IS THERE A ROLE FOR TRANEXAMIC ACID (TXA) IN PEDIATRIC TRAUMA? - 3 CASE STUDIES AND GUIDELINES

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LEARNING OBJECTIVES

• Become familiar with tranexamic acid (TXA) and consider its use in managing hemorrhage in the pediatric trauma patient
• Review one children’s hospital’s TXA guideline

THE CLOTTING CASCADE

FIBRIN

Colored scanning electron micrograph of a whole blood clot. Fibrin is blue. From Y. Veklich and J. Weisel.

FIBRINOLYSIS PATHWAY

FIBRINOLYSIS

From ATVB Feb. 1, 2004, 24(2) 382-6

TXA = AN ANTI-FIBRINOLYTIC

Tranexamic acid – 4-(aminomethyl)cyclohexane-1-carboxylic acid – is a synthetic derivative of the amino acid lysine.

- The antifibrinolytic activity is a result of the TXA molecule reversibly binding to plasminogen which prevents its interaction with fibrin.
- TXA has been shown to blunt the inflammatory response that is thought to contribute to the development of MODS (multiple organ dysfunction syndrome) secondary to hemorrhagic shock.
- Similar actions to aminocaproic acid (Amicar). TXA is 8-10 times more potent in vitro than aminocaproic acid.

- It is typically used systemically, but topical TXA has been shown to be effective in the pericardial sac, which contains high levels of tissue plasminogen activator.

TXA MECHANISM OF ACTION


TXA VS LYSINE

Oral Tranexamic acid has been used on prescription to control heavy menstrual bleeding since 1972.

Why has it taken 40 years to be considered in Pediatric Trauma?
Methods – CRASH-2

- Over 20,000 bleeding trauma patients were randomly allocated to get tranexamic acid or matching placebo.
- We included all adult trauma patients who were within 8 hours of their injury, if their doctor thought that they had or could have significant haemorrhage.
- We then collected data on death in hospital within 4 weeks of injury and all important side effects.

Randomised many trauma patients

- 20,211 patients
- from 274 hospitals
- in 40 countries

This is what CRASH-2 found

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>TXA 10,096</th>
<th>Placebo 10,067</th>
<th>Risk of death</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>489</td>
<td>574</td>
<td>0.85 (0.76–0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>33</td>
<td>48</td>
<td>0.69 (0.44–1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Organ failure</td>
<td>209</td>
<td>233</td>
<td>0.99 (0.75–1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603</td>
<td>621</td>
<td>0.97 (0.87–1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other</td>
<td>129</td>
<td>137</td>
<td>0.94 (0.74–1.20)</td>
<td>0.63</td>
</tr>
<tr>
<td>Any death</td>
<td>1463</td>
<td>1613</td>
<td>0.91 (0.85–0.97)</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

CRASH-2: excellent follow up

- 20,211 randomised
- 10,096 allocated TXA
- 10,115 allocated placebo
- 3 consent withdrawn
- 10,093 baseline data
- 10,114 baseline data
- 33 lost to follow-up
- 47 lost to follow-up
- Followed up = 10,060 (99.7%)
- Followed up = 10,067 (99.5%)

For bleeding deaths – early treatment is better

- ≤1 hour
  - RR (95% CI): 0.68 (0.54–0.86)
  - p = 0.000008
- >1 to ≤3 hours
  - RR (95% CI): 0.79 (0.60–1.04)
- >3 hours
  - RR (95% CI): 1.44 (1.04–1.99)
There was no increase in thrombosis

<table>
<thead>
<tr>
<th></th>
<th>TXA allocated (10,060)</th>
<th>Placebo allocated (10,067)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>40 (0.40%)</td>
<td>41 (0.41%)</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>72 (0.69%)</td>
<td>71 (0.70%)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>35 (0.35%)</td>
<td>55 (0.52%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (0.56%)</td>
<td>66 (0.65%)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>168 (1.63%)</td>
<td>201 (1.95%)</td>
<td></td>
</tr>
</tbody>
</table>

CRASH-2 was conducted on 4 continents and was shown to reduce mortality on each!

Tranexamic acid is highly cost effective

Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial

Tranexamic acid is now being used

- Tranexamic acid reduces mortality in bleeding trauma patients
- Tranexamic acid does not seem to increase unwanted clotting
- Tranexamic acid needs to be given early – within 3 hours of injury
- Tranexamic acid is not expensive and could save hundreds of thousands of lives each year around the world

After the CRASH-2 trial, tranexamic acid was added to the WHO List of Essential Medicines (March 2011)
- The military are using tranexamic acid to treat combat casualties
- Tranexamic acid is being used in hospitals around the world
- Tranexamic acid could be given in ambulances
Antifibrinolytic drugs for acute traumatic injury

Roberts I, Shakur H, Ker K, Coats T; CRASH-2 Trial collaborators. Cochrane Injuries Group, London School of Hygiene & Tropical Medicine, London, WC1E 7HT, UK.

- Tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events.
- TXA should be given as early as possible and within three hours of injury, as treatment later than this is unlikely to be effective.
- Further trials are needed to determine the effects of TXA in patients with isolated traumatic brain injury.

COMPLICATIONS / SIDE EFFECTS

- Possibility of an increased risk of thromboembolic events (e.g. early graft closure in coronary artery bypass grafting, deep vein thrombosis, pulmonary embolism, myocardial and cerebral infarctions), but in practice these adverse events have been reported quite rarely.

Vanek T et al. Cor et Vasa: 55(2) April 2013, Pages e184-9

COMPLICATIONS / SIDE EFFECTS

- Another serious adverse event recently discussed in cardiac surgery seems to be a risk of postoperative convulsive seizures, associated particularly with high-dose regimens. This epileptogenic effect of tranexamic acid may be explained by a similarity between its molecules and the molecules of γ-aminobutyric acid which leads to the occupancy of γ-aminobutyric acid receptors.

Vanek T et al. Cor et Vasa: 55(2) April 2013, Pages e184-9

OUR FIRST 3 PEDIATRIC TXA PATIENTS...
Patient #1
- 16 yo male
- MVC vs. tree
- Restrained passenger
- Aeromed
- HR 165, BP 61/40
- GCS 10
- Trauma Bay
- HR 158, BP 102/64
- 7.24/29/137/12/-15
- INR 1.5, Hgb 12.7

Injury Intervention
1) Depressed skull fx/IPH OR – decompressive craniectomy
2) Bl femur fractures OR – external fixation
3) R lb/lb fracture OR – external fixation
4) L radius/ulna fracture Closed reduction w/splint
5) L PTX, pulmonary contusion Monitor, follow-up chest x-ray
6) 11 th rib fracture Pain control
7) Shock bowel Serial abdominal exams
8) Multiple facial fractures Nonoperative management

Postoperative course – Patient #1
- 20 u PRBC
- 4 u FFP
- 5 u Cryo
- 4 u platelets
- TXA – Pharmacist in Trauma Bay: “Dr., do you want to give TXA?”
  Me: “Sure, what is it?”
- PTD #7 – Persistent RUE swelling = cephalic v. thrombus
- Serial U/S – improved on PTD #16, negative hypercoag w/u
- POD #17 – transferred to MFB for rehab

Patient #2
- 14 yo female
- Bicycle vs. car
- No Helmet
- Trauma Bay
- HR 119, BP 101/62
- 7.50/24/93/19/-5
- Hgb 12.4

Injury Intervention
1) Open L lb/lb fracture OR for IMN
2) R arm degloving OR for biiceps/triceps/supinator tendon repairs, radial/musculocutaneous nerve repair
3) L arm soft tissue injury OR for washout and closure
4) Grade IV splenic laceration Observation, serial H&H
5) L SH/SH lb fractures Pain control
Postoperative course – Patient #2

- 0130 – HR 127, BP 84/27, Hgb 7.8
- 0547 – HR 163, BP 78/59, Hgb 7.6
- 2 u PRBC’s, 1 u Cryo
- 4 TXA doses – first ordered in Trauma Bay by adult trauma surgeon prior to my arrival
  
  Me: “We gave TXA? Okay... what is it again?”

- POD #2 – started clear liquid diet
- POD #4 – transferred to MFB for rehab

Patient #3

- 17 yo male
- Ped vs. auto, 35-55 mph
- Scene
  - GCS 3, pupils fixed
  - 3-5 mins of CPR, 3 doses of epi
  - Significant blood loss
  
  OSH
  - BP range: 153/110 – 74/55
  - 3 liters IVF
  - Venous ph: 6.9, BE: -19.1

Carotid Angiogram – Patient #3

- Occlusion of bilateral carotid arteries at skull base
- Brisk hemorrhage into nasopharynx from Right ICA
- No further interventions undertaken

- 1901: asystole, TOD called by Ped Trauma Surgeon
- Totals: 21 u PRBC’s, 6 u FFP, 3 u platelets, 1 u Cryo, TXA

OUR FIRST 3 PEDIATRIC TXA PATIENTS

- With all 3 patients, since TXA had not been studied in Pediatric Trauma patients, I was questioned about my decision to use it each time at our Trauma Performance Committee meeting (Peer Review).
- ... so we decided to write a guideline for the use of TXA in Pediatric Trauma patients...

Guidelines

- [Dana is possessed by Zuul]
- Dr. Peter Venkman: I make it a rule never to get involved with possessed people.
- [Dana starts passionately making out with him]
- Dr. Peter Venkman: Actually, it’s more of a guideline than a rule...
HDVCH CLINICAL GUIDELINE: USE OF TXA IN PEDIATRIC TRAUMA PATIENTS

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• Background
  • No evidence-based data are available for the use of TXA in pediatric trauma
  • Evidence is available in adult trauma and pediatric operative literature
  • Bleeding trauma patients have a high mortality
  • Children in general have a healthier vasculature than adults, so there is no clear reason for a lower age limit

• Indications for Use:
  • Massive transfusion
  • Uncontrolled vascular bleeding
  • Hemodynamically unstable with active internal bleeding
  • No Indication for Use:
    • Non-bleeding patients
    • Pt.s with crush injury, those receiving TXA beyond the acute phase, and using TXA + factor VIII → ↑ risk of DIC
  • Contraindication:
    • Pt.s with known thrombophilia

• Usage:
  • 20 mg/kg (max 1g) bolus over 10 min, followed by the same dose over 8 hours. Continue up to 24 hours if bleeding persists
  • First dose optimally within 3 hours of injury
  • EMS, Helicopter services
  • Can repeat boluses if infusion line not available
  • TXA should be discontinued once bleeding is controlled

• Clinical guidelines have the potential to improve health outcomes and reduce costs. However, what is best care for the majority of patients, as recommended in the guideline, may be inappropriate for the individual patient. Physicians must continue to use good clinical judgment when deciding when to follow the guideline. (Woolf SH, Grol R, Hutchinson A, Eccles M, Grimshaw J. Clinical guidelines: Potential benefits, limitations, and harms of clinical guidelines. BMJ. February 20, 1999; 318(7182):527-530.)

• Spectrum Health reserves the right to alter, amend, modify or eliminate this guideline at any time without prior notice and in compliance with Administrative Policy Policy and Procedure Structure, Standards and Management.

• Pre-Guideline
  • “Doctor, why did you give TXA?”
• Post-Guideline
  • “Doctor, why DIDN’T you give TXA?”
Summary

- TXA reduces mortality in bleeding trauma patients
- TXA is not associated with increased thrombotic complications
- TXA should be given within 3 hours of injury for optimal results
- TXA is inexpensive and cost-effective
- TXA has been safely used in pediatric surgical patients and adult trauma patients, and appears to be safe for pediatric trauma patients, but further study is needed

HDVCH CLINICAL GUIDELINE: USE OF TXA IN PEDIATRIC TRAUMA PATIENTS

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