Thrombin and Absorbable Hemostatics: Understanding Their Position in Healthcare Institutions

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Speaker Disclosure
No vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation.

Objectives
• Compare the mechanisms of action of thrombin and absorbable hemostatics
• Evaluate the available biomedical literature regarding thrombin and the absorbable hemostatics
• Explain safety concerns related to the use of hemostatic agents
• Discuss formulary issues involving thrombin and the absorbable hemostatics
Introduction

• Surgical complications
  – Intraoperative bleeding
    • Unresponsive to conventional methods (sutures, manual pressure, cautery)
      – Prolonged surgery
      » Increased utilization of resources (personnel, operating room time)
      – Impaired visualization of surgical field
      » Risk for errors
    – Postoperative complications


Introduction

• Surgical complications
  – Transfusions
    • Transfusion Related Lung Injury (TRALI)
      – Rare reaction
      – Third most common cause of transfusion-related death
      – Sudden onset respiratory distress (within 1-6 h)
    • Transfusion Related Immunosuppression (TRIM)
      – Potential for postoperative bacterial infection


Examples of Surgical Complications

• Hepatobiliary surgery
  – Intraoperative blood loss
  – Postoperative rebleeding or bile leakage
• Neurosurgery
  – Bleeding into central nervous system
  – Cerebrospinal fluid leakage at sutured dural closure
• Cardiac/vascular surgery
  – Bleeding at vascular anastomoses

Types of topical agents

- **Hemostat**
  - Stops bleeding

- **Sealant**
  - Prevents leakage of fluids, including blood
    - Synthetic: Duraseal, Coseal
    - Fibrin: Tisseal, Evicel

- **Adhesive**
  - Holds 2 tissue surfaces together
    - BioGlue

Thrombin

- Controlling blood loss for > 60 years
- 3 available products
  - Thrombin JMI: bovine-derived
  - Evithrom: human plasma-derived
  - Recothrom: recombinant human

Thrombin – Mechanism of Hemostasis

- Activates various coagulation factors and platelets
  - Factors V, VII, VIII, XI, and XIII
  - Fibrinolysis inhibitor
- Conversion of fibrinogen to fibrin

Thrombin – Indications

- Thrombin
  - Aid in hemostasis for minor bleeding in various types of surgery; can be used in conjunction with an Absorbable Gelatin Sponge

Thrombin – Clinical Efficacy

- Few comparative trials available
- Efficacy
  - Similar between available products
  - Difference in antibody formation
- Endpoints
  - Cessation of bleeding/incidence of hemostasis
Thrombin – Clinical Efficacy

• Human vs. Bovine Thrombin
- 305 patients undergoing cardiovascular, neurologic, and general surgeries
  - Thrombin applied topically with gelatin sponge
  - Primary endpoint: cessation of bleeding at 10 min
  - Secondary endpoint: cessation of bleeding at 3 and 6 min


• Recombinant vs. Bovine Thrombin
- 463 patients undergoing vascular, spinal, or hepatic procedures
  - Thrombin applied topically with gelatin sponge
  - Primary endpoint: incidence of hemostasis within 10 min
  - Secondary endpoint: safety and presence of antibodies

Thrombin – Clinical Efficacy

• Recombinant vs. Bovine Thrombin
  – Results
    • Incidence of hemostasis within 10 min: 95.1% recombinant vs. 95.4% bovine
    • Nearly all patients had an adverse event within 1 month of the procedure
    • Antibody formation: 21.5% bovine vs. 1.5% recombinant (p<0.0001)


Thrombin – Safety

<table>
<thead>
<tr>
<th>Topical Thrombin</th>
<th>Contraindications</th>
<th>Warnings/Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin-JMI</td>
<td>Hypersensitivity – bovine-origin materials</td>
<td>Hemostasis abnormalities (boxed warning)</td>
</tr>
<tr>
<td>Evithrom</td>
<td>Hypersensitivity to human blood products</td>
<td>Risk of transmitting infectious agents</td>
</tr>
<tr>
<td></td>
<td>Do not use in massive or brisk bleeding</td>
<td>Risk of thrombosis if systemically absorbed</td>
</tr>
<tr>
<td>Recothrom</td>
<td>Do not use in massive or brisk bleeding</td>
<td>Risk of thrombosis if systemically absorbed</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity to hamster or snake proteins</td>
<td></td>
</tr>
</tbody>
</table>


Thrombin – Safety

• Misadministration of Thrombin
  – 4 reports since 1987
    • 3 of the cases – fatality
    • Remaining case – severe hypotension, bradycardia, and respiratory failure
  – Routes of administration
    • Intravenous via dialysis access site
    • Direct injection into splenic tissue
    • Down a nasogastric tube
Thrombin - Safety

- Hemostatic abnormalities – antibody formation
  - Various case reports
  - Repeated exposure may increase risk
  - Effect
    - Bovine factor V in thrombin
    - Subsequent development of antibodies
    - Cross-reaction with human clotting factors

- History
  - 1994: Ortel – case series of 4 patients
  - 2001: Ortel – prospective study
    - 150 patients exposed to bovine thrombin during cardiac surgery
    - 94.3% elevated antibody levels
    - 4 to 8 weeks – 51% elevated antibodies against human coagulation proteins
  - Vast majority – ThromboGen

- Thrombin JMI
  - Described as a purer product than ThromboGen
  - Labeling revised to reflect reduced levels of factor V – January 2008
  - Higher levels of autoreactive antibodies with ThromboGen than Thrombin JMI
  - One report implicating Thrombin JMI – coagulation abnormalities
Absorbable hemostatic agents

- **Uncontrolled Bleeding: Adjunctive therapy**
  - Cellulose, collagen, or gelatin based
  - Sponge, powder, or matrix
  - Biodegrades


Absorbable hemostatic agents

- Mechanism of hemostasis
  - Applied at the site of bleeding
  - Cellulose- and gelatin-based products
    - Contact activation
  - Collagen-based products
    - Dual mechanism
      - Contact activation
      - Promotion of platelet aggregation
      - Result of direct effect of contact of blood and collagen


Absorbable hemostatic agents

[Diagram showing the mechanism of hemostasis involving platelets, intrinsic pathway, extrinsic pathway, and resulting in an insoluble fibrin clot.]
Absorbable hemostatic agents

Uses: adjunctive therapy for control of bleeding during surgery when ligation or conventional methods are ineffective/impractical.

<table>
<thead>
<tr>
<th>Product</th>
<th>Components</th>
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<tr>
<td>Surgicel</td>
<td>Regenerated oxidized cellulose</td>
</tr>
<tr>
<td>Gelfoam</td>
<td>Porcine gelatin</td>
</tr>
<tr>
<td>Surgifoam* / Surgiflo*</td>
<td>Porcine gelatin</td>
</tr>
<tr>
<td>Avitene</td>
<td>Bovine collagen</td>
</tr>
<tr>
<td>Instat*</td>
<td>Bovine collagen</td>
</tr>
<tr>
<td>Helistat*/Helitene*</td>
<td>Bovine collagen</td>
</tr>
</tbody>
</table>

* Excludes neurologic, ophthalmic and/or urologic procedures

Product Characteristics

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<tr>
<td>Surgicel</td>
<td>Pliable woven sheet</td>
</tr>
<tr>
<td>Gelfoam</td>
<td>Fibrillar layered sheet</td>
</tr>
<tr>
<td>Surgifoam</td>
<td>Compressed sponge</td>
</tr>
<tr>
<td>Surgiflo</td>
<td>Powder</td>
</tr>
<tr>
<td>Avitene</td>
<td>Microfibrillar form (flour)</td>
</tr>
<tr>
<td>Instat</td>
<td>Sponge-like pad</td>
</tr>
<tr>
<td>Helistat</td>
<td>Sponge</td>
</tr>
<tr>
<td>Helitene</td>
<td>Microfibrillar form</td>
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</tbody>
</table>

- Combination agents
  - Collagen or gelatin with bovine/human thrombin
  - Components work synergistically
    - Thrombin activates clotting factors to form fibrin
    - Gelatin/collagen potentiates clot formation
Absorbable hemostatic agents

Uses: adjunctive therapy for control of bleeding during surgery when ligation or conventional methods are ineffective/impractical

<table>
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<tr>
<td>FloSeal®</td>
<td>Bovine gelatin and human thrombin</td>
</tr>
<tr>
<td>Vitagel® (formerly Costasis)</td>
<td>Bovine collagen and bovine thrombin</td>
</tr>
</tbody>
</table>

- Excludes ophthalmic procedures; *Excludes neurologic or ophthalmic procedures

Absorbable hemostatic agents

Clinical Efficacy

- Early clinical data
  - Avitene: beneficial effect on:
    - Controlling capillary bleeding
    - Achieving hemostasis during vascular surgery
  - Few clinical trials exist
    - Existing trials compare established agents (Gelfoam) to newer agents (FloSeal) or fibrin sealants


Absorbable hemostatic agents

Clinical Efficacy

- Gelfoam in Thrombin vs. FloSeal
  - 89 patients undergoing reconstructive vascular surgery or arteriovenous access procedures
  - Primary endpoint: hemostasis within 10 min at initial treated site
  - Secondary endpoints: hemostatic outcome of additional bleeding sites and time to bleeding cessation

Absorbable hemostatic agents

Clinical Efficacy

• Gelfoam in Thrombin vs. FloSeal
  – Results
    • Hemostasis within 10 min at initial site: 93% FloSeal vs. 76% Gelfoam plus Thrombin; p=0.036
    • Hemostatic outcome of all treated bleeding sites: 92% FloSeal vs. 79% Gelfoam plus Thrombin; p=0.01
    • Time to bleeding sensation significantly improved with FloSeal for all treated sites (p=0.001; Kaplan-Meier analysis)


• Helistat vs. Actifoam
  – 60 patients undergoing cardiothoracic procedures
  – Main outcomes: hemostasis within 10 min and investigator-rated handling/efficiency characteristics of products


• Helistat vs. Actifoam
  – Results
    • Hemostasis within 10 min: 77% for Helistat vs. 73% for Actifoam
    • Overall, 45 patients achieved hemostasis after application
      – 22 within < 3 min, 16 in 3 to 6 min, and 7 between 6 and 10 min

Absorbable hemostatic agents

- Some adverse events
  - 110 cases reported to the FDA (based on a 2004 report)
  - Paralysis or neural deficits
    - 11 cases
    - Use of agent near or on a bony/neural/confined space
    - Swelling of agent exerted pressure on spinal or neural structures
  - Incomplete absorption
    - Residual material months-years after surgery
  - Local inflammation
  - Bovine components
  - Immune hypersensitivity reaction


FDA Public Health Notification: Paralysis from Absorbable Hemostatic Agent. April 4, 2004

Institutional Approaches to Management

- Pharmacy vs. Central Supply vs. Operating Room
- Absorbable hemostatics: central supply or materials management
- Thrombin: pharmacy
- Pharmacy may handle all products

Institutional Approaches to Management

- What is being used in institutions?
  - No consensus at all for these products
  - No practice guidelines developed for their use
  - Clinician preference/familiarity major driving force
  - Rarely are these products formally reviewed at a P & T Committee
Institutional Approaches to Management

• Formulary issues
  – Thrombin
    • Key Points
      – Efficacy as measured by time to hemostasis appears to be comparable
      – Safety is the big push for differentiation
      – Recothrom – lower incidence of antibody formation compared to bovine
      – Evithrom – human-based and therefore potential for transmission of infectious agents

Is Recothrom safer than both Evithrom and Thrombin JMI?
  – Thrombin JMI – purified further; most cases involved less pure ThromboGen
  – Evithrom – risk of transmission extremely low
  • Recothrom has received a violative advertising and promotional labeling letter

Institutional Approaches to Management

• Formulary issues
  – Absorbable hemostatic devices
    • Key Points
      – Efficacy appears to be similar among products
      – Certain products may be used in conjunction with thrombin
      – Often “out of the hands” of pharmacy
      – Clinician preference drives choice
      – Avoidance of duplicative products
Summary

- Uncontrolled intraoperative bleeding can be a major cause of morbidity and postoperative complications
- Thrombin and absorbable hemostatic agents can effectively control bleeding unresponsive to conventional methods
- Thrombin aid hemostasis by activating various coagulation factors and platelets and affecting the conversion of fibrinogen to fibrin
- Absorbable hemostats include collagen, cellulose, and gelatin based agents and act early in the coagulation cascade
- Appears to be no significant clinical efficacy difference between bovine, human, and recombinant thrombin
- Safety is the main differentiating point; however, the remaining bovine on the market has increased purity over historically available products

Summary

- Clinical efficacy appears comparable among the available absorbable hemostatic agents as well
- Major safety concern with these agents has been the reports of paralysis or neural deficits
- Institutional management has not been standardized historically with absorbable hemostats managed by central supply and thrombin managed by pharmacy
- Use of a particular thrombin product or absorbable hemostatic has been largely driven by clinician preference or familiarity
- Pharmacy may be able to play a larger role in the appropriate use of these agents

Questions??
Learning Assessment Questions:

True or False. Among the various thrombin products, efficacy appears to be similar; however, the incidence of antibody formation differs.

Absorbable hemostatics:
A. are classified as devices by the Food and Drug Administration (FDA).
B. are indicated for use during surgical procedures as an adjunctive therapy when ligature or application of pressure does not control bleeding.
C. have been evaluated in numerous, well-designed clinical trials in a variety of surgical settings.
D. A and B are correct statements.

Which of the following most adequately explains the mechanism of action of thrombin?
A. Initiation of clotting through contact activation.
B. Provides hemostasis through contact activation and promotion of platelet aggregation.
C. Promotes degranulation and release of coagulation factors.
D. Activates various coagulation factors and platelets within the coagulation cascade and converts fibrinogen into fibrin monomers that combine to form polymers resulting in a clot.

Which of the following is NOT a safety concern with thrombin and/or absorbable hemostatics?
A. Possible development of paralysis with absorbable hemostatics
B. Thromboembolic events with all hemostatics
C. Antibody formation with thrombin
D. Inappropriate administration of thrombin

True or False. Clinician preference is a major driving force behind formulary inclusion of a particular thrombin or absorbable hemostatic.