Brain Matters and Blood Splatters: Drug Therapy in the Emergency Trauma Patient
Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.
Blood Splatters

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Assistant Professor, Department of Emergency Medicine
University of Rochester Medical Center
Rochester, NY
Objective

- Determine the appropriateness of pharmacologic agents used for traumatic hemorrhage
- 19 yo male MCC vs. car, level 1 trauma
- SBP reported as 85 and repeat 79
- Bilateral lower extremity bone and soft tissue injuries, concern for pulses on R leg, early compartment syndrome on R leg
- R wrist open fracture, pneumothorax L chest, positive FAST
Which management is the most appropriate for resuscitation?

A. Administer crystalloid fluids
B. Administer blood products alone
C. Administer blood products and tranexamic acid (TXA)
D. Administer blood products and prothrombin complex concentrates (PCC)
Bleeding is the Major Cause of Death in Trauma

- Bleeding: 39%
- CNS: 42%
- MOF: 7%
- Other: 4%
- Unknown: 2%

Sauaia A et al. J Trauma 1995;38:185-93
Lethal Triad → High Mortality Rate

Coagulopathy
↑INR, ↑PT/aPTT, ↓Plt, ↓Fibrinogen

Hypothermia

Acidosis

More Blood, More Problems

Incidence of MOF (%)

Transfused units first 12 hours

P < 0.001

Incidence of Infection (%)

Transfused PRBC units

n=1,593

Tranexamic Acid (TXA)

- Hyperfibrinolysis in trauma
  - Dysfunction from severe shock and major tissue trauma
  - Present 2.5-7% of all trauma patients
CRASH-2 Trial

- Randomized, placebo controlled trial
- 40 countries, 274 hospitals, n = 20,211 with or at risk for bleeding
- Randomization – uncertainty principle
- SBP < 90 mm Hg or HR > 110 bpm or thought to be at risk of significant hemorrhage
- 1 g over 10 minutes, then 1 g over 8 hours or placebo

Crash-2 trial collaborators. Lancet 2010;376:23-32
## CRASH-2 Trial Results

- **Death in the hospital within 4 weeks of injury**

<table>
<thead>
<tr>
<th></th>
<th>TXA (n=10,060)</th>
<th>Placebo (n=10,067)</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause of death</td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85–0.97)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Bleeding</td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85 (0.76–0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69 (0.44–1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>209 (2.1%)</td>
<td>233 (2.3%)</td>
<td>0.90 (0.75–1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603 (6.0%)</td>
<td>621 (6.2%)</td>
<td>0.97 (0.87–1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other causes</td>
<td>129 (1.3%)</td>
<td>137 (1.4%)</td>
<td>0.94 (0.74–1.20)</td>
<td>0.63</td>
</tr>
</tbody>
</table>
### Mortality Subgroup Analysis

<table>
<thead>
<tr>
<th>Time to treatment (h)</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>198/3747 (5.3%)</td>
<td>286/3704 (7.7%)</td>
<td>0.68 (0.57-0.82)</td>
</tr>
<tr>
<td>&gt;1-3</td>
<td>147/3037 (4.8%)</td>
<td>184/2996 (6.1%)</td>
<td>0.79 (0.64-0.97)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>144/3272 (4.4%)</td>
<td>103/3362 (3.1%)</td>
<td>1.44 (1.12-1.84)</td>
</tr>
</tbody>
</table>

\[ \chi^2 = 23.516; p < 0.0000 \]

- Favors TXA
- Favors placebo

Crash-2 trial collaborators. Lancet 2010;376:23-32
## Limitations

<table>
<thead>
<tr>
<th></th>
<th>TXA (n=10,060)</th>
<th>Placebo (n=10,067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood products transfused</td>
<td>5067 (50.4%)</td>
<td>5160 (51.3%)</td>
</tr>
<tr>
<td>Mean units transfused</td>
<td>6.06 (SD ± 9.98)</td>
<td>6.29 (SD ±10.31)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic blood pressure (mm Hg)</th>
<th>TXA (n=10,060)</th>
<th>Placebo (n=10,067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 75</td>
<td>15.5%</td>
<td>15.9%</td>
</tr>
<tr>
<td>76-89</td>
<td>16%</td>
<td>16.8%</td>
</tr>
<tr>
<td>≥ 90</td>
<td>68.4%</td>
<td>67.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart rate (bpm)</th>
<th>TXA (n=10,060)</th>
<th>Placebo (n=10,067)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 77</td>
<td>8.7%</td>
<td>8.6%</td>
</tr>
<tr>
<td>77-91</td>
<td>17.1%</td>
<td>17.5%</td>
</tr>
<tr>
<td>92-107</td>
<td>25.3%</td>
<td>25.2%</td>
</tr>
<tr>
<td>&gt; 107</td>
<td>48.3%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Crash-2 trial collaborators. Lancet 2010;376:23-32
Controversy with CRASH-2

- Design
- Lack of modern trauma systems
- Lack of laboratory monitoring of coagulation function
- No Injury severity scores
- Need for an antifibrinolytic agent since only half required blood transfusion
- NNT 67

- New York Times Article “Cheap drug is found to save lives”
- Death avoidance paper
- WHO essential medications list

Thromboelastometry (TEG, ROTEM)

Coagulation

- Kinetics of clot development
- Reaction time, first significant clot formation

Fibrinolysis

- Angle
- LY30
- MA
- Percent lysis 30 minutes after MA
- Achievement of certain clot firmness
- Maximum amplitude - maximum strength of clot

(t) 020 8371 9908
Hemorrhagic

- Low clotting factors
- Low platelet function
- Low fibrinogen level
- Primary fibrinolysis
- Hypocoagulable state

Thrombotic

- Platelet hypercoagulability
- Enzymatic hypercoagulability
- Platelet & enzymatic hypercoagulability
- Secondary fibrinolysis
MATTERs

- Retrospective, consecutive patients Jan 2009-Dec 2012
- Received at least 1 unit of RBC within 24 hours of injury
- 2009
  - TXA administered at discretion
- 2010 and after
  - TXA administered to those requiring emergent transfusion or based on thromboelastogram data (documented hyperfibrinolysis)
- Loading dose was given, continuation was at discretion
MATTERs Results

- In-hospital mortality
- TXA lower unadjusted mortality
  - 17.4% (n = 293) vs. 23.9% (n = 603), p = 0.03
- Massive transfusion unadjusted mortality
  - 14.4% (n = 125) vs. 28.1% (n = 196), p = 0.004
  - TXA independently associated with survival
    - Odds Ratio 7.228 (95% CI 3-17)
    - NNT 7
## Thromboembolism Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>TXA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRASH-2 (any vasoocclusive event)</td>
<td>1.7%</td>
<td>2%</td>
</tr>
<tr>
<td>MATTERs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>2.7%</td>
<td>0.3%*</td>
</tr>
<tr>
<td>DVT</td>
<td>2.4%</td>
<td>0.2%*</td>
</tr>
<tr>
<td>Massive transfusion + PE</td>
<td>3.2%</td>
<td>0%*</td>
</tr>
<tr>
<td>Massive transfusion + DVT</td>
<td>1.6%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Swendsen, et al. (PE/DVT)</td>
<td>11.5%</td>
<td>0%*</td>
</tr>
<tr>
<td>Cole, et al. (Shock patients: PE/DVT)</td>
<td>8%</td>
<td>2%*</td>
</tr>
</tbody>
</table>

*Statistically significant

TXA Questions

- Unknown mechanism
  - Anti-fibrinolysis vs. anti-inflammatory
- Is there more to the pathophysiology of trauma induced coagulopathy
- Hyperfibrinolysis determination
  - LY30 3% or greater predicts requirement for massive transfusion/risk of mortality
  - Hyperfibrinolysis (18%), physiologic (18%), shutdown (64%)
- Correct dose
- Pre-hospital use (STAAMP trial, The PATCH study, ....)

Clinicaltrials.gov
MASSIVE TRANSFUSION PROTOCOL (MTP)

- SBP ≤ 70 OR SBP 71-90 AND HR ≥ 108

Any of these in the ED:
- Penetrating Torso Injury
- Major Pelvic Fracture
- FAST ⊕ >1 Body Region

ACTIVATE MTP

Transfuse RBC 4 Units and FFP 2 Units

Order Citrated Rapid TEG

Continue to component transfusion based on TEG Results

- ACT > 128 sec
- Angle < 65°
- MA < 55 mm
- LY30 ≥ 5%

Re-assess via Citrated Rapid TEG

CaCl₂ 1 gm IV

FFP 2 Units
Cryo 10 Units
Platelets 1 Unit
TXA 1 gm

if patient is bleeding

Used with permission from Kevin Kaucher, Denver Health
Prothrombin Complex Concentrate (PCC)

- Contain factors IX, II, X, ± VII
- Reversal of trauma induced dilutional coagulopathy
- Retrospective, n = 20 non-warfarin patients (8 TBI)
- Median ISS: 29 (21-44)
- Base deficient > 4: 80%
- 3F-PCC dose: 1,760 ± 576 units (25 units/kg)

<table>
<thead>
<tr>
<th></th>
<th>Before PCC</th>
<th>After PCC</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>2 ± 0.6</td>
<td>1.4 ± 0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>RBC (mean units ± SD)</td>
<td>9.8 ± 6.8</td>
<td>3.8 ± 4.8</td>
<td>0.002</td>
</tr>
<tr>
<td>FFP (mean units ± SD)</td>
<td>6 ± 6</td>
<td>3 ± 3.2</td>
<td>0.077</td>
</tr>
<tr>
<td>Thromboembolic events</td>
<td>= 2 (10%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PCC vs. FFP and Reversal of Coagulopathy

- Retrospective, propensity matched, n = 252 coagulopathic (INR ≥ 1.5) trauma patients, 3F-PCC 25 units/kg
- Median ISS: 27 (16-38)
- Correction of INR: 394 vs. 1,050 min, p = 0.001
- Mortality 23 vs. 28%, p = 0.04

![Graph showing mean units transfused with bars for RBC and FFP transfusions comparing PCC + FFP group and FFP group.]

# PCC Administration Guided by Thromboelastography

<table>
<thead>
<tr>
<th>No. Patients</th>
<th>Criteria for PCC</th>
<th>No. PCC (%)</th>
<th>Dose</th>
<th>Mortality/Transfusion</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>128 (≥ 5 units RBC, fibrinogen concentrate)</td>
<td>EXTEM clotting time &gt; 1.5 x normal</td>
<td>98 (75%)</td>
<td>1800</td>
<td>Mortality 24 vs. 34% (predicted by ISS)</td>
<td></td>
</tr>
<tr>
<td>681 (ISS ≥ 16, fibrinogen concentrate ± PCC vs. FFP)</td>
<td>EXTEM clotting time &gt; 1.5 x normal</td>
<td>43 (54%)</td>
<td>1200</td>
<td>Avoidance of RBCs in 29% combination gp vs. 3% FFP gp)</td>
<td></td>
</tr>
<tr>
<td>144 (ISS ≥ 15, fibrinogen concentrate ± PCC vs. FFP)</td>
<td>PT &lt; 50% or INR &gt; 1.5 or EXTEM clotting time &gt; 90 s</td>
<td>66</td>
<td></td>
<td>RBC 2 vs. 9 units Platelets 0 vs. 1 unit Fewer MOF or sepsis than FFP gp</td>
<td>9%</td>
</tr>
</tbody>
</table>

- 19 yo male MCC vs. car, level 1 trauma
- SBP reported as 85 and repeat 79
- Bilateral lower extremity bone and soft tissue injuries, concern for pulses on R leg, early compartment syndrome on R leg
- R wrist open fracture, pneumothorax L chest, positive FAST
Which management is the most appropriate for resuscitation?

A. Administer crystalloid fluids
B. Administer blood products alone
C. Administer blood products and tranexamic acid (TXA)
D. Administer blood products and prothrombin complex concentrates (PCC)
Combat Gauze

- Impregnated with kaolin
- Kaolin is a negatively charged inert material
- Does not contain animal or human proteins
- Promotes activation of FXII $\rightarrow$ activates FXI $\rightarrow$ initiation of clotting cascade $\rightarrow$ promotes formation of fibrin
Key Takeaways

- **Key Takeaway #1**
  - Trauma induced coagulopathy is complicated and multifactorial

- **Key Takeaway #2**
  - Use of tranexamic acid (TXA) remains controversial but may be guided by thromboelastography

- **Key Takeaway #3**
  - 4F-PCC may decrease overall blood product use but may increase thromboembolic events
Thank You!

UNIVERSITY OF ROCHESTER MEDICAL CENTER
Brain Matters

Sid Patanwala, Pharm.D., BCPS, FCCP, FASHP
Associate Professor
The University of Arizona
Objectives

- Select appropriate pharmacological therapy for the traumatic brain injury patient

- Evaluate the pharmacists role during traumatic resuscitation in the brain injury patient
The Scenario

To TUBE or not to TUBE?

Roc or Sux?
Which agent would you choose?

A. Rocuronium

B. Succinylcholine
## Intubation Success

Analysis of 327 adult patients who received RSI

<table>
<thead>
<tr>
<th></th>
<th>Succinylcholine</th>
<th>Rocuronium</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First attempt success rate</td>
<td>72.6%</td>
<td>72.9%</td>
<td>0.95</td>
</tr>
<tr>
<td>Median number of attempts (IQR)</td>
<td>1 (1-2)</td>
<td>1 (1-2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Median dose</td>
<td>1.6 mg/kg</td>
<td>1.2 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

Multivariate regression: Association of NMBA with intubation success (OR 1.02, 95% CI 0.61-1.7, p=0.95)

Patanwala et al. *Acad Emerg Med* 2011; 18:11-14
## ICP Basic Science - Cats

<table>
<thead>
<tr>
<th></th>
<th>Before SUX</th>
<th>After SUX</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP-Normotensive (n=9)</td>
<td>8.2 ± 1.1</td>
<td>16.3 ± 2.7</td>
<td>0.01</td>
</tr>
<tr>
<td>ICP-Hypertensive (n=8)</td>
<td>27 ± 1.3</td>
<td>47 ± 4.0</td>
<td>0.01</td>
</tr>
</tbody>
</table>

# ICP Basic Science - Dogs

<table>
<thead>
<tr>
<th>Time</th>
<th>SUX (N=6)</th>
<th>Placebo (N=2)</th>
<th>SUX + Pancuronium (N=2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-15 min (% Control)</td>
<td>291 ± 89</td>
<td>138 ± 46</td>
<td>118 ± 39</td>
</tr>
<tr>
<td>15-30 min (% Control)</td>
<td>189 ± 70</td>
<td>127 ± 54</td>
<td>98 ± 48</td>
</tr>
</tbody>
</table>

Lanier et al. Anesthesiology 1986;64:551-9
# Succinylcholine: ↑ICP?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Population</th>
<th>ICP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. 1996</td>
<td>11</td>
<td>RCT</td>
<td>&lt;48 hrs s/p TBI</td>
<td>No Δ</td>
</tr>
<tr>
<td>Kovarik et al. 1994</td>
<td>6</td>
<td>Case Series</td>
<td>1-5 days s/p TBI</td>
<td>No Δ</td>
</tr>
<tr>
<td>Lam et al. 1984</td>
<td>24</td>
<td>Case Series</td>
<td>Aneurism clipping</td>
<td>No Δ (CSF-P)</td>
</tr>
<tr>
<td>McLesky et al. 1974</td>
<td>4</td>
<td>Case Series</td>
<td>Neurosurgery</td>
<td>↑ICP (2/4)</td>
</tr>
<tr>
<td>Marsh et al. 1980</td>
<td>8</td>
<td>Case Series</td>
<td>Neurosurgery</td>
<td>↑ICP (mean Δ 5.2)</td>
</tr>
</tbody>
</table>

Traumatic Brain Injury

Analysis of 233 adult TBI patients who received RSI

# Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe or critical head injury patients</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paralytic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>[Reference]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>4.08</td>
<td>1.18 to 14.13</td>
<td>0.026</td>
</tr>
<tr>
<td>Glasgow Coma Score&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.36</td>
<td>0.20 to 0.68</td>
<td>0.001</td>
</tr>
<tr>
<td>Age&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.04</td>
<td>1.00 to 1.08</td>
<td>0.045</td>
</tr>
<tr>
<td><strong>Less than severe head injury patients</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paralytic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rocuronium</td>
<td>[Reference]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>0.75</td>
<td>0.29 to 1.92</td>
<td>0.548</td>
</tr>
<tr>
<td>Glasgow Coma Scale&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.48</td>
<td>0.31 to 0.74</td>
<td>0.001</td>
</tr>
<tr>
<td>Age&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.03</td>
<td>1.00 to 1.06</td>
<td>0.026</td>
</tr>
</tbody>
</table>

Due to the potential for transtentorial herniation the team would like to initiate a hyperosmolar agent. Which would you recommend?

A. Mannitol

B. Hypertonic saline (NaCl 5%)
EXPERIMENTAL ALTERATION OF BRAIN BULK

LEWIS H. WEED, Capt., Med. Corps

AND

PAUL S. McKIBBEN, 1st Lt., San. Corps

From The Army Neuro-Surgical Laboratory, Johns Hopkins Medical School, Baltimore, Maryland

Received for publication March 22, 1919

- **HyPER**tonic Solution ----> ↑ Size of the brain

- **HyPO**tonic Solution ----> ↓ Size of the brain
Mannitol Versus Hypertonic Saline

- Systematic Review (n=7 RCTs)
  - No difference in mortality, neurological outcome, or ICP reduction
  - Hypertonic saline may lead to fewer treatment failures

Guideline Recommendations

“Although hyperosmolar therapy may lower intracranial pressure, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe traumatic brain injury”

Carney et al. Neurosurgery 0:1–10, 2016 [Ahead of Print]
Mannitol Versus Hypertonic Saline
Quick Lesson About Filters
Quick Lesson About Filters
Seizure prophylaxis is indicated. Which would you choose?

A. Phenytoin

B. Levetiracetam
Levetiracetam Versus Phenytoin

Prospective Observational Study in Blunt Head Trauma

<table>
<thead>
<tr>
<th></th>
<th>Levetiracetam (n=406)</th>
<th>Phenytoin (n=407)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0.997</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>7.9%</td>
<td>10.3%</td>
<td>0.227</td>
</tr>
<tr>
<td>Mortality</td>
<td>5.4%</td>
<td>3.7%</td>
<td>0.236</td>
</tr>
</tbody>
</table>

1000 mg IV q12 hours

Guideline Recommendations

- Phenytoin recommended to decrease early post-traumatic seizures (within 7 days), when benefit outweighs risk for treatment
- Prophylaxis with phenytoin or valproate not indicated for late seizures
- Insufficient evidence to recommend levetiracetam compared to phenytoin

Carney et al. Neurosurgery 0:1–10, 2016 [Ahead of Print]
You plan to use levetiracetam. What dose would you recommend?

A 1000 mg IV q12

B 500 mg IV q12
2 Dosage and Administration

2.1 Dosing for Partial Onset Seizures

Adults 16 Years and Older

Initiate treatment with a daily dose of 1000 mg/day, given as twice-daily dosing (500 mg twice daily). Additional dosing increments may be given (1000 mg/day additional every 2 weeks) to a maximum recommended daily dose of 3000 mg. There is no evidence that doses greater than 3000 mg/day confer additional benefit.
Low Dose Effective?

Retrospective cohort of patients with TBI (n=169)
All patients given levetiracetam 500 mg IV q12

Seizure 2.4%
No Seizure 97.6%

Patanwala et al, Brain Inj. 2016;30(2):156-8
Key Takeaways

- **Key Takeaway #1**
  - Consider rocuronium for RSI (Note: my data is only hypothesis generating)

- **Key Takeaway #2**
  - Insufficient evidence to support mannitol versus hypertonic saline. Consider logistical issues.

- **Key Takeaway #3**
  - Observational studies show levetiracetam equally effective to phenytoin. Adequately powered RCT needed.