Topical Coagulant Agents

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KEYWORDS

• Topical coagulant agents • Hemostatic agents • Surgical hemostasis • Thrombin • Fibrinogen • Chitin • Chitosan • Combat gauze

KEY POINTS

- Bleeding is inevitable in surgical intervention, and the capacity to address bleeding because of different pathways in surgical procedures is important; hence, the need for topical anticoagulant agents.
- Topical anticoagulant agents exist in different forms and are effective based on how they interact with the body's innate coagulation cascade.
- Knowing these different topical anticoagulant agents (how they function, ideal conditions for use, and drawbacks) improves the overall effectiveness of the agents.

BACKGROUND

It is no surprise that most surgical intervention has some degree of bleeding that occurs. Typically, the bleeding is minor and considered acceptable; however, there are times when the situation changes because of pathophysiology, patient disease, or surgical technique (Fig. 1). In these situations, it is essential that bleeding is controlled in a timely and safe manner. Ongoing bleeding limits optimal exposure and visualization of the surgical field, and increases the morbidity and mortality of the surgery.[1,2] The body has its own innate mechanism at resolving bleeding; however, surgical procedures can often overwhelm or impair this system. There are various methods to control bleeding in a surgical site including direct compression, electrocautery, and suture ligation. However, surface area, proximity to surrounding structures, patient pathophysiology, and source of bleeding often limit the surgeon's ability to gain control of bleeding using these traditional methods. In these scenarios, topical hemostatic agents can quickly and safely help achieve hemostasis. The earliest topical adjuncts for hemostasis were developed in 1886, and since that time there has been significant advancement in this area as the understanding of coagulation and pathophysiology has increased.[3] Today, there are dozens of topical hemostats that aid in intraoperative

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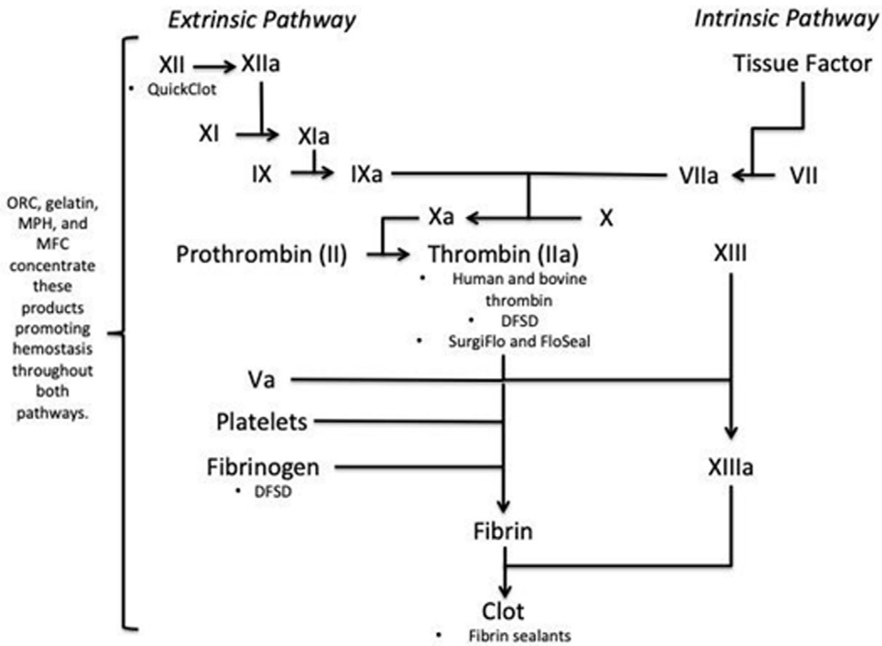

Fig. 1. Coagulation cascade diagram.[52] Clinical use of topical thrombin as a surgical hemostat. DFSD, dry fibrin sealant dressing; MFC, microfibrillar collagen; MPH, microporous polysaccharide hemospheres; ORC, oxidized regenerated cellulose. (*From*: Kustos SA, Fasinu PS. Direct-Acting Oral Anticoagulants and Their Reversal Agents—An Update. Medicines. 2019; 6(4):103. https://doi.org/10.3390/medicines6040103.)

hemostasis. In this article we review the relevant agents (**Box 1**), their roles in surgical hemostasis, and their relevant benefits and drawbacks.

TYPES OF TOPICAL COAGULANT AGENTS

Caustic

Caustic agents are topical hemostats that are applied to the area of bleeding and coagulate tissue by promoting protein precipitation and vessel occlusion.[3] They are predominately used during dermatologic procedures or other procedures confined to the superficial soft tissue. These agents are all stable at room temperature and many have antibacterial properties. As such, these agents are popular for use during in-office procedures.

One of the first caustic agents introduced was Monsel solution, which was developed in the late nineteenth century by a French medic during the Crimean War.[4] Its active ingredient is ferrous sulfate; the ferric ion is a precipitant that promotes local coagulation and provides antibacterial properties.[3] It is still used in dermatologic and gynecologic procedures even today.[3,5] The principal drawbacks of Monsel solution are the tattooing effect that it can have on the skin, the potential injury to surrounding tissues, and possible interference with appropriate histologic interpretation.[5–7]

Mohs paste, first used in 1941 for cutaneous malignancy treatment, has zinc chloride as its active ingredient, which exists in a paste form or impregnated dressings.[3] Another coagulant, silver nitrate, is often used to control local bleeding because the silver ions promote protein precipitation, eschar formation, and coagulation.[3,8] Like

Box 1
Classes of hemostats

Thermal/energy-based methods

Chemical methods
- Systemic pharmacologic agents
- Topical coagulant agents
  - Caustic agents
    - Mohs paste: zinc chloride
    - Monsel solution: 20% ferrous sulfate
    - Aluminum chloride
    - Silver nitrate
  - Noncaustic agents
    - Mechanical
    - Absorbable
    - Cellulose
    - Surgicel (Surgicel, Nu-Knit, Surgicel Fibrillar, Surgicel SNOW, and Surgicel Powder)
    - Oxycel
    - Collagen (bovine)
    - Avitene (flour, Ultrafoam, UltraWrap, EndoAvitene)
    - Instat
    - Helitene
    - Helistat
    - Gelatin (porcine)
    - Gelfoam
    - Gelfilm
    - Surgifoam
    - Ostene
    - Polysaccharide sphere: Arista
    - Nonabsorbable
    - Bone wax
    - Hemostatic dressings
    - Chitin (medical rapid deployment hemostat)
    - Chitosan (HemCon)
    - Mineral Zeolite (QuikClot/combat gauze)
    - Stasilon
    - Dry fibrin sealant dressing
    - Pro or Urgent QR Powder

  - Active
    - Thrombin-JMI (bovine)
    - Evithrom (human)
    - Recothrom (recombinant)

  - Combination agents
    - Flowables
      - FloSeal (bovine gelatin + thrombin)
      - SurgiFlo (porcine gelatin + thrombin)
    - Fibrin sealants
      - Tisseel
      - Evicel (previously Crosseal)
      - Vitagel surgical hemostat/Costasis
      - Vistaseal

  - Synthetic agents
    - Cyanoacrylates (Dermabond)
    - Polyethylene glycol polymers (Coseal)
    - Glutaraldehyde cross-linked albumin (Bioglue)

ferrous sulfate, silver nitrate has local antibacterial benefits. Aluminum chloride is another common topical hemostat. When exposed to water, it causes hydrolysis of hydrogen chloride leading to vasoconstriction and activation of the extrinsic coagulation cascade.[9]

Mechanical and Absorbable

Mechanical hemostatic agents provide a latticework for promotion of platelet aggregation and subsequent fibrin plug formation to stop bleeding expediently. Their function, unlike some other agents, depends on an intact coagulation cascade because they are simply structures to expedite intrinsic coagulation mechanisms. Mechanical agents are further subdivided into absorbable and nonabsorbable mechanical hemostats. Absorbable hemostats have the principal benefit of being able to be left in situ with the product being resorbed over time. Nonabsorbable hemostats, however, are not resorbed by the body and can often be a nidus for infection and/or promote inappropriate inflammation hindering appropriate wound healing.

Hemostatic cellulose products have been used since the 1940s.[3] WoundClot (Core Scientific Creations, Westlake Village, CA) is a commercially available nonoxidized regenerated cellulose product that resorbs water and concentrates coagulation factors to promote clot formation. Unlike its oxidized regenerated counterparts, WoundClot does not rely on acidity to aid in clot formation.[10]

Most commercially available cellulose-based products rely on oxidized cellulose. This includes Surgicel, Nu-Knit, Oxycel, Surgicel Fibrillar, Surgicel SNOW, and Surgicel Powder (Ethicon, Somerville, NJ). The mechanism of action of these products is multifactorial. First, the oxidized cellulose promotes platelet aggregation and adherence to the wound bed. Second, because of its low pH, the product has caustic properties, resulting in coagulative necrosis and clot formation.[3] In addition to promoting hemostasis, the acidity of oxidized cellulose is bacteriostatic against organisms that commonly cause wound infections including methicillin-resistant*Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and *Staphylococcus epidermidis*.[11] It is worth noting that acidity of oxidized cellulose products can inactivate biologically active hemostatic agents that have been concurrently applied to the area, negatively affecting their efficacy.[12] These products are used ubiquitously in a variety of surgical fields including neurologic, cardiac, and general surgery.[13]

Oxidized regenerated cellulose-based products are some of the most widely used topical hemostats in today's operating rooms. They are readily available, easy to store, and intuitive to apply. Multiple studies have demonstrated that these products reduce blood loss and time to hemostasis compared with other products and placebo.[14,15] The chief adverse effects of these products include local acidity leading to granuloma formation and expansion with blood absorption with subsequent compression of surrounding structures, most importantly, nerves. These adverse effects are mitigated by removing excess product after use; however, this can frequently lead to rebleeding because the adherent clot is also removed. Irrigation with sterile saline can help remove excess product while leaving the newly formed clot in situ. Care should be taken when interpreting postoperative imaging because oxidized regenerated cellulose can be mistaken for abscess formation or malignancy on computed tomography scans.[16,17]

Microfibrillar collagen (MFC) is like cellulose, which is an effective topical hemostat that has been formatted into different forms including powder, sheet, and sponge. Commercially available forms of MFC include Avitene (BD, Franklin Lakes, NJ), Helitene (Integra Life Sciences Corporation, Plainsboro, NJ), Helistat (Integra Life Sciences Corporation), and INSTAT (Ethicon).[1,3,18] MFC is used in similar applications as cellulose products, and it functions by promoting platelet aggregation and degranulation resulting in clot formation via the intrinsic pathway.[3] Importantly, because of its reliance on platelet aggregation to promote coagulation, MFC is of limited utility in patients with thrombocytopenia or platelet dysfunction. Additionally, MFC negatively affects bond strength of methylmethacrylate and should not be used on bone if a prosthesis will be inserted.[3,18] In contrast to some other hemostatic agents, MFC does not have bacteriostatic or bactericidal properties. MFC is most used for application over a broad surface area to decrease bleeding.

Gelatin-based products are also widely used for hemostasis and are often combined with other topical hemostats to enhance overall hemostasis. Gelfoam (Pfizer, New York, NY), the first gelatin-based product, was developed in 1945 and remains in use to this day.[3] Surgifoam (Ethicon) and Gelfilm (Pfizer) were later developed and all products use gelatin from porcine skin.[3] They promote coagulation by contact activation and platelet aggregation.[3] On contact with blood, the gelatin sheet is quickly absorbed leaving behind a highly concentrated area of coagulants. Additionally, the meshwork serves as a framework for promoting further clot formation and granulation tissue formation.[9] For this reason, porcine gelatin products have the benefit of promoting wound healing and granulation tissue formation. Because of its neutral pH, porcine gelatin products are easily combined with other hemostatic agents for a synergistic effect. Common combinations include porcine gelatin with thrombin and porcine gelatin wrapped in oxidized regenerated cellulose.[3] Gelatin-based products are used in a wide variety of applications from vascular surgery to trauma.

Ostene (Baxter Healthcare, Deerfield, IL) is a new and specialized topical hemostatic agent. It was developed as an alternative to bone wax to aid in hemostasis from bony surfaces. In contrast to bone wax, Ostene is readily absorbed and does not interfere with bone healing or promote an inflammatory response. Ostene is available as a semisolid stick, which becomes more pliable as it is warmed. Like bone wax, it is applied directly to the bony surface and functions as a mechanical obstruction to ongoing bleeding. Ostene is often used in cardiothoracic and orthopedic surgery to aid in hemostasis from bony surfaces without promoting inflammation or interfering with bone healing.[19]

Microporous polysaccharide hemospheres (MPH) are a new development in topical hemostasis. These particles consist of cross-linked polysaccharides, which are highly hydrophilic. When these particles touch a bleeding surface their hydrophilic nature promotes concentration of erythrocytes, platelets, and various proteins to form a gelatinous matrix and plug formation via the intrinsic pathway.[3] Additionally, this matrix serves as the framework for early fibrin clot formation. These products are distributed as a powder, which is applied to the surgical site to help control venous, capillary, and arteriolar bleeding in general, cardiac, and orthopedic procedures.[20,21] MPH have not been evaluated for safety in neurologic or ophthalmic procedures.[20,21] These products are favored in certain situations, because they provide good hemostasis even in the setting of underlying coagulopathy. Additionally, MPH are absorbed within 48 to 72 hours of application, and do not carry the risk of immunogenicity or allergic reaction that some other hemostatic agents do.[3,20,21] MPH are commercially available in the United States as Arista (BD) and Perclot (Cryolife Inc, Kennesaw, GA), both of which are distributed in a powder form with various applicators for open and endoscopic use.

Mechanical and Nonabsorbable

Bone wax

Bone wax, a combination of beeswax, salicylic acid, and almond oil was first developed in 1886, and it remains in use today, albeit with a slightly different formula.[3]

Bone wax as used today contains beeswax, palmitate, paraffin, and a softening agent. Bone wax, as its name suggests, is used to achieve hemostasis from bony surfaces. When applied, the compound obstructs and tamponades the flow of blood to achieve hemostasis. Bone wax is instantaneous in its effect because it does not rely on the complex physiology of fibrin clot formation or coagulation. The principal drawback of bone wax is that it is nonabsorbable and identified as a foreign body by the innate immune system.[3,22,23] Consequently, bone wax can possibly serve as a nidus for infection and impairs appropriate bone healing.[22,23] Bone wax is broken down by phagocytes over an extended period of time.[3,23]

Hemostatic dressings

This term has been adopted to describe dressings, usually gauze, which have been combined with some other agent with hemostatic properties. These are often used in first aid applications and must be removed before final wound closure.[3]

Chitin is a polysaccharide naturally found in the exoskeletons of arthropods. When applied to the wound, chitin promotes vasoconstriction and the release of PDGF-AB and transforming growth factor-β1.[3,24] Additionally, the positively charged chitin concentrates negatively charged erythrocytes, platelets, and coagulation factors.[24] Importantly, this process remains intact even in situations where the patient is heparinized or defibrinated. Chitin-based products are not readily available; however, Chitin's cousin, chitosan is commonly used in hemostatic dressings.

Chitosan is the deacylated form of chitin and shares the same mechanism for hemostasis.[3,25] Its dressings are commonly used on today's battlefields because of their durability, analgesic, and antimicrobial properties.[24,25] In vivo animal models have demonstrated significantly shorter time to hemostasis when using chitosan dressings.[26] Likewise, chitosan products continue to function as effective hemostatic agents even in heparinized or otherwise coagulopathic patients.[3,27]

QuikClot (Z-Medica LLC, Wallingford, CT), currently known as combat gauze, is a nonwoven mineral zeolite-coated dressing (specifically, kaolin).[28,29] The initial variant of QuikClot was in powder form; this was replaced by the combat gauze version.[30,31] Kaolin, an aluminum silicate, is a potent coagulation initiator that acts through factor XII surface activation to trigger the intrinsic clotting cascade.[28,29] The substance is inert and does not interact with otherwise intact skin surfaces, thereby eradicating the probability of skin reactions or allergies when used. Given the multiple-ply rayon/polyester construction, it is absorbent. In an in vitro study, QuikClot was found to be effective at decreasing the time to clot formation and increasing clot strength not only in nonanticoagulated individuals but also in patients taking antiplatelet therapy, traditional vitamin K antagonist (warfarin), factor Xa inhibitors, direct thrombin inhibitors, and heparin (including low-molecular-weight heparin).[28] QuikClot has been shown to be the most effective hemostatic agent with success rates of 80% to 90% on first application, and 100% after second application in swine models with exsanguinating femoral bleeding and the lethal triad of hypothermia, coagulopathy, and acidosis.[30,32] As such, it has become the first-line treatment of life-threatening hemorrhage caused by combat wounds, hence its name.[30] One disadvantage is that manual pressure must be applied in conjunction with QuikClot gauze for it to be effective.

Stasilon, manufactured and distributed by Entegrion (Durham, NC), is a woven textile composed of allergen-free fibers of continuous filament texturized E-glass yarn as the warp, and bamboo rayon fibers as the weft.[31,33] The fiberglass activates the coagulation cascade while the bamboo rayon fibers absorb the surrounding fluid, thus allowing for aggregation and binding of red blood cells.[31,34] The materials were selected for their thrombogenicity as measured by acceleration of platelet-dependent turnover within the coagulation cascade and subsequent generation of thrombin.[33,34] The nonadherent nature of this product makes it easy to remove from tissue without disrupting clot formation.[33] However, Stasilon has demonstrated poor performance in animal models and further investigation is needed to better delineate the role of this agent in clinical practice.[30]

Dry fibrin sealant dressing (DFSD) is a composite of 15 mg/cm^2 of human fibrinogen, 37.5 U/m^2 of purified human thrombin, and 72 μg/cm^2 $CaCl_2$ freeze-dried onto an absorbable polyglactin mesh backing Vicryl.[31,35,36] It is a three-layer sandwich formation consisting of two fibrinogen layers and one thrombin layer forming the continuous middle layer.[35–37] In a swine model simulating hypothermic coagulopathy, there was an 83% survival rate at 1 hour compared with 0% when plain gauze or gauze containing IgG were used.[36] This was attributed to the rapid achievement of hemostasis despite severe dilutional and hypothermic coagulopathy.[37] The very high concentrations of fibrinogen and thrombin supplied by DFSD seemed to offset the effects of dilutional and hypothermic coagulopathy because the conversion of fibrinogen to fibrin clot is an enzymatic reaction involving thrombin in the final pathway of coagulation.[36–38] With ballistic injuries, DFSD was demonstrated to reduce blood loss and maintenance of blood pressure when compared with gauze wound dressings.[38] Unfortunately, DFSD is expensive.[31] Another product that functions in a similar way is TachoSil (Baxter Healthcare). TachoSil is an equine collagen patch impregnated with pooled human plasma containing fibrinogen and thrombin.[39,40]

Pro or urgent QR Powder

Urgent QR Powder (Biolife, Sarasota, FL) consists of hydrophilic polymers with potassium salts. They function by concentrating the larger components of blood and binding blood to form an overlying, artificial eschar to stop bleeding. Urgent QR Powder is not able to be metabolized by the body and is consequently only able to be applied to wounds that will heal by second intention. One significant benefit of this product is that it is significantly lower cost than many other hemostatic agents.[41]

Active

Thrombin

Thrombin-based hemostatic agents are active in that they are biologically involved in the coagulation cascade.[1,2,31,42] Thrombin, also known as activated factor II, is a procoagulant and anticoagulant.[42,43] In its procoagulant state, it activates platelets, and cleaves fibrinogen to fibrin.[31,42,43] It also upregulates its own production by activating factors V, VIII, and XI.[1,43] Topical thrombin occurs in the forms of “bovine” thrombin (Thrombin-JMI, GenTrac, Inc, Middleton, WI), “human” thrombin (Evithrom, Johnson & Johnson, Brunswick, NJ), and “recombinant” thrombin (Recothrom, ZymoGenetics, Seattle, WA).[1,2,31] The differences in these topical forms are their reactivity, and associated risks. The bovine thrombin has a range of mild to severe coagulopathies associated with it related to antibodies against bovine thrombin and/or factor V that cross-reacts with human coagulation factors.[1] This risk of antibody reactivity increases with re-exposure to bovine thrombin.[1,2] It occurs as a powder in vial form that is used dry or reconstituted in sterile saline to be used within 3 hours of reconstitution.[42] Evithrom, which is a Food and Drug Administration–approved pooled human plasma thrombin, carries a risk of viral transmission even though the final product undergoes viral inactivation treatment to ensure the safety of the product.[2,42] Evithrom is stored frozen and needs to be thawed before use. At this point, it can then be used immediately, kept at room temperature for up to 24 hours, or refrigerated for up to 30 days.[2] It is not recommended for use in combination with human blood salvage or cardiopulmonary bypass systems.[1] Recothrom uses recombinant DNA; hence, it is called recombinant topical thrombin. It does not have bovine or human plasma but was instead produced by using a Chinese hamster ovary host cell protein.[2,42] It exists in a lyophilized powder in vial form that can be stored at room temperature and needs to be used within 24 hours after it is reconstituted in sterile saline.[1]

Combination Agents

Flowables

Flowable hemostatic agents use a combination of passive and active hemostatic agents as a single product application. The two commercially available products are FloSeal (Baxter Healthcare) and SurgiFlo (Johnson & Johnson). These products combine two hemostatic agents for a synergistic stemming of blood flow and leading to the conversion of fibrinogen in blood to fibrin at the bleeding site.[1] The active ingredient in both formulations is pooled human thrombin, whereas the passive agent is the gelatin. In FloSeal bovine gelatin is used, and in SurgiFlo porcine gelatin fills this role.[1,2] When combined and applied with a syringe applicator to a tissue surface, it starts to polymerize into a thick consistency and adheres to surfaces with high concentrations of fibrinogen, which includes blood.[1,44] They both are used in all surgical specialties except ophthalmic surgery.[1] The limitations to use include allergies or sensitivities to the composite materials, blood salvage and cardiopulmonary bypass systems, intravascular use, and use in absence of active blood flow in vessels because of potential for intravascular clotting.[1] In a multicenter trial of 93 cardiac surgery patients, FloSeal was found to be superior to Gelfoam plus thrombin at stopping bleeding within 10 minutes (94% compared with 60%).[1] In a multicenter, prospective, single-arm study, SurgiFlo was effective at hemostasis within 10 minutes of application during endoscopic sinus surgery.[1]

Fibrin sealants

Fibrin sealants form synthetic fibrin clot that acts as an adhesive and covering creating a fluid-impervious barrier that stops most liquids.[31,45] They are typically applied by means of a double syringe system.[45] They have high concentrations of fibrinogen, thrombin, calcium, and factor XIII, which in combination simulate the final stages of the coagulation cascade.[1,31] Tisseel made by Baxter, and Evicel (previously Crosseal) made by Ethicon are based on this mechanism.[1,31] Their drawback, however, is that the components need to be kept frozen, and the thawing and reconstitution process is time consuming, and requires warming with prolonged agitation. They also cannot be used in a significant venous and arterial bleed because the clot formed can be dislodged but do well in low-pressure bleeding and surface oozing.[46] In fact, the effort to address this brought about DFSD. Other products, such as Vitagel (Stryker, Kalamazoo, MI) and Costasis (Orthovita, Malvern, PA), are a combination of microfibrillar bovine collagen and bovine thrombin mixed with the patient's own plasma (obtained during surgery, centrifuged leaving only fibrin and platelets).[1,46,47] Unfortunately, they are expensive.[1,46]

Synthetic Agents/Adhesives

Synthetic agents and adhesives are agents that work by chemical reaction to form a strong seal and limit ongoing bleeding. These hemostatic adhesives exist as liquids that polymerize to form a solid film adhering to tissue surface.[45] Cyanoacrylate monomers polymerize through an exothermic reaction in the presence of local hydroxyl groups.[1,45,48] They form a barrier that is impervious to fluids and provides antimicrobial benefits.[45,48] Dermabond (Johnson & Johnson) is one such adhesive.[1,48]

Table 1
Mechanism of action, advantages/recommended use, and disadvantages/caution against use for topical hemostatic agents

Hemostatic Agent	Products	Mechanism of Action	Advantages/ Recommended Use	Disadvantages/Caution Against Use
Bone wax	Bone wax	Tamponade through occlusion of bleeding channels in bone	Can effectively control bleeding from bone surfaces (eg sternotomy)	Can impede bacterial clearance and act as a nidus for infection, therefore avoid use in a contaminated field May embolize Should not be used where bone fusion is critical, because it is not absorbed by the body
Ostene	Osiene (alkylene oxide copolymers)	Occlude bleeding channels in bone	Recommended for bleeding control on bone surfaces (eg sternotomy) Does not impede bone growth and is absorbed over time	Do not use at sites with active or latent infections Caution when using in areas which lend structural support to bone
Gelatin foams	Gelfoam, Gelfilm, Surgifoam	Provides physical matrix for clotting initiation	Effectively controls small-vessel bleeding May be used to control bleeding from bone Recommended as hemostatic plug wrapped in oxidized cellulose Absorbed by the body within 4–6 wk Nonantigenic Neutral pH allows use with biologic agents	Should not be used in closed spaces because significant swelling may compress nerves Use around brisk arterial bleeding can dislodge sponge May embolize if in an intravascular compartment

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Table 1
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Hemostatic Agent	Products	Mechanism of Action	Advantages/ Recommended Use	Disadvantages/Caution Against Use
Oxidized cellulose	Surgicel	Provides physical matrix for clotting initiation, low pH contributes to coagulative necrosis	Low pH has antimicrobial effect Very good handling characteristics (cotton-like consistency, best when applied dry) Does not stick to instruments Typically dissolves in 2–6 wk	Must not be used with other biologic hemostatic agents (eg thrombin) because of low pH Low pH may increase inflammation of surrounding tissue Caution when using in close proximity of spinal cord because swelling and Surgicel fibers could pass through intervertebral foramen causing cord compression
Microfibrillar collagen	Avitene flour, Avitene Ultrafoam, Avitene Ultra wrap, Helistal, Helitene, Instat, Endoavitene	Platelet adherence and activation	No significant swelling Absorbed in less than 8 wk Can control wide areas of parenchymal bleeding Effective despite profound heparinization because of its mechanism of action	Less effective in patients with thrombocytopenia Sticks to operator's gloves May bind to neural structures Caution with blood scavenging systems, because microfibrillar collagen can pass through fillers
Thrombin	Thrombin-JM 1 (bovine) Evithrom (human plasma-derived), rh	Converts fibrinogen to fibrin to form clots, activation of clotting factors	Effectively controls minor bleeding from capillaries and small venules when pressure or ligature is	We discourage use of bovine thrombin because of immunologic response, and possible

	ThrombinRecothrom (recombinant human)		insufficient Easy application Fast acting	increase in coagulopathy and thrombosis Do not use in individuals known to react to human blood products
Thrombin with gelatin	Floseal	Gelatin granules cross-linked into matrix and swell for tamponade effect; thrombin hemostatic effect	Better control of moderate arterial bleeding than fibrin sealants because of gelatin granule tamponade effect We recommend for use in cardiac surgery, and open and laparoscopic nephrectomies	Needs contact with blood as source of fibrinogen Can swell up to 20% in 10 min after application
Fibrin dressings	Dry fibrin sealant dressings	Freeze-dried (lyophilized) fibrinogen and thrombin on gauze dressing	Initial success with US forces with Iraq and Afghanistan under FDA investigational drag protocol Effectively stops bleeding from large surface abrasions Longer shelf-life than fibrin sealants and does not need mixing at site of application	Not FDA approved Needs strong packaging because of brittleness
Chitin dressings	Rapid Deployment Hemostat	Vasoconstriction, mechanical sealing, mobilization of RBCs, clotting factors, platelets	Intended for emergency field use by first responders Effective for minor wounds in animal model	Varied results for severe wounds, such as splenic lacerations in animal model
Chitosan dressings	HemCon	Deacylated form of chitin, similar mechanism	Intended for emergency field use by first responders	Success rate highly dependent on training of first responders (failure

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Table 1
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Hemostatic Agent	Products	Mechanism of Action	Advantages/ Recommended Use	Disadvantages/Caution Against Use
			Initial success with US forces with Iraq and Afghanistan Has antimicrobial properties	of bandage to adhere undermines effectiveness) Animal testing yields inconsistent results Contains chitosan from shellfish, so do not use in patients with shellfish allergies
Mineral zeolite dressings	QuikClot	Molecular sieves absorb water at site of wound to increase concentration of clotting factors, platelets, RBCs	Intended for emergency field use by first responders Powdered form effective for low-pressure bleeding Zeolite embedded in mesh for high-pressure bleeding Prehydration in newest products avoids exothermic bums of earlier versions	Caution with high-pressure bleeds because they can force powdered form out of wound Intracorporeal use generally effective, but foreign body reactions have been reported to contribute to scar tissue formation and associated complications
Fibrin sealants	Tisseel, Evicel, Crosseal	Thrombin and fibrinogen mixed at site of application; thrombin cleaves fibrinogen to fibrin that forms clots	Effective in heparinized patients; can be used for skin grafting, dural sealing, bone repair, splenic injuries, closure of colostomies, in reoperative cardiac	Before application, wounds must be cleaned of antiseptics containing alcohol, iodine, or heavy metal ions that can denature applied thrombin and fibrinogen

			surgery Recommended for controlling bleeding in urologic surgeries (see text for complete list) Tisseel and Eviceil good for venous oozing from raw surfaces	
Platelet sealants	Vitagel	Microfibrillar collagen and thrombin combined with patient's plasma-derived fibrinogen and platelets	Platelets from patients strengthen clot while proteins in gel facilitate tissue regeneration May be used in orthopedic, hepatic, reconstructive, and general surgical procedures	Need for centrifugation and preuse processing Caution when used in bypass or blood scavenging systems Do not use with methylmethacrylate or other acrylic adhesives because it may reduce their strength Caution when used near renal pelvis or ureters because foci can lead to calculus formation
Polyethylene glycol hydrogels	Coseal	Two synthetic polyethylene glycol polymers that mix and cross-link in wound site	Can prevent pericardial Good mechanical sealant for vascular reconstructions Is not exothermic, does not cause inflammation, and does not potentiate bacterial infection	Swelling up to 4 times initial volume after 1 d, and can continue swelling Does not perform well in partial nephrectomies
Cyanoacrylates	Dermabond	Liquid monomers form polymers in the presence	Use as a replacement for sutures (≤5–0) for wounds on the face,	Difficult to use in jagged lacerations Must not use for bites,

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Table 1
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Hemostatic Agent	Products	Mechanism of Action	Advantages/ Recommended Use	Disadvantages/Caution Against Use
		of water, and glue surfaces together	extremities, and torso Full binding strength within 2.5 min, attains strength of healed tissue after 7 d Forms waterproof barrier	puncture, or crush wounds Not recommended on mucosal surfaces, axilla, or perineum
Glutaraldehyde cross-linked albumin	Bioglue	Glutaraldehyde cross-links bovine albumin to cell proteins at wound site to form tough scaffold	Achieves 65% binding power in 20 s, full strength in 2 min regardless of temperature or whether in air or water Use for sealing holes around sutures or staple lines, good for arterial bleeding Most commonly used in complex cardiovascular procedures involving aortic aneurysms, valve replacements, and aortic dissections, and peripheral vascular procedures, such as carotid endarterectomy, and arteriovenous access	Do not apply circumferentially around developing structures because it can restrict growth Caution in proximity to nerves, because it may cause dysfunction Unreacted glutaraldehyde may have mutagenic effects Do not apply to valve leaflets or intracardiac structures May cause hypersensitivity reactions

A comprehensive review of topical hemostatic agents: efficacy and recommendations for use.

Abbreviations: FDA, Food and Drug Administration; RBC, red blood cell.

Achneck, Hardean E.; Sileshi, Bantayehu; Jamiolkowski, Ryan M.; Albala, David M.; Shapiro, Mark L.; Lawson, Jeffrey H. Annals of Surgery251(2):217-228, February 2010. https://doi.org/10.1097/SLA.0b013e3181c3bcca

Polyethylene glycol polymers (Coseal) made by Baxter is a composite of two biocompatible polyethylene glycols combined with dilute hydrogen chloride solution, rapidly forming a hydrogel that allows for adherence of synthetic graft materials to tissue.[1,49,50] It is used almost exclusively during vascular procedures to reinforce suture lines of graft anastomosis.[50] According to Baxter, it is said to fortify suture lines such that bleeding is decreased or prevented even with significant increases in blood pressure.[50] It remains intact for about 7 days as long as no antibiotic ointment or petroleum jelly is applied and is slowly resorbed by the body over a period of 30 days.[1,49,50] One potential disadvantage is the capacity for Coseal to swell more than four times its initial volume, so should be avoided around structures intolerant to compression.[1]

Another similar product is glutaraldehyde cross-link albumin (Bioglue, Cryolife Inc).[1] This is a semisynthetic form that uses albumin (a biologic agent) in its formulation to create a strong film that is effective at hemostasis in large vascular anastomosis and other thoracic and neurosurgical procedures.[1,45] Bioglue has excellent tensile and shear strength, polymerizes quickly, and is rapidly available.[48] These adhesives, however, do not adhere well to wet surfaces.[51]They are also inflammatory, and the inflammation persists until they are completely degraded.[48,51]

CLINICS CARE POINTS

- Caustic hemostats work best when applied topically for small amounts of bleeding during minor procedures. Avoid contact with surrounding healthy tissue because these products are damaging to surrounding tissues.
- Absorbable hemostats can be left in situ and the wound closed with the agents in place; the amount of inflammatory response and granuloma formation depends on the type of absorbable hemostat used.
- Oxidized regenerated cellulose-based hemostats depend on the presence of appropriate coagulation factors to develop clot and achieve hemostasis. Avoid these products in patients with coagulopathies.
- MFCs rely on platelet aggregation and the intrinsic pathway to achieve hemostasis and should be avoided in patients with thrombocytopenia, platelet dysfunction, or factor deficiencies within the intrinsic pathway.
- Absorbable hemostats often expand as they absorb blood and can compress surrounding structures including vessels and nerves. Use caution to avoid compression of important structures and remove excess product before wound closure.
- Gelatin-based products work well on their own but have a synergistic effect when combined with thrombin products.
- For bleeding from bony surfaces consider bone wax or Ostene, but keep in mind that bone wax can inhibit appropriate wound healing. Use only the minimum required amount to achieve hemostasis.
- MPH products help provide hemostasis over broad surface areas even in the setting of underlying coagulopathy. Their powder form makes them easy to apply over a large area even endoscopically.
- Hemostatic dressings, such as chitin, chitosan, combat gauze, QuikClot, Stasilon, and DFSD, are seldom used during operative intervention. However, these products effectively stop bleeding in first aid and combat situations.
- Thrombin products are potent hemostatic agents but require specific storage practices and time-intensive preparation before use. Thrombin is often combined with other hemostatic agents for a synergistic effect.

- Flowable agents combine gelatin and thrombin in formulations that is easily sprayed or spread over the area of bleeding to provide prompt hemostasis. These agents work rapidly and are easily applied endoscopically or during open procedures.
- Fibrin sealants develop artificial clot overlying the area of bleeding and are not dependent on the patient's physiology to aid in hemostasis. However, they are expensive compared with other products.
- See Table 1 for a full summary of all listed agents.

FUTURE DIRECTIONS

Since their introduction in the 1880s, topical hemostatic agents have continued to develop as knowledge of coagulation physiology and pathophysiology has evolved. The agents commonly used in today's operating rooms, first aid scenes, and battlefields are increasingly effective. The addition of knowledge of hemostatic agents to a surgeon's armamentarium helps to push the boundaries of life-saving care. As understanding of the complex physiology of coagulation and hemorrhage improves, so will the potential for developing hemostatic agents that are safe, affordable, and readily available. Already, scientists, engineers, and surgeons are working to develop better agents to stop hemorrhage (some of which were not mentioned in this article). In today's operating rooms, it is essential to have a firm understanding of how and when to use various hemostatic agents to provide the highest quality care.

DISCLOSURE

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