Massive Transfusion: Controversy Continues

Thrombin-Containing Local Hemostatic Products: Risks and Benefits

Prothrombin Concentrates for Warfarin Reversal: Where are we now in the US?

Presented by:
Dr. Lynn Boshkov, MD
Prof. Pathology, Medicine & Pediatrics
Director Hemostasis & Thrombosis
Associate Director Transfusion Medicine
Oregon Health & Science University, Portland Oregon, USA
E-mail: boshkovl@ohsu.edu

At: Hematology and Breast Cancer Update
Portland, OR January 15, 2011 9:30-10:15 AM
Disclosures: None
Structure of this Talk:

• Massive Transfusion: Controversy Continues……
• Thrombin-containing topical hemostatic agents: risks and benefits
• Prothrombin Concentrates for Warfarin Reversal: Where are we in the US?
Whole blood is being lost—total blood volume = 70 ml/kg--
or between 5000 – 7000 ml in the “average” 70-100 kg adult

What are we giving to replace it?
Blood volume of a 70 kg man and what it’s made of:

\[
\text{Blood Vol} = 70 \text{ ml/kg} \times 70 \text{ kg} = 4900 \text{ ml} \approx 5 \text{ L}
\]

Anticoagulated whole blood

\[\text{c’fuge hard spin}\]

- Plasma 0.60 \(\approx 3 \text{ L}\)
- WBC’s + Platelets
- Red Cells 0.40 \(\approx 2 \text{ L}\) 
  Hct 1.0

Problem ?: Resuscitation starts with crystalloid often and not blood and...
While we collect whole blood from blood donors, we don’t transfuse whole blood in the “Developed World”……

We transfuse “Components” =RBCs, plasma, platelets and sometimes plasma derivatives like cryoprecipitate and albumin—what’s IN these products and how are they made?

HINT: NOT as simple as this……
Whole blood separation into primary components (United States):

(1) 1 ‘U’ Red cell concentrate
≈ 350 - 400 ml total
≈ 250 ml red cells (Hct 0.50 -0.60)
≈ 25 ml plasma
Add 100 ml additive (AS-1) solution

(2) 1 ‘U’ “Random donor” Whole Blood Platelet Concentrate
≈ 6 x 10^{10} platelets
≈ 50 ml plasma

(3) 1 ‘U’ Plasma
≈ 250 ml
(1 ‘U’/ml all clotting factors)

Note: Giving 1 ‘U’ RBCs + 1 ‘U’ plasma will result in a “composite” product of ~ 600-650 ml vs original whole blood donation of 450 ml—thus there will be fewer RBCs and fewer coagulation factors per unit volume than are found in a comparable volume of whole blood; also NO platelets.....
Apheresis Platelet Product:
Note: the only platelet product supplied by Portland Red Cross is apheresis

Donor has double-lumen catheter in arm; whole blood removed and centrifuged by apheresis machine and PRP harvested; remainder of WB minus PRP component is returned to donor

1 ‘U’ “Single donor” Apheresis Platelet concentrate
≈ 35 x 10^{10} platelets
≈ 300 ml plasma
(equivalent to about 6 “whole blood” platelet units)
Cryoprecipitate and plasma derivatives

- **1 ‘U’ Plasma (≈ 250 ml)**
  - (1 ‘U’/ml all clotting factors)
  - spin
  - 4°C

- **1 ‘U’ Cryoprecipitate (≈ 10 ml)**
  - (~1/2 the VWF, FVIII and fibrinogen in the original plasma unit)

- **+ 1 ‘U’ Cryosupernatant plasma**

**Cryo 5 pools:**

- ≈ 50 ml (used as concentrated source of fibrinogen—2 x 5 pool cryo ≈ 100 ml but has as much fibrinogen as 5 x 250 ml ‘U’ or 1250 ml of plasma)

**Plasma pools:**

- **2000 - 20,000 donors**

- **Physical and/or chemical separation (s)**

- **Albumin**

- **Clotting Proteins (FVIII, FIX)**

- **IVIG; RhIg**

- **Many others**
“Classical” teaching re: coagulopathy of trauma (by extension from massive blood loss situations):

• Because initial resus is with crystalloid due to inavailability of blood “in the field” a “dilutional” coagulopathy predominates

• Because the PT INR and PTT begin to prolong when factor levels are < 0.40 as a rule, and because clinical bleeding occurs when factor levels are < 0.30….
  1) a lot of blood (2/3+ blood volumes) can normally be lost before you need to give factors
  2) RBCs should be given first, and you will need to start thinking about giving plasma only after about 5-10 RBC units have been given
  3) Measuring the INR, PTT and fibrinogen should be used to guide blood product replacement
“Classical” teaching re: coagulopathy of trauma (cont’d):

• **Re: plasma use:**
  1) Keep the INR < 1.6-2.0 (normal 0.8-1.2) OR
  2) Keep the PTT < 1.5 x midrange normal (≈ <45-50)

• **Re: platelets:** normal count is 150-450 x 10⁹/l and you
don’t bleed unless the count is < 50 x 10⁹/l so you can start
worrying about platelets about the same time as you start
worrying about plasma…**keep count > 50-100**…

• **Re: fibrinogen:** normal level is 200-400 mg/dl and
coaugulation is only impaired < 50-80 mg/dl—and as plasma
contains physiological amounts of fibrinogen, giving
plasma should keep you on top of any fibrinogen
problems…**keep count > 50-100**
Case: Schreiber from 2004: Typical bad trauma

- 38 yo male fell 25 feet from heating vent
- VS on admit: BP 154/109, P 102, GCS 15
- BP 77/31 with fluid improves to 110/70
- FAST positive for fluid: CT blood in abdo

Hospital Course: Taken to OR

- Grade IV liver laceration, Grade 1 spleen lac
- **Floseal** applied to liver and spleen, abdo packed
- Vacuum pack placed

- **EBL > 3L, 1500cc cell saver, 10 units PRBCs**
**Postop**

- Patient persistently hypotensive
- Bleeding from abdomen
- Platelet count 93,000
- INR 1.4

**Hospital Course**

- Arteriogram negative
- Taken back to OR
- Massive hemoperitoneum
- Injury to SMV, pancreaticoduodenal artery
• Surgical bleeding controlled
• Everything oozing
• INR 1.37, Platelet count 71
• Fibrinogen unknown
• pH 7.08, BD 13.9, T 33C

Hospital Course
• 7 units PRBC’s, 4 units FFP, 2 units platelets, 2 x 5 pools cryo given
• 90 ug/kg rFVIIa given (pH brought to 7.2)
• Abdomen packed……..
This case illustrates many hemostatic interventions in a typical bad 2004 trauma at OHSU including:

- Attempt to use interventional radiology and angioembolization / coiling—still being used

- Use of a **topical hemostatic agent containing thrombin** (Floseal proprietary—made from human plasma)—still being used

- Use of **multiple blood components to assist hemostasis**: plasma, cryoprecipitate, platelets—but only after many RBCs and a lot of crystalloid given first!

- Off-label use of rVIIa (now declining.....)
I agree with John Holcomb (ref below) that a strong argument can be made that, in very severely injured patients,

- **Initial resuscitation predominantly with crystalloid and RBCS** will inevitably lead to significant difficult-to-correct hemodilution of factors and platelets* and

- **Acidosis and hypothermia** will compound the coagulopathy AND

- **rVIIa** will then be reached for in a desperate effort to treat an at-least-significantly *iatrogenic* coagulopathy…..

- Interestingly data to support the now outdating 25 yr advocacy of this method of resuscitation turns out to have been based on 3 papers with largely uncontrolled data from 80 largely elective euvolemic surgery patients, done in the era when “modified whole blood” was being used—that is before modern component preparation (see Holcomb JB, Optimal Use of Blood Products in Severely Injured Trauma Patients, *Hematology* 2010 465-469)
Why? Coagulopathy of Trauma (or Acute Massive Blood Loss) is Complex and Reflects the Sum of…

• Blood loss and dilution

• Coagulation factor and platelet consumption
  • Clot IS platelets and fibrinogen, and factors and platelets are being consumed as clot forms
  • Tissue factor release can be HUGE
  • Ischemia-reperfusion can perpetuate coagulopathy

• Hypothermic platelet dysfunction

• Acidosis-induced ↓ in coagulation factor activity

• Fibrinolysis (hypoperfusion → tPA release +….)

• Perpetuation of the coagulopathy by systemic inflammatory response—IL-6 and TNF-α
Effect of pH and temp on rate of Factor Xa activation: (from paper on use of rVIIa)

a) Want pH > 7.2

b) Temp less important

Therefore, there has been a corollary movement (originating in the military) to “Damage Control Resuscitation” based on the premises that:

• **1:1:1 resuscitation with RBC : plasma: platelets** should ameliorate to some degree the hemodilution component of the coagulopathy

• **Fresh whole blood** should be the ideal fluid for resuscitation in severely injured patients requiring massive transfusion (some data now)

• **Better control of bleeding** should result in less ongoing hypotension, acidosis and hypothermia

• **Less rVIIa** will be needed if these precepts are followed
US Military using:

- Rapid identification coagulopathic pts
- Limited use of crystalloid: hypotensive resus
- 1:1:1 resus ratios using RBCs (grp O), prethawed plasma (AB) and apheresis plts
- Attention to prevention acidosis, hypothermia and coagulopathy

→ Results difficult to unconfound but strongly support decreased mortality with 1:1 plasma:RBCs in these patients
Effect of FFP:RBC Ratio on Overall Mortality

Chi Square
RB: p=0.006
RG: p<0.001
BG: p=0.034

Slide: Marty Schreiber MD

Mortality %

FFP:RBC Ratio

0:22 - 1:4: 65% (n=31)
1:3.9 - 1:2.1: 34% (n=56)
1:2 - 1:0.59: 20% (n=165)
1:1 Ratio Decreases Death from Hemorrhage

Chi Square
1&2: p=0.068
1&3: p<0.001
2&3: p=0.013

38% absolute and 62% relative reduction in hemorrhagic death compared to 1:4 bin

11.5/33 (35%)
18.5/20 (92.5%)
14/20 (70%)

Slide: Marty Schreiber MD
• There is also increasing evidence in civilian contexts that, in the small subset (2-3%) of the most critically injured trauma patients (hypotensive and coagulopathic on presentation --mortality 40-70% in this group) this strategy may save lives (and decrease use of rVIIa)

• By extension this thinking should also apply to any shocky coagulopathic massively bleeding patient.
Downsides and Criticism to this Approach:

• **“Survival Bias” issues:** you’ve got to live long enough to get plasma so bias inherent in 1:1:1 approach (Snyder CW et al, J Trauma 2009; 66: 358-364)

• **Risk and Benefit issues:** ↑ plasma (and other blood products) potentially associated with ↑ risk of allergic reactions, ARDS, TRALI, multiorgan failure

• **Major inventory management issues!!!**
Other unresolved /confounding issues:

• **Age of stored RBCs** (old RBCs > 14 d may be associated with increased risk thrombosis, sepsis, organ failure and death)

• **Equivalency of freshly thawed plasma to stored 5 day old plasma** (old plasma may increase endothelial permeability)

• **Platelet storage age** (old platelets may also increase endothelial permeability)

• **Role of antifibrinolytics** (tranexamic acid may be beneficial—recent trial CRASH-2—Lancet 2010; 376: 23-32)
Clearly this is a job for Superman and we desperately need good randomized controlled trials

In progress:

- US Department of Defense
  --10 center PRospective Observational Multi-center Massive Transfusion sTudy (PROMMTT)—min to min tracking products and complications
- 1200 transfused patients, 300 MT enrolled in 12 mos (to Sept 2010)

Awaiting Date crunch………
Watch this space…..
Structure of this Talk:

• Massive Transfusion: Controversy Continues
• **Thrombin-containing topical hemostatic agents: risks and benefits**
• Prothrombin Concentrates for Warfarin Reversal: Where are we in the US?
Coagulation Factors and In Vivo Clot Formation: Conversion of Fibrinogen to Fibrin by Thrombin Key

- Many “local” clotting agents and fibrin glues basically rely on a source of fibrinogen (often derived from human plasma) activated by thrombin (often bovine) to form a local clot.
- Contaminating bovine FV has given rise in past to anti-FV antibodies and clinical bleeding—and sometimes thrombosis!
A cautionary case history: Abstract Blood Nov 2002

“Bleeding due to acquired antibody to factor V followed by stroke associated with high titer anticardiolipin (ACLA) antibody in a 14 month old congenital cardiac patient exposed to topical bovine thrombin”

Lynn K Boshkov, MD 1, Gregory Thomas, MD 2, Mark Reller, MD 2*, Colin Roberts, MD 2* and Irving Shen, MD 2*. 1Pathology, Oregon Health & Science University (OHSU), Portland, OR, 97201 and 2Pediatrics, OHSU

- 14 mo old with epistaxis 3 ½ wks post uneventful 3rd cardiac surgery: Rastelli for double outlet RV, transposition, VSD, subpulmonic stenosis

- “Homemade” fibrin glue used: cryoppt + bovine thrombin

- PT INR 3.4 with minimal correction on 1:1 mix; PTT 142 sec; FV activity = 0.06 with inhibitor titre of 1.6 Bethesda units
• Bleeding controlled locally; PFA-100 prolonged; ibuprofen d/c’d

• When INR had declined to 1.8 with PTT 50.5 and FV activity of 0.22 patient presented with RUE weakness and a small distal middle cerebral infarct—no arrhythmia; agitated bubble study negative--rx’d with ibuprofen

• 3 days later had 2 focal seizures and flaccid R arm—ACLA IgG strongly positive at > 172 (normal < 20)—he required longterm lovenox therapy for persistant ACLA

--Such bleeding and thrombotic complications are well described in adults exposed to bovine thrombin (Streiff & Ness, Transfusion 42:18-26, 2002; Ortel J Lab Clin Med 133:326-34, 1999) and we saw another milder case in a child again in 2004....
OHSU Pharmacy Services Review of Topical Thrombin Products
Nov 2008:

- 3 topical thrombin products available for control of surgical bleeding:
  - Bovine-derived (Thrombin-JMI)
  - Human plasma derived (Evithrom)
  - Recombinant human thrombin (Recothrom)

- Bovine product carries FDA black box warning re: anti-Factor V antibodies; re-exposure may increase risk

- An older bovine product ThromboGen, now off the market, appears to have been esp pernicious

- More recent (since ? 2004) Thrombin-JMI preparations have used chromatographic processes and been nanofiltered to remove bovine FV and it is reported to be undetectable
Chapman et al. AM Coll Surg 2007; 205: 256-65: Phase 3 double-blind RCT of safety and efficacy of human and bovine thrombin:

--- Antibodies: Thrombin-JMI: 21.5% vs Recothrom 1.5%
--- BUT: No difference in coagulation parameters

--However: antibody patients had slightly higher rates of bleeding and thrombotic complications (19%) vs those with no antibodies (13% for bovine and 15% for Recothrom)

FDA has in past issued warming to Zymogenetics (Recothrom Manufacturer) for misleading statements in advertising re: Immunogenicity and potential safety differences

OHSU currently uses Thrombin-JMI and is saving $90,000 annually by using it vs Recothrom...(5000 unit vial Thrombin-JMI $87.56 vs Recothrom $104.92)—BUT...pricing has been revised now and this is possibly being reconsidered........
Many other topical hemostatic agents use thrombin including human thrombin:

- GelFoam Plus
- FloSeal
- Emerging agents.....

- Such agents appear effective in reducing bleeding and helping achieve superior surgical hemostasis...

- And bleeding and thrombotic sequelae seem rare....
FloSeal (Baxter) = Gelatin matrix + Thrombin Component (Human)

Vascular Surgery

Control = Gelfoam + Thrombin

P < 0.01


Cardiac Surgery

From FloSeal Information Brochure and Internet Sites:

FLOSEAL must not be injected into blood vessels, or allowed to enter blood vessels. Do not apply in the absence of active bleeding. Extensive intravascular clotting and even death may result. ………

Do not use FLOSEAL in patients with known allergies to materials of bovine origin……..

FLOSEAL is made from human plasma. It may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent…..

Related medicine products :
1. Duragen Dural Graft Matrix
2. Duraloc Acetabular Cup System
3. Duraloc 400 Series Cup
4. TISSEEL VH Fibrin Sealant
5. COSEAL Surgical Sealant
FDA Approves Sealant to Control Bleeding During Surgery

On Jan. 2, the U.S. Food and Drug Administration (FDA) expanded the indication for a liquid fibrin sealant to help control bleeding during general surgery. Fibrin is a protein that helps blood clot.

The sealant, called **Evicel**, is sprayed or dripped on small, oozing blood vessels. Once applied, it forms a covering that helps stop bleeding. Evicel was previously approved for use during liver and vascular surgery. This approval expands Evicel's indication to include general surgery applications.

"This approval provides a new option to help control bleeding during general surgery, when other approaches and techniques are ineffective or impractical," said Jesse L. Goodman, M.D., M.P.H., director of FDA's Center for Biologics Evaluation and Research.
Evicel contains fibrinogen and thrombin, two proteins involved in the production of fibrin. Fibrinogen and thrombin are found in human plasma, the liquid portion of blood.

The plasma used to manufacture the product is collected from donors who have been screened and tested for blood-transmitted infections. The fibrinogen and thrombin also undergo a two-step process to further reduce the risk for the transmission of potentially contaminating bloodborne viruses. While the potential risk for infectious disease transmission is remote, it cannot be eliminated.

FDA approved Evicel's predecessor (Crosseal) in 2003 for use during liver surgery. It became Evicel in May 2007 when FDA expanded the indication to include use during vascular surgery. Evicel is manufactured by OMRIX biopharmaceuticals LTD, located in Kiryat Ono, Israel.#RSS

......
Bottom line:

• **Newer bovine thrombin products appear less antigenic but I believe the true safety profile and risk/benefit of these products remains to be determined**

• There is a report in the literature of antibodies with Thrombin-JMI (Lawson JH Ann Thorac Surg 2005; 79: 1037-8)

• I was not reassured to receive the following e-mail on Nov 19, 2008 circulated to Hemophilia MDs and nurses; it originated from Hemophilia & Thrombosis Center at the Henry Ford Health System in Detroit and began: “We have a Factor V inhibitor patient who is bleeding…”
Structure of this Talk:

• Massive Transfusion: Controversy Continues
• Thrombin-containing topical hemostatic agents: risks and benefits
• Prothrombin Concentrates for Warfarin Reversal: Where are we in the US?
<table>
<thead>
<tr>
<th>Serious Bleeding</th>
<th>Vitamin K 10 mg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening Bleeding</td>
<td>FFP or PCC or VIIa</td>
</tr>
</tbody>
</table>

(Slide adapted Tony Giulivi, MD)
“Although FFP can be given in this situation, immediate and full correction can only be achieved by the use of factor concentrates because the amount of FFP required to fully correct the INR is considerable.”

CHEST 2008; 133: 175S
Rule 1: Non-linearity of INR and factor def’y:

INR and Coagulation Reserve

% coagulation Factors

100 %

50 %

30 %

zone of normal hemostasis

zone of anticoagulation

PT (sec) 12 13 15.5 19 21.8 24 30 32

INR 1 1.3 1.7 2.0 2.2 3.0

(Slide adapted from Tony Giulivi MD)
Due to this non-linearity:

1. It should take a lot of plasma (4 L) to take the coagulation factors from 20 to 100% (INR 2.2 to 1.0)

2. Giving 2-4 units of plasma for an INR of 1.3 – 1.8 should do almost nothing!

-- exactly what was found by Abdel-Wahab OI, et al. Transfusion 2006; 46: 1279-85

(Slide adapted from Tony Giulivi, MD)
Treating bleeding on warfarin in USA:

• Problem: Vit K deficiency

<table>
<thead>
<tr>
<th>Factor</th>
<th>t ½ (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F II</td>
<td>60</td>
</tr>
<tr>
<td>F VII</td>
<td>4-6</td>
</tr>
<tr>
<td>F IX</td>
<td>22</td>
</tr>
<tr>
<td>F X</td>
<td>35</td>
</tr>
</tbody>
</table>

Basic principles:

1. PT INR prolongs/correct faster than PTT → target INR < 1.5 - 2.0

2. **Vit K → give IV** (over 30-60 min)--SQ absorption erratic
   - adult: INR 2-4.5: 2.5 mg; INR 4.5-10: 5mg; INR>10: 5-10mg
   - [anaphylaxis ~ 3:10,000; can give 2.5-5 mg PO if not emergent]

3. Earliest effect 4-6 hr; 2-3 days to full effect → **give plasma too**
   - [Large doses needed quickly: 15 ml/kg or 4-5 ‘U’ in an adult]
   - (1 ‘U’ plasma → ↑ factor levels ~ 5%-- at INR 2.0-3.0 baseline levels FX~20-30%)

4. In truly emergent situation (ICH) ??????????
   - → **give rVIIa (? 40 mcgm/kg)** OR **FEIBA (50 ‘U’/kg) ??????*/
Well, wouldn’t it be great if for reversal we could just give what’s missing in warfarinized or Vit K deficient patients (eg II, VII, IX, X, Prot C, Prot S) in a concentrated form?

These products (Prothrombin Complex Concentrates or PCCs) exist—the trouble is the ones licensed in the US are licensed for Hemophilia B and don’t contain much FVII (or PC or PS)
Note: Currently licensed PCCs (prothrombin complex concentrates) in the US are used to treat hemophilia B = FIX def’y and are NOT suitable for warfarin reversal:

<table>
<thead>
<tr>
<th></th>
<th>Profilnine</th>
<th>Bebulin VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Grifols</td>
<td>Baxter</td>
</tr>
<tr>
<td>Contents</td>
<td>Vitamin K dependent factors</td>
<td>Vitamin K dependent factors</td>
</tr>
<tr>
<td>Units/100 units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIX</td>
<td>FII: 148</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>FVII: 11</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>FX: 64</td>
<td>129</td>
</tr>
<tr>
<td>Source</td>
<td>Pooled human plasma</td>
<td>Pooled human plasma</td>
</tr>
<tr>
<td>Dosing</td>
<td>FIX: 75 units/kg</td>
<td>FIX: 50 units/kg</td>
</tr>
<tr>
<td></td>
<td>May repeat q12hr as needed</td>
<td>May repeat q24hr as needed</td>
</tr>
<tr>
<td>Viral attenuation</td>
<td>Solvent detergent</td>
<td>Vapor heat</td>
</tr>
</tbody>
</table>

(Slide adapted from Michael Recht, MD PhD)
• Octaplex, a “balanced” PCC has recently been licensed in Canada for use in warfarin reversal; data being gathered; US trial (Lex-205) is in progress at interim analysis stage…

• Beriplex, another “balanced” PCC has just completed data gathering for their US trial….
<table>
<thead>
<tr>
<th>Name of ingredient</th>
<th>OCTAPLEX Quantity per vial (20mL)</th>
<th>OCTAPLEX Quantity per mL reconstituted solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein:</td>
<td>260 - 820 mg</td>
<td>13 - 41 mg/mL</td>
</tr>
<tr>
<td>Active substances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human coagulation factor II</td>
<td>220 - 760 IU</td>
<td>11 - 38 IU/mL</td>
</tr>
<tr>
<td>Human coagulation factor VII</td>
<td>180 - 480 IU</td>
<td>9 - 24 IU/mL</td>
</tr>
<tr>
<td>Human coagulation factor IX</td>
<td>400 - 620 IU</td>
<td>20 - 31 IU/mL</td>
</tr>
<tr>
<td>Human coagulation factor X</td>
<td>360 - 600 IU</td>
<td>18 - 30 IU/mL</td>
</tr>
<tr>
<td>Further active ingredients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein C</td>
<td>140 - 620 IU</td>
<td>7 - 31 IU/mL</td>
</tr>
<tr>
<td>Protein S</td>
<td>140 - 640 IU</td>
<td>7 - 32 IU/mL</td>
</tr>
<tr>
<td>Excipients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peparin</td>
<td>80 - 310 IU</td>
<td>4 - 15.5 IU/mL</td>
</tr>
<tr>
<td>Sodium Citrate</td>
<td></td>
<td>17.0 - 27.0 mmol/L</td>
</tr>
</tbody>
</table>

Factor IX specific activity is ≥ 0.6 IU/mg proteins.

Further excipient: Solvent (Water for Injections)

Small amounts of the S/D reagents TNPB (<5 μg/ml) and Polysorbate 80 (<50 μg/ml) may remain in the finished product.
Trying to correct an INR below 1.5 with FFP (whether the etiology is Vit K deficiency or liver disease or whatever) is basically an exercise in futility……..

However, balanced PCCs when compared with FFP seem to be able to correct Vit K deficiency:
-- more quickly
-- more fully
-- in a much lower volume, and
-- without some of the other complications of FFP
FFP vs Octaplex

- **FFP**
  - Large volume (15 mL/kg; 770-1500 mL)
  - Risk of TRALI, TACO and anaphylaxis
  - Requires ABO group
  - Needs to be thawed
  - Not virally inactivated

- **PCC**
  - Pooled, virally inactivated
  - Prion reduction process
  - Lyophilized
  - Small volume 40-80 mL

(Slide adapted from Tony Giulivi, MD)
PCC vs rVIIa for reversal of coumadin anticoagulation: PT correction


(Slide adapted from Tony Giulivi, MD)
PCCs vs rVIIa for reversal of coumadin anticoagulation: Effect on blood loss

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Median Difference (CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline vs rFVIIa</td>
<td>261.0 (-628.9 to 1758)</td>
<td>0.55</td>
</tr>
<tr>
<td>Saline vs PCC</td>
<td>905.7 (662.5 to 2487)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>rFVIIa vs PCC</td>
<td>728.9 (363.1 to 1535)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>


(Slide adapted from Tony Giulivi, MD)
The European Experience
J Thromb Haemost 2008; 6: 622-31

- 15 center in Europe (8 countries) over 1 yr
- Beriplex P/N
- Adults, INR>2, needing emergency surgery or bleeding
- 25 IU/kg (2-4), 35 IU/kg (4-6), 50 IU/kg (>6)
- Vitamin K a bit diverse (75% IV, 75% 10mg)

(Slide from Tony Giulivi, MD)
The European Experience
J Thromb Haemost 2008; 6: 622-31

(Slide adapted from Tony Giulivi, MD)
The European Experience
J Thromb Haemost 2008; 6: 622-31

(Slide adapted from Tony Giulivi, MD)
What we are currently doing for ICH in warfarinized patients at OHSU (lead by Tom DeLoughery; approved by P&T Committee):

- Profilnine ("3 component" PCC) 4000 U
- rVIIa 1.0 mg

--Repeat coags and consider redose Profilnine if still significantly prolonged

- Awaiting the FDA’s ultimate approval (hopefully) of a balanced "4 component" PCC for coumadin reversal
And (I cannot tell a lie) I confess I have used this Profilnine + low dose rVIIa combination to treat refractory bleeding in the massive transfusion setting in a patient taken to heart transplant fully coumadinized—and, although a series of anecdotes do not data make, it worked like a charm there too.....