Topical Thrombins: 
Benefits, Risks, and Economic Implications

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LEARNING OBJECTIVES

Upon reading this material, one should be able to:

1. Evaluate the topical biologic hemostatic agents currently used to control surgical bleeding.

2. Discuss the risk for antibody formation and immune response coagulopathy associated with bovine and human thrombins.

3. Describe the clinical implications of immune response coagulopathy.

4. Analyze the economic costs associated with immune response coagulopathy and common treatment interventions to control surgical bleeding.

In the United States, approximately 45 million surgical procedures are performed in the hospital setting each year. Of the potential perioperative complications, bleeding is especially common and occurs in roughly 24,000 of every 100,000 procedures. The risk for perioperative bleeding is higher in surgeries in which uncontrolled surface tissue bleeding occurs, as is seen in patients undergoing liver resections, those who have sustained trauma, and those with congenital or acquired coagulopathies. These outcomes require additional hospital resources (eg, blood supply, hospital beds), increasing related direct and indirect costs. In such cases, the transfusion of blood products is considered the standard treatment for perioperative bleeding. Transfusions can promote the cessation of surgical bleeding—hemostasis. Yet, they also carry a financial burden because of the costs associated with the availability and administration of blood and with transfusion-related complications. In cases of localized bleeding not amenable to suture ligation or electrocauterization, a
Perioperative bleeding is associated with poor outcomes of high-risk procedures. For example, although the overall mortality rate for both elective and urgent surgery is 0.1%, surgeries associated with an increased risk for bleeding carry much higher mortality rates of 5% to 8%, and surgeries associated with severe bleeding have mortality rates of up to 20%. In particular, cardiac and hepatic procedures are associated with high rates of perioperative bleeding and increased in morbidity and mortality, the duration of intensive care unit (ICU) stays, and overall length of hospital stays. In fact, investigators have reported that the incidence of excessive bleeding (defined as blood loss of >2 L) in cardiac surgery ranges from 5% to 7%, and that between 3.6% and 4.2% of patients undergoing these surgical procedures require reoperation because of perioperative bleeding.

In addition to its deleterious effects on clinical outcomes, perioperative bleeding results in increases in direct and indirect costs. The costs include those related to lost work productivity, prolongation of hospital and ICU stays, and significant use of clinical and staff resources during reoperation. Brown and colleagues reported that bleeding and reoperation in patients undergoing coronary artery bypass grafting resulted in increases in hospital resource utilization costs of approximately $12,000 and $19,000, respectively, per patient. Other investigators have reported that perioperative bleeding leads to excess costs of approximately $21,400 for every 1,000 discharges. However, these figures may still underestimate costs because the prolonged operative time and need for reoperation associated with bleeding may delay the surgeries of other patients, incurring additional expenses.

Transfusions: Value and Risks

The mainstay of treatment for perioperative bleeding is the transfusion of blood products. However, the need for a transfusion in a patient with perioperative bleeding entails a significant financial burden. During the last 20 years, the cost of a unit of blood has essentially quadrupled because of the gradual addition of sophisticated tests to detect transfusion-transmitted infections and the move toward universal leukoreduction. Additionally, the costs of acquiring, testing, distributing, and administering blood products are resource-intensive and costly. These burdens are expected to increase, and a recent analysis suggested that by 2010, a unit of blood may cost up to $500. Yet, none of these figures takes into consideration the full breadth of transfusion-related steps and procedures, and the true cost of a unit of blood is likely to be several times higher than the nominal price tag.

Blood transfusions are also associated with a variety of risks, including transmission of infectious diseases, transfusion-related lung injury, and allergic reactions. Several investigators have reported that blood transfusions are associated with worse outcomes in surgical and ICU patients, although it is not entirely clear whether this is a direct effect of the blood transfusion or whether the need for a blood transfusion is a marker for a poor outcome. Regardless, the length of hospital stay on average is about 2 to 2.5 times longer in patients who require transfusions. These potential adverse outcomes and the associated increase in hospital resources needed to address them further complicate the cost–benefit analysis of blood product transfusion.

Achieving Hemostasis

Hemostasis is another critical strategy for the treatment of perioperative bleeding. Hemostasis is usually established with the suture ligation of larger vessels and electrocauterization of small vessels. However, certain surgical procedures can result in bleeding that is not amenable to these techniques; examples include liver resection (in which diffuse raw surface bleeding may occur), spinal surgery (in which bone and the epidural venousplexus are exposed), and vascular surgery (in which needle hole bleeding from anastomotic graft sites may occur). Although the transfusion of plasma, platelet, or factor concentrates can promote hemostasis in these situations, they are limited by the same factors as are red blood cell transfusions—namely, the potential for adverse reactions and high costs. These limitations have led to the development and utilization of biologic agents that can be applied locally to sites of surgical bleeding to induce or enhance endogenous mechanisms of coagulation. The most widely used of these agents are the topical thrombins.

Topical Agents

Although the process of hemostasis is generally complete within a few minutes, an extensive wound may require primary closure and/or the use of hemostatic agents and devices. Fortunately, knowledge of the coagulation system has facilitated the development of targeted strategies to improve hemostasis in surgery. One critical component of the clotting cascade is thrombin, a plasma protein that is activated by both the intrinsic and extrinsic coagulation pathways. Activated thrombin converts fibrinogen to fibrin, which is polymerized and further crosslinked by factor XIII to form a fibrin clot. Thrombin also promotes platelet aggregation and activation, which further enhance clot formation.

On the basis of this mechanism of action, topical thrombin agents have been developed that can be applied directly to sites of bleeding during surgical procedures. In fact, thrombin has been used as a topical hemostatic agent for more than 60 years; an estimated $250 million is spent annually for the topical thrombins applied in more than 1 million surgical procedures—one could infer that an average of $250 is spent on each procedure. A topical thrombin can be applied directly to the wound site (eg, as a topical spray), delivered via hemostatic sponges (eg, gelatin or collagen sponges), or administered as
a component in fibrin and platelet sealants (eg, fibrin glues and platelet gels). The major differences in the efficacy, safety, and cost of thrombin products depend on whether the protein is derived from a bovine source, isolated from human plasma, or generated through recombinant techniques (Tables 1 and 2).

**Bovine Plasma–Derived Thrombin**

Bovine plasma–derived thrombin (Thrombin-JMI) is one of the most commonly used topical surgical hemostatic agents on the US market, with an average of 10,000 IU used per procedure. Following chromatographic purification and further processing by ultrafiltration, the product is supplied as a lyophilized formulation that can be applied to any wound as a dry powder or reconstituted in sterile saline and administered as a solution or spray. Solutions containing approximately 100 IU/mL are frequently used in plastic surgery, dental extractions, and skin grafting. Concentrations of 1,000 to 2,000 IU/mL may be required at sites where bleeding is profuse (eg, in the setting of liver or splenic abrasion). Intermediate strengths to suit the needs of the case may be prepared by diluting the contents with an appropriate volume of sterile isotonic saline.

**Bovine plasma–derived thrombin was originally developed with the mandate to reduce concerns regarding the transmission of viruses from pooled human plasma. Although the possibility of disease transmission from human plasma–derived products has been greatly reduced and recombinant hemostatic products have recently become available, most hemostatic agents still contain bovine thrombin.**

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**Figure. Coagulation cascade.**

The figure shows the stepwise activation of coagulation proteases leading to the generation of thrombin via both extrinsic and intrinsic coagulation pathways. Thrombin converts soluble fibrinogen to insoluble fibrin to form a stable clot and to promote platelet aggregation.
Bovine thrombin is used in an extensive array of procedures, including but not limited to neurologic, orthopedic, general, cardiac, thoracic, vascular, gynecologic, head and neck, and dental surgeries. Thrombin also is commonly used to promote thrombosis to treat vascular pseudoaneurysms and to stop bleeding from cannulation sites in dialysis access grafts. Various clinical trials have demonstrated the efficacy of bovine thrombin in promoting hemostasis in a variety of surgical settings.

Despite its efficacy in promoting hemostasis, bovine thrombin is associated with significant safety concerns, particularly in regard to its immunogenicity. First, the use of bovine thrombin is contraindicated in any patient with hypersensitivity to proteins of bovine origin. Second, initial exposure to topical thrombin may result in sensitization to the product and subsequent immunoglobulin E (IgE)-mediated anaphylaxis on reexposure. Tadokoro and colleagues used a simple skin test to characterize the immune response to bovine thrombin and to identify patients at risk for bovine thrombin–induced anaphylaxis and found that anti-bovine thrombin IgE antibodies develop in at least 11% of patients exposed to bovine thrombin preparations.

The risk for this adverse effect is compounded because no systematic mechanism or central repository exists to document prior exposure to bovine thrombin and that no commercial assay for anti-bovine thrombin IgE is readily available.

Bovine preparations contain small amounts of bovine prothrombin, thrombin, and factor V. Because there is approximately 70% homology between bovine and human coagulation factors, exposure to topical bovine thrombin can result in the development of anti-bovine and anti-human antibodies to any of these components. In fact, a prospective study demonstrated that antibodies to 1 or more bovine coagulation proteins developed in 94.3% of exposed patients, and that antibodies to human coagulation factors, mainly against human factor V and thrombin, developed in 51% of patients. Other studies have reported that cross-reactivity with human factors occurs independently of the thrombin dose or prior surgical procedure, and that the levels of antibodies against human and bovine proteins tend to peak at approximately 4 to 8 weeks postoperatively but may persist at 10 years after exposure. Other studies have reported incidence rates of autoantibody development ranging from 20% to 90%. Factors underlying the variability in the
reported rates of immunogenicity include the method of thrombin purification, type of surgery, method of assay, and history of previous exposure. Regardless, most studies are in agreement that exposure to bovine topical thrombin is the most common cause of acquired factor V inhibitor.39

The development of antibodies against endogenous or xenogenic clotting factors can have significant clinical implications. Various case studies have described alterations in laboratory parameters of coagulation and severe bleeding or thrombosis associated with this form of autoimmunity.40-46 Although the potential development of factor V inhibitors is well recognized, the lack of a commercially available antibody assay makes clinical investigation of this possibility in patients with bleeding or thrombotic complications difficult. More importantly, very little consensus has been reached on the management of immunogenicity secondary to exposure to topical bovine thrombin. For example, Streiff and Ness proposed that patients with asymptomatic elevation of their coagulation parameters might be carefully monitored for signs of bleeding, whereas those with mild to moderate bleeding might be managed initially with steroids and supportive transfusions.39 Other investigators have used I.V. immunoglobulin therapy or plasma manipulation via double-volume exchange transfusion to reduce antibody titers and establish hemostasis in patients with suspected or proven autoantibody-induced coagulopathy.40

Although no studies of the economic implications of these risks have been conducted, the high incidence of autoantibody formation resulting from the use of topical bovine thrombin preparations and the associated potential complications are likely to have an adverse impact on the balance between the cost of reducing perioperative bleeding and the benefit of using topical agents. Even minor coagulopathy in the postoperative setting can result in significant complications, worse outcomes, and high health care costs.39

**Human Plasma–Derived Thrombin**

Human plasma–derived thrombin is isolated by the chromatographic purification of prothrombin from pooled cryo-poor

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**Table 2. Topical Thrombin Agents: Properties**

<table>
<thead>
<tr>
<th>Product</th>
<th>Immunogenicity</th>
<th>Theoretical Risk Of Transmissible Disease</th>
<th>Contraindications</th>
<th>Warnings/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evt throm</td>
<td>++</td>
<td>++</td>
<td>Do not inject directly into circulatory system</td>
<td>May carry risk for transmission of infectious agents (viruses and Creutzfeldt-Jakob disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity to or anaphylaxis in response to human blood products</td>
<td>Potential risk for thrombosis if absorbed systemically</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not for use in treatment of severe or brisk arterial bleeding</td>
<td></td>
</tr>
<tr>
<td>Gelfoam Plus</td>
<td>++</td>
<td>++</td>
<td>Do not use in closure of skin incisions</td>
<td>May carry risk for transmission of infectious agents (viruses and Creutzfeldt-Jakob disease)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not place in intravascular compartments because of the risk for embolization</td>
<td>Do not use for controlling postpartum bleeding or menorrhagia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recothrom</td>
<td>+</td>
<td>NA</td>
<td>Do not inject directly into circulatory system</td>
<td>Potential risk for thrombosis if absorbed systemically</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not for use in treatment of massive or brisk arterial bleeding</td>
<td>Hypersensitivity to hamster proteins or other components</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity to bovine-origin materials</td>
<td></td>
</tr>
<tr>
<td>Thrombin-JMI</td>
<td>++++</td>
<td>+</td>
<td>Do not inject directly into circulatory system</td>
<td>Risk for abnormalities of hemostasis secondary to antibody formation (boxed warning)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not for use in treatment of massive or brisk arterial bleeding</td>
<td>Theoretical risk of prion disease transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitivity to bovine-origin materials</td>
<td></td>
</tr>
</tbody>
</table>

*The use of + indicates the potential and degree for the respective properties.

Although the topical thrombin products vary in terms of the relative risk for transmissible disease, the absolute risk for transmissible disease for each product remains very low.

NA, not applicable

Based on references 16,18-21, and 27.
human plasma obtained from plasma collection centers licensed by the United States. Individual plasma units are evaluated with FDA-licensed serologic tests for hepatitis B and C virus, HIV, and parvovirus. The manufacturing process includes 2 targeted steps for the inactivation or removal of viruses.

Human plasma–derived thrombin is supplied as vials of 2.5 or 20 mL of frozen solution containing 800 to 1,200 IU/mL (Evithrom). The amount required depends on the area of tissue to be treated and the method of application. Another formulation of human plasma–derived thrombin is utilized in conjunction with an absorbable gelatin sponge (Gelfoam Plus). Human plasma–derived thrombin was compared with bovine thrombin in a prospective, randomized, controlled, double-blind Phase III study of 305 subjects at 22 centers in the United States. Subjects undergoing elective cardiovascular, neurologic (spinal), or general surgical procedures were randomized to the local application of bovine thrombin or of human plasma–derived human thrombin when oozing or bleeding of mild intensity could not be controlled by other surgical techniques. The proportions of patients in whom hemostasis was achieved within 10 minutes (primary outcome) were equivalent for human plasma–derived human thrombin and bovine thrombin (97.4% vs 97.4%, respectively; odds ratio, 1.00; 95% confidence interval [CI], 0.96-1.05). The proportions of patients in whom hemostasis was achieved at 6 minutes (94.8% vs 92.8%) and 3 minutes (73.2% vs 72.4%) were also equivalent.

Human plasma–derived thrombin has been used in an effort to overcome the problems associated with the immunogenicity of bovine thrombin. However, the use of human plasma–derived thrombin reduces, but does not eliminate, the potential for the development of autoantibodies against other coagulation factors. In a clinical study, serum samples were collected at baseline and at 5 weeks after surgery for the evaluation of antibodies to bovine thrombin, bovine factor V/Va, human thrombin, and human factor V/Va. Investigators reported that antibodies to any of the 4 antigens developed in 3.3% of the subjects treated with human plasma–derived thrombin and in 12.7% of the subjects treated with bovine thrombin. None of the patients treated with human plasma–derived thrombin developed detectable antibodies to human thrombin or human factor V/Va; of the subjects treated with bovine thrombin, 7.9% developed antibodies to bovine thrombin, 9.52% developed antibodies to bovine factor V/Va, 2.4% developed antibodies to human thrombin, and none developed antibodies to human factor V/Va. Regardless, autoantibody-induced coagulopathy remains a theoretical concern associated with plasma-derived human thrombin.

Although concerns regarding the transmission of bloodborne pathogens by pooled human plasma–derived thrombin have been largely reduced by improved processing, the use of an agent derived from purified plasma still carries a risk for the transmission of pathogens. The development of Creutzfeldt–Jakob disease in humans exposed to prion-contaminated blood products is one of these concerns. Especially given the long latency and invariably fatal outcome of the disease and the lack of screening tests and purification methods, although human plasma–derived thrombin appears to be less immunogenic, persistent concerns regarding potential autoantibody-induced coagulopathy as well as the need for extensive testing in regard to transmissible diseases could impact the effectiveness of treatment with this agent.

Recombinant Human Thrombin

In an effort to eliminate the risks for transmissible diseases and immunogenicity associated with products derived from animal or pooled human blood components, recombinant DNA technology has been used to produce these therapeutic proteins in vitro. Recombinant thrombin (RecoThrom) is a human sequence thrombin protein expressed in and isolated from a genetically modified Chinese hamster ovary (CHO) line. The recombinant thrombin precursor is secreted into culture medium as a single-chain form that is proteolytically converted into a 2-chain active form. Subsequent purification by a chromatographic process yields a high-purity product with hemostatic activities similar to those of native human thrombin. The CHO cell line used to manufacture recombinant thrombin has been extensively tested and shown to be free of known infectious agents. Furthermore, the purification process includes solvent–detergent treatment and nanofiltration—steps dedicated to the clearance of any viral contamination.

The product is supplied in 5,000- and 20,000-IU vials of lyophilized powder that can be reconstituted in sterile saline to yield a solution containing 1,000 IU/mL and applied to the site of bleeding either alone or in combination with an absorbable gelatin sponge. The amount required depends on the area of tissue to be treated and can vary widely depending on the nature and extent of bleeding.

Preclinical trials demonstrated that topical recombinant thrombin was safe in animals, and a Phase II trial demonstrated that it was well tolerated and minimally immunogenic. These findings led to the evaluation of recombinant thrombin in a Phase III study of 411 subjects undergoing spinal surgery, hepatic surgery, peripheral arterial bypass surgery, or placement of an arteriovenous graft. The randomized, double-blind, controlled study, conducted at multiple sites, compared recombinant thrombin with bovine thrombin, each at a nominal concentration of 1,000 U/mL. The agents were topically applied to sites of bleeding with an absorbable gelatin sponge. Overall, hemostasis was achieved within 10 minutes at equivalent rates in the 2 groups (in 95.4% of subjects in the recombinant thrombin arm and in 95.1% of subjects in the bovine thrombin arm). In a post hoc analysis of patients undergoing peripheral arterial bypass surgery, hemostasis was achieved at 3 minutes in a significantly greater proportion of those receiving recombinant thrombin (55%) than of those receiving bovine thrombin (39%; 95% CI, 0.55-0.76).

The development of anti-product antibodies, a prespecified study end point, was also reported in the pivotal Phase III study. Blood samples were collected at baseline and at day 29 from 97% of the subjects in both treatment groups. Specific anti–recombinant thrombin product antibodies developed in 3 of 198 patients in the recombinant thrombin arm (1.5% [95% CI, 0 to 4%]–anti–CHO host cell protein antibodies also developed in 1 patient—and antibodies to prothrombin activated free thrombin developed in none of these subjects. Also, none of the antibodies in the recombinant thrombin group neutralized native human thrombin. By contrast, specific antibodies to bovine thrombin product developed in 43 of 200 subjects (22%; 95% CI, 16% to 28%) in the bovine thrombin arm.

Although these data clearly demonstrate that recombinant thrombin is less immunogenic than bovine thrombin, the development of antibodies in either group did not lead to any adverse
events, such as excessive bleeding. However, a post hoc analysis reported that the presence of anti-bovine thrombin antibodies was associated with a numeric but not statistically significant increase in coagulopathy, which is consistent with observations from other studies.16

Regardless, further research is required to definitively determine whether the reduced immunogenicity of recombinant thrombin translates into a lower incidence of coagulopathy and other adverse events. If this supposition proves true, then the cost-to-benefit ratio of recombinant thrombin, with its reduced potential for transmitting diseases, precluding the need to screen for transmissible diseases, and its lower potential for causing adverse effects, would be more favorable than that of either bovine thrombin or human plasma–derived thrombin.

Cost Considerations for Topical Thrombins

No direct evidence is available on the cost-to-benefit profile of topical thrombin preparations, as noted earlier. Based on Lawson’s data, it can be inferred that their average direct cost should be around $250 per surgical procedure.17 The complications discussed before (e.g., antibodies, coagulopathy) would add to this cost, but it should be noted that such complications occur in only a fraction of the recipients and become clinically significant (and result in additional costs) in yet a smaller number of cases. Moreover, the newer agents (e.g., recombinant human thrombin) are expected to have a more favorable safety profile.

These costs are to be compared with the widely discussed costs associated with bleeding and transfusion, which can easily amount to several hundred dollars per unit of blood transfused and several thousand dollars per surgical patient with excessive bleeding.12 The ultimate question to answer is, what is the number of cases that must be treated with these agents to prevent the transfusion of a unit of blood or to prevent a case of significant surgical bleeding? Although these issues are still under investigation, it is not unreasonable to assume for now that the use of topical thrombins is cost-effective, especially in procedures in which a large amount of bleeding is anticipated, and in patients who are at higher risk for requiring transfusions.

The Pharmacist’s Role

By 1996, clinical reports of immune-mediated events prompted the FDA to require that a black box appear on all bovine thrombin products, warning specifically against reexposure to bovine thrombin.16 Since that specific warning was issued, numerous cases of antibody-related complications in diverse surgical settings have been reported,42,46 suggesting that patients and their physicians are largely unaware of the risks associated with exposure to bovine thrombin.

Despite the availability of other thrombin agents, bovine thrombin is used in more than 1 million surgeries in the United States each year, increasing the risks for immune-mediated coagulopathy.18 With 3 FDA-approved topical derivatives available for coagulation and with the lack of specific medical society guidelines as to which specific agent to use, it becomes imperative that clinicians be educated about the benefits and risks associated with the use of each thrombin.

Hospital pharmacists play a critical role in the selection of these agents and thus need to be aware of the prevalence of perioperative bleeding and the hemostatic agents available to control blood loss. Furthermore, pharmacists should be aware of the most recent data regarding cost–benefit ratios and immunogenicity, and of the ongoing debate about the relationship between immunogenicity and adverse events, so that they can influence the selection of the optimal agent that will produce a safe and efficacious outcome while simultaneously decreasing health care expenditures related to the management of adverse events.

Conclusion

Perioperative bleeding is a relatively common complication, particularly in certain high-risk patients or procedures, and results in unfavorable outcomes and increased health care expenditures. Although commonly used for the treatment of perioperative bleeding, the transfusion of blood products is complicated by limited efficacy, adverse events, and the high costs of acquisition, screening, and administration. Topical thrombin products are a useful adjunct with which to promote hemostasis in patients with localized surgical bleeding. Of the available topical thrombins, human plasma–derived thrombin is associated with a risk for transmitting disease, and both bovine thrombin and human plasma–derived thrombin are associated with immunogenicity that may cause coagulopathic complications. By contrast, the immunogenicity of recombinant thrombin is minimal in comparison with that of other products, and recombinant thrombin is not associated with the transmission of disease. If the link between immunogenicity and coagulopathic complications bears out in future studies, then efficacy and cost–benefit analysis favors the use of recombinant thrombin over the other topical thrombin agents. Pharmacists play a critical role in guiding the appropriate use of topical thrombin agents and should be aware of the current data regarding their comparative efficacy, safety, and cost–benefit profiles.

References

2. Reilly AF, Reilly PM. Medical injuries can increase mortality and incur additional costs. Evid Based Healthcare. 2004;966:62.


