UPDATE OF NEUROCRITICAL CARE PHARMACOTHERAPY

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DISCLOSURE STATEMENT OF FINANCIAL INTEREST

I, Vera Wilson, do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
DISCLOSURE STATEMENT OF UNAPPROVED/INVESTIGATIVE USE

I, Vera Wilson, do anticipate discussing the unapproved/investigative use of a commercial product during this presentation.
OBJECTIVES

• Describe emergent reversal options of warfarin and target-specific oral anticoagulants (TSOACs) for life-threatening bleeding

• Identify contraindications and precautions to ketamine administration

• Recognize evidence-based treatment options and their dosing for elevated intracranial pressure

• Develop monitoring plans for mannitol and hypertonic saline use
EMERGENT PHARMACOLOGIC REVERSAL OPTIONS OF WARFARIN AND TSOACS FOR LIFE-THREATENING BLEEDING
MECHANISM OF ACTION

Extrinsic Pathway

VII → VIIa → X → Xa → Fibrinogen → Fibrin → Clot

Tissue Factor

Xla

IXa

VIIa

VIII

Intrinsic Pathway

XIIa → XII → XI → IX → Xa

Extrinsic and Intrinsic Pathways join at Xa

Xa inhibitors

Warfarin

Inhibits clotting factors II, VII, IX, and X

Dabigatran

II (Prothrombin) → IIa (Thrombin)

NON-ACTIVATED FOUR FACTOR PROTHROMBIN COMPLEX CONCENTRATE (4F-PCC)

• Indicated for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) [e.g. warfarin] therapy in adult patient with acute major bleeding or need urgent surgery/invasive procedure

• Requires individualized dosing based on patient’s baseline INR and body weight

• Administer vitamin K concurrently to maintain factor levels once the effects of 4F-PCC have diminished

• Repeat dosing of 4F-PCC is not recommended
4F-PCC BOXED WARNING

- Both fatal and non-fatal arterial and venous thromboembolic complications have been reported
- Weigh potential benefits of VKA reversal vs. potential risks of thromboembolic events
- Not studied in patients who had a thromboembolic events, MI, disseminated intravascular coagulation (DIC), CVA, TIA, unstable angina or severe PVD within the prior 3 months
- May not be suitable in patients with thromboembolic events in the prior 3 months
4F-PCC CONTRAINDICATIONS

- Known anaphylactic or severe systemic reactions to 4F-PCC or any components in 4F-PCC (including heparin, Factor II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin)
- DIC
- Known heparin-induced thrombocytopenia
## 4F-PCC DOSING

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 – 3.9</th>
<th>4 – 6</th>
<th>Greater than 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F-PCC dose* (units/kg)</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose* (units)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
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*Dose is per units of Factor IX

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<thead>
<tr>
<th><strong>4F-PCC</strong></th>
<th><strong>FFP</strong></th>
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<tbody>
<tr>
<td>Quick onset of action</td>
<td>Quick onset of action</td>
</tr>
<tr>
<td>Less volume</td>
<td>Larger volume</td>
</tr>
<tr>
<td>Short infusion time</td>
<td>Longer infusion time</td>
</tr>
<tr>
<td>Risk of transmitting infectious agents and thromboembolism</td>
<td>Risk of transmitting infectious agents and thromboembolism</td>
</tr>
<tr>
<td>Expensive</td>
<td>Inexpensive</td>
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## MANAGEMENT OF ELEVATED INR FROM VKA

<table>
<thead>
<tr>
<th>INR &amp; Patient Situation</th>
<th>Recommendation</th>
<th>Grade of Evidence</th>
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| VKA-associated major bleeding | - Suggest rapid reversal of anticoagulation with four-factor PCC rather than with plasma  
- Suggest the additional use of vitamin K 5-10mg administered by slow IV injection rather than reversal with coagulation factors alone | Grade 2C          |
SUMMARY OF CHEST RECOMMENDATIONS

- VKA-associated major bleeding
  - Suggest rapid reversal of anticoagulation with 4F-PCC rather than with plasma (Grade 2C)
  - FFP disadvantages include preparation time and higher volume (potential for volume overload)
  - Regardless of which option (FFP or 4F-PCC) is used for VKA-associated major bleeding, vitamin K 5 - 10 mg IV infusion should be given as well
EFFICACY AND SAFETY OF 4F-PCC FOR VKA REVERSAL IN ACUTE MAJOR BLEEDING

- Included patients ≥18 years old receiving VKA therapy with an elevated INR and experiencing acute major bleeding
- Treatment with either 4F-PCC vs. plasma
- Effective hemostasis was 72.4% in the 4F-PCC group vs. 65.4% in the plasma group (95% CI -5.8 – 19.9)
- Rapid INR reduction (INR≤1.3 at 0.5 hour after the end of infusion)
  - 61 patients (62.2%) in the 4F-PCC group vs. 10 (9.6%) in the plasma group
  - Difference demonstrated superiority of 4F-PCC over plasma (difference, 52.6% [39.4 to 65.9])
- Thromboembolic AE occurred 7.8% 4F-PCC group vs. 6.4% plasma group

4F-PCC VS. PLASMA FOR URGENT REVERSAL IN SURGERY OR INVASIVE INTERVENTIONS

• Included patients ≥18 years old needing rapid VKA reversal prior to urgent surgical or invasive procedure

• Demonstrated both non-inferiority and superiority of 4F-PCC over plasma (difference 14.3%, 95% CI 2.8 – 25.8) for effective hemostasis

• Non-inferiority and superiority achieved for rapid INR reduction (≤1.3 at 0.5 h after infusion end) of 4F-PCC over plasma (difference 45.3%, 95% CI 31.9 – 56.4)

ADVERSE EVENTS

• Thromboembolic events (p=0.77)
  • 6 (7%) patients in 4F-PCC group
  • 7 (8%) patients in plasma group

• Fluid overload or similar cardiac events (p<0.05)
  • 3 (3%) patients in 4F-PCC group
  • 11 (13%) patients in plasma group

SUMMARY OF VKA-ASSOCIATED LIFE-THREATENING BLEEDING TREATMENT OPTIONS

• Cochrane Review - Included 4 RCTs (453 participants) – not including most recent Lancet 2015 study
  • Concluded PCC does not appear to reduce mortality or transfusion requirements but demonstrates possibility of reversing VKA induced coagulopathy without the need for transfusion of FFP

• Chest Guidelines
  • Suggest rapid reversal of anticoagulation with 4F-PCC rather than with plasma
  • If 4F-PCC used must be given with vitamin K IV
  • Multiple ongoing clinical trials including one in trauma patients

Chest 2012;141(2)suppl:7S-47S.
TSOACS AND PHARMACOLOGIC OPTIONS FOR TREATMENT OF LIFE THREATENING BLEEDING

- Pharmacologic reversal options are currently off-label
- No high-quality evidence of efficacy and safety of these options for reversal
- Direct thrombin inhibitors (dabigatran)
  - Can be removed by HD
  - Activated PCC (FEIBA) 50 – 80 units/kg IV
    - If unavailable 4F-PCC 50 units/kg IV as a alternative
- Direct Xa inhibitors (apixaban, edoxaban, rivaroxaban)
  - 4F-PCC 50 units/kg IV

POTENTIAL FUTURE OPTIONS

• Under investigation for all TSOACs
  • Perosphere (PER977)
• Direct thrombin inhibitors (dabigatran)
  • Idarucizumab
• Direct Xa inhibitors (apixaban, edoxaban, rivaroxaban)
  • Andexanet alfa in clinical trials

NEJM. 2014;371:2141-2142.
NEJM 2015;373:511-520.
KETAMINE
KETAMINE

• Noncompetitive NMDA antagonist
• Contraindications
  • Conditions in which ↑BP would be hazardous
  • Schizophrenia
• Rapid onset with IV administration
KETAMINE – WARNINGS/PRECAUTIONS

- Emergence reactions
- ↑ ICP?
- ↑ ocular pressure
- ↑ risk of laryngospasm
- Respiratory depression
- CV disease
PRE-HOSPITAL USE OF KETAMINE

- Retrospective trauma database review including patients >15yo
- London helicopter EMS (physician-paramedic team)
- Mostly used on non-trapped awake victims of blunt trauma for analgesia and procedural sedation
  - Procedural sedation 0.5 – 1 mg/kg IV
  - Analgesia 0.1 mg/kg IV
- Mean dose administered 45.5 mg
- No emergence reactions noted however ketamine was co-administered with midazolam in 89% of cases

KETAMINE PRE-HOSPITAL ANALGESIA

• Multiple studies however most with weak level of evidence
• Low doses generally used (0.2 mg/kg)
• Maybe given alone or with an opioid such as morphine for analgesia

Mil Med. 2014;180:304-309.
Mil Med. 2015;180:14-18.
ED EXPERIENCE WITH PREHOSPITAL KETAMINE

• Retrospective, case series of 13 patients

• 11 patients (85%) achieved moderate to deep sedation or were unarousable (5 patients)

• 3 patients developed hypoxia
  • 2 patients required intubation

• 3 patients experienced emergence reactions

KETAMINE USE IN HEAD INJURY

• Controversial
• 2011 ACEP Ketamine Dissociative Sedation Guidelines
  • Head trauma no longer relative contraindication
  • Relative contraindication for CNS masses, abnormalities or hydrocephalus
• Likely best to avoid ketamine in this patient population

HYPEROSMOLAR THERAPY FOR ELEVATED INTRACRANIAL PRESSURE (ICP)
BRAIN TRAUMA FOUNDATION (BTF) GUIDELINE RECOMMENDATIONS FOR SEVERE TBI

- Hypotension should be avoided (SBP < 90) (Level II)
- Treatment should be initiated with ICP > 20 (Level II)
- Cerebral perfusion pressure (CPP) <50 should be avoided (Level III)
BTF GUIDELINE RECOMMENDATIONS FOR MANNITOL

- Mannitol effective for control of raised ICP (Level II)
  - Doses 0.25 – 1 g/kg
  - Avoid arterial hypotension (SBP<90)
- Restrict mannitol use prior to ICP monitoring to patients with (Level III):
  - Signs of transtentorial herniation
  - Progressive neurological deterioration not attributable to extracranial causes

J Neurotrauma. 2007; 24(suppl1):S1-95.
MANNITOL MONITORING

- Serum osmolality
  - Often avoided if >320 mOsm/kg
  - Ideally utilize osmolar gap
- Sodium, potassium, creatinine, glucose
- Urine output

NEJM. 2012; 367:746-752.
Crit Care Med. 2004;32:986-991
BTF GUIDELINE RECOMMENDATIONS FOR HYPERTONIC SALINE (HS) USE IN SEVERE TBI

- No graded recommendations for use of HS
- Studies included suggest that HS as a bolus may be effective adjuvant or alternative to mannitol
- Guidelines are dated (2007)
HYPERTONIC SALINE

• Common doses
  • NaCl 3% 150 – 250 mL
  • NaCl 7.5% 1 – 2 mL/kg
  • NaCl 23.4% 30 mL

• Monitoring
  • Osmolality
  • Sodium, potassium, creatinine
AREAS OF UNCERTAINTY

• Relationship between ICP control and clinical outcomes
• Ideal osmotic agent and method of administration
QUESTIONS