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Introducing a New Topical Hemostatic Agent

Advances in hemostasis agents and techniques can help address the unique bleeding challenges encountered in vascular surgery patients. This review discusses the first and only FDA-approved recombinant human thrombin.

BY ALLAN ALEXANDER, MD

One of the underlying challenges in any surgical procedure is to maintain or regain hemostasis. Classic surgical training reinforces the axiom that careful attention to surgical hemostasis can help reduce blood loss and transfusion and ultimately improve patient outcomes. There are many challenges to hemostasis in the vascular surgery population due to advanced age at presentation, prior procedures/medical history, and the use of prophylactic anticoagulant and antiplatelet medications. Fortunately, advances in preoperative assessment, perioperative care, and topical hemostatic agents have provided new tools for managing hemostasis in surgery. This article highlights a new hemostatic agent developed through the use of recombinant DNA (rDNA) technology.

FACTORS THAT IMPAIR HEMOSTASIS

Complications that affect bleeding in vascular surgery procedures may be related to technical or pathophysiologic factors. In addition, patients who require surgery may be receiving prophylactic or therapeutic anticoagulant medications, which create additional hemostasis challenges. Among the technical causes of intraoperative bleeding are suture line breakage, suture malfunction or malposition, anatomical variation, and unrecognized vascular injury.

Pathophysiologic factors, such as hypothermia and acidosis, may slow the coagulation cascade and impair platelet function; furthermore, loss of adequate blood volume and associated clotting factors can affect hemostasis. Tissue injury, vasculopathy, vascular and extravascular volume shifts, and illness during and after surgery can also disrupt the physiologic balance.¹ Perioperative complications and iatrogenic factors add to the risks of bleeding, including infection, transfusion-related reactions, prolonged procedures, postoperative coagulopathy, and anticoagulant medications.^{2,3} Given the complex and diverse nature of these bleeding challenges, numerous techniques and agents have been developed to speed hemostasis. Once major vascular

bleeding has been controlled and after adequate fluid resuscitation, pharmacologic intervention, including topical and systemic hemostatic agents, may be indicated.

USE OF TOPICAL THROMBIN

Topical hemostatic agents are useful adjuncts in vascular surgery. They are categorized by their mechanism of action and composition and can be considered passive or active, depending on the absence or presence of thrombin.

Thrombin, the central, critical component in coagulation, is formed through a highly regulated series of amplification reactions. Thrombin converts fibrinogen to fibrin and activates platelets and factor XIII. The thrombus develops as gelatinous fibrin polymers bind and entrap additional platelets and red blood cells, gaining added strength from factor XIII-induced cross-linking that ultimately results in hemostasis.

The first report by Warner in 1939 of recognizable efficacy with topical thrombin led to its preparation and use in surgery.⁴ In the ensuing decades, and long before the era of controlled clinical trials, the prominent clinical utility of topical thrombin led to widespread clinical acceptance. Up until recently, only thrombin derived from either bovine or human plasma sources was applied topically in a variety of surgical settings. Thrombin is also included as a hemostatic component in vascular sealing devices, wound dressings, and fibrin sealants. In 2007, an estimated 1 million patients in the US underwent surgical procedures in which topical thrombin was used as a hemostatic agent.⁵

PLASMA-DERIVED THROMBINS

Bovine Thrombin

Thrombin purified from bovine plasma has been used in surgery for more than 60 years; it continues to be widely used and is currently available from King Pharmaceuticals, Inc. (Bristol, TN) as Thrombin-JMI®.^{1,5} In recent years, however, clinicians and researchers have raised concerns about the

immunogenicity of topical bovine thrombin.⁵ In 1990, researchers isolated and characterized antibodies to bovine thrombin and factor V. They demonstrated that high-affinity anti-bovine thrombin antibodies had significant cross-reactivity to human thrombin.⁶

Subsequent research and case reports indicated that bovine-derived thrombin preparations may induce an array of antibodies to coagulation factors associated strongly with hemorrhagic and thrombotic complications.⁷ Clinical studies have suggested that after initial exposure to bovine-derived thrombin preparations, subjects may develop antibodies to the product or its contaminants (eg, bovine factor V), occurring anywhere from 4 to 8 weeks after exposure.⁸⁻¹⁵ Topical bovine thrombin is labeled with a boxed warning regarding the risks of immunogenicity.¹⁶ Because it is an animal-derived protein, bovine thrombin has the potential for antibody development in humans due to differences in amino acid sequences and expression of species-specific epitopes.¹⁷

Human Plasma Thrombin

Thrombin purified from human plasma (Evithrom™, Omrix Biopharmaceuticals, Ltd., Kiryat Ono, Israel) was approved by the FDA as a topical hemostat in August 2007. A randomized, double-blind, controlled clinical study showed that Evithrom was as effective as a bovine plasma-derived thrombin in achieving hemostasis within 10 minutes and resulted in a similar adverse event profile.⁹ The risk of transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viral infections, and by inactivating and removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.¹⁸

The risks associated with thrombin derived from bovine and human plasma created a demand for a plasma-free source of thrombin for topical surgical hemostasis.

USE OF RECOMBINANT DNA TECHNOLOGY

Recombinant DNA (rDNA) results from transplanting or splicing genetic material from one species into the genome of a cell line derived from a different species. The recombinant DNA becomes part of the cellular genetic makeup, resulting in cells that are programmed to produce the protein encoded by that DNA. Numerous products for treating or immunizing against disease have been produced using rDNA technology, starting in 1978 with recombinantly manufactured human insulin. Since that breakthrough, rDNA techniques have been used to manufacture erythropoietin and growth hormone, as well as factors VII, VIII, IX, tissue plasminogen activator, and the vaccine against hepatitis B. Well-recognized benefits of these products include consistent supply and reduction of risks associated with plasma-derived therapies.

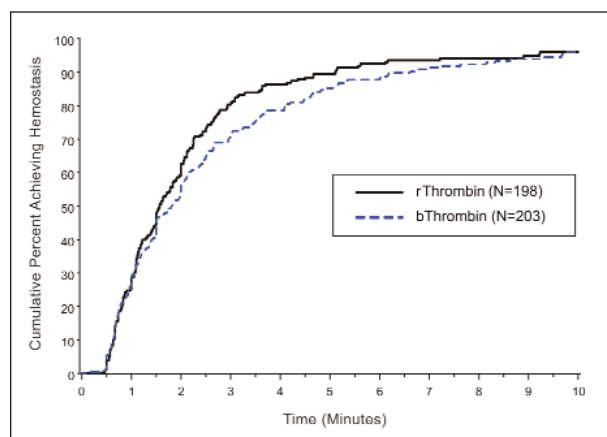


Figure 1. Cumulative incidence of hemostasis over time (rThrombin, recombinant thrombin; bThrombin, bovine thrombin).*

*Three observations in each treatment arm were censored early; observations for 13 additional patients (7 bThrombin; 6 rThrombin) were censored at 10 minutes because hemostasis was not achieved.

RECOMBINANT THROMBIN FOR SURGICAL HEMOSTASIS

Given the utility and widespread use of topical thrombin in the surgical setting and the risks associated with plasma-derived thrombins, recombinant DNA technology was used to develop an alternative topical thrombin that is plasma-free.

In Vitro and Nonclinical Studies Establish Pharmacological Activity

Recombinant thrombin has been shown to be identical in amino acid sequence and structurally similar to native human thrombin. In vitro studies have demonstrated that rThrombin has hemostatic activities similar to those of human plasma-derived thrombin and binds to endogenous inhibitors such as anti-thrombin-III and alpha-2 macroglobulin.¹⁹

The cell line used to manufacture rThrombin has been extensively tested and shown to be free of known infectious agents. The cell culture process used for the manufacture of rThrombin employs no additives of human or animal origin. Studies in animal models have shown that rThrombin applied topically either with a gelatin sponge or spray significantly reduces time to hemostasis when compared to saline control.

Phase 3 Trial Demonstrates Safety, Efficacy of rThrombin

A randomized, double-blinded, pivotal phase 3 clinical trial was conducted at 34 US medical centers to compare the efficacy, safety, and immunogenicity of topical rThrombin and bovine thrombin in surgical hemostasis.⁸ Patients undergoing liver resection, spine, peripheral artery bypass, or dialysis access surgery were randomized to receive rThrombin or bovine thrombin. Enrollment was balanced among surgery types, and baseline demographics were bal-

anced between treatment groups. The primary efficacy endpoint was time to hemostasis. Incidence of hemostasis was similar between treatment groups; 95.4% of patients receiving rThrombin and 95.1% of patients receiving bovine thrombin achieved hemostasis within 10 minutes (Figure 1).

The incidence and severity of adverse events observed in the phase 3 study were similar between treatment groups. The most common adverse events included incision-site complications, nausea, procedural pain, constipation, and vomiting. These adverse events are not uncommon in patients undergoing the types of surgeries evaluated in the study. ZymoGenetics and the FDA concluded that there were no adverse events thought to be causally related to rThrombin application.

Although comparable in efficacy and safety profile, the two thrombins were quite different in immunogenicity. Blood samples were collected from patients at baseline and day 29 to evaluate the presence of antiproduct antibodies. At baseline, fewer patients receiving rThrombin (n=3/198, 1.5%) had antiproduct antibodies than patients receiving bovine thrombin (n=10/200, 5%). The incidence of post-treatment antiproduct antibody development was significantly less in the rThrombin group (n=3/198 or 1.5%) compared with the bovine thrombin group (n=43/200 or 21.5%) (Figure 2). None of the antibodies to rThrombin product neutralized human thrombin. The development of antibodies in either group did not lead to any adverse events such as excessive bleeding.

In January 2008, RECOTHROM™ Thrombin, Topical (Recombinant) (ZymoGenetics, Seattle, WA), became the first and only rThrombin product approved for use in surgical hemostasis. RECOTHROM is indicated as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible, and control of bleeding by standard surgical techniques is ineffective or impractical. In addition, RECOTHROM may be used in conjunction with an absorbable gelatin sponge.²⁰

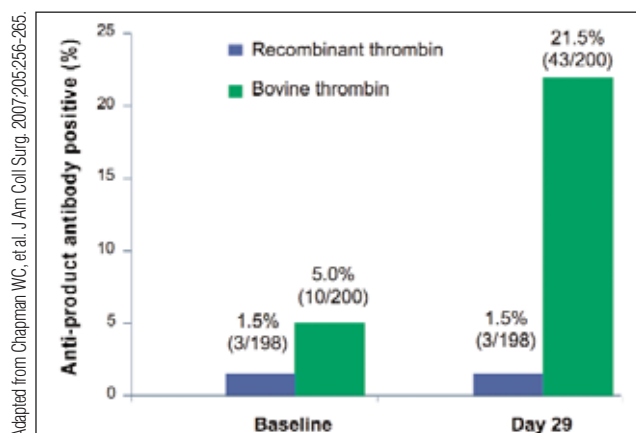


Figure 2. Antibody formation to rThrombin and bovine thrombin in a phase 3 clinical trial. No reported adverse events were considered causally associated with antibody formation in either group.

RECOTHROM: PLASMA-FREE RECOMBINANT THROMBIN

A phase 3 clinical trial has demonstrated that RECOTHROM has comparable efficacy and a lower rate of anti-product antibody formation compared to bovine thrombin. Both treatments were well tolerated and exhibited similar adverse event profiles in the phase 3 trial.⁸ Because it is produced via recombinant technology, RECOTHROM does not rely on the availability of blood from animals or human donors.

After 60 years without an alternative to animal-derived or human plasma-derived thrombin preparations, surgeons now have a new, state-of-the-art active hemostasis option. With efficacy similar to that of bovine thrombin and a potentially improved risk-management profile, RECOTHROM offers surgeons a plasma-free thrombin for use as an aid to surgical hemostasis. ■

Allan Alexander, MD, is Medical Director, BioSurgery and Medical Affairs, ZymoGenetics, Inc., in Seattle, Washington. He is a board-certified anesthesiologist with extensive clinical experience in cardiac anesthesia and intensive care. Dr. Alexander has held academic appointments at Baylor College of Medicine, University of Texas HSC–Houston, and the Texas Heart Institute. Dr. Alexander is a Diplomat of the American Board of Anesthesiology and a Certified Physician Investigator.

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Adapted from Chapman WC, et al. *J Am Coll Surg*. 2007;205:256-265.