Antithrombin III in Cardiac Surgery: An Outcome Study

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ABSTRACT

A retrospective study examined the impact, in heparin resistant patients (HRP), of lyophilized antithrombin III (ATIII) upon five patient outcomes: intensive care unit stay (ICU-S), 24 hour chest tube drainage (CTD in ml), blood and blood product usage (BPU), development of postoperative coagulopathy (PO-Coag), and reoperation for bleeding (Re-Op). Data was collected from the medical records of 311 patients admitted to the hospital between 12/15/95 and 10/24/96.

Subjects were divided into three groups based upon heparin resistance and hemostasis medication. Group 1 (n=109) were HRP treated with increased heparin, Group 2 (n=100) were HRP receiving ATIII, and Group 3 (n=102) were non-HRP and served as controls. Group 2 was also subdivided by use of aminocaproic acid and time of ATIII administration.

No significant differences were found between the groups for PO-Coag and Re-Op. However, significant reduction in CTD (p=0.05) was seen in the aminocaproic acid patients who were treated with ATIII pre-CPB or within the first 20 minutes of CPB. The CTD in this group was (419.37, ±72.96) as compared to Group 1 (782.88, ±360.94) and Group 3 (766.67, ±407.56). Other Group 2 subgroups showed significant differences in BPU, ICU-S and CTD.

The results of this study support the notion that early identification and treatment of HRP with ATIII and aminocaproic acid may decrease postoperative blood loss.

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INTRODUCTION

According to the National Center for Health Care Statistics, 573,000 cardiac surgical procedures were performed on 360,000 individuals in 1995 (Wood, E. 1995 updates for Table 22, CABG procedures for any and all-listed. Unpublished raw data, National Center for Health Statistics, Hyattsville, MD. 1997). The Society of Thoracic Surgeon’s National Cardiac database collected data for 200,555 coronary artery bypass patients between January 1995 and June 1996. This data revealed that, for the study population, 37.5% (75,266) received red blood cell transfusions, 11.5% (23,122) received fresh frozen plasma and 10.8% (21,642) received platelets (1). Other studies report that approximately 60% of cardiac surgical patients receive some type of transfusion during their hospital stay (2,3). Each unit transfused increases the risk of infection, viral disease transmission or transfusion reaction (4-6).

In an effort to reduce homologous blood and blood product transfusion, researchers have studied the etiology of postoperative blood loss in the cardiac surgical population (7,8).

The most common etiology for post-cardiopulmonary bypass microvascular bleeding appears to be platelet dysfunction. Platelets are activated during cardiopulmonary bypass and as time on bypass increases, platelet aggregability decreases (9-11). The precise mechanism for this post cardiopulmonary bypass platelet dysfunction is in debate, but thrombin and plasmin formation during CPB have been strongly implicated as contributing factors (12-14).

Thrombin is formed during CPB through stimulation of both intrinsic and extrinsic coagulation (15,16). Intrinsic stimulation occurs as a result of contact between blood and the foreign surface of the CPB circuit. Extrinsic stimulation occurs in response to tissue dissection. Once coagulation is initiated, thrombin, factor XIIa and tissue plasminogen activator stimulate fibrinolysis through their respective mechanisms (17,18). The conversion of plasminogen to plasmin is greatly accelerated in the presence of fibrin (15). Therefore, during CPB, both procoagulation and fibrinolysis are stimulated. This leads to postoperative platelet dysfunction, which leads to increased transfusion requirements (9,19,20).

During CPB, the heparin-antithrombin III complex suppresses the coagulation system, which minimizes clot formation and fibrinolytic stimulation (15). Antithrombin III (ATIII) binds Factors IXa, Xa and thrombin, which renders them unusable for clot formation (21-24). ATIII activity of less than 60% has been associated with an increased risk of thromboembolism formation in patients with hereditary ATIII deficiency (25). Several studies have linked heparin resistance during CPB with ATIII deficiency (26-30). Clinically, heparin resistance has been linked to subclinical coagulation, depletion of coagulation factors, hyperstimulation of the fibrinolytic system, platelet dysfunction and increased postoperative bleeding (31-35). This leads to the study hypothesis that the addition of ATIII to the heparin resistant population will precipitate better post-CPB outcomes.

MATERIALS AND METHODS

Approximately 1200 cardiac surgical cases were performed at Maine Medical Center between December 1995 and November 1996. The CPB circuit, anesthetic technique and surgical group were the same for all study subjects. Data was collected retrospectively for 310 patients who met the following criteria:

- include only first time CABG x 2-5
- no history of cancer
- no history of liver disease
- no documented coagulation factor deficiency
- no aprotinin used during the surgery
- no documented renal disease
- no preoperative platelet counts below 140,000

The 310 patients were separated into two groups. Those who required a total heparin dose of 5 mg/kg of heparin were labeled “Heparin Resistant” (n=211). The second group were used as controls (n=99).

The 211 heparin resistant patients were further subdivided by the treatment they received for their heparin resistance. Group 1 (n=110) were treated with increased heparin doses. Group 2 (n=101) heparin resistant patients were treated with lyophilized antithrombin III (AT III). The 99 non-heparin resistant control patients were labeled Group 3.

In order to clarify the source of outcome differences detected, use of aminocaproic acid and time of ATIII administration further subdivided Group 2.

DATA COLLECTION FORM: The data collection form was separated into four sections. The title of each section indicated the source of the information contained in that section. The sections were entitled Perfusion Record, Preoperative Data Collection Form, Maine Medical Center Cardiac Surgery Database Outcome Data Sheet and Anesthesia Record. Table 1 lists anthropomorphic, perioperative, CPB variables collected; and Table 2 list outcome variables collected.

STATISTICS: A one way analysis of variance was used to test parametric variables and a Chi-square was used for non-parametric variables and p < 0.05 was considered significant.
RESULTS

Table 3 lists results for the comparison of the three original groups. The anthropomorphic differences between groups were varied. The BSA of Group 2 subjects was significantly larger than Group 3. The height of Group 1 subjects was significantly larger than Group 3. The weight of Group 2 subjects was significantly larger than Group 1. The pre-op hematocrit of Group 3 was significantly larger than groups 1 and 2. There were no significant differences between the groups with respect to age, gender mix, pre-op platelet count, diabetes and pre-op aspirin usage. All three groups were significantly different from one another when they were compared by the use of either pre-op IV nitroglycerine or pre-op IV heparin.

There were no significant differences among the groups regarding the CPB variables: autotransfusion volume given, last CPB hematocrit and lowest nasopharyngeal temperature. The lowest ACT recorded during CPB was significantly larger for Group 3 than both Groups 1 and 2. The perfusion time for Group 1 was significantly larger than Group 3. The perfusion time for Group 2 was significantly larger than Group 1 and Group 3. The amount of protamine required for heparin reversal after bypass was significantly larger for Group 1 than Group 3. Group 2 received significantly more protamine than either Group 1 or Group 3. The heparin-loading dose for Group 1 was significantly larger than Group 3 and Group 2 received significantly more than Group 1 or Group 3. The total heparin given was significantly larger for Group 1 than Group 3 and Group 2 received significantly more than either Group 1 or Group 3.

The results for the outcome variables are listed in Table 4. There was no statistically significant difference between the three groups with regard to the outcome variables: 24-hr. chest tube drainage, length of stay in the surgical intensive care unit (SCU),...
Table 5: Outcome Variables with Group 2 Split by Amicar Usage and Time of ATIII Administration

<table>
<thead>
<tr>
<th>Outcome Variables</th>
<th>Group 1</th>
<th>Group 201</th>
<th>Group 211</th>
<th>Group 200</th>
<th>Group 210</th>
<th>Group 3</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>110</td>
<td>40</td>
<td>41</td>
<td>12</td>
<td>8</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>24 Hour CTD (ml)</td>
<td>782.7 ± 360.9</td>
<td>873.8 ± 681.8</td>
<td>776.9 ± 354.2</td>
<td>621.3 ± 278.3</td>
<td>419.3 ± 72.9</td>
<td>766.7 ± 407.6</td>
<td>1,201,3,211&gt;</td>
</tr>
<tr>
<td>Reop Bleeding (yes/no)</td>
<td>0</td>
<td>2/40</td>
<td>3/41</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Post-Op Coagulopathy (yes/no)</td>
<td>0</td>
<td>3/40</td>
<td>3/41</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>ICU LOS (hours)</td>
<td>22.2 ± 1.19</td>
<td>21.4 ± 1.42</td>
<td>26.1 ± 1.51</td>
<td>19.9 ± 2.5</td>
<td>22.5 ± 2.75</td>
<td>22.3 ± 2.23</td>
<td>211&gt; 1,201,3</td>
</tr>
<tr>
<td>PRBCs (units)</td>
<td>1.19 ± 0.18</td>
<td>1.42 ± 0.45</td>
<td>1.51 ± 0.29</td>
<td>2.5 ± 0.17</td>
<td>2.65 ± 0.75</td>
<td>0.75 ± 0.88</td>
<td>200&gt; 1,3</td>
</tr>
<tr>
<td>FFP (units)</td>
<td>0.88 ± 0.88</td>
<td>0.45 ± 0.45</td>
<td>0.29 ± 0.29</td>
<td>0.17 ± 0.17</td>
<td>0.58 ± 0.17</td>
<td>0.09 ± 0.09</td>
<td>201&gt; 3</td>
</tr>
<tr>
<td>Cryo (units)</td>
<td>0.11 ± 0.09</td>
<td>0.3 ± 0.3</td>
<td>0.98 ± 0.98</td>
<td>0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>0.42 ± 0.42</td>
<td>211&gt; 1,3</td>
</tr>
<tr>
<td>Platelets (units)</td>
<td>0.49 ± 0.49</td>
<td>1.5 ± 1.5</td>
<td>0.8 ± 0.8</td>
<td>2.2 ± 2.2</td>
<td>0.00 ± 0.00</td>
<td>0.49 ± 0.49</td>
<td>201,200&gt; 1,3</td>
</tr>
</tbody>
</table>

Data are mean ± SD. NS = not statistically significant. SIG = statistically significant. Greater than (> ) = statistical significance. CTD LOS = chest tube drainage. ICU LOS = Intensive Care length of stay. PRBC’s = packed red blood cells.

FFP = fresh frozen plasma. Cryo = cryoprecipitate. Early ATIII = ATIII administered either prior to CPB or during the first 20 minutes of CPB. Late ATIII = ATIII administered after the first 20 minutes of CPB.

Group 1 = heparin resistant treated with only heparin. Group 3 = non-heparin resistant (control) group. Group 201 = heparin resistant, received late AT III, no Amicar. Group 211 = heparin resistant, received Amicar and late AT III Group 200 = heparin resistant, received early AT III, no Amicar. Group 210 = heparin resistant, received Amicar and early AT III.

postoperative homologous platelets or fresh frozen plasma received. A significantly greater proportion of patients in Group 2 were re-operated on for bleeding and/or developed a postoperative coagulopathy compared to either of the other two groups. Group 2 received significantly more packed red blood cells and cryoprecipitate.

When the three groups were separated into aminocaproic acid and non-aminocaproic acid groups, two additional variables became significant. The proportion of patients receiving aminocaproic acid in the three groups was not significantly different, but the outcome variable ICU length of stay was significantly longer for Group 2 patients who received aminocaproic acid. Also, platelet use was significantly higher for Group 2 patients who did not receive aminocaproic acid.

Because group 2 was the only group to show outcome differences, this group was separated by not only aminocaproic acid but received early AT III. Group 2 patients who did not receive aminocaproic acid, but received early AT III had significantly more FFP and platelets than the control patients or Group 1 patients. The Group 2 patients who did not receive aminocaproic acid and received early AT III required significantly more platelets and RBCs than the control patients or Group 1 patients. The Group 2 patients who did not receive aminocaproic acid and received late AT III required significantly more cryoprecipitate than Group 1 or Group 3 control patients.

DISCUSSION

Although several significant relationships were found in this study, interpretations are made with caution. The major finding of this study was found in the timing of the AT III administration. Early administration of AT III resulted in improved patient outcomes.

The administration of aminocaproic acid did not precipitate a measurable improvement in 24 hour CTD and transfusion requirements. Contrary to the findings of Penta de Peppo, et al., 1995, this study did not demonstrate a reduction in 24 hour CTD or transfusion requirements when aminocaproic acid was not dispensed. There were however, significant differences in 24-hour CTD when the timing of AT III administration was considered. Group 2 patients who received late AT III, whether they received aminocaproic acid or not, had larger CTD. Additionally, group 2 patients who received aminocaproic acid and late AT III were given significantly more FFP and platelet products than the control group. The other late ATIII subgroup of Group 2, received more cryoprecipitate transfusions and had longer
SCU lengths of stay than control patients. Group 1 patients (heparin resistant but never received AT III) also had significantly more 24-hour CTD than the control group.

In contrast, Group 2 patients who received no aminocaproic acid and early AT III administration had lower CTD than the control group. However, this group did require significantly more RBC and platelet transfusions. One possible explanation for this is that this group had the lowest BSA and pre-op hematocrit of any group studied. Therefore, hemodilution may have played a major role in the transfusion requirements of this group. Finally, Group 2 patients who received aminocaproic acid and early AT III had the lowest 24-hour CTD of all groups and required fewer transfusions than any other subgroup of Group 2. These findings support the notion that administration of AT III in the heparin resistant population is potentially efficacious.

AT III administered pre-CPB or within the first 20 minutes of CPB (Early) in the heparin resistant population will improve patient outcomes. The two groups who received late AT III required significantly more cryoprecipitate, fresh frozen plasma and platelet replacement. They also had significantly more 24-hour CTD than those who received early AT III. Both late AT III groups included patients who developed postoperative coagulopathies and required re-exploration for bleeding. These results support the notion that early identification and treatment of heparin resistance would potentially improve patient outcomes.

These results, taken as a whole, offer limited confirmation of the hypothesis that the administration of AT III in the heparin resistant population will affect outcomes in a positive way. Prospective randomized trials need to be undertaken in order to confirm this hypothesis.

REFERENCES


