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Topical Hemostatic Agents: A Review of the Literature

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Abstract: Inadequate hemostasis in the surgical setting can obscure the surgical field, prolong operating times, and lead to poor patient outcomes. There are a variety of topical agents that can be used when standard methods of achieving hemostasis fail. Knowing about various available products, how they work, and how to use them can help surgeons approach hemostasis in a logical manner. This article reviews some of the products available for use in foot and ankle surgery.

Key words: Topical hemostatic agents, surgical bleeding, mechanical hemostats, flowable hemostats, fibrin sealants, tranexamic acid

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Adequate hemostasis in the operating room is an essential part of any procedure. Poorly controlled bleeding intra-operatively often creates poor visibility at the surgical site and prolongs procedure times [1], and is associated with increased patient morbidity and health care costs [2]. Hemostasis can improve patient outcomes by reducing the need for transfusion, as well as decreasing the risk of delayed wound healing, tissue necrosis, dehiscence, and hematoma formation [2-5].

As general trends have aimed at reducing the number of allogeneic blood transfusions, more emphasis has been placed on utilizing other intraoperative strategies for minimizing blood loss [6-10]. A few of the initial intra-operative measures the surgeon can take to reduce blood loss include conventional strategies such as direct pressure, electro-surgery, and ligation of vessels [9-11].

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There are also a number of topical hemostatic agents available to assist with hemostasis when conventional methods are not sufficient to control bleeding. This article will review some of the intra-operative hemostatic strategies available to the podiatric surgeon that can be used at the site of bleeding.

PHYSIOLOGY OF HEMOSTASIS

Hemostasis is an intricate process that requires a coordinated series of events in order to form a platelet-fibrin clot [12]. There are two main phases of hemostasis: primary and secondary. Primary hemostasis occurs immediately following damage to the blood vessel; collagen in the sub-endothelium is exposed, which provides a surface that promotes platelet adhesion [3]. The first response to vessel damage is local vasoconstriction [13], which slows the flow of blood in the damaged area, giving platelets time to adhere to the injured surface and aggregate [3, 14]. As large numbers of platelets aggregate, they link together and form a primary platelet plug [12]. While the soft platelet plug may be enough to stop bleeding in some cases, it is unstable and can easily be sheared off from the injured vessel [1].

During secondary hemostasis, the primary platelet plug is stabilized and a stronger fibrin clot is formed [4, 14]. The coagulation cascade is a complex process that consists of a series of sequential and dependent reactions that ultimately lead to the enzymatic activation of thrombin. Thrombin cleaves circulating fibrinogen into fibrin and activates factor XIII, which crosslinks fibrin polymers in the platelet plug and creates a fibrin network that stabilizes the clot [1]. A definitive hemostatic plug is formed, effectively stopping the bleeding [4, 14, 15].

Patients with platelet disorders, Von Willebrand disease, or who are taking anti-platelet medications such as aspirin or clopidogrel may have inadequate primary hemostasis [16, 17], which is associated with excessive oozing peri-operatively. Defects or deficiencies in coagulation factors cause disorders of secondary hemostasis. These can include inherited disorders like hemophilias, as well as acquired disorders like liver disease [14, 18]. Anticoagulants such as warfarin, heparin, factor Xa inhibitors, and direct thrombin inhibitors all can interfere with secondary hemostasis and formation of the stable fibrin plug [17, 18].

INTRA-OPERATIVE STRATEGIES TO REDUCE BLOOD LOSS

The various intra-operative approaches to reduce blood loss augment the body's hemostatic mechanisms. Many work simply by slowing or blocking the flow of blood to an area, allowing time for platelets and clotting factors to accumulate and form a plug. Others work by passively providing a surface for platelets to adhere, or actively, by participating in secondary hemostasis at the end of the coagulation cascade.

It is essential for surgeons to be aware of various methods and products that can assist with controlling intra-operative bleeding. The effectiveness and appropriateness of the different hemostatic approaches may be impacted by patient comorbidities or medications. Understanding the mechanisms of each can help the surgeon take a logical approach to achieving hemostasis. It is also important for the techniques to be performed properly to be effective, and the surgeon should be aware of the availability, efficacy, and costs associated with various products.

First-Line Approach

The first line approach for surgical site bleeding typically consists of applying pressure to the area, using electro-surgery to cauterize vessels, and ligation for closing vessels with open lumens. However, in diffuse capillary bleeding, oozing bony surfaces, and inflamed or diseased vessels, these techniques may be ineffective at stopping bleeding [1]. If these fail, topical agents may be used to assist with hemostasis. For further considerations about first-line approaches, refer to Table 1.

TOPICAL HEMOSTATIC AGENTS

Topical agents can be effective adjuncts to achieving hemostasis when bleeding is not controlled with primary methods. Many topical hemostatic agents are available and new products are constantly being added to or taken off the market. Most topical agents can be divided into four main categories: mechanical, active, flowables, and fibrin sealants.

MECHANICAL AGENTS

Mechanical hemostats include porcine gelatins, microfibrillar collagen, oxidized regenerated cellulose, and polysaccharide spheres. These agents provide a physical barrier to block blood flow and act as a scaffold that allows platelets to aggregate and accelerate clot formation [15, 25].

Mechanical agents are often the first choice topical agents when pressure, ligation, and electro-cautery have not provided adequate hemostasis [2, 25]. They are most effective when used for oozing and small amounts of capillary, venous, and arteriolar bleeding. In order for these mechanical agents to work, they require an intact coagulation cascade and fibrin production [26]. Therefore, most mechanical hemostasis will not be effective or adequate if uncontrolled bleeding is caused by a significant coagulopathy [28].

Table 1. First-Line Approaches	
Pressure	• Direct pressure compresses small blood vessels to slow the loss of blood and allow time for platelets to form a plug [17, 19] • When pressure is utilized with gauze or other products, their removal often disrupts the platelet plug and leads to re-bleeding [20] • For most wounds, firm pressure for about 15-20 minutes should be sufficient to tamponade the vessels and allow a more stable clot to form [4, 18]. • If bleeding is severe, applying additional pressure to the supplying artery proximal to the wound can help decrease blood flow to the area and allow platelets to aggregate at the site of disruption [4]. • Pressure alone often fails if there is diffuse bleeding, if the source of bleeding is difficult to identify, or if the patient has a coagulopathy [17].
Electro-surgery	• Works well on identifiable bleeding vessels <2mm in diameter, but not effective for diffuse oozing [20, 21] • The safest and most effective technique is to identify a blood vessel, clamp it with forceps or a hemostat, gently elevate it above the surrounding tissue, then touch the tip of the electrocoagulation device to the surgical instrument [20, 21]. • Excessive charring can create a coagulum that is easily dislodged with blunt dissection and retraction, which can lead to delayed re-bleeding [4, 20]. • Utilizing the lowest power setting for the shortest amount of time that can still create hemostasis will also help avoid unnecessary charring [21, 22] • Excessive use on punctate bleeders in subcutaneous tissues can lead to extensive tissue damage, infection, and wound healing complications [18,20]
Clamping and Ligation	• Generally, any vessel >2 mm in diameter should be ligated with suture [17] • Typically, the ends of vessels are clamped with a hemostat and suture material is used to tie off the vessel at the tip of the hemostat [23, 24]. • The act of clamping assists with hemostasis by increasing surface damage to the vessel while slowing the flow of blood, providing both time and area for platelets and clotting factors to accumulate [3]. • The vessels should be ligated with the smallest size suture possible to reduce the amount of tissue reaction and care should be taken to avoid incorporating surrounding tissue [3].

These products have several advantages, including their immediate availability, ease of use, and relatively low costs [27]. They are stored at room temperature and generally do not require special preparation or need for reconstitution prior to use [28]. They are all absorbable, with time to absorption ranging from 24 hours to 10 weeks depending on the product [11, 29]. They come in multiple formulations, allowing the surgeon to choose a product that fits their needs.

Mechanical hemostatic agents are relatively safe. The most common adverse effects include swelling, infection, foreign body reactions, and allergic reactions, but these are generally minor and well-tolerated [27, 29]. To reduce the risk of complications, it is recommended to use the minimal amount of material that can still achieve hemostasis and to remove any excess material from the site [30]. Also important to consider is that all of these agents come with a risk of thromboembolism if accidentally injected or placed within a blood vessel [25].

Proper use of these products is essential to achieve hemostasis. Any pooled blood should be removed from the area prior to applying the product to allow visualization and accurate placement. Products that come in sheets and sponges should typically be cut to an appropriate size then placed in the area with gauze and manual pressure until hemostasis is achieved [27]. Powders can be applied directly to the area of bleeding, or in some cases they can be combined with saline or thrombin to form a paste, then surgical gauze can be used to hold the agent in place with pressure at the site of bleeding [27]. Most importantly is the removal of the product, which needs to be done carefully to avoid disrupting the newly formed clot [29]. To prevent re-bleeding, the gauze should be adequately moistened with sterile water and rolled off the clotted area slowly [27] .

Microfibrillar collagens are generally considered the most effective of the mechanical agents, while oxidized regenerated cellulose and plain porcine gelatins are considered the least efficacious [2, 26]. Not surprisingly, the cost of the products is generally correlated with effectiveness; so bovine collagen and polysaccharide spheres are generally more expensive than the other options [15, 29]. For information on individual products, see Table 2.

PHYSICAL AGENTS

Two hemostatic agents exist that are indicated specifically for controlling bleeding from bony surfaces. Bone wax (Ethicon, Inc.) is a non-absorbable mixture of beeswax, paraffin, isopropyl palmitate, and wax softening agent. Ostene (Baxter International, Inc.) is an alkylene oxide copolymer with a consistency of bone wax, but a better alternative due to fewer associated risks. Both of these agents strictly work by physically blocking oozing blood from channels in cancellous bone to achieve hemostasis and have no inherent blood-clotting properties and [37]. For further information, refer to Table 3.

ACTIVE AGENTS

Active topical hemostatic agents have biological activity and directly participate in the coagulation cascade by providing thrombin directly to the bleeding site, promoting clot formation [1]. They are approved for broad surgical use for oozing blood and minor bleeding from capillaries and small venules when control of bleeding by standard surgical techniques is ineffective [15].

Unlike the mechanical agents, topical thrombins do not rely as much on a patient's intrinsic clotting mechanisms, so they still work in the presence of most coagulopathies as long as the patient has adequate fibrinogen levels [26]. They are also effective in patients taking antiplatelet and anticoagulation medications [1].

Using liquid thrombin for localized bleeding by dripping it in the area often ineffective because the liquid is easily washed away from the intended sites [26]. To overcome this, thrombin should be applied with an absorbable gelatin matrix or soaked surgical gauze to provide some mechanical assistance and allow the surgeon to apply pressure to the area [30]. If an absorbable gelatin sponge is used, it should be moistened with thrombin but not soaked or it will be ineffective as a scaffold for clot formation [27]. It is also important to be aware that the gelatin matrix or surgical gauze will typically get incorporated into the clotting tissues, so attempting to remove them could lead to significant disruption and re-bleeding [29]. Once hemostasis is achieved, saline can be used to moisten the sponge or gauze so they can be gently lifted off. If the absorbable sponge does not come off easily, it can be left in place [25].

Compared to mechanical agents, active agents are generally more effective at stopping local bleeding, but they are also more expensive and require more preparation with either thawing or reconstitution prior to use [26]. Another advantage compared to mechanical agents is that thrombin does not need to be removed from the site of bleeding prior to closure [1]. Since thrombin initiates a natural physiologic process, no foreign body or inflammatory reactions occur [19].

Table 2. Mechanical Agents

	Mechanism of Action	Advantages	Disadvantages/Cautions
Porcine Gelatins Gelfoam (Pfizer, Inc.) Surgifoam (Ethicon, Inc.)	Swell as they absorb fluid, creating a scaffold that exerts pressure on blood vessels to create a barrier and provides a surface for clot formation [31]	Available as sponges and powders [12]. Can be used dry, moistened with saline, or saturated with topical thrombin [32]. Neutral pH, so will not inactivate thrombin when combined [33]. Works on oozing in irregular wounds [30]. Good alternative for bony bleeding; less infection and inhibition of bone healing than bone wax [32].	Associated with significant swelling, so should not be used in confined areas where they can compress neurovascular structures [15]. Can facilitate bacterial growth or lead to foreign body reactions if left in tissues [4, 34]
Microfibrillar Collagen Avitene, Ultrafoam (C.R. Bard, Inc.) Instat (Ethicon, Inc.) Helistat, Helitene (Integra LifeScience Corp.)	Form a physical matrix; platelets adhere to collagen surface, where they are activated and form a thrombus [15]. Enhance platelet aggregation and activate the intrinsic pathway of coagulation [12, 25].	Most effective mechanical hemostats [25]. Effective in heparinized patients [33]. Available in powders, sheets, and sponges. Generally recommended for large surface areas [19], so role in foot and ankle surgery is unclear.	Require functional platelets, so may not be effective if severe thrombocytopenia or platelet dysfunction [32, 35]. Stick to instruments and gloves if wet [20]. More expensive than other mechanical hemostats [19].
Oxidized Regenerated Cellulose Surgicel, Surgicel Fibrillar, Surgicel Nu-Knit (Ethicon, Inc.)	Create a scaffold for clot formation [12]. Acid within the product promotes coagulative necrosis [32].	Especially useful for control of venous and capillary oozing [30]. Low pH creates bactericidal environment for 7-14 days [36]. Come in multiple different densities [25]. Increased efficacy when used dry [25]. Do not stick to instruments [1]. Less expensive than most other mechanical agents [26].	Less effective than other mechanical hemostats [25]. Low pH inactivates topical thrombin, so cannot be combined [19]. Low pH may increase inflammation and lead to delayed wound healing [32]. Avoid use in bone defects or fractures [15].
Polysaccharide Spheres Arista (C.R. Bard, Inc.) Vitasure (Stryker Corp.)	Hydrophilic effect draws out plasma and dehydrating blood to concentrate platelets and clotting factors [4, 32]. Also creates a physical barrier in the tissue [4].	Comes as a powder in an applicator. Fast absorption (24-48 hrs.)[15], so do not cause foreign body reactions [35]. Free of transmissible viruses and alloantigens, and do not act as a nidus for infection [35]. More effective than cellulose and gelatins [15].	Use <50 grams of product in diabetic patients due to sugar in product [25]. Causes immediate swelling, which can compress surrounding tissues [4].

Table 3. Physical Agents

	Mechanism of Action	Advantages	Disadvantages/Considerations
Bone Wax (Ethicon, Inc.)	Occludes bleeding channels in bone, creating a tamponade effect [33].	Easy to use, affordable, provides almost instantaneous hemostasis [3, 37] Can be warmed and molded prior to use, then pressed against a bony surface [3]	Recent literature advises against using bone wax in favor of other alternatives [33, 37, 38]. Not metabolized or resorbed, so remains at application site indefinitely [38]. Can inhibit osteoblasts from reaching bony defects and lead to impaired bone healing [37, 39]. Associated with infection, foreign body reaction, local inflammation, and pain [19, 38]. May embolize to other areas [33]. Once hemostasis is achieved, as much as possible should be removed [37]. Do not use in bone fusions or in the presence of infection [33].
Ostene (Baxter International, Inc.)	Physically occludes bleeding channels in bone [3].	Better alternative to bone wax as it is water-soluble and eliminated [37]. Does not promote infection and is not associated with chronic inflammation or reduced bone healing [37, 38].	

Table 4. Active Agents

	Mechanism of Action	Considerations	Individual Products
Bovine Thrombin (Thrombin-JMI; Pfizer, Inc.)	Deliver thrombin directly to the site of bleeding, where it participates in the final stages of the coagulation cascade and converts fibrinogen into fibrin to form a fibrin clot [32].	Work in the presence of most coagulopathies [1, 26]. Effective in patients taking antiplatelet and anticoagulant medications [1] Rapid onset of action; hemostasis often within 10 minutes [1]. All are equally effective for local or diffuse bleeding [29]. Can be used with a variety of delivery systems [25]. Easily washed away if not used with sponge or gauze [26]. More effective than mechanical agents, but more expensive and require more preparation [26]. Not associated with foreign body or inflammatory reactions, so does not need to be removed prior to closure [19]. All contain proteins, so can potentially cause an allergic or anaphylactic response [2]. Should never be used intravascularly due to risk of systemic thrombus [40].	Available as lyophilized powder that is stored at room temperature [29]. Requires reconstitution with saline prior to use [40]. Risk of immune-mediated coagulopathy due to antibody formation against bovine thrombin and factor V [29].
Human Pooled Thrombin (Evithro; Ethicon, Inc.)			Comes fully mixed, but is frozen and requires time to thaw prior to use [40]. May be associated with blood-borne disease [11]. Cannot be used in patients allergic to human blood products [25].
Recombinant Human Thrombin (Recothrom; The Medicines Company)			Available as lyophilized powder that is stored at room temperature [29]. Requires reconstitution with saline prior to use [40]. Fewer safety concerns than other thrombins, but theoretical risk in patients with hypersensitivities to snake or hamster proteins [11].

FLOWABLE AGENTS

Flowable hemostats, including Floseal (Baxter International, Inc.) and Surgiflo (Ethicon, Inc.), use gelatin animal matrices with thrombin to create a product that combines both active and mechanical methods to achieve hemostasis [28]. Granules in the product fill and conform to the site, with the granules gradually expanding and restricting blood flow in the area [41]. The blood that continues to flow through is exposed to significant amounts of thrombin, which increases clot formation around the scaffold created by the granules [10].

Overall, flowables are considered some of the most efficacious of the topical hemostatic agents [29]. Advantages of flowable agents include rapid hemostasis, precise application, increased tissue contact, conformability, and absorbability [11]. Unlike other products that have been discussed, in addition to being effective on capillary bleeding and oozing, these may also be effective in situations with arterial bleeding and spurting [41, 42]. Disadvantages include allergic responses to the materials, swelling, increased preparation time, and increased cost [31].

These hemostats create a paste, which allows the product to remain in place at the site of bleeding [26]. The paste needs to be placed directly at the site of bleeding, as the product requires direct contact with blood to work [28]. Gentle pressure should be applied with a moist saline gauze for several minutes to achieve hemostasis [27]. Once hemostasis is achieved, the gauze can be removed and any excess granules not incorporated into the clot should be removed with gentle irrigation [28].

These agents are associated with a higher cost than individual agents in the mechanical or active categories [34]. Their safety profiles are consistent with those of their mechanical and active components and like other topical hemostatic agents. These should not be placed intravascularly due to the risk of thromboembolism [45].

FIBRIN SEALANTS

Fibrin sealants contain a combination of human fibrinogen and human pooled thrombin. These agents function at the end of the coagulation cascade and promote clot formation by providing high concentrations of fibrinogen and thrombin at a local site of bleeding [30]. They do not require active bleeding to be effective [25], and because they act independently of the coagulation cascades, fibrin sealants are ideal for patients with coagulopathies, including those who do not produce enough fibrinogen as well as patients undergoing anticoagulation therapy [11, 19].

Fibrin sealants may be effective for the control of both local and diffuse bleeding as they can be applied locally using a syringe-like applicator, sprayed over a larger area using a gas-driven device[28], or applied in conjunction with a gelatin matrix [30]. Application with a gelatin sponge allows the addition of pressure to facilitate hemostasis, but the sponge typically becomes incorporated into the fibrin clot and is difficult to remove once bleeding stops [29].

Although effective, these agents are some of the most expensive of the topical hemostats and are associated with more complicated preparation and application [29]. Overall, their utility in foot and ankle surgery is probably limited to patients with congenital coagulopathies or patients receiving antiplatelet or anticoagulant therapy undergoing emergent procedures who fail other methods of hemostasis [19, 30]. A new agent, Raplixa, was approved by the FDA in 2015 [46]. It comes premixed to speed up preparation, and it is used in conjunction with a gelatin sponge. This product may be promising for podiatry, but due to its recent release it will likely have limited availability for several years.

TRANEXAMIC ACID

Tranexamic acid is a synthetic anti-fibrinolytic available in both intravenous and topical formulations. It works by competitively inhibiting the activation of plasminogen, reducing the formation of plasmin, which is responsible for the degradation of fibrin clots [19]. The use of tranexamic acid to control surgical site bleeding has been gaining significant interest with favorable results being seen with both intravenous and topical administration [51-57]. Studies in orthopedics have shown that topical

Table 5. Flowable Agents

<table>
<tr><th></th><th>Mechanism of Action</th><th>Advantages of Flowables</th><th>Disadvantages/ Cautions of Flowables</th><th>Considerations of Individual Agents</th></tr>
<tr><td>FLOSEAL

(Baxter International, Inc.)</td><td>Bovine gelatin matrix mechanically obstructs blood flow [15].

Human pooled thrombin converts fibrinogen into fibrin at the site of bleeding to help with clot formation [15].</td><td rowspan="2">Both agents are most effective for localized bleeding [26].

Rapid hemostasis, precise application, increased tissue contact [29].

Mold to irregular surfaces and fill deep spaces [35].

Remain localized better than liquid thrombin alone [26].

May be effective for mild arterial bleeding and spurting [41, 42].

Reduces blood loss, decreases surgical times, and reduces length of hospital stay [42].

More effective and faster than conventional hemostatic methods and passive non-flowable agents [42].</td><td rowspan="2">Both agents require time for reconstitution [25].

Need direct contact with blood to work [28].

More expensive than their individual components [34].

Safety issues consistent with their mechanical and active components [45].

Neither agent should be placed intravascularly due to risk of thrombo-embolism [29].</td><td>May be more effective with fewer compared to Surgiflo [43].

Avoid if hypersensitivity to Bovine material or human blood products [26].

More readily available than Surgiflo [44].</td></tr>
<tr><td>SURGIFLO
(Ethicon, Inc.)</td><td>Porcine gelatin matrix mechanically obstructs blood flow [15].

Thrombin converts fibrinogen into fibrin at the site of bleeding to help with clot formation [15].</td><td>Equivalent or less effective than FloSeal [43, 45].

Avoid if hypersensitivity to Porcine materials or thrombin components [26].</td></tr>
</table>

Table 6. Fibrin Sealants

	Mechanism of Action	Advantages of Fibrin Sealants	Disadvantages/Cautions of Fibrin Sealants
Tisseel (Baxter International, Inc.) **Evicel** (Ethicon, Inc.) **Vitagel** (Stryker, Inc.) **Raplixa** (The Medicine Company)	Function at the end of the coagulation cascade and promote clot formation by providing high concentrations of fibrinogen and thrombin at a local site of bleeding [30].	All are effective for the control of both local and diffuse bleeding [25]. Do not need active bleeding to work [25]. Effective in patients with coagulopathies and taking anticoagulant medications [19]. May be more effective than other topical hemostats [29, 47]. Associated with reduced blood loss and decreased need for allogeneic blood transfusion [47-49].	Most expensive topical hemostats [29]. Require more complicated prep and application [19, 30]. Risks associated with human blood products [50]. Risk of allergic reactions or anaphylaxis [15]. Thromboembolic complications if used intravascularly [34]. Thick layers are associated with infection and poor healing [11].

tranexamic acid is associated with significantly decreased perioperative blood loss and reduces the need for transfusion [54, 56, 58]. Additionally, a 2014 meta-analysis comparing topical versus intravenous use of tranexamic acid in total knee arthroplasty, found no significant difference regarding blood loss, transfusion requirements, or thromboembolic complications [59].

Topical tranexamic acid is dissolved in saline to make a solution that is easy to apply and inexpensive [55]. The topical method maximizes concentration of the active ingredient at the site of bleeding, so it may have a decreased risk of potential systemic complications like thromboembolism compared to intravenous methods [51]. However, typically a higher amount of tranexamic acid needs to be used if applied locally [60].

Despite the promising data, further information on safety, effectiveness, clinical indications, best route of administration, and optimal dosing is still needed [51, 61]. Although a large number of studies have shown that tranexamic acid does not result in an increase of thromboembolic events, it remains a lingering theoretical concern due to its mechanism of action [55].

CONCLUSION

Uncontrolled bleeding is a common and frustrating situation in the surgical setting. Fortunately, a number of effective methods and products exist to assist the surgeon with achieving hemostasis. When primary methods such as pressure, electro-surgery, and ligating vessels fail, topical hemostatic agents are often utilized, with gelatin and thrombin agents being the most commonly used [43]. Understanding how all these products work, the type of bleeding they are indicated for, and how to use them properly will help the podiatric surgeon approach hemostasis methodically.

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