Pharmaceutical Interventions in the Trauma Bay: More than Analgesics
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Disclosure
I do not have (nor does any immediate family member have):
– a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity
– any affiliation with an organization whose philosophy could potentially bias my presentation

Pharmacist Objectives:
• Devise treatment recommendations for patients undergoing massive transfusion resuscitation.
• Describe evidence-based fluid resuscitation recommendations for patients suffering from burn injuries.
• Review the role of a pharmacist in trauma activations and management of burn patients.

Technician Objectives:
• Describe common activities that pharmacy personnel perform in the Emergency Department.
• Identify medications needed as stock in a trauma resuscitation bay to adequately treat patients with burn injuries and hypovolemic shock.
• List blood products utilized to resuscitate patients in hypovolemic shock.

Trauma Facts
• 9 deaths per minute
• 5.8 million deaths from unintentional injuries/violence annually
• 18% of world’s diseases
• Vehicle crashes alone account for over 1 million of these deaths
• 4th highest cause of death in US
• Leading cause of death for those under 45 yo
• High financial burden
• ~$518 billion globally
• ~$37.8 billion annually in US just for TBI disabilities

Trauma Survey

• Primary Survey
  • A = Airway
  • B = Breathing
  • C = Circulation
  • D = Disability
  • E = Exposure/environmental control

• Secondary Survey
  • Only after primary complete, resuscitation started & vitals improved
  • Full physical assessment
  • Complete medical & medication history

Primary Survey

A = Airway
  • Patent or risk for airway loss
  • Intubation with RSI
  • Surgical airway

B = Breathing
  • Secure airway & ventilate
  • Chest injuries that may impede B
  • Sedation/analgesia

C = Circulation
  • Level of consciousness
  • Perfusion
    • Visual assessment
    • BP
      • No longer use pulse location to estimate BP
    • Pulse
      • Utilize central pulse bilaterally
  • Consider shock
  • 40% hemorrhagic shock

Circulation

• Goal: end-organ perfusion & tissue oxygenation
  • Normal BP is not the goal
    • TBI has higher goal: MAP > 80 mmHg
• Warmed isotonic fluids - crystalloids
  • Bolus
    • Adults: 1 liter bolus
    • Pediatrics <40 kg: 20 mL/kg bolus
  • Additional fluid based on patient’s response
    • Include pre-hospital
• Blood products (pRBCs, plasma & platelets)
  • Class III & IV hemorrhage
    • Low ratios 1:1:1 or 1:1:2

Massive Transfusion Protocols

• > 10 units RBC in 24 hrs
• 3% of trauma patients who use 70% of center’s blood
• Example:
  • 6 units of PRBS
  • 4 units of thawed plasma (FFP)
  • 6 units platelets
  • TXA
  • Labs
Hemostasis

- Mechanical
- Thermal
- Mainly OR setting
- Chemical
- Topical Hemostats
- Topical Sealants and Adhesives
- Reverse anticoagulants


Mechanical Hemostasis

- Tourniquets
- Pelvic binders
- Direct pressure
- Minor wounds


Fibrinolysis

Coagulopathy seen in 30% of patients at presentation


TEG In Trauma

<table>
<thead>
<tr>
<th>TEG Value</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEG-ACT &gt; 140</td>
<td>FFP</td>
</tr>
<tr>
<td>R time &gt; 10 min</td>
<td>FFP</td>
</tr>
<tr>
<td>K time &gt; 3 min</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>α angle &lt; 53°</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>MA &lt; 50 mm</td>
<td>Platelets</td>
</tr>
<tr>
<td>LY 30 &gt; 3%</td>
<td>Tranexamic Acid</td>
</tr>
</tbody>
</table>


Tranexamic Acid

Major Trauma
- CRASH-2
- MATTERS & MATTERS 2

Minor Trauma
- Epistaxis
- Oral bleeding
- Topical

Tranexamic Acid

- Severe hemorrhagic shock (systolic BP < 90 mmHg) with bleeding risk
- Part of massive transfusion protocol
- Within 3 hours from time to injury
- Pre-hospital use
- TEG can be utilized but no evidence to guide initial tranexamic acid administration

Dosing:
- 1 gm IV over 10 minutes, then 1 gm IV over 8 hours
- Discussion on single dose


Reversal Agents

- Vitamin K
- Fresh frozen Plasma (FFP)
- Prothrombin complex concentrate
- Idarucizumab
- Andexanet alfa

Warfarin Reversal

<table>
<thead>
<tr>
<th>INR Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
</tr>
<tr>
<td>&lt; 4.5 without bleeding</td>
</tr>
<tr>
<td>&gt; 4.5 but &lt; 10 without bleeding</td>
</tr>
<tr>
<td>&gt; 10 without bleeding</td>
</tr>
</tbody>
</table>

Kinetics:
- IV: onset = 1-2 hours, peak = 12-24 hours
- PO: onset = 6-10 hours, peak = 24-48 hours

Vitamin K (phytonadione)

- Purified, concentrated vitamin K-dependent coagulation factors
- Kinetics:
  - Onset = minutes, duration = 12-24 hours
  - Consider preparation time
  - Adverse effects/concerns:
    - Thrombosis (4-7%)
    - Heparin-induced thrombocytopenia (heparin contained in 4F-PCC)

Prothrombin complex concentrates

- Purified, concentrated vitamin K-dependent coagulation factors
- Kinetics:
  - Onset = minutes, duration = 12-24 hours
  - Consider preparation time
  - Adverse effects/concerns:
    - Thrombosis (4-7%)
    - Heparin-induced thrombocytopenia (heparin contained in 4F-PCC)

- Dosing by INR:
  - > 2.4 = 25 units/kg (max dose 5,000 units)
  - > 4.6 = 35 units/kg (max dose 5,000 units)
  - > 6 = 50 units/kg (max dose 5,000 units)


Fresh frozen Plasma (FFP)

- Centrifuged/separated from cellular components
- Replaces clotting factors
- Typical dose = 10 – 20 mL/kg for full reversal
- FFP has INR of 1.5, therefore other therapies needed to achieve lower INR

- Kinetics:
  - Onset = INR < 2 within 15 min, duration = 6-12 hours
  - Consider 15 min for thawing

Adverse effects/concerns:
- Thrombosis (3-8%)
- Volume overload

FPF vs PCC

Vitamin K vs. FFP vs. PCC
- Incidence of ICH growth – 50% vs. 33% vs. 19%
- No reversal vs. FFP vs. PCC
- Mortality rates – 42% vs. 46% vs. 37%
- FFP vs. Vitamin K vs. PCC
- Time to INR < 1.4 – ~ 30 hours vs. < 30 minutes
- FFP vs. PCC
- Thromboembolism – 8% vs. 7%** 3-8% in large trials

FFP vs. PCC
- Thromboembolism – 8% vs. 7%** 3-8% in large trials

Fixed-dose vs Variable
- FDA approved dosing is driven by INR & weight
- Studies evaluating fixed-dosing vs FDA dosing:
  - Khorsand et al. 2012: Unable to determine non-inferiority with INR
  - Fixed-dosing resulted in favorable outcomes
  - Rowe et al. 2018: As effective
  - No increased thrombotic events
  - More studies evaluating
- Take Away:
  - May consider
  - Follow up with INR to assess

Dabigatran Reversal
- Decreased absorption
  - Activated charcoal
  - If within 2-4 hrs of ingestion
- Elimination
  - Can consider dialysis in renal impaired
- Idarucizumab
  - RE-VERSE AD trial
- PCC
  - Mixed results
    - Healthy subjects – 1 showed lab improvement, 2 others had no change
    - DCAC reversal study with FEIBA® – may be effective
    - Utilized in RE-VERSE AD

Guidelines Speak

Factor X_A Inhibitor Reversal
Factor Xa Inhibitor Reversal

- Activated charcoal
- Apixaban – within 6 hours of ingestion
- Rivaroxaban – within 2 hours of ingestion
- Prothrombin complex concentrates
- Coagulation factor X1 (recombinant)


Prothrombin complex concentrates

- Reversal studies:
  - A low-dose of 4F-PCC produced hemostasis in the majority of patients without thromboembolic complications
  - PCC immediately and completely reverses anticoagulant effect of rivaroxaban
- Guidelines recommend:
  - ASH 2018 VTE Guidelines: can be utilized in addition to stopping agent in life-threatening bleeding
  - Not given with or after andexanet alfa


Andexanet alfa (Andexxa®)

- Coagulation factor Xa (recombinant) inactivated-zhzo
- Binds to NOAC 1:1, high affinity
- Indications:
  - Life-threatening or uncontrolled bleeding in patients treated with apixaban or rivaroxaban
- Kinetics:
  - Elimination t½ = 5-7 hours, pharmacodynamic t½ = ~1 hour
- Adverse effects/concerns:
  - Infusion reactions, urinary tract infections, pneumonia
  - Black boxed warning: thromboembolic risks, ischemic events, cardiac arrest & sudden death
  - Cost ~$27,500 to $50,000 per dose


ANNEXA-A & ANNEXA-R

- Phase-3 trail in healthy patients (50-70 years old)
  - ANNEXA-A → bolus only or bolus + infusion or placebo following 3.5 days apixaban
  - ANNEXA-R → bolus only or bolus + infusion or placebo following 4 days rivaroxaban
- Conclusion:
  - Andexanet effectively reverses apixaban and rivaroxaban within minutes
  - Rebound elevation of unbound factor Xa inhibitor and anti-Xa activity occurs at 3-4 hours
  - Potential immunogenic effects are unknown


ANNEXA-4

- Phase 3b-4 trail, adults with acute major bleed & Fxa inhibitor within 18 hours
- Exclusions:
  - Surgery within 12 hrs
  - Poor outcomes (e.g. GCS, ICH size)
  - Certain medications or blood products
- Study take away:
  - Efficacy in reduction of anti-Xa levels seen in both healthy and bleeding patients
  - Potential lower thrombotic risk given late-onset & low rates of AC
  - Unknown efficacy in more severe bleeds
  - No control group or interaction with plasma products

Guidelines Speak Out

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>ACC 2017 Bleeding on Oral Anticoagulants</td>
<td>Mentioned, but pending further investigation</td>
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</table>

Controversies & Conundrums

- Head to Head studies
  - None for idarucizumab or andexanet alfa vs PCC
  - Expect to see some soon
- Renal dysfunction
- Rebound bleeding – redosing of andexanet alfa?
- Combinations
  - Andexanet alfa not studied with PCC (unlike idarucizumab)
- Availability
- Cost

Primary Survey

**D = Disability**
- Neurologic assessment
  - Changes assessed
  - Spinal cord injury

**E = Exposure/Environmental Control**
- Full body visual
- Prevention of hypothermia
  - Warming blankets
  - Warmed IV fluids

Adult GCS Response Score

<table>
<thead>
<tr>
<th>Eye Opening</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>To pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
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<td>2</td>
<td>3</td>
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</table>

<table>
<thead>
<tr>
<th>Best Verbal Response</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>None</td>
<td></td>
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<tr>
<td>Incomprehensible</td>
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<tr>
<td>Inappropriate words</td>
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<td></td>
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<tr>
<td>Patient confused</td>
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<tr>
<td>Patient oriented</td>
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<table>
<thead>
<tr>
<th>Best Motor Response</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
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</tr>
<tr>
<td>Extensor to pain</td>
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</tr>
<tr>
<td>Flexion to pain</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Withdraws to pain</td>
<td></td>
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<tr>
<td>Localizes to pain</td>
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<tr>
<td>Obeys commands</td>
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<td></td>
</tr>
</tbody>
</table>

Total x/15

Adapted from: Teasdale G et al. Nurs Times. 2014; 110: 12-16

Secondary Survey

- Once primary survey complete & resuscitation initiated
  - Improvement in vitals
  - Full body assessment
  - Head-to-toe, front-to-back
  - Physical exam
  - Complete medical history
  - Medication history
  - Continuous vital assessment

If patient’s mental status or vitals change – Restart Primary Survey!!

Unique Areas of Trauma

- Traumatic Brain Injury
- Spinal Cord Injury
- Burn & Inhalation Injury
- Ocular Injuries
- Mass-Casuality
- Special Populations
  - Pediatric
  - Geriatric
  - Pregnancy

### Topical Hemostasis

<table>
<thead>
<tr>
<th>Category</th>
<th>Type</th>
<th>Examples</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostatic dressings</td>
<td>Calcium silicate, chitosan,</td>
<td>QuickClot®, Combat Gauze®</td>
<td>Heavy arterial bleeding, inexpensive, potential for exothermic reaction.</td>
</tr>
<tr>
<td>Physical &amp; absorbable</td>
<td>Bone wax, gelatin products,</td>
<td>Collagen (Instat®, Avitene®), Cellulose (Surgicel®), Gelatin (Gelfoam®, Surgifoam®)</td>
<td>Small vessel bleeding, may embolize, possible interference with healing.</td>
</tr>
<tr>
<td>Synthetic sealants</td>
<td>Chitosan, polyurethane glucoside</td>
<td>Dermabond®, Coseal®</td>
<td>Arterial bleeding, antifibrinolytic, topical only, difficult in irregular wounds.</td>
</tr>
<tr>
<td>Biologically active</td>
<td>Pooled/recombinant thrombogen,</td>
<td>Thrombins (Thrombin®, Evithrom®, Recothrom®), Fibrin sealant (Evicel®), Albumin (Bioglue®)</td>
<td>Mild to moderate bleeding, effective in epistaxis, easy to apply, immunological response.</td>
</tr>
</tbody>
</table>

### Burn Resuscitation

**Burn Injuries**
- Burn with >25% TBSA associated with pathological fluid shifts
- Increased inflammatory and vasoactive mediators
- Inhalation injury
- Increases mortality & fluid resuscitation
- Early airway evaluation & intubation critical
- Injury
- Etoma
- Oxygenation needs
- Estimation of burn TBSA

**Burn Management**
- Fluid resuscitation: warmed lactated ringers
  - <30% = oral fluid candidates
  - >30% = IV fluid
- Analgesics & sedation
- Wound care
- No systemic antibiotics
- Topical antibiotics
- Tetanus vaccination

**Fluids in Burn Management**
- >20% TBSA have increased capillary permeability
- Warmed lactated ringers
  - Initial estimation:
    - Adults: 2 mL/kg x % TBSA
    - Pediatric: 3 mL/kg x % TBSA
  - Electrical Injury: 4 mL/kg x % TBSA
  - Administer half in first 8 hrs, then second half over 16 hrs
  - Titrate to renal output:
    - Adults: 0.5 – 1 mL/kg/hr
    - Pediatric: 1 – 1.5 mL/kg/hr + maintenance fluids
  - Add glucose source

**Pharmacy in Trauma**

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**Pharmacists Role in Trauma**

- Participate as part of the trauma team (adult and pediatric)
- Decrease medication errors
- Procure medications for patients in a timely manner
- Evaluate medications for safety & appropriateness
- Advocate for the patient
- Follow guidelines national/international & institution specific
- Evaluate and stock medications needed in trauma in appropriate locations


**Value of Pharmacy in Trauma**

- Postintubation sedation & analgesia
  - Improved time = 9/21 min vs 28/44 min
  - Improved appropriateness selection
- Management of pain
  - Improved time to administration = 17 min vs 21 min
- Antibiotics in open fractures
  - Improved appropriate antibiotic selection = 81% vs 47%
  - Improved time to administration = 1 min vs 20 min
- Pediatric medication errors


**Tips & Tricks**

- Have tools ready
  - Sharpie & tape
- Intubation & pain/sedation meds 1st
  - Typical ACLS medications used less
  - “Epi makes the heart beat faster = Pt bleeds out faster”
- Prepare for epi in thoracotomy
  - 1mg epinephrine (conc 1 mg/mL)
  - Spinal needle (or at least 1 inch)
- Diluent


**References**

- Behrens AM, Sikorski MJ, Kofinas P. Hemostatic strategies from traumatic and surgical bleeding.

**Conclusion**

- The ABCDEs should be utilized during the primary survey and when vital signs or mental status changes.
- Hemorrhagic shock is commonly seen in trauma and resuscitation and MTP should be utilized.
- Patients presenting with burn injuries require boluses and the guided resuscitation with warmed lactated ringers.
- Pharmacy plays a key role in the trauma team and improves patient access to medications, increases appropriateness of medications, and reduces errors.


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