Hemostatic Resuscitation, Viscoelastic Monitoring, and Pharmacologic adjuncts

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Objectives

• Review of viscoelastic monitoring

• Review evidence regarding the impact of viscoelastic monitoring on outcomes

• Overview of pharmacologic adjuncts in hemorrhagic resuscitation
  o Tranexamic Acid (TXA)
  o Factor VIIa
  o Prothrombin Complex Concentrate (PCC)
Viscoelastic Monitoring Overview
Conventional Coagulation Tests

Do NOT assess:

• Involvement of endothelium or blood cells

• Generation of thrombin, clot formation, stabilization

• Hypercoagulability and fibrinolysis
Viscoelastic Monitoring

- **Thromboelastography** (TEG®, Haemonetics)
  - *cup spins* around a stationary detection pin

- **Rotational Thromboelastometry** (ROTEM®, Haemoview Diagnostics)
  - *pin spins* in a stationary cup

- Cannot compare values directly
  - Similar in clinical applicability
<table>
<thead>
<tr>
<th>Measurement</th>
<th>TEG</th>
<th>ROTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting Time (to 2mm)</td>
<td>Reaction Time (R)</td>
<td>Clotting Time (CT)</td>
</tr>
<tr>
<td>Clot Kinetics (2-20mm)</td>
<td>Kinetics (K)</td>
<td>Clot Formation Time (CFT)</td>
</tr>
<tr>
<td>α-Angle</td>
<td>Slope between R and K</td>
<td>Slope of tangent at 2mm</td>
</tr>
<tr>
<td>Amplitude at Fixed Time</td>
<td>(A30, A60)</td>
<td>(A10-30)</td>
</tr>
<tr>
<td>Max Strength</td>
<td>Max Amplitude(MA)</td>
<td>Max Clot Firmness(MCF)</td>
</tr>
<tr>
<td>Lysis at a fixed time</td>
<td>CL30, CL60</td>
<td>CLY30, CLY60</td>
</tr>
<tr>
<td>Maximum Lysis</td>
<td></td>
<td>ML &lt;15%</td>
</tr>
</tbody>
</table>

Coagulation Activation & Clot Polymerization

Rapid TEG (rTEG): activated clotting time (T-ACT)

• Initial fibrin formation

• Intrinsic and extrinsic pathways

• If abnormal, give FFP
Coagulation Activation & Clot Polymerization

R (reaction time) = Clotting Time (CT) = Time to start clot

- **Initial** fibrin formation is at 2mm amplitude

- Reflects *coagulation factors* & intrinsic clotting cascade

- If abnormal give FFP or Prothrombin Complex Concentrate if need to restrict volume
Coagulation Activation & Clot Polymerization

**Ktime (kinetics) = Clot Formation Time (CFT)**

- Time to *fixed strength*
- From 2 mm-20 mm amplitude (normal 1-3 min)
- Relates to *fibrinogen* and *platelet number*
- In trauma, low fibrinogen correlated with mortality & reversal with improved survival
- **If >3 min, give cryoprecipitate**

![Diagram of clot formation and degradation process](image-url)
Coagulation Activation & Clot Polymerization

Alpha Angle

- Between baseline and tangent to clotting curve through 2mm
- Rate of clot formation, fibrinogen & fibrin build up & X-linking
- Relates to fibrinogen and platelet number
- Normal 53-72 degrees

- If $\alpha$ angle < 53 give Cryoprecipitate +/- platelets
Clot Firmness

Maximum Amplitude (MA) = Maximum Clot Firmness (MCF)

- Dependent on *platelet number & function* (80%) & *fibrin*
- If < 50 mm, give platelets or DDAVP

Amplitude times (A5, A10...A-30..Max)

- Time between 2mm & amplitude at any given time up to max
- Coagulation Time (R) + X min
Clot Lysis

Lysis at 30 minutes (CL30 or LY30)
- Percent Δ amplitude/clot lost 30 min after maximum
- Fibrinolysis phase
- If >3%, consider anti-fibrinolytic agent
- Last value produced on a TEG
- Consider empiric TXA, but will alter further values

Maximum Lysis (ML)
- Difference between max clot firmness/amplitude & lowest firmness/amplitude
- ML ≥ 15% is consistent with hyperfibrinolysis
Table 2: Suggested TEG-guided transfusion

<table>
<thead>
<tr>
<th>TEG Value</th>
<th>Transfuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEG-ACT &gt; 140</td>
<td>FFP</td>
</tr>
<tr>
<td>R time &gt; 10</td>
<td>FFP</td>
</tr>
<tr>
<td>K time &gt; 3</td>
<td>cryoprecipitate</td>
</tr>
<tr>
<td>$\alpha$ angle &lt; 53</td>
<td>cryoprecipitate +/- platelets</td>
</tr>
<tr>
<td>MA &lt; 50</td>
<td>platelets</td>
</tr>
<tr>
<td>LY30 &gt; 3%</td>
<td>tranexamic acid</td>
</tr>
</tbody>
</table>

Viscoelastic Monitoring Evidence
PTS MTP Guidelines Committee PICO Question 1: In severely injured pediatric trauma patients, are viscoelastic abnormalities better than conventional coagulation test (CCT) abnormalities for predicting trauma induced coagulopathy?

• Only one study met criteria

Study Characteristics

- Non-randomized, retrospective, 86 patients ≤14 years
- Media median ISS 21; 88% blunt
- 76 survivors (88%) and 10 non-survivors (12%)
- Overall certainty of evidence very low
- ACT ($r=0.68$), $k$-time ($r=-.77$), $\alpha$-angle ($r=-0.75$) showed strong correlation to PTT
- MA ($r=0.46$) showed good correlation to platelet count
**Viscoelastic Vs. Conventional Coagulation Tests (CCT): MORTALITY**
(controlling for age, gender, and ISS)

<table>
<thead>
<tr>
<th>r-TEG</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT*</td>
<td>1.04</td>
<td>1.008-1.066</td>
</tr>
<tr>
<td>r-value*</td>
<td>33.89</td>
<td>2.355-487.81</td>
</tr>
<tr>
<td>k-time*</td>
<td>4.61</td>
<td>1.662-12.75</td>
</tr>
<tr>
<td>α angle*</td>
<td>0.84</td>
<td>0.754-0.946</td>
</tr>
<tr>
<td>mA*</td>
<td>0.79</td>
<td>0.694-0.899</td>
</tr>
<tr>
<td>LY-30</td>
<td>1.20</td>
<td>0.779-1.852</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CCT</th>
<th>Odds Ratio</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>1.27</td>
<td>0.681-2.362</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.74</td>
<td>0.465-1.180</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.99</td>
<td>0.983-1.001</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.78</td>
<td>0.082-73.74</td>
</tr>
<tr>
<td>PTT*</td>
<td>1.18</td>
<td>1.039-1.347</td>
</tr>
<tr>
<td>Base value*</td>
<td>0.69</td>
<td>0.541-0.881</td>
</tr>
</tbody>
</table>
Does goal directed hemostatic resuscitation using viscoelastic monitoring result in decreased Total Blood Products Transfused

Vogel et al. (2013)

• All rTEG and CCT values predicted RED CELL transfusion volumes except LY30 and fibrinogen levels

• All rTEG and CCT values predicted PLASMA transfusion volumes except hemoglobin and aPTT

• Only INR and hemoglobin level predicted PLATELET transfusion volumes

• Only k-time and α-angle predicted CRYOPRECIPITATE transfusion volumes
Viscoelastic Vs. Conventional Coagulation Tests (CCT):
**ICU FREE DAYS**
(Controlling for age, gender, and ISS)

<table>
<thead>
<tr>
<th>r-TEG</th>
<th>Coef.</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT*</td>
<td>-0.121</td>
<td>-0.199, -0.040</td>
</tr>
<tr>
<td>r-value*</td>
<td>-11.21</td>
<td>-18.562, -3.861</td>
</tr>
<tr>
<td>k-time*</td>
<td>4.294</td>
<td>-6.608, -1.980</td>
</tr>
<tr>
<td>α angle*</td>
<td>0.471</td>
<td>0.211, 0.713</td>
</tr>
<tr>
<td>mA*</td>
<td>0.508</td>
<td>0.223, 0.792</td>
</tr>
<tr>
<td>LY-30</td>
<td>-0.482</td>
<td>-1.949, 0.983</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CCT</th>
<th>Coef.</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>-1.634</td>
<td>-4.117, 0.849</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.858</td>
<td>-0.636, 2.353</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.017</td>
<td>-0.005, 0.039</td>
</tr>
<tr>
<td>Fibrinogen*</td>
<td>0.500</td>
<td>0.010, 0.089</td>
</tr>
<tr>
<td>PTT*</td>
<td>-0.245</td>
<td>-0.349, -0.142</td>
</tr>
<tr>
<td>Base value*</td>
<td>0.847</td>
<td>25.595, 35.876</td>
</tr>
</tbody>
</table>
Pediatric Society MTP Guidelines Committee PICO Question 2: Does goal directed hemostatic resuscitation using viscoelastic monitoring compared to CCT result in decreased mortality, blood products transfused, and increased ICU-free days, or vent-free days?

Four Studies (n=1330) met criteria for evaluating mortality and total blood products, only two (n=1111) looked at ICU and vent free days.


2. Leeper, C. M., Neal, M. D., McKenna, C., Sperry, J. L., Gaines, B. A. (2016) The Journal of Trauma and Acute Care Surgery 82(1), 27-34.


Study Characteristics

• Indirect comparisons (e.g. interventions to placebo but not each other)

• Confidence intervals were not reported

• One with confounding bias

• One with selection bias

• Certainty of evidence very low
CCT VS. TEG MORTALITY

Aladegbami et al. (2018)
Univariate analysis of MORTALITY
- 1.92% CCT group, 18.18% rTEG group (p<0.001)
- rTEG group less favorable ISS, RTS, GCS, Hgb, and PTT

Leeper et al. (2016)
- Mortality rate 9%, all but one had disturbance in fibrinolysis
- Mortality
  - fibrinolytic shutdown (SD) 15.7%
  - hyperfibrinolysis (HF) 11.5%
  - normal fibrinolysis 1.8%
Liras et al. (2017)

• Arrival rTEG values: 57% coagulopathic, 43% were not

• 30 day mortality:
  o 12% coagulopathic group, 3% control group
  o admission coagulopathy = independent predictor of death
    OR 3.67 (95% CI 1.768 to 7.632)
CCT VS. TEG
Total Blood Products Transfused

Aladegbami et al. (2018)
• Unadjusted analysis at 6 and 24 hrs
  o No coagulation assessment received the least volume, rTEG the most (p<0.001)

• Adjusted analysis showed same trend, but not significant

• Conclusion: not affected by TEG with adjusted analysis
CCT VS. TEG
Total Blood Products Transfused

Leeper et al. (2016)

• HF associated with hemorrhagic injuries (p<0.001) and need for pRBC’s within 24 hours (p<0.001)

• SD associated with hemorrhagic injuries (p=0.014) and the need for early blood transfusion (p=0.001)

• Both SD and HF were associated with elevated INR
Liras et al. (2017)

- Used TEG on everyone, so can comment on use, not on comparison to CCT

- Coagulopathic patients received more pRBCs, plasma and platelet transfusions in the first 24 hours
CCT VS. TEG

ICU & Vent Free Days

Aladegbami et al. (2018)

- rTEG use associated with longer ICU length of stay and longer time on ventilator

Liras et al. (2017)

- Coagulopathic patients had fewer ICU and ventilator free days
Viscoelastic Monitoring Summary

Benefits

- Faster turnaround time compared to CCT
- Assesses coagulation, clot growth
- Differentiates hyperfibrinolysis from fibrinolytic shutdown
- Likely can measure response to blood product therapy
- Possibly reduced bleeding and transfusions

Challenges

- Lack of standardization
- Variability of reagents, machines, algorithms
- Mostly observation data, lack of controls, small studies
Pharmacologic Adjuncts
Recombinant Activated Human Factor VII (Factor VIIa)

- Approved for hemophilia with factor VIII or IX antibodies
- Initial off-label use by the Israeli military
- Reduces bleeding in hemorrhaging patients
- No effect on mortality
- Increased risk of arterial thrombotic events
- Meta-analysis in adults: *Not recommended in trauma*
Prothrombin Complex Concentrate (PCC)  
K-Centra®

• Contains II, VII, IX, X, protein C, protein S

• Current use mostly for emergency reversal of vitamin K antagonist pharmacologic anticoagulation

• Adverse Reactions
  o Venous & arterial thrombosis (higher risk than plasma)
  o MI
  o DIC
  o HIT
Tranexamic Acid (TXA)

- Interacts with the lysine-binding sites on plasminogen inhibiting conversion to plasmin
- Decreased cleavage of fibrin into fibrin split products
- Blocks fibrinolysis and stabilizes clot formation
Safety

• Adverse effects of TXA rare and mostly minor

• Potentially serious include:
  o Hypotension with rapid administration
  o Hypersensitivity/anaphylaxis
  o Seizures: may be due to the antagonistic effect of TXA on GABA receptors

• Likely no increased risk of thrombosis
50% of MTP patients demonstrated SD physiology
SD is associated with death, disability, and DVT
Severe TBI is associated with sustained shutdown
Extreme HF was lethal
HF without associated shutdown was not related to poor outcome, despite no TXA use
Selective use of anti-fibrinolytics if documented HF
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

- Large multi-center European RCT
- Early TXA reduced mortality adult trauma patients
- Push to give TXA early, maybe even prehospital especially in remote areas
The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients

I Roberts, H Shakur, T Coats, B Hunt, E Balogun, L Barnetson, L Cook, T Kawahara, P Perel, D Prieto-Merino, M Ramos, J Cairns and C Guerriero

Early administration of TXA

• Safe
• Reduced the risk of death
• Highly cost-effective
• Treatment beyond 3 hrs of injury unlikely effective
Additional TXA Trials

• No benefit to TXA in single urban US trauma center

• Standardized massive hemorrhage protocol including TXA did reduce mortality in Haiti
Additional TXA Trials


• 3.9% received TXA

• Recipients more seriously injured

• TXA in adult combat trauma patients independently associated with decreased mortality and improved neurologic outcomes

• No increase in thromboembolic events
TBI related death within 28 days was primary outcome

22% were < 25 yrs of age

TBI related death reduced when TXA given within 3 hrs
  - in mild to mod TBI

No difference in disability

No increased risk of thrombosis

Multinational more resource poor countries
### CRASH-3

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid</th>
<th>Placebo</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>855/4613 (18.5%)</td>
<td>892/4514 (19.8%)</td>
<td>0.94 (0.86–1.02)</td>
</tr>
<tr>
<td>Excluding patients with GCS score of 3 or bilateral unreactive pupils*</td>
<td>485/3880 (12.5%)</td>
<td>525/3757 (14.0%)</td>
<td>0.89 (0.80–1.00)</td>
</tr>
</tbody>
</table>


**Table 2: Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury**

- CI crosses 1 when GCS included, hits 1 when excluded
- A priori sensitivity analysis excluded those expected to have a poor outcome
If reactive pupils and GCS 9-15, TXA may help (i.e. mild to moderate TBI)
## CRASH-3

### Head injury-related death, n/N (%)

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRASH-2 (2011)&lt;sup&gt;6&lt;/sup&gt;</td>
<td>14/133 (10.5%)</td>
<td>24/137 (17.5%)</td>
<td>0.60 (0.33-1.11)</td>
</tr>
<tr>
<td>Yutthakasemsunt al (2013)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>12/120 (10.0%)</td>
<td>18/120 (15.0%)</td>
<td>0.67 (0.34-1.32)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.63 (0.40-0.99)</td>
</tr>
<tr>
<td>New evidence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRASH-3 (2019)</td>
<td>485/3880 (12.5%)</td>
<td>525/3757 (14.0%)</td>
<td>0.89 (0.80-1.00)</td>
</tr>
<tr>
<td>NCT01990768 (2019)</td>
<td>93/603 (15.4%)</td>
<td>50/285 (17.5%)</td>
<td>0.88 (0.64-1.20)</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>0.89 (0.80-0.99)</td>
</tr>
</tbody>
</table>

**Figure 5:** Evidence on the effect of tranexamic acid on head injury-related death
RR = risk ratio.
Tranexamic Acid Use in Children's Hospitals

• Only 0.31% of TXA use was for trauma in American pediatric hospitals

• TXA given on the first day of the hospitalization in 65% of trauma patients

• Only 19% who received TXA were transfused, despite indication for TXA being hemorrhage requiring transfusion

• Over one-third received TXA after 24h
  o Early administration most likely to benefit
  o Late administration might be harmful
TXA in Pediatrics

- Retrospective review pediatric trauma admissions, Afghanistan, 2008 to 2012. 73% penetrating injury.

- 9% received TXA
  - had greater ISS, hypotension, acidosis, coagulopathy

- TXA independently associated with decreased mortality among all
  - Similar trends for subgroups of severely injured and transfused patients
  - Propensity analysis suggested improvements in discharge neurologic status and ventilator dependence

- No significant difference in thromboembolic or cardiovascular complications
TXA in Pediatrics

Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC). Pilot randomized controlled trial.

TIC-TOC Collaborators of the Pediatric Emergency Care Applied Research Network

- Trial at four pediatric level I trauma centers
- Severe trauma and hemorrhagic injuries to the torso and/or brain
- Three arms
- Outcome Measures
  - coagulation biomarkers
  - intracranial hemorrhage progression at 24 h
  - total blood products transfused in initial 48 h
  - global functioning  Pedsql and GOS-E Ped
  - working memory (digit span test)
  - thromboembolic events and seizures
TXA in Pediatrics Summary

- Safe
- Cost effective
- Current studies suggest may decrease mortality
  - unclear if only in resource poor settings
- Ideally should be used only when known hyperfibrinolysis
- Some conflicting data on empiric use
  - possible harm if in fibrinolytic shutdown
  - some data suggest potential for improved neurological outcomes, yet other data indicate that fibrinolytic shutdown is more likely if severe TBI
References


References


- Hunt H, Stanworth S, Curry N, Woolley, Cooper C, Ukoumunne O, Zhelev Z, Hyde C. Thromboelastography (TEG) and Rotational Thromboelastometry (ROTEM®) for Trauma Induced Coagulopathy in Adult Trauma Patients with Bleeding (Review.) The Cochrane Library. 2015. Issue 2.


References


References


END