Disclosure

- I will be discussing the off-label use of recombinant activated factor VIIa in massive obstetric hemorrhage.
- Recombinant activated factor VIIa has been approved by the US FDA for the prevention and treatment of bleeding in hemophilic patients.

Objectives

- Maternal Mortality and Hemorrhage
- Historical & Traditional Management of Massive Transfusion
- Current Massive Transfusion Protocol Considerations
- Use of Factor VIIa and Cell Salvage

WHO Analysis of Causes of Maternal Death Systematic Review

<table>
<thead>
<tr>
<th></th>
<th>Developed Countries</th>
<th>Africa</th>
<th>Asia</th>
<th>Latin Am. Caribbean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>13.4%</td>
<td>33.9%</td>
<td>30.8%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Hypertensive Disorders</td>
<td>16.1%</td>
<td>9.1%</td>
<td>9.1%</td>
<td>25.7%</td>
</tr>
<tr>
<td>Infections</td>
<td>2.1%</td>
<td>9.7%</td>
<td>11.6%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Abortion</td>
<td>8.2%</td>
<td>3.9%</td>
<td>5.7%</td>
<td>12.0%</td>
</tr>
<tr>
<td>Embolism</td>
<td>14.9%</td>
<td>2.0%</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

The CMQCC OB Hemorrhage Task Force

This project was supported by funds received from the California Department of Public Health; Maternal, Child and Adolescent Health Division

Co-Chairs of the OB Hemorrhage Task Force:
- David Lagrew, MD
- Audrey Lyndon, PhD, RN

Slide Source: CMQCC California Maternal Quality Care Collaborative
CMQCC Hemorrhage Task Force:

- Developed a Tool Kit for OB services:
  - Set of Best Practices (short summaries of key aspects of OB hemorrhage)
  - Checklist for managing OB hemorrhage
  - Flow-Chart and Table Chart Summaries of approach
  - Implementation tools such as sample policies, procedures, charting examples, implementation hints

- All resources on-line at: www.cmqcc.org/ob_hemorrhage

Source: CMQCC California Maternal Quality Care Collaborative

14 Cases of > 5 Liter blood loss within 48 hours
12 of 14 died (86% Mortality)

Traditional Management

Replace hemorrhage with:
1. Crystalloid or Colloid
2. PRBCs (cross-matched if possible)
3. If continued bleeding AND:
   - coagulation tests >1.5X normal -> FFP
   - fibrinogen < 100 mg/dL -> give cryoprecipitate
   - platelet < 75-100K -> platelets
“Patients who were hypothermic and acidotic developed clinically significant bleeding despite adequate blood, plasma, and platelet replacement.”

- Hypothermia
- Acidosis
- Coagulopathy

90% Mortality if all 3 present

- Coagulopathy persisted at ICU admission
  Pre-ICU resuscitation:
  - 9 ± 1 L crystalloid
  - 12 ± 1 units PRBC
  - 5 ± 0.4 units FFP
  FFP was not given until after 6 units PRBCs

- In the ICU during resuscitation, patients received 10 ± 1 units FFP for coagulopathy; the ratio of FFP:PRBC was 1:1. Mean INR < 1.4 within 8 hours

- Volume restoration is accomplished by using thawed plasma as a primary resuscitation fluid in at least a 1:1 or 1:2 ratio with PRBCs
- Crystalloid is minimized and serves mainly as a carrier
- The blood bank activates the massive transfusion protocol and deliver 6 units of plasma, 6 units of PRBCs, 6 packs of platelets, and 10 units of cryoprecipitate
- Recombinant FVIIa is occasionally used
“Using the damage control resuscitation approach, the lack of intraoperative coagulopathic bleeding has been remarkable, allowing surgeons to focus on surgical bleeding.”

“Patients treated in this fashion almost always arrive in the ICU warm, euvoletic, and nonacidotic, with a normal INR and minimal edema.”

“In the majority of patients the abnormalities of the lethal triad are absent.”

“These patients appear to be easily ventilated and more quickly extubated than patients with similar blood loss treated with the standard crystalloid resuscitation volumes and blood component ratios.”

Iraq Theatre Experience

- Retrospective review of soldiers with massive transfusion (>10u RBC in 24 hr)
- Increased FFP/PRBC ratios more effective:

![Graph showing mortality rates for different Plasma:RBC ratio groups]

Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

![Graph showing Kaplan-Meier survival plot for different plasma:RBC ratios]

Annals of Surgery Volume 248, Number 3, September 2008
Not sure what this bullet point is trying to say

Stanford, 4/2/2010
Principles to Reducing Maternal Hemorrhage

- Screen and identify patients at high risk
- Active management of 3rd stage
- Ongoing quantification of blood loss
- Ongoing evaluation of patient’s vital signs
- Sequential use of medications & procedures
- Timely request for blood products
- Massive transfusion protocol and team
- Periodic hemorrhage drills and simulations

Adapted from CMQCC California Maternal Quality Care Collaborative – OB Hemorrhage Task Force

Graphic Source: CMQCC California Maternal Quality Care Collaborative
Considerations in Massive Transfusion Protocol

- Activate "Massive Transfusion" protocol to blood bank
- O-neg Emergency blood vs Type-Specific vs Cross-Matched
- RBC:FFP:PLT in ratio of 4:4:1 to 6:4:1
- Do not wait for lab results to transfuse
- Mobilize Team
- Consider assigned runners for blood products/labs
- Move to OR if not already there, place monitors
- Consider IR consultation and other surgical options

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Considerations in Massive Transfusion Protocol - Continued

- Consider arranging for blood salvage
- Place large bore IVs (16G-14G)
- Place invasive monitoring (a-line & CVP)
- Repeat labs frequently (CBC, ABG, lytes, iCa, coags)
- Fluid warmers & forced air warmer for patient
- Prime rapid infusion pump or pressure bags
- Point of care testing (Hb, blood gas, coags, lytes)
- Direct communication with blood bank & central lab

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SFHG Massive Transfusion Policy No 2.06
CMQCC Hemorrhage Task Force. www.cmqcc.org
Considerations in Massive Transfusion Protocol - Continued

- Prepare for general anesthesia
- Vasopressors immediately available
- All uterotonics immediately available
- Supply of calcium chloride to prevent low ionized calcium levels from rapid transfusion
- Foley to measure urine & SCDs
- Reserve ICU bed

- Request additional blood products as needed in “packs” of correct ratio (Prbcs:FFP:Plts)
- Consider cryoprecipitate (Fibrinogen < 100 mg/dL)
- Consider factor VIIa (off-label hemostatic use)
  - Only after approximately 10 units prbcs and factor replacement
- Person for recording/tallying blood products & EBL
- Bring “Code Cart” into OR
- Plan for Blood Bank to prioritize Transfusion labs
- Make time to debrief after event with all disciplines

Additional Topics

- Recombinant Factor VIIa
- Cell Salvage

Thromboembolic Adverse Events After Use of Recombinant Human Coagulation Factor VIIa

- A review of the FDA’s Reporting System from 1999 to 2004
- A total of 431 AE reports for rFVIIa were found, of which 168 reports described 185 thromboembolic events
- Unlabeled indications accounted for 151 of the reports, most with active bleeding (n=115)
- In 36 (72%) of 50 reported deaths, the probable cause of death was the thromboembolic event
- Conclusion: RCTs are needed to establish the safety and efficacy of rFVIIa in patients without hemophilia
A 2008 review noted 118 cases of massive postpartum hemorrhage treated with rFVIIa.

- Median dose was 71.6 mcg/kg
- rFVIIa was reported to be effective in stopping or reducing bleeding in 90% of reported cases
- Caution in interpreting results as they are from uncontrolled studies
- RCTs needed to determine efficacy, dose, & safety

Blood scavenged through regulated suction and heparinised in tubing
- Blood is collected in reservoir and centrifuged to remove plasma and debris
- Saline wash is added and blood is hemoconcentrated
- Salvaged RBC product is filtered with leukocyte reduction filter
- Returned PRBCs have a hematocrit of 55-80%

Tissue factor is a potent initiator of coagulation
- Cell salvage unit completely removes tissue factor from blood contaminated with amniotic fluid (1)
- Since the mechanism of AFE is not known, Waters(2) chose to measure the effectiveness of cell washing examining:
  - Potassium
  - Lamellar bodies
  - Squamous cells
  - Bacterial culture

### Amniotic Fluid Components

- Potassium
- Lamellar bodies
- Squamous cells
- Bacterial culture

### Overview of Cell Salvage

- Blood scavenged through regulated suction and heparinised in tubing
- Blood is collected in reservoir and centrifuged to remove plasma and debris
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### Stepwise Analysis of Cell Salvage

<table>
<thead>
<tr>
<th></th>
<th>Maternal (1)</th>
<th>Prewash (2)</th>
<th>Postwash (3)</th>
<th>Postfilter (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potassium (mEq/L)</strong></td>
<td>3.8 (3.7-4.0)</td>
<td>3.8 (2.4-4.0)</td>
<td>1.5 *(1,2) (1.1-1.5)</td>
<td>1.4 *(1,2) (1.0-1.5)</td>
</tr>
<tr>
<td><strong>Lamellar (K/µl)</strong></td>
<td>31.0 (24.0-49.9)</td>
<td>22.0 (18.5-29.5)</td>
<td>3.0 *(1,2) (2.0-3.5)</td>
<td>0.0 *(1,2) (0.0-1.0)</td>
</tr>
<tr>
<td><strong>Squamous (#/HPF)</strong></td>
<td>0.0*(2,3) (0.0-0.0)</td>
<td>8.3 (4.0-10.5)</td>
<td>4.4 (3.0-7.6)</td>
<td>0.0 *(2,3) (0.0-0.1)</td>
</tr>
<tr>
<td><strong>Bacteria (CFU/ml)</strong></td>
<td>0.0*(2,3) (0.0-0.1)</td>
<td>3.0 (0.6-7.7)</td>
<td>1.3 (0.4-6.1)</td>
<td>0.1 *(2,3) (0.0-0.2)</td>
</tr>
<tr>
<td><strong>Fetal Hb (%)</strong></td>
<td>0.5 (0.3-0.7)</td>
<td>1.1 *(1) (0.7-1.5)</td>
<td>1.7 *(1) (1.0-2.1)</td>
<td>1.9 *(1) (1.1-2.5)</td>
</tr>
</tbody>
</table>

Cell Saver Benefits

- Safely used in 400 case reports without AFE
- Better quality of red cells
- Eliminates transmitted disease exposure
- Reduces post-op anemia
- Cost effective with larger blood losses [1,2]
- Rate of return of 60% of lost cells can be achieved


Cell Saver Concerns

- No randomized controlled trials
- One case report of death after salvaged blood reinfused, although patient severely ill and no pathologic diagnosis
- Efficacy dependent on volume of blood loss
- Concerns of amniotic fluid and fetal cells remain
- Trained and dedicated staff required to avoid possible complications


Opinion Statements

- "If the diagnosis or strong suspicion of placenta accreta is formed before delivery...Cell saver technology should be considered if available as well as the appropriate location and timing for delivery..."
  (ACOG Committee Opinion No. 266, January 2002 – Placenta Accreta)

- "Cell salvage may be considered in cases of high risk of massive haemorrhage"
  (RCOG Guideline No. 27, October 2005 – Placenta Praevia and Placenta Accreta)

Summary

- The “Standard” for massive transfusion is changing
- Utilizing appropriate ratios of FFP and platelets with prbcs is key to improving successful transfusion management
- A massive transfusion protocol, planning, communication, and teamwork are all critical to optimal outcomes