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A Review of Topical Thrombin by Dragos Plesca, Pharm.D., Ph.D.

Introduction: After cardiovascular surgical interventions, abnormal blood loss occurs in 3% to 14% of cases. Post-operative hemorrhage control is managed in several ways, and more than one method may be used to achieve hemostasis. In addition to surgical re-exploration, blood products (e.g., platelets, plasma, cryoprecipitate, or red blood cells) or the administration of injectable pharmacological agents such as desmopressin (DDAVP[®]), tranexamic acid (Cyklokapron[®]), aminocaproic acid (Amicar[®]), or Factor VIIa (NovoSeven[®]) are used. Additionally, another hemostatic agent used is topical thrombin. Since it was initially approved by the Food and Drug Administration (FDA) more than 60 years ago, topical thrombin has been used in a variety of surgeries including cardiac, thoracic, vascular, neurology, orthopedic, gynecology, head and neck, and dental. Currently, there are three commercially available FDA-approved thrombin products: bovine thrombin, human purified thrombin, and recombinant human thrombin (See Table 1).

Regardless of the initiating event, coagulation is the result of fibrin formation and stabilization. Fibrin results from the conversion of fibrinogen under the catalytic activity of thrombin. In addition to its role in the common pathway of the coagulation cascade, thrombin also causes vasoconstriction which facilitates hemostasis.

Despite its efficacy in achieving hemostasis through bypassing the initial steps of the coagulation pathway, the use of thrombin has been associated with an increased risk of anaphylaxis, thrombosis, and immune-mediated coagulopathy (IMC). The manifestations associated with IMC range from asymptomatic alterations in coagulation tests (e.g., prothrombin time, activated partial thromboplastin time, international normalized ratio, or thrombin time) to severe hemorrhage and death. Immune-mediated coagulopathy may result from the emergence of cross-reacting antibodies against thrombin and factor V, which the original FDA-approved bovine thrombin contained as an impurity. Cross-reacting antibodies against human thrombin and factor V are from the 75% homology that human and bovine clotting factors share.

These antibodies may be detected as early as 1 to 2 days after administration, may peak at 4 to 8 weeks post-exposure, and may persist for years following re-exposure of the patient to the thrombin-containing product. These antibodies inhibit thrombin and factor V at that convergence of the intrinsic and extrinsic coagulation pathways and can profoundly alter clot formation resulting in abnormal coagulation.

Table 1. Comparison Between Commercially Available Thrombin Products

	Bovine Thrombin (Thrombin-JMI®)						Human Thrombin (Evithrom®)	Human Recombinant Thrombin (Recothrom®)
Formulation	Pad	Powder for Reconstitution				Sponge	Solution (topical)	Powder for Reconstitution (topical)
		Powder	Epistaxis Kit	Spray Kit	Syringe Spray Kit			
Strength	≥200 units	5,000 units and 20,000 units	5,000 units	20,000 units	20,000 units	≥1000 units and ≥2000 units	800-1200 int. units/mL (2 mL, 5 mL, and 20 mL)	5,000 units and 20,000 units
FDA-approved	1995						2007	2008
Manufacturer	King Pharmaceuticals						OMRIX Biopharmaceuticals	ZymoGenetics
Warning	Black Boxed – Patients with antibodies to bovine thrombin should not be re-exposed						None	None
Average Wholesale Price (AWP)	\$43	\$87, \$345	\$90	\$362	\$362	\$59, \$142	\$82, \$117, \$458	\$104, \$420
Formulary	No	Yes	Yes	Yes	Yes	No	No	No

Bovine thrombin: Bovine thrombin (Thrombostat®, Parke-Davis) was the first thrombin product to be approved by the FDA in 1943. Afterwards, the following products received FDA-approval: Thrombinar® (Armour Pharmaceutical Co, 1982), Thrombogen® (Ethicon Inc., 1986), and Thrombin-JMI® (King Pharmaceuticals Inc., 1995). The purity of bovine thrombin ranged from 20% to 30% with early bovine products to 81% to 96% with later products (e.g., Thrombin-JMI®). The incidence of IMC is 95% with the earlier products (Thrombostat®, Thrombinar®, and Thrombogen®) but only 10% with Thrombin-JMI®. In 2008, Thrombin-JMI® underwent a manufacturing change involving chromatographic purification which resulted in very low factor V concentrations (<92 ng/mL). However, the incidence of IMC with the new, purified form of Thrombin-JMI® is unknown.

In 1996, the FDA placed a black-boxed warning on all bovine thrombin products to warn that bovine-source topical thrombin may be associated with abnormal hemostasis, ranging from asymptomatic laboratory alterations to severe bleeding and/or thrombosis. Consequently, it is recommended that patients who have developed antibodies to bovine thrombin should not be re-exposed to bovine thrombin-containing preparations, and if further invasive interventions are necessary, different hemorrhagic control methods should be considered. Furthermore, the incidence of IMC may be underestimated, because of not being diagnosed or the bleeding is attributed to other causes of coagulopathies (e.g., therapeutic anticoagulation, hemodilution, sepsis, disseminated intravascular coagulation, liver disease, and vitamin K deficiency). These other causes would have to be ruled out before IMC can be diagnosed.

Bleeding may not occur until months after bovine thrombin exposure due to delayed production of anti-thrombin antibodies which contributes to misdiagnosis and underreporting of these cases. Additionally, poor documentation in patient medical records of the use of medical devices containing bovine thrombin (e.g., fibrin sealants, gelatin sponges and granules, gauze sponges, collagen, or cellulose preparations) can lead to the inadvertent re-exposure of patients to bovine thrombin and result in the production of anti-thrombin antibodies. Several different treatment approaches have been attempted in patients with anti-thrombin antibodies that were symptomatic. The use of corticosteroids has been suggested in treating mild bleeding cases while red blood cells and platelets transfusion may be useful as the factor V contained in the platelet granules has not been exposed to circulating antibodies. However, in more severe cases aggressive immunosuppression with cyclophosphamide, azathioprine, cyclosporine or even the use of intravenous immunoglobulin or plasmapheresis may be needed.

Human purified thrombin: Human purified thrombin (Evithrom[®], Johnson & Johnson) was approved by the FDA in 2007. The manufacturing process involves purification from pooled, human plasma followed by inactivation and removal of viruses; therefore, human purified thrombin has a risk of carrying different infectious agents such as viruses. To date, no cases of viral seroconversion have been reported in the United States, but the FDA-approved product labeling carries a warning with respect to potential infectious agents. Another concern with the use of human purified thrombin is its stability. It is recommended to be stored in the freezer and after thawing, it is stable for no more than 30 days when refrigerated or for no more than 24 hours when stored at room temperature.

A Phase III randomized, double-blind, multicenter study by Doria and colleagues evaluated the efficacy and safety of human purified thrombin (Evithrom[®]) compared to bovine thrombin (Thrombin-JMI[®]) in 305 patients undergoing elective cardiovascular, neurologic, or general surgical procedures. The incidence of hemostasis within 10 minutes was the same between the human purified thrombin and bovine thrombin [97.4% vs. 97.4%, respectively (95% CI, 0.96 to 1.05; p=NS)]. Seroconversion or an increase of ≥ 1 unit in antibody titer was observed in 3.3% patients administered human purified thrombin compared to 12.7% of patients administered bovine thrombin (p=0.01). The authors concluded that human purified thrombin and bovine thrombin have similar efficacy and comparable safety profiles.

Human recombinant thrombin: The newest topical thrombin product received FDA approval in 2008 and is known as human recombinant thrombin (Recothrom[®], ZymoGenetics Inc). Human recombinant thrombin is obtained through activation of prothrombin-1 by snake venom enzymes; therefore, caution is recommended when used in patients who are allergic to snake venom. The highly controlled purification steps ensure that the final product is free of non-thrombin impurities and infectious agents.

A Phase III, randomized, double-blind, multicenter trial by Chapman and colleagues compared the efficacy and safety of human recombinant thrombin (Recothrom[®]) and bovine thrombin (Thrombin-JMI[®]) for hemorrhage management in 463 adult patients undergoing liver resection, spinal surgery, peripheral arterial bypass surgery, or dialysis access surgery. The primary efficacy endpoint was the incidence of hemostasis within 10 minutes. This endpoint was achieved in 95.4% of patients treated with human recombinant thrombin compared to 95.1% of patients receiving bovine thrombin (95% CI, -3.7 to 5.0; p=NS). The incidence of anti-thrombin antibody formation was 1.5% (3/198 patients) in the human recombinant thrombin group and 21.5% (43/200 patients) in the bovine thrombin group (p<0.001). Patients with antibodies against bovine thrombin had numerically higher incidences of bleeding or thromboembolic events compared to patients without these antibodies (19% and 13%, respectively). The authors concluded that the human recombinant thrombin had comparable efficacy, a similar safety profile, and was less immunogenic than the bovine thrombin.

Another Phase III, randomized, double-blind, multicenter study by Weaver and colleagues assessed the efficacy and safety of human recombinant thrombin (Recothrom[®]) compared to bovine thrombin (Thrombin-JMI[®]) as adjuncts to surgical hemostasis. The study enrolled 164 patients undergoing peripheral arterial bypass or arteriovenous graft procedures. The primary endpoint was incidence of hemostasis at 1.5-, 3-, 6-, and 10-minutes, while the secondary endpoint was seroconversion, or ≥ 1 unit increase in anti-thrombin antibody titer at day 29. The incidence of hemostasis at 10 minutes was comparable between the two groups (human recombinant thrombin 91% compared to bovine thrombin 94%; p=0.28). No patients in the human recombinant thrombin group developed anti-recombinant thrombin antibodies at day 29 while 27% of patients who received bovine thrombin developed antibodies (p<0.0001). The authors concluded that the human recombinant and the bovine thrombin had similar efficacy as topical hemostatics, while the human recombinant thrombin demonstrated a significantly lower immunogenicity.

Finally, a Phase IIIb, open-label, single-group, multicenter study by Singla and coworkers examined the risk for secondary immune response to bovine thrombin in patients being treated with human recombinant thrombin while undergoing spinal or vascular surgical interventions. The trial enrolled 209 patients whose anti-thrombin antibody status was evaluated at baseline and approximately 29 days post-exposure. All patients had documented (45%) or highly likely (55%) prior exposure to bovine thrombin-containing products. Of the 200 patients that were evaluated for immunogenicity, 15.5% were seropositive for anti-bovine thrombin antibodies while 2% were seropositive for anti-recombinant human thrombin antibodies. However, none of these patients became seropositive for the anti-recombinant human antibodies or had a ≥ 10 -fold increase in their antibody titer. The authors concluded that these results confirmed the low immunogenicity of human recombinant thrombin, and it could be safely used in the hemorrhage control in patients with or without preexisting anti-bovine thrombin antibodies.

Formulary: The current topical thrombin products on the Cleveland Clinic Formulary are: Thrombin-JMI® (5000 units and 20,000 units), Thrombin-JMI Epistaxis Kit (5000 units), Thrombin-JMI® Spray Kit (20,000 units), and Thrombin-JMI® Syringe Spray Kit (20,000 units).

Conclusion: Topical thrombin is a hemostatic agent commonly used in a wide variety of surgical interventions. The use of bovine-derived thrombin products has resulted in the appearance of anti-thrombin antibodies which may cause abnormal coagulation and lead to severe bleeding. In the near future, more information regarding the immunogenicity of the new, highly purified form of Thrombin-JMI® as well as that of the human recombinant thrombin will emerge. Human recombinant thrombin can be considered as a safe and effective agent for future surgical interventions in patients who were previously exposed to bovine-derived thrombin.

References:

1. Boucher BA, Traub O. Achieving hemostasis in the surgical field. *Pharmacother* 2009 Jul;29(7 Pt 2):2S-7S.
2. Dunn B, Uber W, Ikonomidis JS. Topical thrombin preparations and their use in cardiac surgery. *Open Access Surgery* 2009;2;15-34.
3. Ortel TL, Mercer MC, Thames EH, Moore KD, Lawson JH. Immunologic impact and clinical outcomes after surgical exposure to bovine thrombin. *Ann Surg* 2001;233:88–96.
4. Greenhalgh DG, Gamelli RL, Collins J, Sood R, Mozingo DW, Gray TE, et al. Recombinant thrombin: safety and immunogenicity in burn wound excision and grafting. *J Burn Care Res* 2009;30:371–9.
5. Chapman WC, Singla N, Genyk Y, McNeil JW, Renkens KL Jr, Reynolds TC, 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;205:256–65.
6. 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 Mar;24(3):785-94.
7. Weaver FA, LewW, Granke K, Yonehiro L, Delange B, Alexander WA, et al. A comparison of recombinant thrombin to bovine thrombin as a hemostatic ancillary in patients undergoing peripheral arterial bypass and arteriovenous graft procedures. *J Vasc Surg* 2008;47:1266–73.
8. Singla NK, Ballard JL, Moneta G, Randleman CD Jr, Renkens KL, Alexander WA. *J Am Coll Surg*. 2009 Jul;209(1):68-74.

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