Introduction: Anti-thrombin (AT) is crucial for heparin to be effective and for the prevention of thrombosis and levels are known to be low in infants. We tested the hypothesis that pre-cardiopulmonary bypass (CPB) normalization of AT levels to 100% would improve anticoagulation during CPB, attenuate activation of the coagulation cascade, as measured by fibrin degradation products (D-Dimer), and mitigate microthrombin in the post-operative period.

Methods: This is a randomized, double blinded, placebo controlled study in infants with AT levels less than 70% undergoing CPB at 2 tertiary centers. Half were given AT (Troxobin) to normalize to 100% functional AT and the other half received placebo. We recorded demographics, laboratory values, hemostatic agents, blood products administered, operating room times, 24-hour chest tube output, and occurrence of post-operative thrombosis. Summary statistics, pooled T test and Fisher exact test were used. Data are presented as mean and ± SD, with statistical significance defined as p<0.05.

Results: Over a 24 month period, 223 patients were screened: 68 met inclusion criteria, 40 were randomized, and 1 (in placebo group) was withdrawn during the study due to ECMO initiation in the operating room. Thirty percent of screened patients had AT levels <70%. Table 1 shows demographic and peri-operative variables. Notable differences were observed between the two groups including higher first post-heparin activated clotting time (ACT) and AT levels in the treatment group. Table 2 shows laboratory values; no differences were noted between the two groups with CPB circuit red blood cell and FFP prime usage, or intraoperative blood, platelet, cryoprecipitate, recombinant Factor VIIa (NovoSeven) and Prothrombin Complex Concentrate usage. Significantly, 24 hours post-operative chest tube output, overall blood product transfusions and D-Dimer production were lower in the AT group. No difference in major adverse events (significant bleeding, stroke, allergic reaction, ECMO initiation, chest exploration or death) was noted.

Conclusion: Replacement of AT improves anticoagulation during CPB without increased rates of bleeding or adverse events. Furthermore our results suggest extension of these beneficial effects into the postoperative period.

Introduction: Anti-thrombin III (ATIII) plays a critical role in achieving adequate heparinization for cardiopulmonary bypass (CPB) and preventing vascular thrombosis. It is recognized that neonates and infants, less than 7 months, have decreased ATIII. Insufficient ATIII levels in infants undergoing congenital heart surgery may be responsible for the increased frequency of hematoma resistance, compressive coagulopathy due to deficient anticoagulation, and postoperative thrombotic events in this population.

Purpose
- Normalization of ATIII levels to 100% pre-cardiopulmonary bypass in infants undergoing congenital cardiac surgery would result in:
  - Improved anticoagulation during CPB
  - Decreased total heparin and protamine dose
  - Less intraoperative bleeding due to attenuation of coagulation cascade
  - Decreased thrombosis in postoperative period

Methods
- Randomized, double blinded, placebo controlled trial
- 2 academic centers
- Inclusion
  - Infants < 7 months
  - Cardiac surgery requiring CPB
- Exclusion
  - < 2.5 kg
  - Hereditary ATIII deficiency
- ACT at time of surgery
- History of thrombosis
- Prematurity < 37 weeks GA
- History intracranial hemorrhage
- Prior ATIII supplementation
- Prior therapeutic anticoagulant use
- Units required = (100%−baseline ATIII level) x 1.2 x body wt

Results
- 24 month period, screened 223 patients
- 30% patients had ATIII <70% (68 met inclusion criteria)
- 40 randomized (1 placebo group withdrawn due to ECMO initiation in OR)

Demographics and Perioperative Variables (Table 1)
- Treatment group demonstrated higher:
  - First post-heparin activated clotting time (ACT)
  - ATIII levels (persisted into early ICU stay)

Demographic and Perioperative Variables (Table 1)
- No differences:
  - CPB circuit RBC and FFP prime usage
  - Intraoperative blood, platelet, cryoprecipitate, recombinant Factor VIIa (NovoSeven) and Prothrombin Complex Concentrate usage
  - Significant differences: Treatment group showed lower:
    - 24 hour postoperative chest tube output
    - Overall blood product transfusion
    - D-dimer production
    - POC: reflecting attenuation of coagulation cascade during CPB resulting in less fibrinolysis

Conclusion
- ATIII replacement to 100%
  - Improved anticoagulation during CPB
  - No increased rates of intraoperative bleeding or adverse events
- Beneficial effects persisted in postoperative period
  - Less bleeding
  - Decreased blood product transfusion
  - Reduced fibrinolysis (D-Omers)

Normalization of ATIII with exogenous AT is helpful in infants undergoing cardiac surgery on CPB.

Table 1. Demographics and Perioperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment Group (n=20)</th>
<th>Placebo Group (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)</td>
<td>9.8 ± 15.7</td>
<td>12.2 ± 30.2</td>
<td>0.174</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14:06</td>
<td>13:06</td>
<td>0.915</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.4 ± 0.5</td>
<td>3.5 ± 0.6</td>
<td>0.784</td>
</tr>
<tr>
<td>ATIII functional assay (%)</td>
<td>71.9 ± 10.4</td>
<td>66.2 ± 15.4</td>
<td>0.195</td>
</tr>
<tr>
<td>ACT post heparin (sec)</td>
<td>105.1 ± 18</td>
<td>119.0 ± 13</td>
<td>0.141</td>
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<tr>
<td>Total CPB time (min)</td>
<td>185 ± 80</td>
<td>212 ± 16</td>
<td>0.186</td>
</tr>
<tr>
<td>Total cross clamp time (min)</td>
<td>87.4 ± 14</td>
<td>101.4 ± 22</td>
<td>0.329</td>
</tr>
<tr>
<td>Protease inhibitor dose normalized to HMX machine (mlg/kg)</td>
<td>11 ± 7.6</td>
<td>9.2 ± 2.8</td>
<td>0.545</td>
</tr>
<tr>
<td>Prothrombin time (min)</td>
<td>100.8 ± 15.6</td>
<td>101.7 ± 15.9</td>
<td>0.727</td>
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</tbody>
</table>

Table 2. Study Lab Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time Point</th>
<th>ATIII functional assay (%)</th>
<th>AT (n=20)</th>
<th>Placebo (n=19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT1 functional assay (%)</td>
<td>T1 (Baseline)</td>
<td>54 ± 12</td>
<td>54 ± 13</td>
<td>0.382</td>
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<tr>
<td>AT (n=20)</td>
<td>T2 (24 hr after study drug)</td>
<td>58 ± 16</td>
<td>49 ± 18</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>AT (n=19)</td>
<td>T4 (post CPB)</td>
<td>55 ± 17</td>
<td>56 ± 15</td>
<td>0.643</td>
<td></td>
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<tr>
<td>AT1 functional assay (%)</td>
<td>T5 (Arrest in ICU)</td>
<td>62 ± 18</td>
<td>63 ± 19</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>AT1 functional assay (%)</td>
<td>T6 (POD 2)</td>
<td>78 ± 15</td>
<td>57 ± 14</td>
<td>0.84</td>
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<tr>
<td>AT1 functional assay (%)</td>
<td>T7 (POD 4)</td>
<td>70 ± 20</td>
<td>65 ± 17</td>
<td>0.475</td>
<td></td>
</tr>
</tbody>
</table>

Results reported by Mean ± SD. RBC/machine = Hemostasis Management System machine; CPB = cardiopulmonary bypass; AT = Anti-Thrombin Postoperative

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