Achieving Hemostasis in the Operating Room and Critical Care Setting: What the Pharmacist Needs to Know

A knowledge-based CPE activity presented during the
2013 MSHP-ICHP Spring Meeting

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ADVANTAGE

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Achieving Hemostasis in the Operating Room and Critical Care Setting: What the Pharmacist Needs to Know

ACTIVITY FACULTY

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Dr. Boucher received his Bachelor of Science and Doctor of Pharmacy degrees from the University of Minnesota and completed a critical care fellowship at the University of Kentucky. In addition, he is a board-certified pharmacotherapy specialist and a fellow of the American College of Clinical Pharmacy (ACCP) and American College of Critical Care Medicine. Dr. Boucher has received several professional honors, including being elected as a pharmacy member of the National Academy of Practitioners and receiving the 2011 ACCP Clinical Practice Award.

Dr. Boucher's current research interests include pharmacokinetic and therapeutic issues in the critically ill surgical patient and medical management of the neurotrauma patient. He has published over 75 peer reviewed articles and 15 book chapters during his career. He has also served as an editorial board member for several medical journals, including *Critical Care Medicine* and *American Journal of Pharmaceutical Education*, and he is currently serving on the editorial board of *Critical Care Research and Practice.* Dr. Boucher has served as President of ACCP and maintains active membership in numerous professional scientific and professional organizations, including ACCP, American Society of Health-System Pharmacists, and Society of Critical Care Medicine.

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ACTIVITY OVERVIEW

Bleeding is a major complication of surgery and is associated with poor clinical outcomes. A number of techniques and products for achieving surgical hemostasis are available. Although pharmacists may not be present in the surgical suite, they need to be aware of surgery-related processes that decrease the need for blood transfusions and improve patient safety in the operating room and critical care practice areas. This educational activity will review key clinical, safety, economic, and regulatory factors that pharmacists need to consider when evaluating local and systemic hemostatic agents for use in the institutional setting.

There will be time for questions and answers at the end of the presentation.

LEARNING OBJECTIVES

At the conclusion of this knowledge-based CPE activity, attendees should be able to

- Discuss the clinical and economic impact of surgical complications that result in bleeding and transfusion.
- Demonstrate knowledge of local and systemic hemostatic agents, including clinical, safety, economic, and regulatory factors.
- Describe the role of the health-system pharmacist in the use of hemostatic agents to manage surgical bleeding.

CONTINUING EDUCATION ACCREDITATION

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity # 0204-0000-13-416-L01-P).

Attendees must complete a Continuing Pharmacy Education Request online and may print their official ASHP statements of continuing pharmacy education credit at the ASHP eLearning site (elearning.ashp.org) immediately following this activity.

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   Note: The Enrollment Code was announced at the end of the live activity.
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Date of Activity	Activity Title	Enrollment Code	Credit Hours
Friday, April 12, 2013	Achieving Hemostasis in the Operating Room and Critical Care Setting: What the Pharmacist Needs to Know	_ _ _ _ _	1.0

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Achieving Hemostasis in the Operating Room and Critical Care Setting: What the Pharmacist Needs to Know

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Learning Objectives

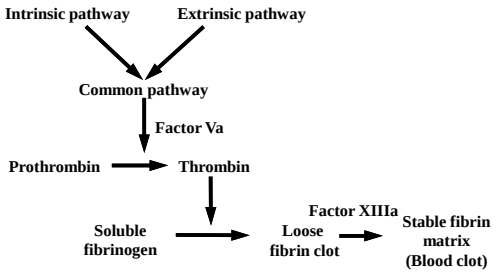
- Discuss the clinical and economic impact of surgical complications that result in bleeding and transfusion.
- Demonstrate knowledge of local and systemic hemostatic agents, including clinical, safety, economic, and regulatory factors.
- Describe the role of the health-system pharmacist in the use of hemostatic agents to manage surgical bleeding.

Biologic Processes of Hemostasis

- Clotting is complicated process
  - Platelet-mediated primary hemostasis
  - Thrombin generation
  - Conversion of fibrinogen to fibrin
  - Stable fibrin and platelet network or clot produced
- Complex interaction between vascular wall, platelets, coagulation factors, fibrinolysis
- Response to traumatic or surgical injury

Porte RJ et al. *Drugs*. 2002; 62:2193-211.

The Coagulation Cascade



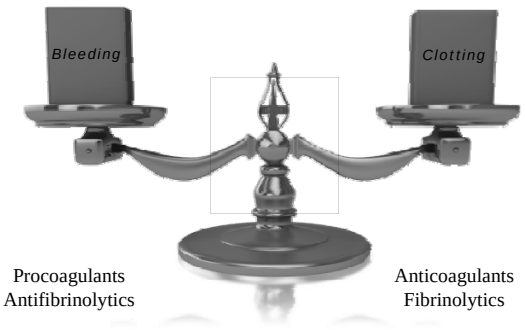
Cell-Based Coagulation Model

Newer Complement to Cascade Model

- Integrates components from cascade model
- Consists of 3 overlapping phases, each involving thrombin
  - Initiation
    - Tissue factor primary initiator of coagulation
  - Amplification (priming)
    - Critical role of thrombin activating platelets, activation of FV, FXI; cleavage of FXIII
  - Propagation
    - Large of amounts of thrombin generation, clot formation
- Thrombin (FIIa) active in all phases

Zimmerman LH. *Pharmacotherapy*. 2007; 27(9 Pt 2):45S-56S.

Maintaining Hemostasis



Consequences of Perioperative Bleeding

- Clinical consequences
  - Reduction in oxygen delivery
  - Increased morbidity
  - Increased mortality
- Economic consequences
  - Increased duration of operative procedure; returns to the OR
  - Transfusions of blood products, hemostatic costs, clotting time tests
  - Prolonged LOS

Zimmerman LH. *Pharmacotherapy*. 2007; 27(9 pt 2):45S-56S.

Bleeding Interventions

- Mainstays of therapy
  - Reversal of hypothermia and acidosis
  - Calcium
  - RBC transfusions
  - Fresh frozen plasma (FFP)
  - Platelets
  - Cryoprecipitate
  - Prothrombin complex concentrates (PCCs)

Prothrombin Complex Concentrates

- Concentration of coagulation factors II, VII, IX, X
  - 3-factor PCCs (lack FVII)
  - 4-factor PCCS (preferred – presently not available in U.S.)
- Most countries outside U.S. use PCCs vs. FFP as primary treatment for warfarin reversal
  - Quicker for INR correction
  - Small infusion volume
  - No need for cross-matching
- Low levels of evidence (?)

Godier A et al. *J Thromb Haemost*. 2010; 8:2592-5.
Sniecinski RM et al. *Curr Opin Anaesthesiol*. 2012; 25:74-9.

Blood Transfusion Truism

"Blood transfusion is like marriage: it should not be entered upon lightly, unadvisedly or wantonly or more often than is absolutely necessary."

- Robert Beal

Former Director, Blood Department
International Federation of Red Cross/Red Crescent Societies

Alter HJ et al. *Blood*. 2008; 112:2617-26.

Risks of Allogeneic Transfusions

- Infectious complications
  - Viral (HIV-1, -2, HBV, HCV, others)
    - Less than 1:1,000,000 units transfused
  - Bacterial
    - 1:2000-3000 platelet transfusions
- Mistransfusions
  - Approximately 1:12,000 – 19,000 units transfused
- Transfusion-related acute lung injury (TRALI)
  - Leading cause of transfusion-related morbidity and mortality: 1:500 platelet transfusions, 1:1000-5000 plasma, RBC transfusions

Boucher BA et al. *Pharmacotherapy.* 2007; 27:1394-411.
Hendrickson JE et al. *Anesth Analg.* 2009; 108:759-69..

Risks of Allogeneic Transfusions (cont.)

- Transfusion-related immunomodulation (TRIM)
- Transfusion-associated circulatory overload (TACO)
- Potential risks associated with use of RBC stored for longer than 28 days include
  - Increased DVT: 34.5% (old blood) vs. 16.7% (new blood)
  - Increased mortality: 26.7% (old blood) vs. 13.9% (new blood)

Hendrickson JE et al. *Anesth Analg.* 2009; 108:759-69.
Spinella PC et al. *Crit Care.* 2009; 13(5):R151.
Weinberg JA et al. *J Trauma.* 2010; 69:1427-32.

RBC Transfusion Adult Trauma and Critical Care Clinical Practice Guideline (2009)

- Developed by joint taskforce of EAST and ACCM
- Key recommendations
  - Restrictive transfusion trigger (Hgb <7 g/dL) although should not be sole transfusion determinant
  - Use single RBC transfusion units in the absence of acute hemorrhage
  - Avoid transfusions in patients at risk for ALI or ARDS

EAST = Eastern Association for Surgery of Trauma
ACCM = American College of Critical Care Medicine
ALI = acute lung injury
ARDS = acute respiratory distress syndrome

Napolitano LM et al. *Crit Care Med.* 2009; 37:3124-57.

CDC Blood Transfusion Surveillance Program

- First national surveillance system to monitor adverse events in patients receiving blood products
- Program goals: summarize standardized data to better understand prevention of transfusion-related events, reduce heathcare costs
- CDC encouraging healthcare facilities in U.S. to enroll in surveillance program

Kuehn BM. *JAMA*. 2010; 303:1467.

Joint Commission

- *Patient Blood Management Performance Measures Project*
- Implementation Guide published in 2011
- Purpose: identify, develop and test set of standardized measures to assess consistent and efficacious use of blood transfusions in hospitals

The Joint Commission. Patient blood management performance measures project. (URL in handout).

Minimization of Blood Products: Preoperative and Intraoperative Planning

- Discontinue anticoagulants including NSAIDS, antiplatelet agents, herbals
- Minimize blood draws
- Anemia tolerance: lower transfusion trigger
- Minimally invasive procedures: laparoscopy, robotics
- Iron therapy: enteral/parenteral
- Administration of erythropoiesis-stimulating agents

Boucher BA et al. *Pharmacotherapy.* 2007; 27:1394-411.

Local Hemostatic Agents

Local Hemostatic Agent Characteristics

- Useful adjunct to surgical care for improved outcomes
- Identified by FDA as device intended to produce hemostasis by accelerating the clotting process of blood
- Available in a variety of forms
- Used in conjunction with collagen, gelatin, cellulose matrices

Spotnitz WD et al Burks S. *Transfusion*. 2008; 48:1502-16.
Gabay M. *Am J Health-Syst Pharm*. 2006; 63:1244-53.

Ideal Local Hemostat Qualities

- Prompt and reliable bleeding control
- Ease of storage
- Easy preparation
- Immediate availability and usability
- Reduced OR time for surgical staff

Fagan NL et al. *US Pharm*. 2010; 35(11):HS2-HS8.

Local Hemostats:
Classification Based on Functional Characteristics

- Mechanical hemostats (passive)
  - Gelatin
  - Collagen
  - Regenerated cellulose
  - Polysaccharide spheres
- Flowable hemostats (combination)
  - Gelatin granules + thrombin
- Adhesives
  - Cyanoacrylate
  - Albumin + glutaraldehyde
  - Octyl and butyl lactoyl cyanoacrylate
- Active hemostats: topical thrombins (3 biologic origins)
  - Bovine
  - Pooled human plasma-derived
  - Recombinant human
- Sealants
  - Human plasma-derived fibrinogen + thrombin
    - Fibrin sealant (pooled human plasma)
  - Bovine collagen, bovine thrombin for mixing with autologous plasma.
  - PEG polymers

Spotnitz WD et al. *Transfusion*. 2008; 48:1502-16.

Mechanical Agents

- Gelatin foams *(Gelfilm, Gelfoam, Surgifoam)*
  - Provide physical matrix for initiation of clotting
  - Film, sponge, powder forms
- Oxidized cellulose *(Surgicel Fibrillar, Surgicel Nu-Knit)*
  - Superior handling compared to gel foams
  - Low pH, resulting in antimicrobial effect against a variety of pathogenic organisms
- Microfibrillar collagen *(Avitene, Instat, Helitene, Helistat)*
  - Conforms well to irregular surfaces
  - Provides for large surface area
- Polysaccharide spheres (*Arista, Hemostase, Vitasure*)

Achneck HE et al. *Ann Surg*. 2010; 251:217-28.
Spotnitz W et al. *Transfusion*. 2008; 48:1502-16.

Active Agents: Thrombin

- Bovine thrombin (*Thrombin-JMI*)
- Plasma-derived thrombin (*Evithrom*)
- Recombinant thrombin (*Recothrom*)

Acquired Specific-Factor Inhibitors: Bovine Thrombin-Associated Coagulopathy

- Boxed warning on bovine thrombin preparations notes occasional association with coagulopathies
  - Range from laboratory abnormalities to serious bleeding
- Related to antibodies against bovine thrombin and/or factor V that cross-react with human coagulation factors
- True incidence of coagulopathy associated with bovine thrombin is unknown
- Antigen exposure may not be documented

Lomax C et al. *Pharmacotherapy.* 2009; 29(7 pt 2):8S-12S.

Flowables *(FloSeal, Surgiflo)*

- Contain bovine or porcine gelatin matrix
  - Possible addition of topical thrombin
- Effective in difficult-to-reach surfaces, wet surgical field
- Conforms to topography of underlying tissue

Spotnitz WD et al. *Clin Appl Thromb Hemost*. 16:497-514.

Sealants

- Fibrin Sealants: thrombin + fibrinogen (*Tisseal, Evicel, Tachosil, Evarrest)*
  - FDA approved first commercial hemostat/sealant in 1989
  - 2 components interact during application to form stable fibrin clot
  - Effective for localized and diffuse bleeding.
- Fibrin sealant: suspension of bovine collagen, bovine thrombin for mixing with autologous plasma (*Vitagel*)

Achneck HE et al. *Ann Surg*. 2010; 251:217-28.
Spotnitz WD et al. *Clin Appl Thromb Hemost.* 2010; 16:497-514.
Gabay M et al. *Pharmacotherapy.* In press.

Other Local Sealants, Adhesives

- Form barrier to flow of liquids including blood
- Local sealant: PEG polymers (*Coseal, Duraseal, Progel*)
- Local sealants/Adhesives
  - Cyanoacrylates (*Dermabond Advanced, Indermil, Histoacryl*)
  - Albumin and Glutaraldehyde (*BioGlue*)
  - Octyl and butyl lactoyl cyanoacrylate (*Omnex*)

Achneck HE et al. *Ann Surg*. 2010; 251:217-28.
Spotnitz WD et al. *Transfusion*. 2008; 48:1502-16.

Systemic Pharmacologic Hemostatic Agents

Anticoagulant Reversal Agents

- Vitamin K
  - Reversal of warfarin
- Protamine
  - Reversal of unfractionated heparin (not low molecular weight heparin products)
  - Potential for adverse reactions, including anaphylaxis, acute pulmonary vasoconstriction, hypotension

Sniecinski RM et al. *Curr Opin Anaesthesiol*. 2012; 25:74-9.

Desmopressin

- Analog of vasopressin
- Stimulates release of vWF multimers from endothelial cells
- Prevent or control bleeding in patients with von Willebrand syndrome
- Cochrane Library review of surgical patients: no benefit from administration of desmopressin to cardiac surgery patients

vWF = von Willebrand factor

Sniecinski RM et al. *Curr Opin Anaesthesiol*. 2012; 25:74-9.
Carless PA et al. *Cochrane Database Syst Rev*. 2004; (1):CD001884.

Antifibrinolytic Agents: The Lysine Analogs

- Indications: hemorrhaging in hemophilia
- Mechanism of action: competitively inhibit activation of plasminogen to plasmin
- Epsilon aminocaproic acid
- Tranexamic acid
  - CRASH-2: Prospective, randomized, controlled trial of tranexamic acid or placebo in adult trauma patients with, or at risk of, significant bleeding within 8 hours of injury
  - All-cause mortality: 14.5% tranexamic acid group, 16.0% placebo group (P=.0035); no significant differences in vascular occlusive events except MI favoring tranexamic acid
  - Conclusion: should be considered for use in bleeding trauma patients

Sniecinski RM et al. *Curr Opin Anaesthesiol*. 2012; 25:74-9.
CRASH-2 trial collaborators et al. *Lancet.* 2010; 376:23-32..

Recombinant Factor VIIa (rFVIIa)

- Indication: treatment of bleeding episodes in hemophilia A or B with inhibitors to factor VIII or IX
- Off-label uses: uncontrolled, life-threatening bleeding
- Dosing: wide range for off-label uses (15 to 400 mcg/kg)
- Safety: risk of thromboembolic events
- Pharmacoeconomics: some evidence that high acquisition cost offset by reduced blood product use, decreased morbidity, mortality

Sniecinski RM et al. *Curr Opin Anaesthesiol*. 2012; 25:74-9.
Stanworth SJ et al. *Cochrane Database Syst Rev.* 2007; (2):CD005011.
O'Connell KA et al. *JAMA*. 2006; 295:293-8.

Recombinant Factor VIIa (cont.)

- Cochrane Database meta-analysis: uncertain hemostatic effectiveness either prophylactically (6 RCTs) or therapeutically (7 RCTs) in patients without hemophilia
- Meta-analysis of 10 case series in major abdominal surgery patients: reduction or cessation of bleeding in 73.2% patients; survival in 66% responders (19 of 29) vs. 10% nonresponders (1 of 10)
- CONTROL Trial: Phase III randomized clinical trial of rFVIIa vs. placebo in trauma patients with refractory hemorrhage
  - rFVIIa group (n=273) dose: 200 mcg/kg, then 100 mcg/kg at 1 and 3 hours, or placebo (n=300)
  - Results: no differences in mortality for blunt or penetrating trauma patients (>0.05); significant reduction in RBC transfusions in rFVIIa group (P=0.04), no difference in thrombotic adverse events
- Overall equivocal risk/benefit ratio for off-label indications

Stanworth SJ et al. *Cochrane Database Syst Rev.* 2007; (2):CD005011.
von Heymann C et al. *Crit Care.* 2008; 12(1):R14.
Hauser CJ et al. *J Trauma.* 2010; 69:489-500.

Pharmacist Roles in Surgical Hemostasis

Pharmacy and Therapeutics Committee

- Evaluative
  - Appraisal of published efficacy, safety data relative to hemostatic products undergoing formulary review
    - Hemostatic agent class reviews
    - Preparation of drug monographs including storage requirements, pharmacoeconomic evaluations
- Advisory
  - Provision of general safety information (e.g., ISMP, FDA newsletter)
  - Hospital wide alerts, sentinel events

Gabay M, Boucher BA. *Pharmacotherapy*. In press.

Distribution, Monitoring

- Create safe use/handling protocols
  - Labeling, addition of auxiliary warning labels e.g., "do not inject" for local hemostatic agents
  - Storage, preparation
- Surveillance
  - Hemostatic medication-use evaluation
  - Adverse event reporting
- Monitoring of hemostatic agents entering institution via central supply versus pharmacy department

Gabay M, Boucher BA. *Pharmacotherapy*. In press.

Patient Care

- Knowledge of bleeding causes, consequences and hemostasis
- Familiarity with characteristics , clinical use of hemostatic agents
  - Blood products
  - Local agents
  - Systemic agents
- Development of therapeutic guidelines, pathways
- Education: inservices, newsletters, institutional websites

Gabay M, Boucher BA. *Pharmacotherapy.* In press.

Overcoming Barriers to Pharmacist Involvement in Surgical Hemostasis

- Bridge existing knowledge gap relative to bleeding, hemostatic agents
- Engage with other healthcare professionals in other departments
  - Physicians, nurses, laboratory personnel, and others interested in patient safety, clinical outcomes, quality of care, and cost
  - Direct patient care settings
  - Committees: P&T, Blood Conservation, Quality Council/Patient Safety, Medication Safety

Gabay M, Boucher BA. *Pharmacotherapy*. In press.

Conclusion

- Perioperative bleeding is a significant cause of increased morbidity and mortality in surgery patients
- Local and systemic hemostatic agents are important adjunctive therapy for reestablishing hemostasis in surgical patients, although have associated risks
- Pharmacists can play an important role relative to minimizing blood product use and maximizing benefits of local and systemic hemostatic agents

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S E L F – A S S E S S M E N T Q U E S T I O N S

1. Which of the following risks of allogeneic red blood transfusions is considered to be the leading cause of morbidity and mortality?

    a. Bacterial or viral infection.
    b. Mistransfusion.
    c. Transfusion-related acute lung injury.
    d. Transfusion-related circulatory overload.

2. Which of the following products is an example of a mechanical local hemostat?

    a. Recombinant thrombin.
    b. Gelatin.
    c. Cyanoacrylate.
    d. Polyethylene glycol polymers.

3. Which of the following local hemostats has been associated with immune-mediated coagulopathy?

    a. Bovine thrombin.
    b. Human pooled plasma thrombin.
    c. Recombinant human thrombin.
    d. Human pooled fibrinogen and thrombin.

4. Which of the following is a key role for pharmacists within pharmacy and therapeutic committees relative to systemic and local hemostatic agents?

    a. Placement of auxiliary labels when distributing these products.
    b. Monitoring physician prescribing patterns for these agents.
    c. Evaluation of cause of bleeding within a particular intensive care unit.
    d. Evaluation of efficacy and safety data within hemostatic agent class.

Answers
1. c
2. b
3. a
4. d