

# Topical Hemostatic Agents in Surgery: A Surgeon's Perspective

SRINATH SAMUDRALA, MD

**M**anagement of hemostasis during surgery has many key components that start, first and foremost, with good surgical technique and anesthetic support.<sup>1</sup> Beyond this, a surgeon may use various hemostatic products to help control surgical bleeding when it is encountered. These agents range from the absorbable hemostats, such as gelatins and collagens, to biologically active topical hemostats, such as thrombin and combined agents, to systemically delivered agents, such as coagulation factors used for more extensive bleeding.<sup>1</sup> This review focuses on topically applied hemostatic agents and the value they provide during surgery to both the patient and surgical team.

## ABSTRACT

**GOOD HEMOSTASIS IN SURGERY** can provide multiple advantages to the patient, surgical team, and health care facility. Active and passive hemostatic agents have been widely used for many years and have extensive history supporting effective and safe use in a wide variety of surgical procedures.

**THE TYPE OF SURGICAL PROCEDURE**, type of bleeding, hemostatic agent availability, and patient characteristics will influence the choice of topical hemostatic agent that is used by the surgeon. By actively participating in the coagulation cascade, active topical hemostatic agents are more able to meet the criteria of an ideal hemostatic agent in cases of oozing blood and minor bleeding during surgical procedures. Active agents can be used alone or in combination with passive agents.

**FAMILIARITY WITH THE PRODUCTS** used to achieve hemostasis and their preparation can facilitate optimal use by surgical teams. *AORN J* 88 (September 2008) S1-S11. © AORN, Inc, 2008.

## THE BIOLOGY OF HEMOSTASIS

Understanding the mechanisms of hemostasis and thrombosis is critical to the management and stabilization of a patient undergoing any surgical procedure. Hemostasis can be defined as a tightly regulated process that maintains the blood flow through the vasculature simultaneously as a thrombotic response to tissue damage occurs.<sup>2</sup> Maintaining hemostasis requires a complex interaction of the vessel wall, platelets, and the coagulation and fibrinolytic systems (Figure 1).<sup>3-5</sup> There are two main phases of hemostasis: primary (ie, the cellular phase) and secondary (ie, the humoral phase).<sup>2</sup>

Primary hemostasis begins immediately after endothelial disruption and is characterized by vasoconstriction, platelet adhesion, and formation of a soft aggregate plug.<sup>5</sup> After the injury occurs, there is a temporary local contraction of vascular smooth muscle and the blood flow slows, promoting platelet adhesion and activation.<sup>5</sup> Within 20 seconds of the injury, circulating von Willebrand factor attaches to the subendothelium at the site of injury and adheres to the glycoproteins on the surface of platelets.<sup>5</sup> As platelets adhere to the injured surface, they are activated by contact with collagen-exposing receptors that bind circulating fibrinogen. A soft plug of aggregated platelets and fibrinogen is formed.<sup>2,5</sup> This phase of hemostasis is short lived, and the soft plug can easily be sheared from the injured surface.<sup>5</sup>

The soft platelet plug is stabilized during secondary hemostasis to form a clot. Vasoconstriction and the resultant reduction in blood flow are maintained by platelet secretion of serotonin, prostaglandin, and thromboxane while the coagulation cascade is initiated

---

*Publication of this supplement article is provided by commercial support from King Pharmaceuticals<sup>®</sup>, Inc.*

(Figure 2).<sup>2,5</sup> The coagulation cascade is a series of dependent reactions involving several plasma proteins, calcium ions, and blood platelets that lead to the conversion of fibrinogen to fibrin.<sup>2,5</sup> Coagulation factors are produced by the liver and circulate in an inactive form until the coagulation cascade is initiated. Then each step of the cascade is initiated and completed via a series of sequential and dependent coagulation factor activation reactions.<sup>5,6</sup> In the final steps, thrombin converts the soluble plasma protein fibrinogen to the insoluble protein fibrin, while simultaneously converting factor XIII to factor XIIIa. This factor conversion stabilizes the fibrin and results in cross-linking of the fibrin monomers, producing a stable clot.<sup>2,6</sup>

### THE IMPORTANCE OF MAINTAINING HEMOSTASIS DURING SURGERY

During surgery, it is important to maintain a fine balance between bleeding and clotting, such that blood continues to flow to the tissues at the surgical site without excessive loss of

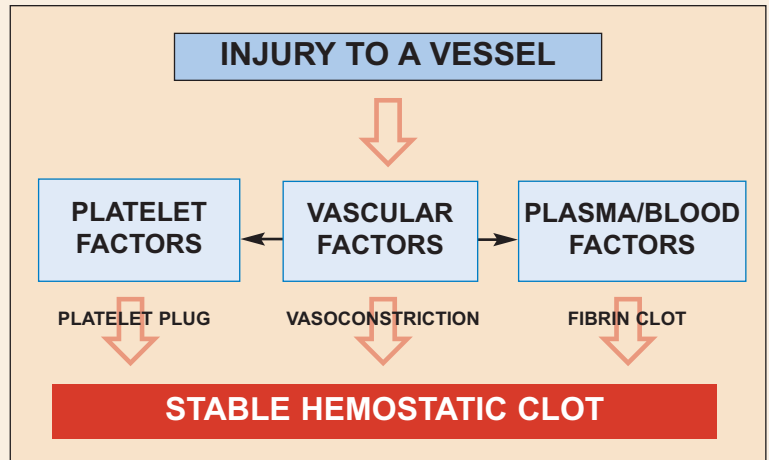


Figure 1 • The synergy of factors that contribute to normal hemostasis.

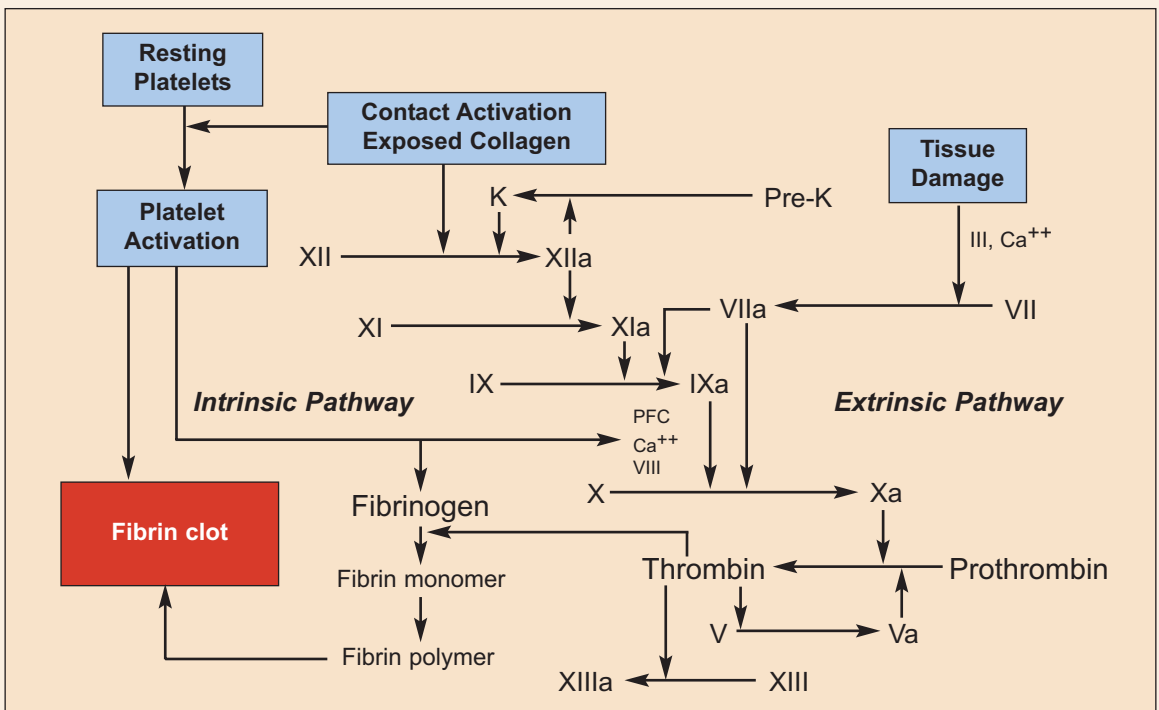


Figure 2 • The clotting cascade. Thrombin catalyzes the conversion of fibrinogen to fibrin, one of the last steps of the coagulation cascade. (Adapted from Oz MC, Rondinone JF, Shargill NS. FloSeal Matrix: new generation topical hemostatic sealant. J Card Surg. 2003;18(6):486-493, with permission from Blackwell Publishing, Oxford, United Kingdom).

blood, to optimize surgical success and patient outcome. Continuous bleeding from diffuse minor capillaries or small venules during surgery can obscure the surgical field, prolong operating time, increase the risk of physiologic complications, and expose the patient to risks associated with blood transfusion.<sup>7,8</sup>

Several factors can contribute to the occurrence of intraoperative bleeding related to either the surgical procedure itself or the individual patient (Table 1).<sup>6,9,10</sup> To combat these factors, a surgeon must adopt effective surgical techniques that reduce the amount of exposed, bleeding tissue during surgery to decrease blood

loss and avoid the risks and costs associated with transfusion.

Effective hemostasis in surgery can offer various advantages to the patient, surgeon, and health care facility (Table 2). As a result of intraoperative blood loss, the need for allogenic or autologous blood transfusions and the risks associated with blood transfusions are increased.<sup>10-12</sup> Reduced length of stay in the intensive care unit (ICU) and overall length of hospital stay have been related to reductions in the amount of blood transfused.<sup>11</sup> For example, blood transfusion has been identified as an independent risk factor for infection, respiratory complications, and admission to the ICU after surgery for traumatic spleen injury; risk of complications and ICU admission was doubled in patients who received more than two units of blood.<sup>11</sup> Excessive intraoperative blood loss also has been shown to significantly increase the risk of major perioperative complications.<sup>10,13,14</sup>

Rapid and effective hemostasis allows the surgeon to retain visualization of the surgical field.<sup>7</sup> This can both reduce the procedure time and the risk of accidental injury.<sup>7</sup> In turn, a reduction in surgery time may lead to potential savings in OR costs.<sup>7,11,12</sup> Effective hemostasis also should decrease the morbidity and mortality associated with surgical procedures.<sup>7</sup>

**TABLE 1**  
**Factors Contributing to Intraoperative Bleeding<sup>1-3</sup>**

- Exposed bone (eg, spinal reconstructive procedures)
- Diffuse capillaries (eg, large surfaces)
- Unseen sources of bleeding (eg, retroperitoneal spaces)
- Surgical incisions
- Tissues not amenable to suturing
- Low-pressure suture lines
- Stripped adhesions
- Anticoagulant medications
- Coagulopathies and platelet dysfunction

1. Oz MC, Rondinone JF, Shargill NS. FloSeal Matrix: new generation topical hemostatic sealant. *J Card Surg.* 2003;18(6):486-493.  
 2. Morikawa T. Tissue sealing. *Am J Surg.* 2001;182(2 Suppl):29S-35S.  
 3. Block JE. Severe blood loss during spinal reconstructive procedures: the potential usefulness of topical hemostatic agents. *Med Hypotheses.* 2005;65(3):617-621.

**TABLE 2**  
**Advantages of Effective Hemostasis During Surgery**

- Fewer transfusions
- Better visualization of surgical field
- Reduced surgical time
- Decreased morbidity and mortality

**TECHNIQUES USED TO MAINTAIN HEMOSTASIS IN SURGERY**

Surgeons have an array of options to control bleeding, including mechanical and thermal techniques and devices as well as pharmacotherapies and topical agents (Table 3). Application of direct pressure or compression at a bleeding site is often the surgeon's first choice to assist in the control of bleeding. Other mechanical methods, including sutures, staples, and ligating clips, are useful if the source of bleeding is easily identifiable and able to be sealed. Compression or other mechanical methods, however, may not be appropriate during all surgical procedures<sup>6,8</sup>—for example, if the source of bleeding is diffuse or hard to identify or the patient has an inherent or surgery-induced coagulopathy resulting from the type of surgical procedure

(eg, hemodilution, hypothermia) or prior administration of antiplatelet or anticoagulant medications.<sup>6,11</sup>

In recent years, thermal techniques, such as hemostatic scalpels and lasers, also have become viable surgical options to reduce bleeding; however, the frequent use of cautery and other thermal techniques can have its drawbacks.<sup>8</sup> Depending on the procedure and location of the bleeding tissue, it may be impractical or impossible to effectively stop blood loss via mechanical or thermal hemostatic techniques. For example, in bony surfaces, parenchymal tissues, inflamed or friable vessels, or tissues containing multiple and diffuse capillaries, it is extremely difficult to maintain hemostasis with these methods.<sup>8-10</sup>

The use of effective pharmacological methods during surgery can be a useful option or an adjunct to other methods in these situations. The pharmacological methods seek to augment surgical hemostasis by enhancing the natural coagulative mechanisms.<sup>11</sup> This may include the use of pharmacological agents, such as epinephrine, desmopressin, topical hemostatic agents, tissue sealants, and tissue adhesives.<sup>2,6,10,12,15,16</sup>

One of the earliest topical hemostatic agents was cotton, in the form of gauze sponges. Although such materials concentrate blood and coagulation products via physical adsorption, they are not absorbed by the body, and upon removal, the clot may be dislodged, leading to further

### TABLE 3

## Techniques for Maintaining Hemostasis in Surgery<sup>1-6</sup>

#### Mechanical techniques

- Direct pressure
- Sutures
- Staples
- Ligating clips
- Fabric pads
- Gauzes
- Sponges
- Blood component/replacement therapy

#### Thermal techniques

- Electrocautery
- Hemostatic scalpel
- Laser

#### Chemical techniques

- Pharmacotherapy
  - Hypotensive anesthesia
  - Epinephrine
  - Vitamin K
  - Protamine
  - Desmopressin
  - Aminocaproic acid
  - Tranexamic acid
- Topical hemostats
  - Collagen
  - Cellulose
  - Gelatins
  - Thrombins
- Topical sealants and adhesives
  - Fibrin sealants
  - Synthetic glues

1. Oz MC, Rondinone JF, Shargill NS. FloSeal Matrix: new generation topical hemostatic sealant. *J Card Surg.* 2003;18(6):486-493.
2. Sabel M, Stummer W. The use of local agents: Surgicel and Surgifoam. *Eur Spine J.* 2004;13(Suppl 1):S97-S101. Epub May 15, 2004.
3. Block JE. Severe blood loss during spinal reconstructive procedures: the potential usefulness of topical hemostatic agents. *Med Hypotheses.* 2005;65(3):617-621.
4. Tomizawa Y. Clinical benefits and risk analysis of topical hemostats: a review. *J Artif Organs.* 2005;8(3):137-142.
5. Krebs VE, Higuera C, Barsoum WK, Helfand R. Blood management in joint replacement surgery: what's in and what's out. *Orthopedics.* 2006;29(9):801-803.
6. Albala DM, Lawson JH. Recent clinical and investigational applications of fibrin sealant in selected surgical specialties. *J Am Coll Surg.* 2006;202(4):685-697. Epub February 20, 2006.

bleeding.<sup>11</sup> Absorbable topical hemostatic agents have since been developed and provide useful adjunctive therapy when conventional methods of hemostasis are ineffective or impractical (Figure 3).<sup>3</sup> Topical hemostatic agents can be applied directly to the bleeding site and may prevent continuous unrelenting bleeding throughout the entire procedure and into the postoperative recovery period.<sup>10</sup> Hemostasis using topical agents also can avoid the adverse effects of systemic hemostatic medications, such as “unwanted” blood clots.<sup>12</sup> The flexibility associated with topical agents can also make them an attractive option. In surgical procedures where the amount of blood loss is unpredictable, topical hemostats can be used sparingly when blood loss is minimal and more liberally during severe bleeding.<sup>10</sup> Furthermore, as hemostasis is attained and maintained at the bleeding site, there may be prolonged benefit with respect to postoperative blood loss.<sup>10</sup>

**ACTIVE VERSUS PASSIVE HEMOSTASIS**

A number of topical hemostatic agents are currently available for use in surgery. They can be divided into two categories: those that provide their mechanism of action on the clotting cascade in a biologically active manner and those that act passively through contact activation and promotion of platelet aggregation.<sup>6</sup> Passive topical hemostatic agents include collagens, cellulose, and gelatins, while active agents include thrombin and products in which thrombin is combined with a passive agent to provide an active overall product.<sup>3,6</sup> Tissue sealants and glues are appropriate for rapid arterial bleeding.

**PASSIVE HEMOSTASIS.** The basic mechanism of action of passive hemostatic agents is to provide a physical structure around which platelets can aggregate so a clot can form.<sup>17</sup> Passive topical hemostatic agents come in multiple forms and methods of application that can be important factors in determining their effectiveness.<sup>12</sup> Gauze, sheets,

sponges, and fleece are most popular among surgeons; however, fleece and powdered forms may have high electrostatic charge, causing them to stick to instruments and gloves and rendering them unsatisfactory in terms of handling characteristics.<sup>12</sup>

Collagen-based products provide hemostasis through contact activation and the promotion of platelet aggregation, which occur as a direct result of contact between blood and the collagen.<sup>3,6</sup> The collagen may be applied to the site of bleeding as a powder, paste, or sponge.<sup>3,6</sup> As with any product of animal origin, bovine-derived collagen has the potential to cause allergic or immune reactions to develop.<sup>3</sup> Between 2% and 4% of the total population has an allergy to bovine collagen, but this is a relatively low incidence compared with other common allergies.<sup>18</sup>

Cellulose-based products contain regenerated oxidized cellulose.<sup>3</sup> They initiate clotting via contact activation; however, the exact mechanism is not completely understood.<sup>3,6</sup> Cellulose products may be cut to size to fit the wound, and when cut into small pieces, the knitted strips of material conform well to different shapes, are easily manipulated, and do not stick to instruments.<sup>3,8</sup> It has been suggested, however, that oxidized cellulose is not absorbed as well as other products. Several case reports have indicated that residue of oxidized cellulose can be recognized at reoperation.<sup>12</sup> Differences in biodegradability may depend on the amount used, the site of implantation, or environmental factors.<sup>12</sup> It is therefore recommended that only the minimum amount of

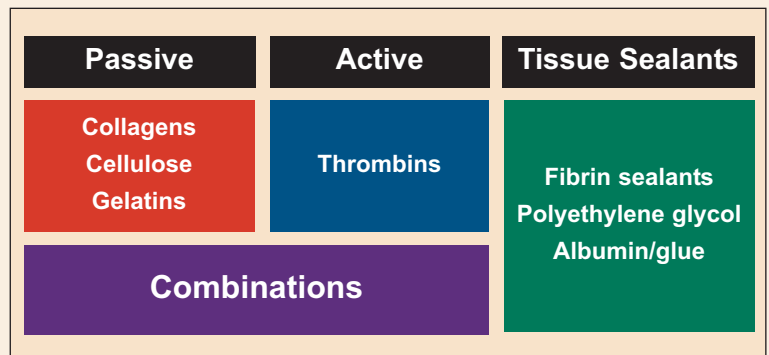


Figure 3 • Available topical hemostatic modifiers.

material be used and, as far as possible, it should be removed from the site of application when hemostasis is achieved.<sup>8,12</sup>

The properties of gelatin can allow it to conform to irregular wound geometries.<sup>6,8</sup> When held in place at the site of bleeding, gelatin will conform to the wound and swell, providing a tamponade effect in confined spaces.<sup>6</sup> The swollen gelatin particles restrict blood flow and provide a stable matrix around which a clot can form.<sup>6</sup> Clotting is initiated via contact activation.<sup>3,6</sup> Gelatin-based products are available in granular or sponge forms from bovine or porcine sources.<sup>3,6</sup> Gelatin-based products also can have their drawbacks; for example, blood-soaked gelatin tends to stick to surgical instruments, making handling difficult. Furthermore, gelatin sponges are easily dislodged because they do not form a tight bond with the bleeding source.<sup>8</sup>

An *in vitro* evaluation of the coagulation mechanisms of passive topical hemostatic agents found that microfibrillar collagen was the most effective, followed by collagen sponge, gelatin sponge, and oxidized regenerated cellulose.<sup>12,19</sup> Due to the nature of surgical hemostasis, however, it has not been possible to conduct surgeon-blinded trials; therefore, studies comparing the efficacies of different topical hemostats *in situ* are open to bias and should be interpreted with caution.<sup>12,20,21</sup>

As more surgical procedures are performed through minimally invasive incisions with laparoscopic, endoscopic, and robotic approaches, tools that can reduce bleeding by causing blood to clot, sealing vessels, or gluing tissues are gaining increasing importance.<sup>22</sup> There is little doubt that positive hemostatic effects can be achieved with glues, sealants, and topical hemostats, with a beneficial effect on blood loss.<sup>23</sup> The efficiency of sealants in promoting hemostasis is difficult to quantify in clinical practice, however, for both practical and ethical reasons. The effect on total perioperative blood loss can only be indirectly inferred from drain output and the number of units transfused.<sup>23</sup>

**ACTIVE HEMOSTASIS.** Active topical hemostatic agents have biological activity and directly participate at the end of the coagulation cascade to induce a clot at the site of bleeding.

Active agents used in surgery include thrombin and combination products containing thrombin.<sup>2</sup> The active topical hemostatic agent thrombin has been widely used in surgery for years. In the late 1970s, the US Food and Drug Administration (FDA) approved topical bovine thrombin as an aid to hemostasis in surgery, and the agent has had a long history of clinical efficacy and safety in many surgical procedures.<sup>2</sup> Currently, there are three active topical hemostatic agents available on the US market as a single agent: Thrombin-JMI<sup>®</sup> (Thrombin, Topical, Bovine Origin, USP); Evithrom<sup>™</sup> (Thrombin, Topical [Human], Omrix<sup>™</sup> Biopharmaceuticals, Ltd); and Recothrom<sup>™</sup> (Thrombin, Topical [Recombinant]; ZymoGenetics<sup>®</sup>, Inc).

As active agents are directly involved in the final physiologic events of the coagulation cascade and bypass the initial enzymatic steps, other aspects of the coagulation cascade can be dysfunctional without significantly impairing the local hemostatic efficacy of the products. The presence of circulating fibrinogen is necessary for hemostatic efficiency because thrombin exerts its primary hemostatic action via interaction with the fibrinogen in the patient's blood to form a fibrin clot.<sup>6,24</sup> Failure of thrombin to clot blood occurs only in the rare cases in which the primary clotting defect is the absence of fibrinogen. The fact that thrombin is active at the last stages of the clotting cascade is important because its action is less susceptible to coagulopathies caused by clotting factor deficiencies or platelet malfunction.<sup>6</sup> Indeed, it can provide a useful adjunct in the presence of antiplatelet and/or anticoagulation agents, which are increasingly used in the general population.<sup>6,7</sup>

Thrombin is commonly used in combination with certain passive topical hemostatic agents, such as a gelatin sponge, to increase the utility and effectiveness of the final product. Thrombin is also a component in many fibrin sealant products. Indeed, it was not until fibrinogen was combined with concentrated plasma thrombin in the late 1990s that the use of sealants became common in surgical practice.<sup>9</sup> When the fibrinogen and thrombin components are combined, thrombin cleaves the fibrinogen into monomers that polymerize to

form a soft plug before the soluble fibrin is converted into the insoluble fibrils that form a stable clot.<sup>2</sup>

### ADVANTAGES AND DISADVANTAGES OF TOPICAL HEMOSTATIC AGENTS

There are a number of factors to consider when choosing a topical hemostatic agent. The selection of the topical agent and delivery method are highly dependent on both the source and magnitude of bleeding and the local anatomy of the patient.<sup>23</sup> The relative advantages and disadvantages of different topical hemostatic methods also need to be considered.

**PASSIVE TOPICAL HEMOSTATIC AGENTS.** Passive topical hemostatic agents offer improved blood conservation by reducing blood loss.<sup>12</sup> These agents form a "lattice-like" structure that adheres to the bleeding site, providing a platform for platelet aggregation while reinforcing the fibrin clot.<sup>12</sup> Passive topical hemostatic agents can be useful in situations of heavier bleeding because of their larger absorption capacity and greater mass provided by their more fibrous/dense structures.<sup>12</sup> Passive topical hemostatic agents can absorb up to several times their own weight in fluid. For example, oxidized cellulose can absorb seven times its own weight in physiological saline, while cotton-type collagen can absorb 32 times its own weight.<sup>12</sup> Any portion of passive topical hemostatic agent retained in the wound that has not participated in the hemostasis will absorb effusion and moisture and expand.<sup>12</sup> Their broad label usage in surgical procedures is accompanied by availability in a variety of sizes, shapes, and forms.<sup>12</sup>

The expansion of a passive topical hemostatic agent can result in complications such as pressing nerves in surrounding tissue against bone or hard tissue; an extreme case of this has resulted in spinal cord compression leading to paraplegia.<sup>8,12,25,26</sup> It is therefore recommended that the minimum amount of hemostatic agent necessary to achieve hemostasis be used and as much of the agent as possible be removed after hemostasis is achieved when a passive topical hemostatic agent is used on or near bony or neural spaces.<sup>12,27</sup> Also, passive topical hemostatic

agents do not adhere strongly to wet tissue and have little impact on actively bleeding wounds.<sup>12</sup>

The physical presence of passive topical hemostatic agents can lead to confusion on subsequent diagnostic imaging because it may be difficult to distinguish between residual local topical hemostatic product and a tumor or abscess.<sup>12</sup> For this reason, information on the hemostatic agents used, including the name of the agent, the site, and the amount used, should be documented in the patient's surgical record to avoid misinterpretation of future diagnostic images.<sup>12</sup> Any residual product that may remain at the site also can possibly potentiate a foreign-body reaction, chronic inflammation, or infection, which could promote granuloma formation and prevent optimal healing. Granulomas have been reported at a number of different sites after the use of passive topical hemostatic agents.<sup>12</sup> Consequently, absorbable passive hemostatic agents should be used in small quantities when a risk of bacterial contamination or perceived risk of anaphylaxis exists.<sup>12</sup>

**ACTIVE TOPICAL HEMOSTATIC AGENTS.** Like passive topical hemostatic agents, active agents improve blood conservation by reducing blood loss.<sup>6</sup> Unlike passive agents, which rely on the presence of normal clotting processes, however, the active agent thrombin acts at the end of the clotting cascade, rendering its action less susceptible to coagulopathies caused by clotting factor deficiencies or platelet malfunction.<sup>6</sup> Thrombin can provide a logical and useful choice in patients receiving antiplatelet and/or anticoagulation agents, which is occurring in an increasing proportion of surgical cases.<sup>6,7</sup> Thrombin relies on the presence of fibrinogen in the patient's blood, however, so it is ineffective in patients who have afibrinogenemia, a rare condition reported to affect one in 1 million people.<sup>6</sup> Additionally, thrombin itself does not need to be removed from the site of bleeding before wound closure, unlike many of the passive topical hemostatic agents, and degeneration and reabsorption of the resulting fibrin clot is achieved during normal wound healing.<sup>9,12</sup>

Active topical hemostatic agents have a rapid onset of action, providing hemostasis within 10 minutes in most patients.<sup>6,11,28,29</sup>

Indeed, in a comparison of collagen-based products at diffusely bleeding sites after surgical tumor resection, the combination collagen-thrombin product (n = 23) achieved complete hemostasis three times faster than the collagen sponge alone (n = 30); median time to hemostasis was 78 seconds versus 243 seconds, respectively ( $P = .0001$ ).<sup>19</sup> Furthermore, approximately four of every five patients achieved complete hemostasis within two minutes with the active topical hemostatic agent compared with only one-third of patients receiving the passive topical hemostatic agent.<sup>20</sup>

The sprayable formulation of thrombin offers potential advantages in the surgical setting because wide surfaces can be treated instantaneously without the need for tamponade.<sup>21</sup> Bovine thrombin, for example, can be administered to the site of bleeding as a powder without reconstitution, and this may be particularly advantageous on oozing surfaces.<sup>3</sup> The concentration of thrombin solution also can be varied according to the severity and type of bleeding. Increasingly, surgeons may find themselves using a topical hemostatic agent in multiple ways during one procedure, thus flexibility in the range of delivery options becomes important.

The use of thrombin as a hemostatic agent was reported as far back as 1939,<sup>2,30,31</sup> followed by reports many years later regarding the antigenicity of bovine thrombin.<sup>2,32</sup> More than six decades later, however, bovine thrombin remains a widely used hemostatic agent.<sup>23</sup> Indeed, it is conservatively estimated that at least 1 million patients are treated with topical applications of thrombin every year in the United States alone.<sup>1</sup> Today's topical thrombin products are very different from those used even 10 years ago because of different sources and formulations as well as enhanced manufacturing techniques that significantly improved the purity of the products.

In recent years, awareness of the potential of bovine thrombin products to induce antibodies has been raised; however, the clinical implications are still largely unclear.<sup>1,2,23,33,34</sup> Although many patients will demonstrate no clinical or laboratory abnormalities after the development of antibodies to thrombin preparations, abnor-

malities in blood coagulation tests are occasionally reported and have rarely been fatal.<sup>25,35,36</sup> In 2007 and 2008, human plasma-derived and recombinant human thrombin were introduced to the US market. These thrombins, much like bovine thrombins, have the potential to produce antibodies,<sup>28,29</sup> although the clinical consequences of these antibodies are largely unknown because so few patients have been exposed to the newer products. In many cases, an individual surgeon will have many years of experience using thrombin and other topical hemostatic agents. The surgeon's history and experience of appropriate use with the product, including adverse events, procedure, and patient types, will contribute to continued use of a hemostatic agent in any given surgical situation.

It should be acknowledged that both passive and active topical hemostatic agents are not envisioned to supplant ligation or surgical repair of major vascular disruption. Rather, they provide a useful adjunct to assist in the control of diffuse oozing blood and minor bleeding from capillaries and small venules.<sup>21</sup>

### PROPERTIES OF THE IDEAL TOPICAL HEMOSTATIC AGENT

Although the precise properties of the ideal topical hemostatic agent will vary according to surgical specialty as a result of the varying requirements, some features are universally valued, including:

- rapid and effective in control/cessation of bleeding;
- ability to make effective contact with the bleeding surface;
- an acceptable adverse-event profile;
- reliable and easy to handle;
- simple to prepare;
- available in multiple, versatile delivery options appropriate for different types of bleeding; and
- active and compatible with the patients' own physiology.<sup>9</sup>

By actively participating in the coagulation cascade and bypassing the initial enzymatic steps, active topical hemostatic agents are more able to meet the criteria for an ideal agent than passive agents.<sup>23</sup> Active topical hemostatic

agents have been shown to achieve hemostasis rapidly, provide ease of use, have an acceptable adverse-event profile, have multiple delivery options, decrease the number of necessary blood transfusions, improve postoperative outcomes, reduce the length of surgical procedures, and be cost-effective.<sup>1,9,11,19,20,36,37</sup> In many cases, a surgeon may choose to combine an active agent with a passive agent to improve the overall hemostatic effect.

### CONCLUSION

Intraoperative bleeding can be life threatening in some cases; therefore, a fast and effective blood management plan incorporating topical hemostatic agents may be essential for achieving optimal patient outcomes. The use of topical hemostatic agents may improve blood conservation, avoid potential adverse events of systemic hemostatic medications, reduce overall procedure time, and contribute to faster patient recovery times.<sup>9,11,12</sup> Active hemostatic agents provide rapid and effective hemostasis, are available in multiple delivery forms, and can be used in combination with topical passive hemostatic agents.

Familiarity with the products used to achieve hemostasis and their preparation can facilitate their optimal use within the OR. Appropriate and correct use of these products has the potential to improve outcomes for patients, the surgical team, and health care facilities. — **AORN** —

### REFERENCES

1. Lawson JH. The clinical use and immunologic impact of thrombin in surgery. *Semin Thromb Hemost.* 2006;32(Suppl 1):98-110.
2. Lundblad RL, Bradshaw RA, Gabriel D, Ortel TL, Lawson J, Mann KG. A review of the therapeutic uses of thrombin. *Thromb Haemost.* 2004;91(5):851-860.
3. Gabay M. Absorbable hemostatic agents. *Am J Health Syst Pharm.* 2006;63(13):1244-1253.
4. Adams GL, Manson RJ, Turner I, Sindram D, Lawson JH. The balance of thrombosis and hemorrhage in surgery. *Hematol Oncol Clin North Am.* 2007;21(1):13-24.
5. Hemostasis. In: Porter RS, ed. *The Merck Manuals Online Medical Library.* <http://www.merck.com/mmpe/sec11/ch134/ch134a.html>. November 2005. Accessed July 29, 2008.
6. Oz MC, Rondinone JF, Shargill NS. FloSeal Matrix: new generation topical hemostatic sealant. *J Card Surg.* 2003;18(6):486-493.
7. Renkens KL Jr, Payner TD, Leipzig TJ, et al. A multicenter, prospective, randomized trial evaluating a new hemostatic agent for spinal surgery. *Spine.* 2001;26(15):1645-1650.
8. Sabel M, Stummer W. The use of local agents: Surgical and Surgifoam. *Eur Spine J.* 2004;13(Suppl 1):S97-S101. Epub May 15, 2004.
9. Morikawa T. Tissue sealing. *Am J Surg.* 2001;182(Suppl):29S-35S.
10. Block JE. Severe blood loss during spinal reconstructive procedures: the potential usefulness of topical hemostatic agents. *Med Hypotheses.* 2005;65(3):617-621.
11. Bochicchio G, Dunne J, Bochicchio K, Scalea T. The combination of platelet-enriched autologous plasma with bovine collagen and thrombin decreases the need for multiple blood transfusions in trauma patients with retroperitoneal bleeding. *J Trauma.* 2004;56(1):76-79.
12. Tomizawa Y. Clinical benefits and risk analysis of topical hemostats: a review. *J Artif Organs.* 2005;8(3):137-142.
13. Carreon LY, Puno RM, Dimar JR 2nd, Glassman SD, Johnson JR. Perioperative complications of posterior lumbar decompression and arthrodesis in older adults. *J Bone Joint Surg Am.* 2003;85-A(11):2089-2092.
14. McDonnell MF, Glassman SD, Dimar JR 2nd, Puno RM, Johnson JR. Perioperative complications of anterior procedures on the spine. *J Bone Joint Surg Am.* 1996;78(6):839-847.
15. Krebs VE, Higuera C, Barsoum WK, Helfand R. Blood management in joint replacement surgery: what's in and what's out. *Orthopedics.* 2006;29(9):801-803.
16. Albala DM, Lawson JH. Recent clinical and investigational applications of fibrin sealant in selected surgical specialties. *J Am Coll Surg.* 2006;202(4):685-697. Epub February 20, 2006.
17. Hemostasis, surgical bleeding, and transfusion. In: Brunicaardi FC, Anderson DK, Billiar TR, Dunn DL, Hunter JG, Pollock RE, eds. *Schwartz's Principles of Surgery.* 8th ed. New York, NY: McGraw-Hill; 2005:93.
18. Lynn AK, Yannas IV, Bonfield W. Antigenicity and immunogenicity of collagen. *J Biomed Mater Res B Appl Biomater.* 2004;71(2):343-354.
19. Wagner WR, Pachence JM, Ristich J, Johnson PC. Comparative in vitro analysis of topical hemostatic agents. *J Surg Res.* 1996;66(2):100-108.
20. Chapman WC, Wren SM, Lebovic GS, Malawer M, Sherman R, Block JE. Effective management of bleeding during tumor resection with a collagen-based hemostatic agent. *Am Surg.* 2002;68(9):802-807.
21. Chapman WC, Clavien PA, Fung J, Khanna A, Bonham A. Effective control of hepatic bleeding with a novel collagen-based composite combined with autologous plasma: results of a randomized controlled trial. *Arch Surg.* 2000;135(10):1200-1204.
22. Spotnitz WD, Burks S. Hemostats, sealants,

- and adhesives: components of the surgical toolbox. *Transfusion*. 2008;48(7):1502-1516. Epub April 14, 2008.
- 23.** Kraus TW, Mehrabi A, Schemmer P, Kashfi A, Berberat P, Buchler MW. Scientific evidence for application of topical hemostats, tissue glues, and sealants in hepatobiliary surgery. *J Am Coll Surg*. 2005;200(3):418-427.
- 24.** Bishop PD, Lewis KB, Schultz J, Walker KM. Comparison of recombinant human thrombin and plasma-derived human alpha-thrombin. *Semin Thromb Hemost*. 2006;32(Suppl 1):86-97.
- 25.** Banerjee T, Goldschmidt K. "Surgiceloma" manifested as cauda equina syndrome. *South Med J*. 1998;91(5):481-483.
- 26.** Brodbelt AR, Miles JB, Foy PM, Broome JC. Intra-spinal oxidised cellulose (Surgicel) causing delayed paraplegia after thoracotomy—a report of three cases. *Ann R Coll Surg Engl*. 2002;84(2):97-99.
- 27.** FDA Public Health Notification: Paralysis from absorbable hemostatic agent. US Food and Drug Administration. <http://www.fda.gov/cdrh/safety/040204-hemostatics.html>. April 2, 2004. Accessed July 29, 2008.
- 28.** Chapman WC, Singla N, Genyk Y, et al. A phase 3, randomized, double-blind comparative study of the efficacy and safety of topical recombinant human thrombin and bovine thrombin in surgical hemostasis. *J Am Coll Surg*. 2007;205(2):256-265.
- 29.** Doria C, Fischer CP, Wood CG, Li PM, Marra S, Hart J. Phase 3, randomized, double-blind study of plasma-derived human thrombin versus bovine thrombin in achieving hemostasis in patients undergoing surgery. *Curr Med Res Opin*. 2008;24(3):785-794.
- 30.** Seegers WH, Warner ED, Brinkhous KM, Smith HP. The use of purified thrombin as an hemostatic agent. *Science*. 1939;89(2300):86.
- 31.** Warner ED, Brinkhous KM, Seegers WH, et al. Further experience with the use of thrombin as a hemostatic agent. *Proc Soc Exp Biol*. 1939;41:655-657.
- 32.** Light RU. The antigenicity of bovine thrombin: clinical evaluation. *J Neurosurg*. 1945;2:516-523.
- 33.** Ortel TL, Charles LA, Keller FG, et al. Topical thrombin and acquired coagulation factor inhibitors: clinical spectrum and laboratory diagnosis. *Am J Hematol*. 1994;45(2):128-135.
- 34.** Schoenecker JG, Johnson RK, Fields RC, et al. Relative purity of thrombin-based hemostatic agents used in surgery. *J Am Coll Surg*. 2003;197(4):580-590.
- 35.** Nelson PA, Powers JN, Estridge TD, et al. Serological analysis of patients treated with a new surgical hemostat containing bovine proteins and autologous plasma. *J Biomed Mater Res*. 2001;58(6):710-719.
- 36.** Winterbottom N, Kuo JM, Nguyen K, et al. Antigenic responses to bovine thrombin exposure during surgery: a prospective study of 309 patients. *J Applied Res*. 2002;2(1). <http://jrnlappliedresearch.com/articles/Vol2Iss1/winterbottom.htm>. Accessed July 29, 2008.
- 37.** Mathiasen RA, Cruz RM. Prospective, randomized, controlled clinical trial of a novel matrix hemostatic sealant in children undergoing adenoidectomy. *Otolaryngol Head Neck Surg*. 2004;131(5):601-605.

**Srinath Samudrala, MD**, is a neurosurgeon at Cedars-Sinai Medical Center, Los Angeles, CA.