Achieving hemostasis in dermatology-Part II: Topical hemostatic agents

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ABSTRACT

Bleeding is a common occurrence during any dermatologic surgery that disrupts blood vessels. The complications of excess bleeding can include delayed wound healing, hematoma formation, infection, dehiscence, and necrosis. In part one of this review, we discussed the pre-operative, intra-operative, and post-operative management of patients undergoing dermatologic surgery. In Part two, we discuss traditional and new topical hemostatic agents used to achieve hemostasis in dermatological procedures and surgery. We will evaluate the caustic and non-caustic hemostatic agents as well as hemostatic dressings. The mechanisms of action, side effect profile, and advantages and disadvantages of the topical hemostatic agents are provided. Sources for this article were found searching the English literature in PubMed for the time period 1940 to March 2012. A thorough bibliography search was also performed and key references examined.

Key words: Dermatologic surgery, hemostasis, topical hemostatic agents

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INTRODUCTION

Bleeding is an inevitable consequence of any dermatologic surgery that disrupts blood vessels of any size. The complications of excess bleeding are significant and can include, delayed wound healing, hematoma formation, infection, dehiscence of the wound, and necrosis. In part one of this review, we discussed the pre-operative, intra-operative and post-operative management of patients undergoing dermatologic surgery. In this section, we will focus on the topical hemostatic agents used to obtain hemostasis in skin surgery.

In order to best evaluate hemostatic agents, it is important to understand the physiologic progression of coagulation. Coagulation can be thought of as occurring in three main phases: Initiation, amplification, and propagation.[1] The initiation phase begins with injury to the endothelium and tissue factor release ultimately leading to thrombin formation. Platelet aggregation and activation occur during the amplification phase. Finally, fibrin formation and stabilization of the platelet clot occur during the propagation phase.

The authors conducted a literature review evaluating, the hemostatic agents used in dermatology. The following keywords were included in the search: "Hemostasis," "dermatology," "dermatologic surgery," "topical hemostats," "hemostatic agents," and "topical hemostatic agents." The sources for this article were identified by searching the English literature by PubMed for the time period of 1940 to March 2012. A thorough bibliography search using the articles found in the PubMed search was also conducted and key references were used for this review.

Topical hemostatic agents are beneficial as adjunctive treatments to conventional hemostatic means such as electrocautery, electrocoagulation and vessel ligation. The ideal agent should have high efficacy, minimal tissue reactivity, non-antigencity, low-cost, and easy absorbability.[2] Topical hemostatics are commonly classified as either non-caustic or caustic. Table 1 depicts the currently available topical agents used in dermatology.

CAUSTIC AGENTS

Topical caustics include, aluminum chloride, ferric sulfate (Monsel's solution), silver nitrate, and zinc chloride paste; all are effective tools

Table 1: Topical hemostatic agents for use in dermatology

Name (generic)	Trade name	Manufacturer, location	Website	Approximate cost per use ($)	Advantages	Disadvantages
Caustic agents						
Aluminum chloride 20-70%	Drysol	Person and Covy Inc., Glendal, CA		$10-$20/bottle, few cents per use	Inexpensive, less likely to cause pigmentation	Used only on superficial wounds
	Hypercare	Stratus Pharmaceuticals, Miami, FL		$10/bottle, few cents per use		
Ferric Subsulfate 20%	Monsel's solution			$0.20-0.60/mL	Inexpensive	Tattoo effect
Silver nitrate 10-50%				$0.10-0.15/ applicator stick	Inexpensive	Pigments skin, causes thick eschar
Non-caustic agents						
Porcine gelatins	Gelfoam	Pfizer, Memphis, TN	www.pfizer.com	$11/gelatin square	Absorbs several times its weight, non-antigenic, absorbable	Swelling can lead to damage of surrounding tissues, granulomatous foreign body reaction
	Spongostan	Ethicon, Somerville, NJ	www.ethicon360.com	$8-14/gelatin square		
	Surgifoam	Ethicon, Somerville, NJ	www.ethicon360.com			
Microporous polysaccharide spheres (MPH)	Arista AH	Medafor, Minneapolis, MN	www.medaforcom	$107/1 g applicator	Arista AH is a 100% plant based polysaccharide which contains no animal or human components. All are used in closed wounds and wounds that heal by secondary intention; absorbable	Expensive, Perclot only available in Europe
	Perclot	Cryolife, Kennesaw, GA	www.perclot.com	Perclot not available in US		
	Vitasure	Orthovita, Malvern, PA	www.orthovita.com			
Hydrophilic polymers with potassium salts (HPPS)	Wound Seal/ BioSeal/Pro QR	Biolife, Sarasota, FL	www.biolife.com	$0.99/packet (biopsy size)	Inexpensive, available over the count	Only used in wounds that heal by secondary intention
Oxidized Cellulose	Surgicel	Ethicon, Somerville, NJ	www.ethicon360.com	$1 for 2" square	Antibacterial, absorbable	Granulomatous foreign body reaction, acidic pH may inactivate thrombin
	Oxycel	Becton Dickinson, Franklin Lakes, NJ	www.oxycel.co.uk	$25-40/5.5×8 cm pad		
Microfibrillar Collagen	Avitene, Ultrafoam	Davol, Cranston, RI	www.davol.com	$150-$160/1 oz powder	No significant swelling, absorbable	Cannot be used as a surface dressing or for packing wounds, Granulomatous foreign body reaction
	Instat	Ethicon, Somerville, NJ	www.ethicon360.com	$80-$189/sponge		
	Helistat, Helitene	IntegraLifeScience, Plainsboro, NJ	www.integralife.com	$150/1 g powder		
Hemostatic dressings						
Alginate					Wound protective, Inexpensive	Not effective for high pressure bleeding
Mineral zeolite	Quickclot	Z-medica, Wallingford, CT	www.quikclot.com	$ 7-8/packet	Inexpensive	foreign body reactions
Chitin/chitosan	Celox	SAM Medical, Wilsonville, OR	www.celox.edical.com	$55-63/4×2" square	Antibacterial	
	ChitoFlex, HemCon	HemCon Medical Technologies, Portland, OR	www.hemcon.com			

CA = California, FL= Florida, TN = Tennessee, NJ = New Jersey, MN = Minnesota, GA = Georgia, PA = Pennsylvania, RI = Rhode Island, CT = Conneticut, OR = Oregon

for hemostasis. They work by coagulating proteins leading to tissue necrosis and eschar formation enhancing thrombus formation and hemostasis. Aluminum chloride does not lead to pigmentation of the skin and is the most frequently used caustic agent.[3] Monsel's solution is a 20% ferric subsulfate solution used in creating hemostasis. Silver nitrate is commonly used in the treatment of small wounds and is particularly effective in the cauterization of pyogenic granulomas of the hand.[4] Application of the silver nitrate creates a thin eschar, which sloughs off within several days. Silver nitrate may cause permanent skin pigmentation. Zinc chloride was pioneered early on in the use of Mohs surgery[5] and is uncommonly used at present. Caustic agents are applied to a wound using either gauze or a Q-tip applicator after the wound has been dried of blood.

NON-CAUSTIC AGENTS

Non-caustic hemostatic agents include physical and physiological hemostatic agents. The physical agents are comprised of porcine gelatins, microporous polysaccharide spheres, hydrophilic polymers with potassium salts (HPPS), oxidized regenerated cellulose and microfibrillar collagens. These products are active in the amplification and propagation phases of hemostasis and create a physical mesh that facilitates platelet aggregation and coagulation.[3] These hemostatic agents should be used if bleeding continues even after standard methods of hemostasis like electrocoagulation are applied. Physical hemostatics may create a granulomatous foreign body reaction and should be avoided in an infected surgical field and near the conjunctiva. The physical hemostatics are the most practical and cost-effective agents for use in dermatologic surgery.[3]

Porcine Gelatins

Porcine gelatins exist as sponges and powders. These agents work by forming a matrix that creates a mechanical barrier to bleeding. Porcine gelatins can be used effectively as monotherapy or in combination with topical thrombin. Achieving hemostasis after nail biopsy can be particularly difficult due to the rich vascular supply of the nail bed. A recent report demonstrated, the effectiveness of combining an absorbable gelatin sponge saturated in aluminum chloride in stopping bleeding after nail biopsy.[6] The combination was found to be more effective than either agent alone.[6] Another recent study investigated, the use of Gelfoam® (Pfizer, Memphis, TN) in Mohs micrographic surgery (MMS) and staged melanoma excisions. Results demonstrated that Gelfoam® promoted healing by secondary intention and was associated with improved hemostasis and cosmesis.[7] In addition to the adverse reactions of physical hemostats mentioned earlier, the porcine gelatins may swell during use and can lead to injury of neighboring structures such as nerves. These agents are absorbed by the body in approximately 4-6 weeks.[8,9]

Microporous polysaccharide hemospheres (MPH)

MPH are bio-inert particles derived from purified potato starch. The products hydrophilic effect concentrates the solid particles of blood enhancing the activity of platelets and clotting factors and accelerating the natural coagulation cascade.[10] The product is effective within minutes. A recent study of 29 volunteers compared the efficacy of MPH to control in the treatment of two small skin incisions.[11] Results indicated the MPH treated lesions stopped bleeding 5 minutes faster than the control area. Additionally, hemostasis occurred in 79% of the patients treated with MPH. There was no significant difference in wound healing between groups.[11] MPH can be used on open wounds that heal by secondary intention. Additionally, MPH can be used in wounds that will be sutured closed as they are absorbed by the body usually within 24-48 h.[10] To apply MPH, sprinkle it over the wound to create a thin covering. If bleeding continues to occur after 15-45 seconds, the agents can be reapplied in the same manner.[12]

Hydrophilic polymers with potassium salts (HPPS)

We find the use of the hydrophilic polymer with potassium salt to be particularly effective, as this hemostatic agent seems to work the fastest. The product was originally marketed as Urgent Quick Release (QR) powder® (Biolife, Sarasota, FL) but is currently marketed under several names including, Wound Seal, Pro QR Powder®, and Bioseal® (Biolife, Sarasota, FL). The hydrophilic polymers are able to dehydrate and concentrate the blood while the potassium ferrate acts as a binding agent creating an artificial eschar. The eschar ultimately falls off in the same manner as a natural scab. The powder is sprinkled on to the wound as pressure is applied. The powder creates a seal over the bleeding wound and does not permit anything to enter or exit, allowing the agent to function as a wound dressing. Wound seal QR powder® can be used effectively during MMS, removal of cancerous lesions and treatment of a skin tear.[13] It is also effective in patients on anticoagulant and antiplatelet therapy as it works independently of the body's innate coagulation system.[13] In a recent study, Wound Seal was found to have a 96% success rate in treating lacerations, skin tears, and abrasions. Moreover, bleeding was stopped in less than 15 seconds in 70% of lesions.[14] Similarly, to MPH, HPPS can be used on open wounds that heal by secondary intention. However, HPPS cannot be used in wounds that will be sutured closed, as it is not absorbed by the body.

Oxidized regenerated cellulose

Oxidized regenerated cellulose products are derived from plant cellulose and act as a physical barrier to facilitate clotting. These agents are useful for capillary, venous, and small arterial bleeding.[15] The products are acidic and thus, create a bactericidal environment.[15-17] Oxidized regenerated cellulose products have been shown to be useful in achieving hemostasis in the skin in several case reports.[18,19] Oxidized

cellulose is absorbed by the body in 7-14 days.[16] A recent study demonstrated, the effectiveness of using a micro-dispersed oxidized cellulose carrier to deliver an antibiotic in the treatment of full-thickness skin infections.[20] The oxidized cellulose carrier and antibiotic system also proved effective in providing hemostasis.[20]

Microfibrillar Collagen

Microfibrillar collagen is derived from purified bovine collagen. The agent works by causing aggregation of platelets. As the platelets aggregate on the collagen surface, they de-granulate and release coagulation products and facilitate hemostasis.[21] Prior to product use, the wound should be sponge dried and the product should be placed directly on the wound with pressure applied using a dry gauze and forceps.[21] Hemostasis usually occurs between 1 and 5 minutes. According to one review article, mircofibrillar collagens should be used primarily to control bleeding and not for the closure of skin incisions as some products have been shown to disrupt skin healing.[22] The article cited no primary reference on this subject.

Physiological Hemostatics

Physiological hemostatics include fibrin sealants, thrombin, and platelet gels that provide activity during the augmentation and/or propagation phase of hemostasis. In addition, to providing hemostasis, fibrin sealants may enhance wound healing. Although, effective in achieving hemostasis, the physiologic agents are rather costly and are not as commonly used in dermatologic surgery.[3] Antifibrinolytic hemostats include aminocaproic acid, aprotinin, and tranexamic acid. These agents delay the lysis of fibrin and are more commonly used systemically though topical application has been reported.[3]

HEMOSTATIC DRESSINGS

An excellent wound dressing can prevent excessive bleeding and save the patient from unplanned emergency department and/or office visits. An appropriate wound dressing should not only compress the suture line but also include areas of undermining and potential dead space. Certain dressings also function as effective hemostatic agents and are discussed below.

Alginate based dressings

Alginate based dressings are sold as wound dressings but are also very good hemostatics. Alginate dressings are able to absorb fluids through an ion exchange reaction as a result of calcium ions present in the material. The dressing is an occlusive dressing creating a protective barrier for the wound. Alginate dressings should be used in wounds with mild blood loss and are not as effective for high-pressure bleeding wounds. A study by Steenfos *et al*. demonstrated significantly higher amounts of blood absorption after 10 min with alginate dressings compared to mesh gauze dressings.[23] Alginate dressings are also rather inexpensive and appropriate for use in dermatology. One author, Daniel Siegel uses small pre-cut 2 cm × 2 cm squares in between Mohs stages to minimize the need for destructive modalities.

Mineral Zeolite

The mineral zeolite, QuickClot® (Z-Medica, Wallingford, CT) is comprised of a kaolin impregnated polyester gauze. When kaolin contacts the blood it immediately initiates the clotting process by transforming Factor XII to its activated form.[24] The active form of Factor XII then activates Factor XI and pre-kallikrien. Factor XII is capable of activating pre-kallikrien without kaolin but, in the presence of kaolin the activation is markedly enhanced. It is the activation of Factor XI and Factor XII that subsequently leads to the activation of the rest of the coagulation cascade. A clot is formed that can be left in place for up to 24 h and then painlessly removed. A recent animal study also demonstrated the use of QuickClot® in both normal and anti-coagulated hosts.[25]

Chitin and Chitosan Dressings

Chitosan is the deacylated form of chitin, an organic polymer derived from shrimp and crab exoskeletons.[26] Chitosan and chitin are believed to have hemostatics capabilities.[27] Chitosan dressings work by adhering to tissue and sealing wounds. Chitosan dressings also possess antimicrobial properties and are able to disrupt the membranes of gram-negative bacteria.[28,29] In two mouse model studies, chitosan was applied to wounds infected with bacteria and was able to prevent the spread of infection through the bloodstream.[30,31]

In addition to the hemostatic agents discussed above, there are a number of products employed in other surgical specialties not commonly used in dermatology, as they are too expensive or not appropriate for skin closure. For example, sealants are agents that prevent leakage of fluids from tissues and include the fibrin sealants, polyethylene glycol polymer and albumin, and glutaraldehyde.[32] These products are used more commonly in neurosurgery and/or cardiac surgery. Among the newest of the hemostatic agents is Legoo® (Pluromode Inc., Woburn, Mass). Legoo® is a reversible thermo-sensitive polymer that is a liquid at room temperature but immediately solidifies when reaching body temperature.[33] It appears to be effective by creating a physical compression to tamponade vessels. A recent study demonstrated, the effectiveness of Legoo® in facilitating an anastomosis necessary for an off-pump coronary artery bypass surgery.[34]

CONCLUSION

There are number of available hemostatic agents used in dermatologic surgery. These agents are often used in conjunction with more traditional hemostatic modalities such as electrosurgery and suturing. The caustic agents are

effective as they coagulate proteins causing tissue necrosis and eschar formation. The non-caustic agents are active during the amplification and propagation phases of hemostasis. The physical agents are among the most useful tools available for dermatologists. Finally, there are several wound dressings that can also be used effectively as hemostatic agents in dermatology.

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