FORMULARY REVIEW

Absorbable hemostatic agents

MICHAEL GABAY

Purpose. The pharmacology, clinical efficacy, adverse effects and toxicities, drug interactions, dosage and administration, and safety issues related to the use of absorbable hemostatic agents are reviewed.

Summary. Absorbable hemostatic agents exert their pharmacologic effects at various points within the coagulation cascade. These agents are indicated for use during surgical procedures as adjunctive therapy when bleeding is not controlled by conventional methods. Early clinical data on absorbable hemostatic agents revealed a beneficial effect with regard to controlling capillary bleeding, achieving hemostasis during vascular surgery, and controlling bleeding from fistula-puncture sites. Few randomized controlled clinical trials have directly compared available agents, but case reports describing the efficacy of absorbable hemostatic agents in specific situations, especially unlabeled uses of thrombin, abound. Existing trials have compared the efficacy of established agents with newer agents, including fibrin sealants, with varying results. A variety of rarely occurring adverse effects have been reported with the administration of absorbable hemostatic agents; some of these rare effects, such as paralysis, are quite severe. No standardized dosing regimens are available for these agents, although surgeons may have a preference for a particular regimen based on their own clinical experience. No drug interactions involving absorbable hemostatic agents have been published; however, the use of these agents with other medications that affect hemostasis may disrupt clot formation.

Conclusion. Absorbable hemostatic agents are useful as adjunctive therapy during surgical procedures when conventional methods do not control bleeding. Although rare adverse effects have occurred with these agents, their careful administration will prevent serious adverse outcomes.

Index terms: Dosage; Drug administration; Drug interactions; Fibrin; Hemostatics; Surgery; Thrombin; Toxicity

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The process of hemostasis refers to the ability of the human body to maintain blood flow within the vasculature and to prompt a thrombotic response when blood escapes the vascular system.[1,2] Maintaining hemostasis involves a complex interaction of the vessel wall, platelets, and the coagulation and fibrinolytic systems.[2] After an injury, the vessel wall reacts by constricting, aiding in the formation of a platelet plug, and regulating the coagulation and fibrinolytic processes. Platelets respond by adhesion, secretion, aggregation, and promotion of procoagulant effects. Finally, the coagulation and fibrinolytic systems promote the formation and dissolution, respectively, of a fibrin clot, with the subsequent restoration of normal blood flow.

During surgical procedures, various therapeutic agents are generally administered that have a direct effect on hemostasis. One device, an absorbable hemostatic agent, is often used as adjunctive therapy when bleeding is not controlled by ligature or the application of pressure. The absorbable hemostatic agents Gelfoam (Pfizer) and Oxycel (Becton Dickinson) have been commercially available since the 1940s. Since the introduction of these early devices, many more absorbable hemostatic agents have been approved for use by the Food and Drug Administration (FDA).

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This article reviews the pharmacology, clinical efficacy, adverse effects and toxicities, drug interactions, dosage and administration, and safety issues related to the use of absorbable hemostatic agents. Fibrin sealants, such as Tisseal (Baxter) and Crosseal (Johnson & Johnson), are not included within this classification scheme[3]; however, these agents may be mentioned when a published clinical trial compares an absorbable hemostatic agent with a fibrin sealant. In 1999, the University HealthSystem Consortium published a technology assessment of the fibrin sealants, which provides more in-depth information on these products. Although thrombin (Gen Trac) is not formally classified as an absorbable hemostatic agent by FDA, this agent was included in this review because of its standard use as a hemostatic aid and the breadth of biomedical literature involving thrombin in the hemostatic arena.

Product description

Originally, absorbable hemostatic agents were regulated as drugs and required a new drug application for marketing approval. In 1976, with the Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, a number of products regulated as drugs, including absorbable hemostatic agents, were transferred to device regulations because these regulations were more appropriate. The absorbable hemostatic agents approved via the regulatory process to date contain porcine or bovine gelatin, bovine collagen, or regenerated oxidized cellulose. The two most recently approved absorbable hemostatic agents, FloSeal (Baxter) and CoStasis (Cohesion Technologies), contain bovine thrombin and are therefore combination products.[3] A list of the absorbable hemostatic agents available is provided in Table 1.

Pharmacology

Absorbable hemostatic agents exert their pharmacologic effects at various points within the coagulation cascade. It has been theorized that the cellulose-based product, Surgicel (Johnson & Johnson), and gelatin-based products, such as Gelfoam and Surgifoam (Johnson & Johnson), initiate clotting through contact activation; however, the exact mechanism is not completely understood.[4-7] Collagen-based products, such as Avitene (Davol), Instat (Johnson & Johnson), Helistat (Integra LifeSciences), and Helitene (Integra LifeSciences), provide hemostasis through a dual mechanism: contact activation and the promotion of platelet aggregation, which occur as a direct effect of contact between blood and the collagen in the products.[8] Once platelet aggregation is under way, degranulation and release of coagulation factors occur. Coagulation factors, in conjunction with plasma factors, result in the formation of fibrin and, subsequently, a clot. FloSeal contains both a gelatin matrix and thrombin. These two components work synergistically to produce a stable clot at the bleeding site by restricting blood flow, providing a matrix around which a clot can form, and delivering thrombin to the surface of the tissue. Thrombin activates various coagulation factors and platelets within the coagulation cascade and converts fibrinogen into fibrin monomers[4] that combine to form polymers. The result is a fibrin clot. CoStasis, a variant on fibrin sealants, is used in conjunction with a patient's plasma.[4,9] The thrombin component of CoStasis converts plasma fibrinogen to fibrin. Subsequently, fibrin comes into contact with the collagen in CoStasis, thereby

Table 1.
Absorbable Hemostatic Agents and Their Approval Dates[a]

Topical Hemostatic	Composition	Approval Date
Surgicel (Johnson & Johnson)	Regenerated oxidized cellulose	October 14, 1960
Gelfoam (Pfizer)	Porcine gelatin molded into a sponge	Available 1945; approved July 8, 1983
Surgifoam (Johnson & Johnson)	Porcine gelatin sponge	September 30, 1999
Avitene (Davol)	Bovine collagen	August 26, 1976 (as a drug); October 24, 1980 (as a device)
Instat (Johnson & Johnson)	Bovine collagen	October 10, 1985
Helistat (Integra LifeSciences)	Bovine collagen	November 8, 1985
Helitene (Integra LifeSciences)	Bovine collagen	November 8, 1985
CoStasis (Cohesion Technologies)	Flowable bovine collagen and bovine platelets	June 13, 2000
FloSeal (Baxter)	Flowable bovine gelatin matrix and bovine thrombin	December 8, 1999

[a]Adapted from reference 3.

resulting in a collagen–fibrin gel matrix that potentiates the formation of a clot.

Indications

Absorbable hemostatic agents are indicated for use during surgical procedures as adjunctive therapy when bleeding is not controlled by conventional methods, such as ligature or application of pressure.[5-14] Even though the product labeling explicitly states that thrombin is for absorbable use only, it has been administered via a variety of routes for unlabeled indications, including oral administration for the control of upper gastrointestinal bleeding[15] and direct injection for the treatment of pseudoaneurysms.[16-18] Table 2 summarizes the labeled indications for the available absorbable hemostatic agents.

Clinical efficacy

Clinical trials and case reports for this review were identified by performing a MEDLINE search and evaluating bibliographies of pertinent articles. Although case reports are the weakest form of biomedical literature, reports were included if they were the only source describing a particular use.

Early clinical data on absorbable hemostatic agents, particularly older agents (e.g., microcrystalline collagen [Avitene] and thrombin), revealed a beneficial effect with regard to controlling capillary bleeding,[19] achieving hemostasis during vascular surgery,[20] and controlling bleeding from fistula-puncture sites in patients receiving hemodialysis.[21,22] Few randomized, controlled clinical trials have directly compared available agents, but case reports describing the efficacy of absorbable hemostatic agents in specific situations, especially unlabeled uses of thrombin, abound.[17,18,23,24] Existing trials have compared the efficacy of established agents, such as Gelfoam, with newer agents, including FloSeal and fibrin sealants (Crosseal or Tisseal), with varying results. A summary of clinical trials and case reports of absorbable hemostatic agents is presented in Table 3.

Adverse effects and toxicities

Various adverse effects have been associated with absorbable hemostatic agents (Table 4). Many of these reported effects are observed when absorbable hemostatic agents are used during specific surgical procedures such as laminectomy, craniotomy, lobectomy, and nasal surgery.

Adverse effects involving thrombin have been reported in the biomedical literature. These reports generally entail either allergic reactions to thrombin or the development of inhibitory antibodies that interfere with the hemostatic process.[13] Because thrombin preparations are of bovine origin, patients may develop antibodies to bovine coagulation factors that may cross-react with endogenous human clotting proteins.[38] Although thrombin is widely used in health care institutions, some case reports describing adverse events (i.e., bleeding complications, coagulopathies, rashes) associated with thrombin administration have been reported.[39-44]

Drug interactions

There are no published drug interactions involving absorbable hemostatic agents; however, the use of these agents with other medications

Table 2.
Labeled Indications for Absorbable Hemostatic Agents[5-14]

Hemostatic Agent	Labeled Indication(s)
Surgicel	For use in surgical procedures when conventional methods of hemostasis, such as pressure and ligature, are ineffective or impractical; for endoscopic procedures, may be used by cutting to size.
Gelfoam	For use in surgical procedures, including those that may result in cancellous bone bleeding, when conventional methods of hemostasis are ineffective or impractical; may be used with or without thrombin.
Surgifoam	For use in surgical procedures, except urologic and ophthalmic procedures, when conventional methods of hemostasis are ineffective or impractical.
Avitene	For use in surgical procedures when conventional methods of hemostasis are ineffective or impractical.
Instat	For use in surgical procedures, except ophthalmic procedures, when conventional methods of hemostasis are ineffective or impractical; for endoscopic procedures, may be used by cutting to size.
Helistat	For use in surgical procedures, except urologic and ophthalmic procedures, when conventional methods of hemostasis are ineffective or impractical.
Helitene	For use in surgical procedures, except urologic and ophthalmic procedures, when conventional methods of hemostasis are ineffective or impractical.
CoStasis	For use in surgical procedures, except neurosurgical, ophthalmic, and urologic procedures, when conventional methods of hemostasis are ineffective or impractical.
FloSeal	For use in surgical procedures, except ophthalmic procedures, when conventional methods of hemostasis are ineffective or impractical.
Thrombin	For use as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules are accessible; may be used in combination with absorbable gelatin sponge for hemostasis; may be used in conjunction with any other device that has been approved by FDA[a] with a specified dosage of topical thrombin.

[a]FDA = Food and Drug Administration.

Table 3.

Summary of Selected Clinical Trials and Case Reports on Absorbable Hemostatic Agents[a]

Ref.	Study Design	Dosing Regimen	Efficacy Results	Comments
Gelatin based				
25	P, R, MC	GEL soaked in THR (n = 46) FLO (n = 43)	Primary endpoint: percentage of pts. achieving hemostasis at the initial treated site within 10 min after application of GEL plus THR or FLO. Secondary endpoints: hemostatic outcome of additional bleeding sites and time to bleeding cessation. A significant improvement in the percentage of pts. achieving hemostasis at the initial treated site within 10 min was observed with FLO compared with GEL plus THR (93% vs. 76%; p = 0.036). This significant difference favoring FLO was also seen when evaluating the hemostatic outcome of all treated bleeding sites (92% vs. 79%; p = 0.01). The time to bleeding cessation was significantly improved with FLO compared with GEL plus THR for all treated bleeding sites (p = 0.001; Kaplan-Meier analysis).	All pts. underwent reconstructive vascular surgery or arteriovenous access procedures. Occurrence of adverse events was similar between groups. Selected adverse hematologic or infectious adverse events included anemia, hemorrhage, hypotension, arterial thrombus, and wound infection. Antibodies to both bovine THR and factor Va were observed in a significant no. of pts.; however, the presence of these antibodies is rarely of clinical significance. FLO provided more rapid and effective hemostasis than conventional GEL plus THR.
26	P, R, MC	GEL soaked in THR (n = 62) PRO (also referred to as FLO) (n = 65)	Primary endpoint: percentage of pts. achieving hemostasis at the initial treated site within 10 min after application of GEL plus THR or PRO. Secondary endpoints: hemostatic outcome of additional bleeding sites and time to bleeding cessation. A significant improvement in the percentage of pts. achieving hemostasis at the initial treated site within 10 min was observed with PRO compared with GEL plus THR (98% vs. 90%; p = 0.042). This significant difference favoring PRO was also seen when evaluating the hemostatic outcome of all treated bleeding sites (99% vs. 93%; p = 0.001). For pts. receiving PRO, the median time to hemostasis was 1.5 min vs. 3 min for pts. receiving GEL plus THR.	All pts. underwent spinal surgery. Adverse-event profiles were similar between groups. Investigators rated the handling characteristics of the 2 products, including ease of application, ability to conform to surfaces, and ease of delivery to the bleeding site. PRO was the preferred agent for all product-handling characteristics (p < 0.001 for all comparisons).
27	P, R, MC	GEL soaked in THR (n = 45) FLO (n = 48)	Main efficacy measures: achievement of hemostasis within 10 min at the initial bleeding site and for all treated bleeding sites. Achievement of hemostasis within 10 min for the initial bleeding site improved with FLO vs. GEL plus THR (94% vs. 60%; p = 0.0001). This statistical improvement was observed with all treated bleeding sites (88% vs. 57%; p < 0.001).	All pts. underwent cardiac operations. Handling characteristics of the 2 products, including ease of application, ability to conform to surfaces, and access to difficult-to-reach locations, were rated. FLO was preferred in ease of application and conformance to surfaces (p = 0.002 and p = 0.04, respectively). Adverse-event profile was similar for the 2 groups.
28	P, R, PG	GEL (n = 23) Investigational fibrin sealant (human) (n = 24)	Primary endpoint: percentage of pts. achieving hemostasis within 15 min after application of GEL or investigational fibrin sealant. Secondary endpoints: amount of blood loss and the time to hemostasis.	All pts. were undergoing expanded polytetrafluoroethylene patch angioplasty during carotid endarterectomy. The efficacy of the investigational fibrin sealant was deemed to be equivalent to that of the conventional absorbable hemostatic (GEL).

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Table 3 (*continued*)

Ref.	Study Design	Dosing Regimen	Efficacy Results	Comments
			No significant differences in either primary or secondary endpoints were seen (GEL vs. fibrin sealant): achievement of hemostasis within 15 min: 52.2% vs. 50%; $p = 0.882$, amount of blood loss (mL ± S.D.): 94.3 ± 121.2 vs. 105 ± 107.8; $p = 0.551$, time to hemostasis (min): 19.5 ± 15.1 vs. 17.8 ± 13.6; $p = 0.749$.	None of the pts. in the study experienced a perioperative stroke, transient ischemic attack, or death. There were no bleeding complications in either group. If persistent suture bleeding occurred, the investigational fibrin sealant tended to "float off" during the procedure. The investigators theorized that this effect was due to the poor adhesive properties of the sealant.
Collagen based				
29	P, R, MC	HET ($n = 30$) ACT (no longer available in the United States) ($n = 30$)	Main outcomes: percentage of pts. achieving hemostasis within 10 min and the investigator-rated handling/efficiency characteristics of products. No statistically significant difference between groups was observed with regard to the percentage of pts. achieving hemostasis within 10 min: 77% for HET and 73% for ACT. Of 45 pts. who achieved hemostasis after application of either product, 22 (49%) reached hemostasis within <3 min, 16 (36%) in 3 to 6 min, and 7 (16%) between 6 and 10 min. As to handling/efficiency characteristics, ACT was determined to be easier to handle than HET.	All pts. underwent a cardiothoracic procedure. Follow-up at 2–4 days, 1–4 wk, and 6–10 wk revealed no significant differences in coagulation profile between products. Occurrence of adverse events was similar between groups. Of the 12 complications reported, none was deemed related to use of the hemostatic product.
30	P, R	AVI ($n = 31$) BER (fibrin glue not available in the United States) ($n = 31$)	Efficacy of both products was evaluated in terms of hemostatic efficacy during surgery (a dry cut surface), postoperative rebleeding, bile leakage, and other complications. No. pts. with a dry cut surface reflecting hemostatic efficacy during surgery did not significantly differ between groups (27 [AVI] vs. 25 [BER]; p = NS). No difference between groups in postoperative rebleeding, bile leakage, and morbidity or mortality rates. Rebleeding or postoperative bile leakage was observed in 3 pts. in the AVI group who had a dry cut surface vs. none in the BER group with a dry cut surface.	All pts. underwent elective hepatic resection; most pts. had hepatocellular cancer. Although neither agent had an advantage in efficacy outcome measures, BER may be more reliable in the postoperative period because of reduced rebleeding rates and reports of bile leakage.
Thrombin				
17	CR	Single injection of 0.3 mL (300 units) ($n = 1$)	Injection of THR into brachial artery pseudoaneurysm resulted in immediate thrombosis. Brachial artery remained patent, oxygen saturation remained normal, and no evidence of distal embolization was documented. Sonography at 24 hr and 4 wk after the procedure revealed continued thrombosis of pseudoaneurysm with no adverse events with THR administration noted.	Neonate developed the pseudoaneurysm after an attempted right brachial artery puncture for blood gas analysis. Pt. safely sedated with i.v. fentanyl and midazolam during the procedure. General anesthesia was not required. Data on use of THR in pediatric pts. with pseudoaneurysms are limited.
18	CS	Both pts. received a single injection of 1,000 units ($n = 2$)	Injection of THR into brachial artery pseudoaneurysm resulted in thrombosis within 10 sec. Follow-up at 2 wk and 6 mo revealed that both pts. remained symptom free.	Although this procedure resulted in an almost immediate benefit, more data are needed to determine which pts are appropriate candidates for THR.

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Table 3 (*continued*)

Ref.	Study Design	Dosing Regimen	Efficacy Results	Comments
16	P, OL	All pts. received an injection of 0.5–1 mL (1,000 units/mL solution) of THR (n = 20) Additional injections of 0.5–1 mL could be administered if needed.	Injection of THR resulted in successful occlusion in 20 (95%) of 21 pseudoaneurysms. 15 of 20 were occluded within 20 sec after the first injection.	All pts. had a postcatheterization femoral artery pseudoaneurysm. No factor related to success or failure of occlusion with THR was identified. Pseudoaneurysm volume might have role in successful occlusion after 1 injection vs. multiple injections of THR. Pts. with larger pseudoaneurysm volume tended to need an additional THR injection for successful occlusion (p = 0.059).
31	P, R, OL	EPI 1:100,000 alone (n = 70) EPI 1:100,000 followed by 2.8 mL (600 international units) of THR (n = 70) Multiple injections of EPI could be administered.	Study endpoints: rebleeding, surgical operation, units of blood transfused, duration of hospitalization, and 30-day mortality rates. Rebleeding occurred in 14 (20%) of pts. receiving EPI alone and 3 (4.5%) pts. receiving EPI + THR (p < 0.005). 7 pts. receiving EPI alone died vs. no pts. receiving EPI + THR (p < 0.013). No. pts. retreated: 10 pts. (EPI alone) vs. 1 pt. (EPI + THR) (p not reported) Permanent hemostasis achieved in 63 pts. (EPI alone) vs. 67 pts. (EPI + THR) (p not reported) Emergency surgery required for 5 pts. (EPI alone) vs. 3 pts. (EPI + THR) (p not reported) Overall median units of blood transfused and duration of hospitalization similar between groups.	All pts. had documented major peptic ulcer hemorrhage. EPI + THR combination was compared with the standard therapy of EPI alone. Human THR, not bovine THR, was used. Reported fatalities occurred in pts. with severe comorbid disease; 3 pts. developed secondary bleeding after admission for an unrelated medical condition. EPI + THR provided an improved therapeutic effect over EPI alone. However, larger efficacy and safety studies of this combination are needed.
32	P, R, OL	THR: 20,000 units in 20 mL of 0.9% sodium chloride for irrigation (n = 57) 0.9% sodium chloride for irrigation (n = 59) The irrigation solution was applied to the wound after it was sponged free of blood.	Main outcome measure: occurrence of incisional hematoma at time of wound closure. Effect of THR wound irrigation on coagulation parameters also evaluated. No pts. in either group developed major hematoma (a collection of blood that disrupted the wound or required opening the wound for drainage). Minor hematomas (ecchymoses of the skin surrounding the incision) were documented in 6 pts. receiving wound irrigation with THR vs. 12 pts. receiving saline irrigation (p = 0.33). Evaluation of coagulation parameters revealed no difference between groups, either preoperatively or postoperatively.	All pts. underwent elective exploratory laparotomy for gynecological cancer or benign gynecological disease. Wound irrigation with THR resulted in no greater benefit in the prevention of hematoma than irrigation with saline alone.
23	CS	Intraocular infusion of human THR 80 units/mL in BSS Plus (n = 8)	Reported bleeding time in all pts. who received THR ranged from 2 to 15 sec. Vitreous space was reported to be clear in 5 pts. 1 day after surgery and in 6 pts. 1 mo after surgery.	Diffuse hemorrhages were observed in 2 pts. on first day after surgery; however, these hemorrhages cleared in 1 pt. 1 mo after procedure. Presence of postoperative inflammation was reduced compared with studies where bovine THR was administered. Use of human THR in these pts. resulted in a reduction in immunogenic stimuli compared with bovine THR.

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Table 3 (*continued*)

Ref.	Study Design	Dosing Regimen	Efficacy Results	Comments
33	P, R, SB	THR 100 units/mL intravitreal infusion (n = 17) Placebo intravitreal infusion (n = 17)	Main efficacy measure: mean intraocular bleeding time, which was significantly reduced in pts. receiving THR vs. placebo (7 ± 10 sec vs. 118 ± 24 sec; $p < 0.0001$). THR was not associated with a significant increase in postoperative inflammation. Rebleeding at the operation site occurred in 2 eyes that received THR vs. 8 eyes that received placebo (p not reported).	At 6-mo follow-up, all eyes had fibrous proliferation at the operation site; no differences between groups were observed with regard to this outcome. Similar no. of eyes in both groups required reoperation (7 in the THR group vs. 8 in the placebo group). A larger study is needed to confirm results.
24	CS	THR diluted with BSS Plus (concentration: 100 units/mL) infusion (n = 26) BSS Plus solution infusion (n = 10)	Study evaluated the rates of bleeding intraoperatively and at wound closure. The severity of bleeding was also quantified using a 4-point scale (0 = no bleeding and 4 = uncontrollable bleeding). Percentage of pts. with intraoperative bleeding was similar in both groups: 88% for THR + BSS Plus vs. 100% for BSS Plus alone. Bleeding at wound closure was reduced by the use of THR + BSS Plus vs. BSS Plus alone (19% vs. 80%; p not reported). In addition, the occurrence of significant bleeding (> grade 2) was more prevalent among pts receiving BSS Plus alone (4% vs. 30%; p = not reported).	All pts. underwent vitrectomy for stage V retinopathy of prematurity. Pts. were not randomized. The initial 26 pts. were administered THR + BSS Plus, followed by 10 pts. who received BSS Plus alone. Investigation stopped early because of reduced rates of bleeding at wound closure and significant bleeding observed with THR. Two pts. receiving THR developed mild vitreous haze.

[a]P = prospective, R = randomized, MC = multicenter, GEL = Gelfoam, THR = thrombin, FLO = FloSeal, PRO = Proceed, PG = parallel group, HET = Helistat, ACT = Actifoam, AVI = Avitene, BER = Beriplast, NS = not significant, CR = case review, CS = case study, OL = open label, EPI = epinephrine, SB = single blind, BSS = balanced salt solution.

that affect hemostasis may result in alterations in the clotting process.

Dosage and administration

Typically, absorbable hemostatic agents are not administered according to a standardized dosing regimen. In general, the minimal amount of product needed to achieve hemostasis should be applied.[5-14] Many of the product inserts recommend removal of excess hemostatic before wound closure. Surgeons may have a preference for a particular dosing regimen based on their own clinical experience with these agents. The directions for administering the newer topical hemostatic agents, FloSeal and CoStasis, are much more complex than they are for the older agents. The product labeling for absorbable hemostatic agents contains specific directions for use, but no published consensus papers or guidelines on proper dosing or selection of these agents have been published. Table 5 provides a general overview of the dosage and administration of absorbable hemostatic agents.

Safety issues

In April 2004, FDA issued a public health notification on the possible development of paralysis following the use of absorbable hemostatic agents.[46] Since 1996, FDA has received more than 110 reports of adverse events related to the use of absorbable hemostatic agents; 11 of these reports included paralysis or other neural deficits. The last of the adverse neurologic events associated with the use of absorbable hemostatic agents was reported to FDA in October 2003.

In all of the 11 reported events, an absorbable hemostatic agent was administered on or near a "bony or neural space" and left inside the patient.[46] In most cases, the adverse events occurred once the hemostatic agent was wet and began to swell. This swelling resulted in pressure against the spinal cord or other neu-

Table 4.
Reported Adverse Reactions with Absorbable Hemostatic Agents[5-12,14,34-37]

Arachnoiditis	Hearing loss
Bladder and bowel dysfunction	Hematomas
Blindness	Impotence
Brain and spinal cord compression	Infections and abscesses
Burning and stinging sensations	Laryngospasm
Difficulty passing urine	Meningitis
Edema	Pain
Excessive fibrosis	Paralysis
Fever	Paresthesias
Fluid encapsulation	Sneezing
Foreign body/allergic reactions	Subgaleal seroma
Granuloma at the implant site	Toxic shock syndrome
Headaches	Wound dehiscence

ral structures, and pain, numbness, or paralysis ensued. In some instances, a hematoma formed and exerted pressure on neural tissues when blood pooled behind the absorbable hemostatic agent.

To prevent the occurrence of these potentially serious adverse events, FDA recommends that clinicians who use an absorbable hemostatic agent on or near bony or neural spaces should apply the minimal amount of hemostatic needed to control bleeding and should remove as much of the agent as possible once hemostasis has been achieved.[46]

Misadministration of topical thrombin is another important safety concern.[47] Since 1987, FDA, through the MedWatch program, has received a total of four reports that illustrate the serious consequences of misadministration of topical thrombin. In three of these cases, a fatality ensued. The remaining patient developed severe hypotension, bradycardia, and respiratory failure but eventually recovered. Two of the four patients were administered topical thrombin intravenously via a dialysis access site, one patient received a direct injection of thrombin into the splenic tissue, and the final patient was given the drug through a nasogastric tube.[47]

Because of these reports, the manufacturer of topical thrombin added the following wording to its carton and container labeling: "For topical use only—do not inject." In addition, FDA informed medical providers about this safety issue through a Dear Doctor letter and other appropriate communications.[47]

Economic issues

There are no published pharmacoeconomic analyses that evaluate the cost-effectiveness of absorbable hemostatic agents. Issues that may influence formulary inclusion and product selection are contract availability and pricing for similar devices, such as fibrin sealants. Generally, the average wholesale prices of absorbable hemostatic agents are not available. Prices may be obtained by consulting with the purchasing agent at your institution. Table 6 illustrates the relative expense of absorbable hemostatic agents. Surgicel, Gelfoam, and Surgifoam may be used with thrombin in some circumstances, and therefore the total cost of providing hemostasis would increase significantly.

Therapeutic interchange

There are no formal published studies discussing the potential for therapeutic interchange among the absorbable hemostatic agents. Since clinician preference can be the driving force behind formulary inclusion of a particular absorbable hemostatic agent, a therapeutic interchange program involving these agents may not be feasible. Health care institutions may try to minimize the number of absorbable hemostatic agents on the formulary by avoiding duplicate products and, in the case of thrombin, building a consensus among providers regarding the appropriate strengths (i.e., 5,000, 10,000, or 20,000 units) for formulary inclusion.

Summary

Absorbable hemostatic agents have been available since the 1940s. These agents are indicated for use as adjunctive therapy during surgical procedures when conventional methods, such as ligature and application of pressure, do not control bleeding. Their procoagulant effects are exerted at various points within the coagulation cascade.

Good clinical data evaluating the efficacy of absorbable hemostatic agents are lacking. There are few randomized, controlled clinical trials directly comparing available agents. Most of the published comparative trials evaluate the efficacy of older products, such as Gelfoam, against newer agents, including FloSeal and fibrin sealants. The results of these trials vary, with some revealing a statistically significant advantage to using fibrin sealants[48] or FloSeal,[25,27] and others concluding that no advantage exists.[28] Whether a statistically significant reduction in bleeding time is clinically significant in the surgical arena is also debatable.

A variety of rarely occurring adverse effects have been reported with the administration of absorbable hemostatics; some of these rare effects, such as paralysis, are quite severe. No standardized dosing regimens are available for the absorbable hemostatic agents, although surgeons may have a preference for a particular regimen based on their own clinical experience.

The cost-effectiveness of the older absorbable hemostatic agents versus

Table 5.
Dosage and Administration for Absorbable Hemostatic Agents[5-14,45]

Hemostatic Agent	Dosage and Administration
Surgicel	Apply minimal amount needed, with concurrent application of pressure, at the surgical site to achieve hemostasis. Use dry forceps to remove Surgicel from its container.
Gelfoam	Apply minimal amount needed, with concurrent application of pressure, at the surgical site to achieve hemostasis. Product may be saturated with sterile, isotonic sodium chloride before use. Open powder packet and pour contents into a sterile beaker. Add 3–4 mL of sodium chloride to powder to form paste. Paste can be administered to bleeding surface to achieve hemostasis. Wound may be closed over paste, if necessary. If applied to mucosal surfaces, product may be left in place until it liquefies. Gelfoam may also be used in conjunction with thrombin. Consult thrombin package insert for specific administration concerns.
Surgifoam	Apply minimal amount needed, with concurrent application of pressure, at the surgical site to achieve hemostasis. Surgifoam powder comes with a self-contained sterile mixing vessel. To administer, open mixing vessel and add 3–4 mL of sterile saline. Vessel lid should then be reattached and the vessel shaken or stirred until a paste forms. Paste can subsequently be administered to the bleeding surface to achieve hemostasis. Surgifoam sponge should be dry or saturated with sterile sodium chloride solution when applied to the source of bleeding. Sponge should be removed once hemostasis has been achieved to prevent dislodgement or compression of nearby structures.
Avitene	Apply directly to source of bleeding. Amount of product required depends on severity of bleeding. Ideally, surface should be compressed with dry sponges before product administration. Pressure should be applied with a dry sponge after Avitene is applied. The duration of pressure application varies with the severity of bleeding, ranging from a minute for capillary bleeds to 3–5 min for major artery suture holes. For bleeding from cancellous bones, Avitene may be packed into the spongy bone surface. After 5–10 min, excess Avitene may be teased away by using blunt forceps and wetting product with sterile normal saline. Additional Avitene may be applied to areas of breakthrough bleeding. Preloaded applicator devices are available.
Instat	Amount of product required depends on severity of bleeding. Hemostasis usually achieved within 2–5 min after product application. Excess product should be removed before wound closure.
Helistat	Apply directly to source of bleeding. Amount of product required depends on the severity of bleeding. After application, apply pressure for 1–5 min. Use dry forceps to place Helistat at source of bleeding. Remove excess Helistat before wound closure.
Helitene CoStasis	Apply directly to source of bleeding. Amount of product required depends on severity of bleeding. After application, apply pressure for 1–5 min. CoStasis contains a suspension of collagen and thrombin and is used in conjunction with a patient's own plasma. The CellPaker Plasma Collection Device is used to collect the patient's plasma, which will eventually be administered with CoStasis. Site should be dry before applying CoStasis. Apply as a thin, uniform coating. Edges of coating should overlap to ensure coverage. The coating should not be disturbed. Apply additional CoStasis for discrete bleeding. If bleeding does not halt completely, remove original coating and reapply.
FloSeal	Refer to product labeling for an in-depth description of administration process. Directions for use include preparation of thrombin solution, mixing of thrombin solution with gelatin matrix, and specific techniques for application.
Thrombin	Apply to bleeding site in a dry form or after reconstitution with sterile isotonic saline. Appropriate concentration varies with the severity and type of bleeding. For profuse bleeding, 1000 units/mL may be required. A 100-unit/mL concentration may be appropriate for general use in plastic surgery, dental extractions, and skin grafting. Diluting product with appropriate amount of sterile isotonic saline may compound other concentrations.

the newer agents and fibrin sealants is another area of debate because no pharmacoeconomic analyses have been performed.

Overall, no consensus recommendations favor the use of one particular absorbable hemostatic over another, nor do available data strongly favor the use of a particular agent. However, limited comparative information on FloSeal versus the older absorbable hemostatic agents has shown an improved hemostatic response with FloSeal, although the clinical significance of this response remains questionable.

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Table 6.
Relative Expense of the Topical Hemostatics

Topical Hemostatic	Relative Expense[a]
Surgicel, Gelfoam, Surgifoam[b]	$
Avitene, Instat, Helistat, Helitene	$$
CoStasis, FloSeal	$$$
Thrombin	$$

[a]$ = least expense, $$ = moderate expense , $$$ = most expense. Expense may vary based on the formulation of the hemostatic agent. Data obtained from the University HealthSystem Consortium's Clinical Data Base—Pharmacy.
[b]May be used with thrombin in some circumstances, which would increase the total cost of hemostasis significantly.

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