Coagulation Factors in Controlling Traumatic Bleeds: FFP, PCC, or Lucky Sevens?

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Learning Objectives:
1. Explain the pathophysiology of coagulopathies due to traumatic bleeding
2. Describe the role of warfarin in coagulopathies
3. Explain mechanisms and places in therapy of fresh frozen plasma (FFP), prothrombin complex concentrate (PCC), and recombinant factor VII (rFVIIa) in traumatic bleeds
4. Devise a treatment plan for coagulopathic patients with traumatic bleeds
I. Trauma
   a. International endemic affecting persons of all ages
   b. Leading cause of death in individuals aged 1-44 years in 2003

II. Hemorrhagic shock (SEE APPENDIX A)
   a. Precipitated by traumatic event, resulting in acute blood loss
   b. Severe impairment of tissue perfusion and oxygenation
   c. Standard of care
      i. Goals: control source of bleeding and resolve shock
      ii. Surgical exploration – direct "hands-on" examination (ie. exploratory laparotomy); mechanical control by direct pressure (ie. ligation of severed blood vessels, excision of damaged solid organs, surgical packing)
      iii. Initial fluid therapy
         1. Warmed isotonic electrolyte solutions
         2. "3-for-1 rule": for each 1 mL of blood loss, replace with 3 mL of crystalloid fluid
         3. Guided by goal of restoring normal blood pressure
   v. Risks of aggressive fluid resuscitation
      1. Reverse compensatory vasoconstriction
      2. Dilute blood’s oxygen-carrying capacity and hemostatic factors
      3. “Wash away” early clots
      4. Result: coagulopathy, rebleeding, and recurrent hypotension → provoke further fluid administration

III. Coagulopathy
    a. Definition: a defect in the body’s mechanism for blood clotting
    b. Laboratory diagnosis: PT (prothrombin time) ≥ 1.5 times normal, aPTT (activated partial thromboplastin time) ≥ 1.5 times normal, INR (international normalized ratio) > 1.5, platelet count < 50 x 10^9 L, fibrinogen < 50-100 mg/dL
    c. Generalized non-surgical bleeding from wounds, skin edges, vascular access sites

IV. Mechanisms of blood coagulation (SEE APPENDIX B)
i. Several circulating proteins interact in a cascading series of limited proteolytic reactions

ii. Tissue factor (TF)
   1. Transmembrane protein expressed outside the vasculature
   2. Binds FVIIa when exposed on damaged endothelium or to blood that has extravasated tissue
   3. TF-FVIIa complex: main initiator of blood coagulation – activates FIX and FX
      i. Tissue factor pathway inhibitor (TFPI): inhibits catalytic action of TF-FVIIa complex
   4. FXa and FVa form prothrombinase complex on activated cell surfaces →
      catalyze conversion of prothrombin (FII) to thrombin (FIIa)

iii. Thrombin (FIIa) functions
   1. Allows fibrinogen to polymerize and form a fibrin clot, an essential component of a functional clot
   2. Activates upstream clotting factors (V, VIII, IX)
   3. Potent platelet activator and mitogen
   4. Activates protein C pathway, lessening the clotting response

b. Endothelial cell layer
   i. Setting of vascular injury
      1. Series of changes, resulting in a more procoagulant phenotype

2. Amplification phase:
   Vessel damage → extravascular migration of platelets and FVIII-von Willebrand complex →
   platelet adherence and activation, secretion and synthesis of vasoconstrictors and platelet
   recruiting and –activating molecules

3. Propagation phase:
   Large numbers of activated platelets → increased rates of thrombin generation with
   subsequent fibrin generation → formation of platelet plug

c. Hemostasis
   i. Definition: a complex process that limits blood loss following vascular injury
      1. Maintains blood fluidity
      2. Repairs vascular injury
      3. Prevents vessel occlusion (thrombosis) and inadequate perfusion of vital organs
   ii. Both excessive bleeding and thrombosis represent a breakdown of the hemostatic mechanism

d. Disseminated intravascular coagulation (DIC)
   i. Coagulation and fibrinolytics systems pathologically activated
   ii. Hemostatic system "careens out of control"
   iii. Leads to generalized intravascular clotting and bleeding
   iv. May follow massive tissue injury
   v. Often fatal when underlying disease process not controlled
V. “Lethal triad” of coagulopathy

a. Aggressive resuscitation resulting in rebleeding, hypothermia, and dilution → perpetuate coagulopathy and the “lethal triad”

b. Hypothermia
   i. Core body temperature < 35°C
   ii. Reduced heat production
      1. Decreased oxygen consumption during hemorrhagic shock
      2. Operative interventions → further heat loss from peritoneal and pleural surfaces
      3. Fluid resuscitation \[\text{heat} = \text{mass} \times \text{specific heat} \times (T_{\text{body}} - T_{\text{fluid}})\]
   iii. Largest effect on platelet activation and adhesion
      1. Inhibits interaction between von Willebrand factor (vWF) and platelet glycoprotein Ib-IX-V complex
      2. Slows metabolic rate of coagulation factor enzymes
   iv. Occurs in 80% of trauma non-survivors and 36% of trauma survivors
   v. Effects on specific clotting factor deficiencies
      1. At 35°C, without dilution, decreased activity in all coagulation factors
      2. FXI and FXII only functioning at 65% of normal at 35°C
      3. At 32°C, activity of FXI and FXII reduced to 17% and 32%, respectively

c. Acidosis
   i. Reduces activity of proteases in coagulation system
   ii. pH reduction of 7.4 to 7.0
      1. Activity level of FVIIa reduced by 90%
      2. Activity of TF-FVIIa complex reduced by 55%
      3. Rate of prothrombin activation by FXa-FVa complex reduced by 70%

d. Hemodilution
   i. Hemorrhage: direct loss of coagulation factors
   ii. Dilutional coagulopathy: losses restored with fluids without clotting factors
      1. Reduced plasma and coagulation factors in circulating blood volume → reduced ability of clot formation
      2. Crystalloids given en route to trauma center
      3. Packed red blood cells (pRBCs) given prior to laboratory tests (INR, fibrinogen, hemoglobin, platelets) becoming available
      4. Abnormal results trigger request for fresh frozen plasma (FFP)
         i. Takes 20-30 min to thaw → further delay to correct ongoing coagulopathy
      5. Perpetuating cycle delays diagnosis and treatments and contributes to dysfunctional clotting capabilities

e. Risk factors for coagulopathy

- Massively transfused
  - >10 units pRBC/24 hrs

- ISS** > 25
- pH < 7.1
- Temp < 34°C
- SBP ≤ 70mmHg

98% likelihood of developing life-threatening coagulopathy

*(See Appendix C)*
i. Patients with none of these risk factors had 1% chance of developing life-threatening coagulopathy
ii. Patients with coagulopathy on admission had significantly higher mortality rates than those with normal clotting on admission (46% vs. 10.9%)  
iii. Abnormal admission PT increases adjusted odds of dying by 35%; abnormal aPTT increases adjusted odds of dying by 326%  
1. PT: evaluates adequacy of the extrinsic pathway; clotting ability of factors I, II, V, VII, X  
2. PTT: measures efficacy of both the intrinsic and common coagulation pathways; evaluates factors I, II, V, VIII, IX, X, XI, and XII

WARFARIN

VI. Warfarin + Trauma = Bad

a. Increasing need to manage trauma patients who receive anticoagulation  
i. Expanding warfarin use due to expanding aging population  
   1. Use increased from 2.3% to 4.0% from 2002 to 2006  
   2. Use in patients > 65 years increased from 7.3% to 12.8% from 2002 to 2006  
   3. 1-10% annual incidence of major bleeding in warfarin patients  
ii. Increasing trauma rates in patients ≥ 65 years  
   1. 2009: 20.8% trauma cases in patients ≥ 65 years – increased from 15.3% in 2004  
b. Traumatically injured patients receiving warfarin at higher risk for severe intracranial hemorrhage and uncontrolled bleeding  
i. Four- to five-fold increased risk of death in anticoagulated trauma patients vs. non-anticoagulated trauma patients  
ii. Increased anticoagulation intensity increases risk of hemorrhagic events  
   1. 98,900 patient years of observation  
   2. Evaluated how under- and over-anticoagulation influence patient outcomes  
   3. Compared with INR 2.0-3.0, relative risk of hemorrhagic events was 2.7 (absolute risk 3.7%/year) at INR 3.0-5.0, and 21.8 (absolute risk 30.1%/year) for INR >5.0  
iii. Rapid reversal of anticoagulation in trauma patients necessary to prevent or minimize hemorrhagic complications  
   1. Protocol of rapid identification of intracranial bleeding and warfarin reversal decreased intracranial hemorrhage progression and reduced mortality

VII. Pharmacology  
a. Vitamin K antagonist (VKA)  
b. Commonly prescribed for treatment and prevention of thromboembolic events  
c. Inhibits enzyme, vitamin K epoxide reductase (VKORC1)  
   blocks formation of reduced vitamin K from vitamin K epoxide  
i. Reduced form of vitamin K required for biological activity of extrinsic coagulation factors  
d. Response to warfarin influenced by several factors (medications, diet, pharmacogenomics, etc.)  
e. PT used in clinical practice as a therapeutic response marker  
   i. INR used to standardize its reporting [INR = (patient PT/mean PT)]  
   ii. Moderate intensity anticoagulation (INR 2.0-3.0) recommended for most indications  
   iii. Safety and efficacy depend on maintaining INR within therapeutic range

VIII. Questions to answer  
a. What treatment strategies should be used in traumatic bleeding patients on warfarin pre-injury?  
b. What treatment strategies should be used in traumatic bleeding patients NOT on warfarin pre-injury?
REVERSAL OF COAGULOPATHY

IX. Discontinue warfarin\textsuperscript{15,20}
   a. Allow natural increase in synthesis of associated clotting factors
   b. Long $t_{1/2}$ (average 40 hrs); takes several days for reversal, therefore not enough in setting of traumatic bleed

X. Vitamin K (phytonadione)\textsuperscript{21}
   a. Highly effective at reversing effects of warfarin
      i. Ineffective in patients with severe liver failure – poor synthesis of coagulation factors
   b. Large doses directly converted to reduced vitamin K via the enzyme vitamin K reductase
   c. Subcutaneous inferior to oral or intravenous (IV) administration – unpredictable and delayed response
   d. Under normal circumstances, no considerable difference in how fast oral or IV administration will work
      i. Guidelines recommend 10 mg IV for urgent reversal of anticoagulation due to high risk of delayed enteral uptake in severely bleeding patient\textsuperscript{21,22}
      ii. Dilute and administer as slow IV infusion, no faster than 1 mg/min
   e. Increased synthesis of factors within 1-3 hrs; however, clinical effect cannot be detected until 4-6 hrs; maximum effect after 24-36 hrs\textsuperscript{21}

XI. Resuscitation solution\textsuperscript{23}
   a. Necessary to restore and support tissue oxygenation and perfusion\textsuperscript{14}
   b. 1960s: whole blood used effectively as resuscitation solution\textsuperscript{23}
      i.Contained all elements needed for hemostasis
   c. Early 1970s: blood suppliers began separating whole blood into components and supplying blood products in the form of pRBCs, platelets, plasma, etc.
      i. Current standard of practice in civilian communities
      ii. Whole blood only available for “walking blood banks” in the military
      iii. Currently left with pRBCs, crystalloid fluids, replacement of various coagulation factors piecemeal using cryoprecipitate and FFP
   d. Good for: patients with congenital or acquired coagulopathy – advantageous to allocate resources according to the needs of individual patients\textsuperscript{14,23}
   e. Problem: replacement of lost blood volume with crystalloid and pRBCs alone does not replenish coagulation factors in acutely hemorrhaging trauma patients\textsuperscript{23}
      i. Recent emphasis on hemostasis with replacement of FFP, platelets, cryoprecipitate, and rFVIIa
   f. Response to discontinuation of whole blood and the adoption of component therapy
      i. 3 L crystalloid for each 1 L of blood loss\textsuperscript{24}
         1. Problem: massive fluid overload $\rightarrow$ significant edema, acute respiratory distress syndrome, hepatic failure, renal failure, sepsis
         2. Does not contain necessary clotting factors for complete resuscitation
      ii. Fluid replacement as near to whole blood as possible in severely injured military patients — 1:1:1 ratio of blood, plasma, and platelets\textsuperscript{25}
         1. Mortality improved from \textasciitilde80\% to < 30\% in severely injured patients who required > 10 units of blood in 8 hrs\textsuperscript{26}
         2. Shorter length of stay and less blood required for resuscitation
         3. Early use of pRBCs, FFP, and platelets offers best chance of limiting coagulopathy in early phases of care\textsuperscript{14}
   g. Current approaches as a solution to hemorrhage\textsuperscript{23}
      i. 1:1:1 ratio – plasma, platelets, pRBCs (cryoprecipitate PRN)
      ii. 1:1 ratio – plasma, pRBCs (cryoprecipitate and platelets PRN)
   h. “Ideal” resuscitation fluid\textsuperscript{14}
      i. Efficacous
      ii. Safe
      iii. Inexpensive
      iv. Easy to store and transport
      v. Assist in carrying oxygen and nutrients to cells
XII. Fresh frozen plasma (FFP)\textsuperscript{15,21,23}

a. Recommended in massive bleeding or bleeding complicated by coagulopathy
b. Contains factors II, VII, IX, X, fibrinogen, vWF, and antithrombin
   i. Blood group specific (requires ABO group testing)
   ii. Total FFP pack volumes can range between 150-250 mL; institutionally-dependent

   c. Widely available and most common means of replacing depleted coagulation factors and urgently reversing coagulopathy
      i. Indications: active bleeding and PT or PTT > 1.5 times normal, or an INR > 1.5
      ii. Many protocols suggest transfusing FFP after patient has received 4-6 units pRBCs; however, becoming more common to transfuse earlier due to development of post-traumatic coagulopathy\textsuperscript{12}

   d. Drawbacks\textsuperscript{15,23}
      i. Low and variable amounts of coagulation factors $\rightarrow$ unpredictable reversal of VKA therapy
      ii. Recommended dosage of $\sim$15 mL/kg often insufficient to correct coagulopathy
         1. Some recommend 10-30 mL/kg\textsuperscript{21}
      iii. Large volume $\rightarrow$ risk of volume overload
         1. Patients on VKA often elderly, may have compromised and vulnerable cardiovascular system
         2. Thawed plasma: FFP that has been thawed and kept at 1-6°C for up to 5 days – except for differences in FVII levels, thawed plasma and FFP considered equivalent in terms of factor concentrations\textsuperscript{27,28}
         v. Risk of transfusion-related acute lung injury (TRALI) – estimated incidence of 8-25%
            1. Most common cause of transfusion-related death in the US
            vi. Citrate toxicity
            vii. Transmission of viral illness (low risk)

XIII. Prothrombin complex concentrate (PCC)\textsuperscript{14,21,23,29}

a. FDA labeled indication: prevention and control of bleeding due to factor IX deficiency in hemophilia B
   i. Produced from pooled human plasma
   ii. Contains standardized, although variable, amount of coagulation factors
   iii. Virus-inactivated
   iv. Not blood-group specific
   v. Minimal risk of volume overload
      1. 10 mL diluent per vial

b. Formulations\textsuperscript{30} (SEE APPENDIX D)
   i. Contains factors II, +/- VII, IX, X, +/- coagulation inhibitors protein C and S, +/- heparin (0.2-15 units/mL)
   ii. Low levels FVII = 3-factor PCC (Profilnine\textsuperscript{®}, Bebulin\textsuperscript{®}VH) – only formulations available in the US
   iii. High levels FVII = 4-factor PCC (Beriplex\textsuperscript{®}VH, Octaplex\textsuperscript{®})
   iv. Dose expressed as units of FIX
   v. Considerable differences between PCCs in quantities of coagulation factors
   vi. 2012 CHEST guidelines\textsuperscript{22} recommend 4-factor PCC over FFP for VKA-associated bleeding

c. 3-factor PCC ± thawed plasma in supratherapeutic INR reversal\textsuperscript{27}
   i. Retrospective case series
   ii. 82 patients with INR > 5.0, excluded intracranial hemorrhage
   iii. Administration of thawed plasma alone OR 3-factor PCC (25 units/kg or 50 units/kg) alone not sufficient in providing satisfactory INR correction (< 3.0) in 42-62% patients
   iv. Addition of 2.1 units thawed plasma to PCC significantly improved proportion of patients achieving adequate INR (89-93%)

   d. Optimal dosage for a given situation is unclear\textsuperscript{31}
      i. Influenced by several factors: urgency of reversal, risks for thrombosis, traumatic injury, and level of anticoagulation before and after administration of reversal strategy
      ii. Recommended maximum rate of infusion is 3 mL/min; up 10 mL/min has been reported without complications (ie. thrombosis)
      iii. Reversal of INR occurs within 10-30 min, duration 6-96 hrs
e. Major drawback: risk of thrombotic complications\textsuperscript{15,30,32,33}
   i. Hemophilia B: deep vein thrombosis, DIC, pulmonary embolisms, and acute myocardial infarctions reported (1960s-80s)\textsuperscript{33}
      1. Supra-physiological levels of other factors (besides IX) in the preparation
      2. Repetitive dosing
   ii. Cause may be due to activated factor IX or presence of procoagulant phospholipids\textsuperscript{33}
      1. Reduction in thromboembolic complications among hemophilia B patients when highly-purified factor IX began to replace PCCs – despite higher levels of factor IX compared with PCC
      2. Prothrombin cited to be major determinant of excessive thrombin generation in PCC
   iii. Inclusion of coagulation inhibitors – heparin, antithrombin, protein C, S, Z – may provide "balance" to coagulation factors, avoiding excessive increase in thrombin generation and reducing thrombotic risk\textsuperscript{33}
   iv. Incidence unknown – varies based on PCC content, dosage, concurrent use of procoagulants, and patient-specific risk factors (age, liver disease, surgery, history of thrombosis)
   v. No evidence to suggest difference in thromboembolic risk between 3- and 4-factor PCCs\textsuperscript{33}

| Dickneite G, et al. Prothrombin complex concentrate vs. fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model. 2009.\textsuperscript{34} |
|---|---|
| **Design** | Randomized, placebo-controlled trial in pigs |
| **Population** | 47 anaesthetized, mildly hypothermic (36°C) pigs |
| **Interventions** | ● 65-70% of total blood volume substituted in phases with hydroxyethyl starch and pRBCs  
                   ● Randomized to receive: 15 mL/kg isotonic saline, 25 units/kg PCC, or standard-dose (15 mL/kg) or high-dose (40 mL/kg) porcine FFP  
                   ● 4-factor PCC used  
                   ● Immediately after treatment given, standardized injury inflicted |
| **Endpoints** | PT, thrombin generation, time to hemostasis, volume of blood loss |
| **Results** | ● PCC therapy fully reversed prolonged PT and corrected reduced peak thrombin generation  
             ● Compared with 15 mL/kg FFP, PCC shortened time to hemostasis after either bone or spleen trauma, and reduced volume of blood loss |
| **Take Home Points** | ● PCC 25 units/kg effective in correcting dilutional coagulopathy and controlling bleeding when administered prior to trauma |

| Grottke O, et al. Increasing concentrations of prothrombin complex concentrate induce disseminated intravascular coagulation in a pig model of coagulopathy with blunt liver injury. 2011.\textsuperscript{30} |
|---|---|
| **Design** | Randomized, placebo-controlled trial in pigs |
| **Population** | 27 anaesthetized pigs |
| **Interventions** | ● Coagulopathy induced by replacing ~70% blood volume with hydroxyethyl starch and Ringer's lactate solution  
                          ● RBCs collected and re-transfused  
                          ● 10 min after trauma, animals randomly received 4-factor PCC (35 or 50 units/kg) or saline |
| **Endpoints** | Blood loss; survival; presence of emboli |
| **Results** | ● Total blood loss significantly lower and survival higher in low- and high-dose PCC groups vs. saline group (p <0.05)  
             ● Thromboembolism found in all animals treated with PCC 50 units/kg |
| **Take Home Points** | ● PCC 35 units/kg safely improved coagulation and attenuated blood loss  
                              PCC 50 units/kg increased risk of thromboembolism |

XIV. Recombinant FVIIa (rFVIIa)\textsuperscript{35}
   a. Recombinant form of human factor VIIa
   b. FDA labeled indications: treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia; prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors in acquired hemophilia; treatment of bleeding episodes in congenital FVII deficiency
   c. Acts at site of injury to enhance thrombin generation, leading to stable fibrin clot\textsuperscript{36}
   d. Rationale: FVII is single coagulation factor with the most pronounced clotting ability affected by VKA\textsuperscript{21}
   e. Administration gives biochemical rapid reversal of INR within 10 min
      i. Short $t_{1/2} < 1$ hr
Theories behind mechanism

i. Original thought: supra-physiological concentrations speed up tissue FVIIa-mediated reaction, resulting in more thrombin generation

1. Problem: concentrations of rFVIIa required for hemostatic efficacy were far greater than what would be required to saturate TF

ii. Cell-based system: rFVIIa can bind to platelets and directly activate FX and FIX without TF

iii. Recent data: when administered in doses sufficient to bypass need for FVIII or FIX, rFVIIa binds to surface of activated platelets in TF-independent manner and promotes FX activation and thrombin generation

XV. Summary of available options

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<th>FFP</th>
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<td>1.5-2 days</td>
<td>6-8 hrs</td>
<td>&lt; 60 min</td>
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**CLINICAL EVIDENCE: WITH PRE-INJURY WARFARIN**


<table>
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<tr>
<th>Design</th>
<th>Retrospective before-and-after study</th>
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| Population | ● 40 patients with pre-injury warfarin use, traumatic intracranial hemorrhage, and INR ≥ 1.3  
● Protocol: administration of 1.2 mg rFVIIa in the ED and standard treatment (FFP + vitamin K) |
| Endpoints | ● Primary: in-hospital mortality  
● Secondary: mortality at 48 hrs and 30 days; successful reversal of anticoagulation (INR <1.3); time to coagulopathy reversal; worsening Marshall score (SEE APPENDIX E); neurosurgical intervention; time to neurosurgical intervention; prevalence of in-hospital VTE |
| Results | ● Patient characteristics: median age 80.5 years; most common injury fall from standing height or less; median Glasgow Coma Scale (SEE APPENDIX F) 14; median initial INR 2.72 (2.17-3.51) - similar patient characteristics between groups  
● Median rFVIIa dose 17.7 mcg/kg; average treated 2.1 hrs after ED arrival; 1/20 received 2 doses  
● All 40 patients received FFP; decreased number of units in rFVIIa cohort (2.3 vs. 4.6 units, p=0.001)  
● Identical in-hospital mortality (35.0%), 48 hr mortality (5.0%), and 30 day mortality (35.0%)  
● Greater number of patients achieved correction of INR in rFVIIa cohort (100% vs. 68.4%, p=0.02) and faster time to INR correction in rFVIIa cohort (17.5 vs. 4.8 hrs, p <0.001)  
● No difference in worsening Marshall score  
● Numerically greater neurosurgical intervention in rFVIIa cohort (35.0% vs. 20.0%, p=0.29); and decreased time from ED arrival to neurosurgical intervention in rFVIIa cohort (5.6 vs. 74.6 hrs, p=0.30); no difference in survival between patients with neurosurgical intervention  
● Trend towards more thromboembolic complications (PE or DVT) in standard cohort (5.0%) vs. rFVIIa cohort (20.0%), p=0.15 |
| Take Home Points | ● No mortality benefit  
● Relatively low dose rFVIIa improved INR correction  
● Risk of venous thromboembolism? |

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<th>Design</th>
<th>Retrospective case series</th>
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| Population       | - 31 total patients: received warfarin pre-injury; INR > 1.5; received vitamin K, FFP, and/or PCC  
- Exclusion criteria: received rFVIIa |
| Endpoints        | Achievement of INR ≤ 1.5; time to INR ≤ 1.5; INR change from baseline (%); mortality: LOS |
| Results          | - Baseline: PCC patients had higher ISS (17.8 vs. 9.1, p < 0.001) and more required surgical intervention (7 vs. 2, p=0.017); otherwise, no differences  
  - Average age ~70 years, mean GCS ~14, ~one-third with “fall”, ~25% with traumatic brain injury  
  - Mean INR 3.03 in PCC group, 2.77 in no-PCC group (p=0.78)  
  - Treatment:  
    - PCC group: 36% received vitamin K, 85% received FFP (average ~4 units), average dose ~25.6 units/kg  
    - No-PCC group: 61% received vitamin K, 89% received FFP (average ~5.1 units)  
  - INR outcome:  
    - Similar proportion achieving INR ≤ 1.5 (~90%)  
    - Shorter time to INR ≤ 1.5 in PCC group (17 hrs vs. 30 hrs, p=0.048)  
    - Similar change from baseline INR between groups  
  - Mortality: 3 in PCC group (23.1%) vs. 0 in no-PCC group (p=0.06)  
  - LOS: ICU LOS similar between groups (9.1 vs. 6.1 days, p=0.17); hospital LOS similar (11.4 days vs. 9.7 days, p=0.26) |
| Take Home Points | - 3-factor PCC ~25 units/kg allows faster achievement to goal INR when used in trauma  
- Sicker baseline characteristics in 3-factor PCC group likely cause of mortality and LOS difference |


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| Population       | - 46 patients admitted for warfarin-related intracerebral hemorrhage  
- “Trauma Coumadin Protocol” (TCP) group = 3-factor PCC 4000 units + rFVIIa 1.0 mg + vitamin K 5 mg IV daily x 3 days  
- Control group: historical, received FFP or FFP + 3-factor PCC, unknown amounts of vitamin K |
| Endpoints        | Pre/post-TCP INR; INR at 24 hrs; time to INR correction; thromboembolisms; mortality |
| Results          |  
| Treatment        | Mean baseline INR | Mean time from blood bank dispense to next INR | Mean post-infusion INR | Mean INR at 24 hrs |
| TCP: 3-factor PCC + rFVIIa + vitamin K (n=46) | 3.4 | 176 min | 1.0 | 1.2 |
| FFP (n=3)        | 2.6 | 406 min | 1.6 | 1.6 |
| FFP + PCC (n=9)  | 3.3 | 217 min | 1.4 | 1.3 |
| p-value          | NS | 0.048* | 0.0036*, 0.0019** | 0.0056*, 0.025** |

*TCP vs. FFP  
**TCP vs. FFP + PCC
- TCP group: 2 NSTEMIs (1 received 2.4 mg rFVIIa); 4 died within 24 hrs; 3 died within 72 hrs  
- 30 days post-TCP: 10 died, 17 survived, 19 lost to follow-up |
| Take Home Points | - Combination 3-factor PCC + low-dose rFVIIa improved INR correction in intracerebral hemorrhage, despite shorter time from blood bank dispense to next INR measurement  
- No comparison group for thrombotic events and mortality |

### XVI. PCC and thrombosis in VKA reversal

- Possible underlying thrombotic risk factors may be unmasked when anticoagulation is reversed  
- Review of 14 studies (460 patients) in anticoagulation reversal showed no evidence of DIC  
  - Seven thrombotic complications (4/7 not attributable to PCC therapy)  
  - Three cases attributed to PCC were in patients with extensive co-morbidities  
- Possibility that PCC therapy increases thrombotic risk, but unlikely that PCC alone is the cause

| **Purpose** | To evaluate efficacy and safety of a Proplex T protocol for rapid reversal of warfarin-induced coagulopathy |
| **Design** | Study group: prospective  
Control group: historical |
| **Patient Population** | Inclusion  
- Trauma patients  
- History of prescribed warfarin therapy  
- Intracranial hemorrhage on CT scan  
- INR >1.5  
Control group: historical; received FFP + vitamin K |
| **Outcomes** | ICU length of stay; hospital length of stay; INR; Delta INR; Time to complete reversal of coagulopathy; Time to operation procedure; Use of FFP and vitamin K; Mortality |
| **Methods** | Patients who met inclusion criteria received weight-based dose of PCC, Proplex T, according to manufacturer guidelines for normalization of coagulopathy  
- 1 unit/kg * body weight in kg * % desired increase in plasma factor IX  
- Proplex T: contains concentrated forms of factors II, VII, IX, and X  
- Control group: historical; received FFP + vitamin K  
Statistics  
- Performed using Chi² and Fisher’s exact test for nominal variables  
- Mann Whitney U for non-normally distributed continuous variables  
- Significance denoted by a P ≤0.05 |
| **Results** | **Control group (n=65) vs. study/protocol group (n=46):**  
**Patient groups:**  
- 111 trauma patients → 46 patients in the study group, 65 patients in the control group  
- Mean age ~77 years  
- GCS ~12 in both groups  
- 100% of patients were involved in blunt trauma – falls and motor vehicle accidents  
- Similar demographics, ISS, GCS, and head AIS  
- Increased number of patients receiving PCC (54.3% vs. 35.4%, p=0.047)  
- Use of FFP and vitamin K was similar between groups  
**Parameters of coagulopathy reversal & outcomes:**  
- Improved time to normalization of INR (INR ≤1.5) in study group (331.3 vs. 737.8 min, p=0.048)  
- Improved number of patients with a therapeutic reversal of coagulopathy in study group (73.2% vs. 50.9%, p=0.026)  
- Improved time to the operating room in study group (222.6 vs. 351.3 min, p=0.045)  
- No significant difference in ICU length of stay (~6-7 days), hospital length of stay (~10-13 days), or mortality (~23%) between groups  
**PCC use (n=48) vs. no PCC use (n=63):**  
**Patient groups:**  
- Patients who received PCC had higher head AIS scores (4 vs. 3, p=0.003); lower GCS scores (10 vs. 13, p=0.002)  
**Parameters of coagulopathy reversal & outcomes:**  
- Longer ICU days (7 vs. 5 days, p=0.01), and longer hospital days (14 vs. 9 days, p=0.02) in PCC group  
- Improved time to normalization of INR in PCC group (327 vs. 758 days, p <0.001)  
- Increased number of therapeutic reversals of coagulopathy (82.6% vs. 40.4%, p < 0.001)  
- Improved times to operative intervention (189 vs. 748 min, p=0.005)  
**Safety:**  
- 3/48 patients who received PCC were found to have deep vein thrombosis during their hospitalization; no occurrences of pulmonary embolism or myocardial infarction  
- Two patients died as a result of their traumatic injuries and one was diagnosed with a below-knee deep vein thrombosis requiring no intervention  |
| **Authors’ Conclusions** | The Proplex T protocol is practical and effective, expediting the identification of patients on outpatient warfarin with traumatic intracranial hemorrhage, affording a rapid and reliable reversal of warfarin-induced coagulopathy, and decreasing time to operative intervention |
| **Take Home Points** | In patients with blunt trauma and pre-injury warfarin, receiving PCC, there is an improved time to normalization of INR, increased number of therapeutic reversals of coagulopathy, and improved times to operative intervention  
- No difference in mortality nor LOS in patients receiving PCC vs. not receiving PCC |
| **Critique** | Delta INR calculated by subtracting first check INR 4 hrs after reversal from initial INR drawn in ED → discrepancy because mean time to operation more rapid than mean time to coagulopathy reversal  
- Power not mentioned  
- Used hemophiliac dosage, based on desired percent increase in FIX – factors not typically measured in trauma
XVII. Review of rFVIIa for refractory bleeding in non-hemophilic patients\textsuperscript{42}

a. 26 trauma cases of excessive bleeding (13 blunt, 13 penetrating)
b. Average administered pre-treatment: 38 units pRBC + 24 units FFP + 24 units platelets
c. rFVIIa achieved hemostasis in 20/26 (77%); 17/20 (85%) with achieved hemostasis survived
   i. All 3 who died after achieving hemostasis died from sepsis and multi-system organ failure

XVIII. Review of rFVIIa in life-threatening hemorrhage in trauma patients\textsuperscript{43}

a. 126 different patients with trauma-related bleeding and associated coagulopathy
b. Dosing ranged from 36-240 mcg/kg (single or multiple doses)
   i. Variable nature and severity of refractory bleeding
c. Efficacy results
   i. In 100/126 (79%) evaluable patients, rFVIIa administration associated with rapid reduction or
      cessation of blood loss, decrease in pRBC requirements, and prevention of imminent death
      1. ~21% failed to respond to rFVIIa; all non-responders died from exsanguination
   ii. Long-term survival available for 116/126
      1. 59 (51%) survived to recovery or rehabilitation
d. Safety results
   i. No non-thrombotic adverse events reported in any publications
   ii. Thromboembolic events observed in 5/126 (4%) patients
      1. Necrotic bowel (n=3), DVT (n=1), cerebral sinus thrombosis (n=1)
      2. Unclear whether cases of necrotic bowel attributable to rFVIIa; possibility that rFVIIa allowed
         survival of patients who would have otherwise exsanguinated before traumatic bowel injury
         apparent
   iii. 11/17 available autopsy results (Dutton), no evidence of inappropriate vascular thrombosis
   iv. “These findings suggest that rFVIIa may not present any immediate safety concerns”

| Boffard KD, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. 2005.\textsuperscript{44} |
|---|---|
| **Purpose** | To evaluate efficacy and safety of rFVIIa as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma |
| **Design** | Two parallel randomized, placebo-controlled, double-blind trials (one in blunt trauma, one in penetrating trauma) conducted simultaneously |
| **Patient Population** | Patients with severe blunt and/or penetrating trauma |
| Inclusion: | Severe trauma, defined as those suffering physical injury requiring 6 units of RBCs within 4 hrs of admission |
| & | Known age 16-64 years |
| Exclusion: | Cardiac arrest pre-hospital or in the emergency or operating room before trial drug administration |
| & | Gunshot wound to the head |
| & | GCS < 8 unless in the presence of a normal CT scan |
| & | Base deficit > 15 mEq/L or severe acidosis with pH < 7.0 |
| & | Transfusion of ≥ 8 units RBCs before arrival at the trauma center |
| & | Injury sustained ≥12 hrs before randomization |
| **Outcomes** | Primary: number of RBC units transfused during 48-hr period after first dose of trial product |
| & | Secondary: requirement for other transfusion products, mortality, days on the ventilator, days in the ICU |
| **Methods** | Patients assigned to either blunt or penetrating trauma trial |
| & | On receiving 6 units of RBCs within a 4-hr period, eligible patients within each trial equally randomized to receive either three IV injections of rFVIIa (200 + 100 + 100 mcg/kg) or three placebo injections |
| & | First dose of trial product administered after transfusion of 8 units RBCs; second and third doses followed 1 and 3 hrs after the first dose, respectively |
| **Statistics** | 140 patients required in each trauma trial to detect difference with 80% power and 5% type 1 error |
| & | One-sided Wilcoxon-Mann-Whitney rank test: total number of RBC units transfused within 48 hrs from the start of trial product treatment compared between treatment groups |
| & | Hodges-Lehmann estimate: difference in RBC transfusions |
| & | Fisher’s exact test: number of patients requiring massive transfusion (> 20 units of RBCs – defined post-hoc) and number of patients experiencing either MOF, ARDS, or death within 30 days |

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### Results

**Patient groups:**
- 143 patients eligible for analysis in blunt trauma trial: 74 placebo + 69 rFVIIa
- 124 patients eligible for analysis in penetrating trauma trial: 64 placebo + 70 rFVIIa
- Treatment groups well-matched in both trauma populations
- Predominantly male patients; characterized by being coagulopathic, acidotic, and hypothermic
- Causes of penetrating trauma primarily gunshots (68%) and stab wounds (30%); 77% of blunt trauma due to traffic-related injury

**Transfusion requirements:**
- Blunt trauma patients: rFVIIa reduced 48-hr requirements by 2.6 units (p=0.02); need for massive transfusion reduced from 33% of patients in placebo group to 14% of patients in the rFVIIa group (p=0.03)
- Penetrating trauma patients: no significant effect of rFVIIa in 48-hr RBC requirements; need for massive transfusion reduced from 19% in the placebo group to 7% in the rFVIIa group (p=0.08)
- No statistical difference in patients who died to the worst outcome
- No significant differences in administration of fresh frozen plasma, platelets, or cryoprecipitate

**Clinical outcome and safety:**
- Positive trends in favor of rFVIIa for death, critical complications (MOF and ARDS)
- Overall similar ADR profiles between groups in both trials
- 12 thromboembolic ADRs reported during both trials: 6 in rFVIIa-treated patients, 6 in placebo-treated patients

### Authors' Conclusions

- rFVIIa significantly improved bleeding control, as reflected by the decrease in RBC transfusion requirements and the number of patients requiring massive transfusion in a population of blunt trauma patients with severe bleeding and coagulopathy secondary to the traumatic injury
- rFVIIa appears to be a promising adjunct to existing therapy within trauma

### Take Home Points

- In blunt trauma patients, rFVIIa reduced RBC requirements and need for massive transfusion
- No difference between placebo and rFVIIa groups in mortality
- Similar thromboembolism ADRs reported between groups in both trials

### Critique

- Power not met on RBC transfusion endpoints in penetrating trauma population; likely explained by higher proportion of surgically treatable bleeding
- Data on thromboembolic complications collected through adverse event reporting only – likely underreporting of asymptomatic thromboembolic events
- Differences in patient management across regions and trial centers due to complexity of study population and diversity of choices faced by trauma teams – despite adherence to trial protocol
  - Potential influence of site-specific effects on RBC reduction assessed by parametric analysis of the ranks including a site effect and a site-treatment interaction – effect of treatment was independent of site (p=0.24) for the site vs. treatment interaction
- Transfusion therapy not standardized care; confounding variable, yet used as primary endpoint
  - Placebo group acted as control across census
- Upper limit dosage used to assess safety
- Per author, total rFVIIa dose of 400 mcg/kg achieved FVII level of 40 mcg/L in the plasma
  - FFP and cryoprecipitate (unknown dose) approach ~1/3 of this, and contribute to dilutional coagulopathy

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**XV. Safety of rFVIIa in off-label trials**

a. Review of 26 studies involving 4419 patients
b. All reported thrombotic or embolic were confirmed by means of objectives tests
  - Arterial (coronary, cerebrovascular, other) and venous
c. Rate of thromboembolic events similar between groups (10.2% in rFVIIa vs. 8.7% in placebo, p=0.16)
e. Higher arterial thromboembolic event rate in rFVIIa group vs. placebo group (5.5% vs. 3.2%, p=0.003)
  - No significant difference in incidence of venous thromboembolisms
e. Three trauma studies, n=837 (included Boffard et al.)
  - 428 placebo + 409 rFVIIa (20% of total population assessed)
  - Mean age 36.5 years, all in rFVIIa group received > 120 mcg/kg
  - 4.6% incidence arterial thrombosis vs. 3.5% in placebo group (p=0.36)
  - Boffard et al. trial makes up 32% (277/837); likely underreporting of asymptomatic thromboembolic events

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XX. NovoSeven® package insert

a. Black Box Warning: serious thrombotic adverse events associated with the use of NovoSeven® RT outside labeled indications
   i. Two meta-analyses: increased risk of thrombotic events (10.0% in rFVIIa vs. 7.5% in placebo)
   ii. Arterial thrombosis (ie. myocardial infarction, myocardial ischemia, cerebral infarction, cerebral ischemia) statistically increased with rFVIIa use vs. placebo (5.3-5.6% vs. 2.8-3.0%)
   iii. Meta-analysis of clinical trials did not suggest increased risk of venous thromboembolic events (4.8% in rFVIIa vs. 4.7% in placebo)

XXI. Cost

<table>
<thead>
<tr>
<th></th>
<th>FFP</th>
<th>PCC</th>
<th>rFVIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost</td>
<td>$69.00 per unit</td>
<td>$0.70 per unit</td>
<td>$1.38 per mcg</td>
</tr>
<tr>
<td>Dosage</td>
<td>15 mL/kg (~250 mL/units)</td>
<td>25 units/kg</td>
<td>90 mcg/kg</td>
</tr>
<tr>
<td>Dosage per 80 kg patient</td>
<td>1200 mL (4.8 units)</td>
<td>2000 units</td>
<td>7.2 mg (7 mg – nearest whole vial)</td>
</tr>
<tr>
<td>Cost per 80 kg patient</td>
<td>~$330</td>
<td>~$1400</td>
<td>~$9660</td>
</tr>
</tbody>
</table>

XXII. Summary

a. What treatment strategies should be used in traumatic bleeding patients on warfarin pre-injury?
   i. YES: Discontinue warfarin
      1. Natural increase in synthesis of clotting factors
   ii. YES: Vitamin K 10 mg IV over 10 min
      1. Directly converted to reduced vitamin K, increased production of extrinsic clotting factors
   iii. YES: PCC 25 units/kg – can repeat dose in 30 min if inadequate effect
      1. Improved time to normalized INR and improved number of patients with therapeutic reversals of coagulopathy in blunt trauma patients41
      i. ... But, does the INR represent an adequate assessment of level of hemostasis?
      2. No difference in mortality, LOS, worsening intracranial hemorrhage41
      3. CHEST guidelines22 recommend 4-factor PCC vs. FFP for VKA-associated major bleeding (grade 2C); however, unavailable in the US
      4. Benefit of improved INR vs. risk of thromboembolism
         i. Indication of anticoagulation – benefits vs. risks
         ii. In 460 patient review, 0.65% thrombotic events attributable to PCC therapy33
   iv. YES: FFP 5-10 mL/kg
      1. Provides FVII, which is lacking in 3-factor PCC – would theoretically provide advantage of promoting clotting cascade27
      2. Increased proportion of patients achieved reversal of anticoagulation after FFP administration (post-PCC)27
   v. NO: rFVIIa
      1. Improved time to normalized INR and number of patients achieving corrected INR39
      2. No difference in mortality39
      3. Risk of arterial thrombosis – questionable in trauma patients35,45,46
      4. Cost ~7x greater than PCC

b. What treatment strategies should be used in traumatic bleeding patients NOT on warfarin pre-injury?
   i. YES: 1:1:1 ratio FFP, pRBCs, platelets (+ fibrinogen PRN < 100 mg/dL)14
      1. Standard of treatment
   ii. YES: PCC 25 units/kg – can repeat dose in 30 min if inadequate effect
      1. Consider use in refractory bleeding as “last effort” if inadequate response to FFP, pRBCs, platelets, and cryoprecipitate
      2. Animal studies – improved coagulation and attenuated blood loss30,34
      3. Consider use if volume-sensitive patient
      4. No retrospective nor prospective trials to support nor refute

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iii. NO: rFVIIa

1. Decreased pRBCs used and decreased number of required massive transfusions in blunt trauma patients
2. Achieved hemostasis in 77% trauma patients
3. No difference in mortality, LOS
4. Risk of arterial thrombosis significant in off-label usage – although not significant in trauma patients – based 32% of patients from Boffard et al. trial; likely underreporting of asymptomatic thromboembolic events
5. Cost ~7x greater than PCC

XXIII. Conclusion
REFERENCES


REFERENCES (continued)

APPENDICES

APPENDIX A

Estimated blood loss based on patient’s initial presentation

<table>
<thead>
<tr>
<th>Blood loss (mL)</th>
<th>CLASS I</th>
<th>CLASS II</th>
<th>CLASS III</th>
<th>CLASS IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss (% blood volume)</td>
<td>Up to 15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt; 40%</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>&lt;100</td>
<td>100-120</td>
<td>120-140</td>
<td>&gt; 140</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>Normal or increased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>14-20</td>
<td>20-30</td>
<td>30-40</td>
<td>&gt; 35</td>
</tr>
<tr>
<td>Urine output (mL/hr)</td>
<td>&gt;30</td>
<td>20-30</td>
<td>5-15</td>
<td>Negligible</td>
</tr>
<tr>
<td>CNS/mental status</td>
<td>Slightly anxious</td>
<td>Mildly anxious</td>
<td>Anxious, confused</td>
<td>Confused, lethargic</td>
</tr>
<tr>
<td>Fluid replacement</td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crystalloid and blood</td>
<td>Crystalloid and blood</td>
</tr>
</tbody>
</table>

APPENDIX B

Blood Coagulation Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Synonym</th>
<th>Biologic Half-Life</th>
<th>Blood Product Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Fibrinogen</td>
<td>100-150</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>II</td>
<td>Prothrombin</td>
<td>50-80</td>
<td>FFP, PCC</td>
</tr>
<tr>
<td>V</td>
<td>Proaccelerin</td>
<td>12-36</td>
<td>FFP</td>
</tr>
<tr>
<td>VII</td>
<td>Proconvertin</td>
<td>4-6</td>
<td>rFVIIa, FFP, PCC</td>
</tr>
<tr>
<td>VIII</td>
<td>Antihemophilic factor</td>
<td>12-15</td>
<td>FFP, factor concentrates, cryoprecipitate</td>
</tr>
<tr>
<td>IX</td>
<td>Christmas factor</td>
<td>18-30</td>
<td>FFP, PCC, factor concentrates</td>
</tr>
<tr>
<td>X</td>
<td>Stuart-Power factor</td>
<td>25-60</td>
<td>FFP, PCC</td>
</tr>
<tr>
<td>XI</td>
<td>Plasma thromboplastin antecedent</td>
<td>40-80</td>
<td>FFP</td>
</tr>
<tr>
<td>XII</td>
<td>Hageman factor</td>
<td>50-70</td>
<td>Not associated with bleeding diathesis</td>
</tr>
<tr>
<td>XIII</td>
<td>Fibrin-stabilizing factor</td>
<td>150</td>
<td>FFP, cryoprecipitate, factor concentrate</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
<td>8-12</td>
<td>FFP, cryoprecipitate, factor concentrate</td>
</tr>
</tbody>
</table>

APPENDIX C

Injury severity score (ISS): anatomical scoring system that provides an overall score for patients with multiple injuries. Each injury is assigned an abbreviated injury scale (AIS) and is allocated to one of six body regions. The three most injured body regions have their score squared and added together to produce the ISS score. The ISS score takes values from 0-75. If an injury is assigned an AIS of 6, the ISS score is automatically assigned to 75.

Abbreviated injury scale (AIS): Injuries are ranked on a scale of 1 to 6, with 1 being minor, 5 severe, and 6 a non-survivable injury. This represents the “threat to life” associated with an injury and is not meant to represent a comprehensive measure of severity.
## APPENDIX D

### Comparison of PCC Products (available in the US)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Profilnine® SD</th>
<th>Bebulin® VH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source material</td>
<td>Pooled human plasma</td>
<td>Vapor heated</td>
</tr>
<tr>
<td>Microbial reduction</td>
<td>Solvent detergent</td>
<td>Vapor heated</td>
</tr>
<tr>
<td>Formulation</td>
<td>Lyophilized concentrate in single-dose vials</td>
<td>Lyophilized concentrate in single dose vials with ~0.15 units heparin per unit factor IX</td>
</tr>
<tr>
<td>Factor composition</td>
<td>Potency per 1 unit factor IX 100-150 units/mL factor IX ≤ 1.5 units factor II ≤ 1 unit factor X ≤ 0.35 units factor VII</td>
<td>Potency per 1 unit factor IX 24-37.5 units/mL factor IX ~1 unit/mL factor II ~1 unit/mL factor X ≤ 0.20 units factor VII</td>
</tr>
<tr>
<td>Approved indication</td>
<td>Factor IX deficiency due to hemophilia B</td>
<td></td>
</tr>
<tr>
<td>Storage/shelf-life</td>
<td>Refrigeration at 2-8 ºC until expiration date Room temperature (≤ 30 ºC) up to 3 months After reconstitution, use within 3 hrs</td>
<td>Refrigeration at 2-8 ºC until expiration date Room temperature stability not available After reconstitution, use within 3 hrs</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Thrombosis Infectious disease transmission Infusion reactions</td>
<td>Thrombosis Infectious disease transmission Infusion reactions Heparin-induced thrombocytopenia</td>
</tr>
</tbody>
</table>

## APPENDIX E

### Marshall CT Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse injury I (no visible pathology)</td>
<td>No visible intra-cranial pathology on CT scan (9.6% mortality)</td>
</tr>
<tr>
<td>Diffuse injury II</td>
<td>Cisterns present with midline shift 0-5 mm and/or lesion densities present; no high or mixed density lesion &gt; 25 mL (13.5% mortality)</td>
</tr>
<tr>
<td>Diffuse injury III</td>
<td>Cisterns compressed or absent with midline shift 0-5 mm; no high- or mixed-density lesion &gt; 25 mL (34% mortality)</td>
</tr>
<tr>
<td>Diffuse injury IV</td>
<td>Midline shift &gt; 5 mm; no high- or mixed-density lesion &gt; 25 mL (56.2% mortality)</td>
</tr>
<tr>
<td>Evacuated mass lesion</td>
<td>Any lesion surgically evacuated</td>
</tr>
<tr>
<td>Non-evacuated mass lesion</td>
<td>High or mixed density lesion &gt; 25 mL; not surgically evacuated</td>
</tr>
</tbody>
</table>

## APPENDIX F

### Glasgow Coma Scale & Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Scale Response</th>
<th>Score Notation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye opening</td>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>To voice command</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>To pain stimuli</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No response</td>
<td>1</td>
</tr>
<tr>
<td>Verbal response</td>
<td>Oriented and converses</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confused</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Words (inappropriate)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Sounds (incomprehensible)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No sounds</td>
<td>1</td>
</tr>
<tr>
<td>Best motor response</td>
<td>Obey commands</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Localizes to pain</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Withdrawals from pain</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Decorticate posturing</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Decerebrate posturing</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Total Coma Score</td>
<td></td>
<td>3/15 – 15/15</td>
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</table>