to limit the amount of blood loss. Trauma and orthopedics as a specialty also presents some unique challenges, with operations having significant blood loss and in trauma, junctional injuries on the battlefield with hemorrhage that is hard to control by conventional means. In addition, patients may be complex and frequently have platelet or coagulation disorders that preclude the use of certain classes of hemostatic agents. As mentioned before, these compounds are diverse, with different mechanisms of actions and indications, both in an elective and an emergency trauma setting. A comprehensive knowledge of these products is essential in modern-day trauma and orthopedic practice.

Despite recent developments, the perfect hemostatic or biosurgical agent still remains elusive and each of these products has their own drawbacks, side effects and unique indications and future research will hopefully continue to improve on these.

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References

[1] Morikawa T. Tissue sealing. American Journal of Surgery. 2001;**182**(2 Suppl):29S-35S

[2] Block JE. Severe blood loss during spinal reconstructive procedures: The potential usefulness of topical hemostatic agents. Medical Hypotheses. 2005;**65**(3):617-621

[3] Morrison CA. The prehospital treatment of the bleeding patient—Dare to dream. The Journal of Surgical Research. 2013;**180**(2):246-247

[4] Sambasivan CN et al. A highly porous silica and chitosan-based hemostatic dressing is superior in controlling hemorrhage in a severe groin injury model in swine. American Journal of Surgery. 2009;**197**(5): 576-580; discussion 580

[5] Renkens KL Jr et al. A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. Spine (Phila Pa 1976). 2001;**26**(15):1645-1650

[6] Sabel M, Stummer W. The use of local agents: Surgicel and Surgifoam. European Spine Journal. 2004;**13**(Suppl 1):S97-S101

[7] Bochicchio G et al. The combination of platelet-enriched autologous plasma with bovine collagen and thrombin decreases the need for multiple blood transfusions in trauma patients with retroperitoneal bleeding. The Journal of Trauma. 2004;**56**(1):76-79

[8] Tomizawa Y. Clinical benefits and risk analysis of topical hemostats: A review. Journal of Artificial Organs. 2005;**8**(3):137-142

[9] Lemos MJ, Healy WL. Blood transfusion in orthopaedic operations. The Journal of Bone and Joint Surgery. American Volume. 1996;**78**(8):1260-1270

[10] Popovsky MA, Audet AM, Andrzejewski C Jr. Transfusion-associated circulatory overload in orthopedic surgery patients: A multi-institutional study. Immunohematology. 1996;**12**(2):87-89

[11] Li G et al. Long-term survival and quality of life after transfusion-associated pulmonary edema in critically ill medical patients. Chest. 2010;**137**(4):783-789

[12] Carreon LY et al. Perioperative complications of posterior lumbar decompression and arthrodesis in older adults. The Journal of Bone and Joint Surgery. American Volume. 2003;**85**(11):2089-2092

[13] McDonnell MF et al. Perioperative complications of anterior procedures on the spine. The Journal of Bone and Joint Surgery. American Volume. 1996;**78**(6):839-847

[14] Lundblad RL et al. A review of the therapeutic uses of thrombin. Thrombosis and Haemostasis. 2004;**91**(5):851-860

[15] Gabay M. Absorbable hemostatic agents. American Journal of Health-System Pharmacy. 2006;**63**(13):1244-1253

[16] Adams GL et al. The balance of thrombosis and hemorrhage in surgery. Hematology/Oncology Clinics of North America. 2007;**21**(1):13-24

[17] Oz MC, Rondinone JF, Shargill NS. FloSeal matrix: New generation topical hemostatic sealant. Journal of Cardiac Surgery. 2003;**18**(6):486-493

[18] Krebs VE et al. Blood management in joint replacement surgery: What's in and what's out. Orthopedics. 2006;**29**(9):801-803

[19] Albala DM, Lawson JH. Recent clinical and investigational applications of fibrin sealant in selected surgical specialties. Journal of the American College of Surgeons. 2006;**202**(4):685-697

[20] Samudrala S. Topical hemostatic agents in surgery: A surgeon's perspective. AORN Journal. 2008;**88**(3):S2-S11

[21] Taylor LM Jr 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. Journal of Vascular Surgery. 2003;**38**(4):766-771

[22] Lynn AK, Yannas IV, Bonfield W. Antigenicity and immunogenicity of collagen. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2004;**71**(2):343-354

[23] Bishop PD et al. Comparison of recombinant human thrombin and plasma-derived human alpha-thrombin. Seminars in Thrombosis and Hemostasis. 2006;**32**(Suppl 1):86-97

[24] Saleh A et al. Use of hemostatic agents in hip and knee arthroplasty: A critical analysis review. JBJS Reviews. 2014;**2**(1)

[25] Dhillon S. Fibrin sealant (evicel(R) [quixil(R)/crosseal]): A review of its use as supportive treatment for haemostasis in surgery. Drugs. 2011;**71**(14):1893-1915

[26] Patel S, Rodriguez-Merchan EC, Haddad FS. The use of fibrin glue in surgery of the knee. Journal of Bone and Joint Surgery. British Volume (London). 2010;**92**(10):1325-1331

[27] Thoms RJ, Marwin SE. The role of fibrin sealants in orthopaedic surgery. The Journal of the American Academy of Orthopaedic Surgeons. 2009;**17**(12):727-736

[28] Chapman WC et al. A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis. Journal of the American College of Surgeons. 2007;**205**(2):256-265

[29] Doria C et al. Phase 3, randomized, double-blind study of plasma-derived human thrombin versus bovine thrombin in achieving hemostasis in patients undergoing surgery. Current Medical Research and Opinion. 2008;**24**(3):785-794

[30] Wagner WR et al. Comparative in vitro analysis of topical hemostatic agents. The Journal of Surgical Research. 1996;**66**(2):100-108

[31] Chapman WC et al. Effective management of bleeding during tumor resection with a collagen-based hemostatic agent. The American Surgeon. 2002;**68**(9):802-807

[32] Lawson JH. The clinical use and immunologic impact of thrombin in surgery. Seminars in Thrombosis and Hemostasis. 2006;**32**(Suppl 1):98-110

[33] Carraway JW et al. Comparison of a new mineral based hemostatic agent to a commercially available granular zeolite agent for hemostasis in a swine model of lethal extremity arterial hemorrhage. Resuscitation. 2008;**78**(2):230-235

[34] Yucel N et al. Trauma associated severe hemorrhage (TASH)-score: Probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. The Journal of Trauma. 2006;**60**(6):1228-1236; discussion 1236-1237

[35] Khoshmohabat H et al. Overview of agents used for emergency hemostasis. Trauma Monthly. 2016;**21**(1):e26023

[36] Gruen RL et al. Haemorrhage control in severely injured patients. Lancet. 2012;**380**(9847):1099-1108

[37] Leonard J et al. A multi-institutional study of hemostatic gauze and tourniquets in rural civilian trauma. Journal of Trauma and Acute Care Surgery. 2016;**81**(3):441-444

[38] Bulger EM et al. An evidence-based prehospital guideline for external hemorrhage control: American College of Surgeons Committee on Trauma. Prehospital Emergency Care. 2014;**18**(2):163-173

[39] Jacobs LM Jr. Joint Committee to Create a National Policy to enhance survivability from mass casualty shooting events: Hartford Consensus II. Journal of the American College of Surgeons. 2014;**218**(3):476-478

[40] Kelly JF et al. Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003-2004 versus 2006. The Journal of Trauma. 2008;**64**(2 Suppl):S21-S26; discussion S26-S27

[41] Granville-Chapman J, Jacobs N, Midwinter MJ. Pre-hospital haemostatic dressings: A systematic review. Injury. 2011;**42**(5):447-459

[42] Vournakis JN et al. The RDH bandage: Hemostasis and survival in a lethal aortotomy hemorrhage model. The Journal of Surgical Research. 2003;**113**(1):1-5

[43] Mabry RL et al. United States Army Rangers in Somalia: An analysis of combat casualties on an urban battlefield. The Journal of Trauma. 2000;**49**(3):515-528; discussion 528-529

[44] Navein J, Coupland R, Dunn R. The tourniquet controversy. The Journal of Trauma. 2003;**54**(5 Suppl):S219-S220

[45] Bilgili H et al. Hemostatic efficacy of Ankaferd blood stopper in a swine bleeding model. Medical Principles and Practice. 2009;**18**(3):165-169

[46] Ward KR et al. Comparison of a new hemostatic agent to current combat hemostatic agents in a swine model of lethal extremity arterial hemorrhage. The Journal of Trauma. 2007;**63**(2):276-283; discussion 283-284

[47] Pusateri AE et al. Effect of a chitosan-based hemostatic dressing on blood loss and survival in a model of severe venous hemorrhage and hepatic injury in swine. The Journal of Trauma. 2003;**54**(1):177-182

[48] Pusateri AE et al. Making sense of the preclinical literature on advanced hemostatic products. The Journal of Trauma. 2006;**60**(3):674-682

[49] Smith AH et al. Haemostatic dressings in prehospital care. Emergency Medicine Journal. 2013;**30**(10):784-789

[50] Clay JG et al. Dextran polymer hemostatic dressing improves survival in liver injury model. The Journal of Surgical Research. 2009;**155**(1):89-93

[51] Kilbourne M et al. Hemostatic efficacy of modified amylopectin powder in a lethal porcine model of extremity arterial injury. Annals of Emergency Medicine. 2009;**53**(6):804-810

[52] Ragusa R et al. Use of gelatin powder added to rifamycin versus bone wax in sternal wound hemostasis after cardiac surgery. Interactive Cardiovascular and Thoracic Surgery. 2007;**6**(1):52-55

[53] Lewis KM et al. Comparison of regenerated and non-regenerated oxidized cellulose hemostatic agents. European Surgery. 2013;**45**:213-220

[54] Brodbelt AR et al. Intraspinal oxidised cellulose (Surgicel) causing delayed paraplegia after thoracotomy—A report of three cases. Annals of the Royal College of Surgeons of England. 2002;**84**(2):97-99

[55] Chiara O et al. A systematic review on the use of topical hemostats in trauma and emergency surgery. BMC Surgery. 2018;**18**(1):68

[56] Wagenhauser MU et al. Oxidized (non)-regenerated cellulose affects fundamental cellular processes of wound healing. Scientific Reports. 2016;**6**:32238

[57] Sabino L et al. Evaluation of renal defect healing, hemostasis, and urinary fistula after laparoscopic partial nephrectomy with oxidized cellulose. Journal of Endourology. 2007;**21**(5):551-556

[58] Emmez H et al. Radiological and histopathological comparison of microporous polysaccharide hemospheres and oxidized regenerated cellulose in the rabbit brain: A study of efficacy and safety. Turkish Neurosurgery. 2010;**20**(4):485-491

[59] Echave M, Oyaguez I, Casado MA. Use of Floseal(R), a human gelatine-thrombin matrix sealant, in surgery: A systematic review. BMC Surgery. 2014;**14**:111

[60] Bruckner BA et al. Microporous polysaccharide hemosphere absorbable hemostat use in cardiothoracic surgical procedures. Journal of Cardiothoracic Surgery. 2014;**9**:134

[61] Spotnitz WD. Fibrin sealant: The only approved hemostat, sealant, and adhesive—A laboratory and clinical perspective. ISRN Surgery. 2014;**2014**:203943

[62] Chalmers RT et al. Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. The British Journal of Surgery. 2010;**97**(12):1784-1789

[63] Fischer CP et al. A randomized trial of aprotinin-free fibrin sealant versus absorbable hemostat. Clinical and Applied Thrombosis/Hemostasis. 2011;**17**(6):572-577

[64] Xu D et al. A randomized controlled trial on effects of different hemostatic sponges in posterior spinal fusion surgeries. BMC Surgery. 2016;**16**(1):80

[65] Dumville JC et al. Tissue adhesives for closure of surgical incisions. Cochrane Database of Systematic Reviews. 2014;**11**:CD004287

[66] Kim KD, Wright NM. Polyethylene glycol hydrogel spinal sealant (DuraSeal spinal sealant) as an adjunct to sutured dural repair in the spine: Results of a prospective, multicenter, randomized controlled study. Spine (Phila Pa 1976). 2011;**36**(23):1906-1912

[67] Wright NM 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):505-513

[68] Allen MS et al. Prospective randomized study evaluating a biodegradable polymeric sealant for sealing intraoperative air leaks that occur during pulmonary resection. The Annals of Thoracic Surgery. 2004;**77**(5):1792-1801

[69] Coselli JS et al. Prospective randomized study of a protein-based tissue adhesive used as a hemostatic and structural adjunct in cardiac and vascular anastomotic repair procedures. Journal of the American College of Surgeons. 2003;**197**(2):243-252; discussion 252-253

[70] Robinson K. Controlling bleeding in the field: Hemostatic powders and dressings debut in the prehospital setting. Journal of Emergency Nursing. 2004;**30**(2):160-161

[71] Saha SP et al. A prospective randomized study comparing fibrin sealant to manual compression for the treatment of anastomotic suture-hole bleeding in expanded polytetrafluoroethylene grafts. Journal of Vascular Surgery. 2012;**56**(1):134-141

[72] Fischer CP et al. 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. Journal of the American College of Surgeons. 2013;**217**(3):385-393

[73] Koea J et al. Safety and hemostatic effectiveness of the fibrin pad for severe soft-tissue bleeding during abdominal, retroperitoneal, pelvic, and thoracic (non-cardiac) surgery: A randomized, controlled, superiority trial. World Journal of Surgery. 2015;**39**(11):2663-2669

[74] Colombo GL et al. Economic and outcomes consequences of TachoSil(R): A systematic review. Vascular Health and Risk Management. 2014;**10**:569-575

[75] Rhee P et al. QuikClot use in trauma for hemorrhage control: Case series of 103 documented uses. The Journal of Trauma. 2008;**64**(4):1093-1099

[76] Shina A et al. Prehospital use of hemostatic dressings by the Israel defense forces medical corps: A case series of 122 patients. Journal of Trauma and Acute Care Surgery. 2015;**79**(4 Suppl 2): S204-S209

[77] Wedmore I et al. A special report on the chitosan-based hemostatic dressing: Experience in current combat operations. The Journal of Trauma. 2006;**60**(3):655-658

[78] Arnaud F et al. Exothermic reaction in zeolite hemostatic dressings: QuikClot ACS and ACS+. Annals of Biomedical Engineering. 2008;**36**(10):1708-1713

[79] Dai C et al. Molecular imprinted macroporous chitosan coated mesoporous silica xerogels for hemorrhage control. Biomaterials. 2010;**31**:7620-7630

[80] Wright JK et al. Thermal injury resulting from application of a granular mineral hemostatic agent. The Journal of Trauma. 2004;**57**(2):224-230

[81] Cox ED et al. New hemostatic agents in the combat setting. Transfusion. 2009;**49**(Suppl 5):248S-255S

[82] McManus J et al. A case series describing thermal injury resulting from zeolite use for hemorrhage control in combat operations. Prehospital Emergency Care. 2007;**11**(1):67-71

[83] Velmahos GC et al. Self-expanding hemostatic polymer for control of exsanguinating extremity bleeding. The Journal of Trauma. 2009;**66**(4):984-988

[84] Sambasivan CN, Schreiber MA. Emerging therapies in traumatic hemorrhage control. Current Opinion in Critical Care. 2009;**15**(6):560-568

[85] Clay JG, Grayson JK, Zierold D. Comparative testing of new hemostatic agents in a swine model of extremity arterial and venous hemorrhage. Military Medicine. 2010;**175**:280-284

[86] Gerlach T et al. Preliminary study of the effects of smectite granules (WoundStat) on vascular repair and wound healing in a swine survival model. The Journal of Trauma. 2010;**69**(5):1203-1209

[87] Kheirabadi BS et al. Safety evaluation of new hemostatic agents, smectite granules, and kaolin-coated gauze in a vascular injury wound model in swine. The Journal of Trauma. 2010;**68**(2):269-278

[88] Te Grotenhuis R et al. Prehospital use of hemostatic dressings in

emergency medical services in the Netherlands: A prospective study of 66 cases. Injury. 2016;**47**(5):1007-1011

[89] Kheirabadi BS et al. Comparison of new hemostatic granules/powders with currently deployed hemostatic products in a lethal model of extremity arterial hemorrhage in swine. The Journal of Trauma. 2009;**66**(2):316-326; discussion 327-328

[90] Devlin JJ et al. Comparison of ChitoFlex(R), CELOX, and QuikClot(R) in control of hemorrhage. The Journal of Emergency Medicine. 2011;**41**(3):237-245

[91] Millner RW et al. A new hemostatic agent: Initial life-saving experience with Celox (chitosan) in cardiothoracic surgery. The Annals of Thoracic Surgery. 2009;**87**(2):e13-e14

[92] Pozza M, Millner RW. Celox (chitosan) for haemostasis in massive traumatic bleeding: Experience in Afghanistan. European Journal of Emergency Medicine. 2011;**18**(1):31-33

[93] Malmquist JP et al. Hemostasis of oral surgery wounds with the HemCon dental dressing. Journal of Oral and Maxillofacial Surgery. 2008;**66**(6):1177-1183

[94] Waibel KH et al. Safety of chitosan bandages in shellfish allergic patients. Military Medicine. 2011;**176**(10):1153-1156

[95] Ong SY et al. Development of a chitosan-based wound dressing with improved hemostatic and antimicrobial properties. Biomaterials. 2008;**29**(32):4323-4332

[96] Lawton G, Granville-Chapman J, Parker PJ. Novel haemostatic dressings. Journal of the Royal Army Medical Corps. 2009;**155**(4):309-314

[97] Bennett BL, Littlejohn L. Review of new topical hemostatic dressings for combat casualty care. Military Medicine. 2014;**179**(5):497-514

[98] Collaborators C-T et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet. 2010;**376**(9734):23-32

[99] Morrison JJ et al. Military application of Tranexamic acid in trauma emergency resuscitation (MATTERs) study. Archives of Surgery. 2012;**147**(2):113-119

[100] Levy O et al. The use of fibrin tissue adhesive to reduce blood loss and the need for blood transfusion after total knee arthroplasty. A prospective, randomized, multicenter study. The Journal of Bone and Joint Surgery. American Volume. 1999;**81**(11):1580-1588

[101] Wong J et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: A randomized, controlled trial. The Journal of Bone and Joint Surgery. American Volume. 2010;**92**(15):2503-2513

[102] Notarnicola A et al. Comparative efficacy of different doses of fibrin sealant to reduce bleeding after total knee arthroplasty. Blood Coagulation & Fibrinolysis. 2012;**23**(4):278-284

[103] Wang GJ et al. Fibrin sealant reduces perioperative blood loss in total hip replacement. Journal of Long-Term Effects of Medical Implants. 2003;**13**(5):399-411

[104] Lassen MR et al. A pilot study of the effects of Vivostat patient-derived fibrin sealant in reducing blood loss in primary hip arthroplasty. Clinical and Applied Thrombosis/Hemostasis. 2006;**12**(3):352-357

[105] Mawatari M et al. Effectiveness of autologous fibrin tissue adhesive in reducing postoperative blood loss during total hip arthroplasty: A prospective randomised study of 100 cases. Journal of Orthopaedic Surgery (Hong Kong). 2006;**14**(2):117-121

[106] Bloomfield MR et al. Prospective randomized evaluation of a collagen/thrombin and autologous platelet hemostatic agent during total knee arthroplasty. The Journal of Arthroplasty. 2012;**27**(5):695-702

[107] Mannucci PM. Hemostatic drugs. The New England Journal of Medicine. 1998;**339**(4):245-253

[108] Tse EY et al. Reducing perioperative blood loss and allogeneic blood transfusion in patients undergoing major spine surgery. The Journal of Bone and Joint Surgery. American Volume. 2011;**93**(13):1268-1277

[109] Crescenzi G et al. Desmopressin reduces transfusion needs after surgery: A meta-analysis of randomized clinical trials. Anesthesiology. 2008;**109**(6):1063-1076

[110] Flordal PA et al. Effects of desmopressin on blood loss in hip arthroplasty. Controlled study in 50 patients. Acta Orthopaedica Scandinavica. 1992;**63**(4):381-385

[111] Karnezis TA et al. The hemostatic effects of desmopressin on patients who had total joint arthroplasty. A double-blind randomized trial. The Journal of Bone and Joint Surgery. American Volume. 1994;**76**(10):1545-1550

[112] Schott U et al. Desmopressin acetate does not reduce blood loss during total hip replacement in patients receiving dextran. Acta Anaesthesiologica Scandinavica. 1995;**39**(5):592-598

[113] Leino KA et al. The effect of desmopressin on blood loss in patients with rheumatoid arthritis undergoing hip arthroplasty. Acta Anaesthesiologica Scandinavica. 2010;**54**(7):863-870

[114] Ellis MH et al. The effect of tourniquet application, tranexamic acid, and desmopressin on the procoagulant and fibrinolytic systems during total knee replacement. Journal of Clinical Anesthesia. 2001;**13**(7):509-513

[115] Zohar E et al. A comparative study of the postoperative allogeneic blood-sparing effects of tranexamic acid and of desmopressin after total knee replacement. Transfusion. 2001;**41**(10):1285-1289

[116] Sukeik M et al. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. Journal of Bone and Joint Surgery. British Volume (London). 2011;**93**(1):39-46

[117] Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: A meta-analysis. The Journal of Bone and Joint Surgery. American Volume. 2012;**94**(13):1153-1159

[118] Lin PC et al. The blood-saving effect of tranexamic acid in minimally invasive total knee replacement: Is an additional pre-operative injection effective? Journal of Bone and Joint Surgery. British Volume (London). 2012;**94**(7):932-936

[119] Ishida K et al. Intra-articular injection of tranexamic acid reduces not only blood loss but also knee joint swelling after total knee arthroplasty. International Orthopaedics. 2011;**35**(11):1639-1645

[120] Roy SP et al. Efficacy of intra-articular tranexamic acid in blood loss

reduction following primary unilateral total knee arthroplasty. Knee Surgery, Sports Traumatology, Arthroscopy. 2012;**20**(12):2494-2501

[121] Seo JG et al. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surgery, Sports Traumatology, Arthroscopy. 2013;**21**(8):1869-1874

[122] Harley BJ et al. The effect of epsilon aminocaproic acid on blood loss in patients who undergo primary total hip replacement: A pilot study. Canadian Journal of Surgery. 2002;**45**(3):185-190

[123] Ray M et al. Aprotinin and epsilon aminocaproic acid are effective in reducing blood loss after primary total hip arthroplasty—A prospective randomized double-blind placebo-controlled study. Journal of Thrombosis and Haemostasis. 2005;**3**(7):1421-1427

[124] Camarasa MA et al. Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: A randomized clinical trial. British Journal of Anaesthesia. 2006;**96**(5):576-582

[125] Miscusi M et al. The use of surgical sealants in the repair of dural tears during non-instrumented spinal surgery. European Spine Journal. 2014;**23**(8):1761-1766

[126] Menovsky T et al. Massive swelling of Surgicel(R) Fibrillar hemostat after spinal surgery. Case report and a review of the literature. Minimally Invasive Neurosurgery. 2011;**54**(5-6):257-259