Tranexamic acid and congenital cardiac surgery

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Promotor: dr. Layth Al Tmimi
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Cardiac surgery in UZ Leuven
Cardiac surgery in UZ Leuven

- Tranexamic acid and congenital cardiac surgery

- Valvesurgery (37%)
- Congenital heart surgery (22%)
- CABG (22%)
- Heart TX (2%)
- Others (2%)
- Aortic dissection (1%)
- PM (4%)
- VAD (9%)
- PTEA (1%)

2011
Cardiac surgery: Bleeding

- Increased risk of bleeding
  - CPB:
    - hyperfibrinolysis, coagulation, inflammatory
    - hemodilution
  - Congenital heart disease
    - Coagulation abnormalities, platelet dysfunction
    - Particularly cyanotic hearth disease
How to reduce blood loss and transfusion?

- Blood-sparing surgery
- Cell saving, autologous predonation…
- Procoagulantia (rec factor VIIa, PPSB)
- Antifibrinolytics
Antifibrinolytics

• Lysine analogues
  – Tranexamic acid (TXA, Exacyl)
  – Epsilon-aminocapronacid (EACA)

• Serine protease inhibitors
  – Aprotinin
  – Nafamostat
  – Ecallantide
Tranexamic acid and congenital cardiac surgery

Eaton M P Anesth Analg 2008;106:1087-1100
Tranexamic acid (Exacyl)

Fig. 2. Antifibrinolytic action of tranexamic acid. Plasminogen normally binds to lysine residues on fibrin and is converted to plasmin in the presence of tissue plasminogen activator; plasmin then digests fibrin. Tranexamic acid reversibly binds to plasminogen at the lysine binding site, preventing the binding of plasminogen to fibrin and the subsequent degradation of fibrin [reproduced from Dunn and Goa. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999 Jun; 57 (6): 1005-32 with permission from Adis (© Adis Data Information BV 1991. All rights reserved)]. t-PA = tissue plasminogen activator.
Blood loss TXA vs. placebo

Tranexamic acid and congenital cardiac surgery

Blood loss (ml/kg/24h)

- TXA
- Placebo

Bulutçu, Chauhan, Reid, Zonis, Levin, Shimizu, Chauhan, p > 0.05
Blood loss TXA vs. placebo

Tranexamic acid and congenital cardiac surgery

Blood loss (ml/kg/24h)

- TXA
- Placebo

- Tranexamic acid bolus and congenital cardiac surgery
  - p > 0.05

- Tranexamic acid CPB prime
  - p > 0.05

- Tranexamic acid bolus and CPB prime
  - p > 0.05

- Tranexamic acid bolus and CPB prime
  - p > 0.05

Cyanotic
Blood loss TXA vs antifibrinolytics

Tranexamic acid and congenital cardiac surgery

- TXA
- Aprotinin
- Epsilon aminocaproic acid
Transfusion TXA vs. placebo

RBC Transfusion TXA vs. Placebo

- TXA
- Placebo

Bulutçu
Chauhan
Reid
Shimizu
Chauhan
Chauhan
Chauhan
Chauhan
Chauhan

RBC Transfusion (ml/kg/24h)

p > 0.05
Tranexamic acid and congenital cardiac surgery

Transfusion TXA vs. placebo

RBC Transfusion TXA vs. Placebo

- Bulutçu
- Chauhan
- Reid
- Shimizu
- Chauhan

TXA vs. Placebo

- 100 mg/kg bolus
- 50 mg/kg CPB prime
- 100 mg/kg bolus
- 15 mg/kg/h infusion
- 100 mg/kg bolus
- 10 mg/kg CPB prime
- 10 mg/kg bolus
- 20 mg/kg bolus
- 20 mg/kg CPB prime
- 1 mg/kg/h infusion
- cyanotic

p > 0.05
Transfusion TXA vs. placebo

**FFP Transfusion TXA vs. Placebo**

- Bulutçu
- Chauhan
- Shimizu
- Chauhan
- Chauhan
- Chauhan
- Chauhan

**PL Transfusion TXA vs. Placebo**

- Chauhan
- Shimizu
- Chauhan
- Chauhan
- Chauhan
- Chauhan
- Chauhan

P > 0.05
Transfusion TXA vs antifibrinolytics

RBC Transfusion TXA vs antifibrinolytics

FFP Transfusion TXA vs antifibrinolytics

Bulutçu
Chauhan

TXA
Aprotinin
EACA

TXA
Aprotinin
EACA
Safety of tranexamic acid

- insufficient data.
- hypotension
- thrombosis
- seizures
  - GABA A R-antagonist effect?
- renal injury
Safety of tranexamic acid

- Thrombotic, seizures, renal injury

<table>
<thead>
<tr>
<th></th>
<th>TXA (n=114)</th>
<th>Aprotinin (n=85)</th>
<th>p</th>
<th>EACA (n=120)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Renal injury</td>
<td>11 (9,6%)</td>
<td>9 (10,6%)</td>
<td>0,83</td>
<td>16 (13,3%)</td>
<td>0,38</td>
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<tr>
<td>Renal failure</td>
<td>2 (1,8%)</td>
<td>0</td>
<td>0,51</td>
<td>5 (4,2%)</td>
<td>0,45</td>
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<td>Seizures</td>
<td>4 (3,5%)</td>
<td>0</td>
<td>0,14</td>
<td>1 (0,8%)</td>
<td>0,20</td>
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<tr>
<td>Other neurologic events</td>
<td>3 (2,6%)</td>
<td>4 (4,7%)</td>
<td>0,46</td>
<td>2 (1,7%)</td>
<td>0,68</td>
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<tr>
<td>In-hospital mortality</td>
<td>3 (2,6%)</td>
<td>3 (3,5%)</td>
<td>0,7</td>
<td>4 (3,3%)</td>
<td>&gt;0,99</td>
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<tr>
<td>Revision for bleeding</td>
<td>11 (9,6%)</td>
<td>2 (2,4%)</td>
<td>0,04</td>
<td>10 (8,3%)</td>
<td>0,73</td>
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<tr>
<td>Vascular thrombosis (any kind)</td>
<td>5 (4,4%)</td>
<td>6 (5,0%)</td>
<td>0,82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table: Postoperative outcome out of Martin et al. and Breuer et al. 
Tranexamic acid as compared with aprotinin (Breuer et al) and with ε-aminocaproic acid (Martin et al) with p-values
Dosing regimes

• Different dosage forms
• Lack of PK, PD data, mostly based on clinical effectiveness
  – 2 compartment model
  – In vitro conc >10 µg/ml.
  – Plasma conc TXA >127 µmol
Dosing regimes

• Dose comparison Chauhan: triple bolus
  • 10 mg/kg bolus + 10 mg/kg CPB prime + 10 mg/kg bolus

• Proposal weight-adjusted dosing regime: 1 loading dose (6.4 mg/kg) + continuous infusion (3.1 – 2.0 mg/kg/h)
Conclusion

• TXA is effective in congenital cardiac surgery
  – Especially in cyanotic children
  – Dose dependent
• Safety: lack of data
  – Increased risk of seizures
• Dosing regime
  – 1 loading dose + continuous infusion
Thank you for your attention!