Original Article

Supplemental Use of Antithrombin III Concentrate in the Pediatric Patient

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ABSTRACT

Decreased AT-III levels during cardiopulmonary bypass (CPB) have been observed in pediatric patients and are attributable to hemodilution. Prebypass administration of AT-III to the pediatric patient has been shown to prevent decreases in serum AT-III levels and elevated fibrinopeptide A (FPA) levels before and after bypass. We compared the clinical outcome of patients receiving supplemental AT-III injectate to control patients. Patients with preoperative AT-III levels less than 80% received AT-III injectate prior to heparinization.

A retrospective analysis of 149 patients (31 study patients vs. 118 controls) revealed that a greater percentage of patients receiving AT-III were cyanotic ($p=0.001$) and underwent more complex cardiac repairs ($p=0.001$). Compared to patients not receiving AT-III, surgeries were performed at lower temperatures ($p=0.040$) with longer CPB times ($p=0.031$) and circulatory arrest times ($p=0.047$). Baseline AT-III levels were significantly lower in the treated group ($p<0.0001$) but were significantly higher during CPB ($p=0.0001$). Total postoperative blood loss, blood product administration, rate of reoperation, total time in ICU and mortality proved not to be significantly different between the groups after adjusting for above covariates (p=NS). It appears that maintenance of higher AT-III levels did not affect the clinically measurable outcome variables associated with hemostasis.

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INTRODUCTION

Cardiopulmonary bypass (CPB) alters the physiological hemostatic mechanism of the human body (1). During bypass, the patient's blood is exposed to many foreign surfaces, and this contact results in the activation of the kallikrein, complement, coagulation and fibrinolytic systems (2). Safe patient management during CPB requires the temporary inhibition of the coagulation mechanism. Heparin, a heterogeneous mucopolysaccharide, is the anticoagulant of choice for CPB because of its fast action and easy neutralization with protamine sulfate. However, heparin alone has no effect on coagulation (3).

Adequate Antithrombin III (AT-III) levels are necessary for heparin to exert its inhibitory function (4). Synthesized in the liver, AT-III is a circulating plasma protein that neutralizes the activity of thrombin and other serine proteases of the intrinsic coagulation cascade (5). In addition to enzymatically converting fibrinogen to fibrin, thrombin activates cofactors V and VIII, notably increasing the rate of fibrin clot being formed via the intrinsic and common pathways (6). AT-III inactivates thrombin by the formation of a covalent bond resulting in an inactive 1:1 stoichiometric complex. In addition, this glycoprotein also inhibits kallikrein and factors XIIa, XIa, Xa, and IXa by binding to their active sites at a serine residue. Heparin functions as a catalyst by attaching to AT-III and altering the configuration of the molecule. The rate of reaction between thrombin and antithrombin (TAT) increases at least 1000-fold when heparin serves as a catalytic template (7). Heparin is subsequently released from AT-III for catalyzation of other TAT complexes (8). Nonetheless, the effectiveness of heparin as a catalyst relies on adequate AT-III levels.

Decreased AT-III levels during CPB have been observed in pediatric patients. One variable that may contribute to this is the great hemodilution produced from higher prime volume to patient volume ratios (3). Moreover, preoperative AT-III levels of term newborns have been shown to be 25% to 56% of adult normal levels. Depending on gestational age, premature infants have demonstrated levels 20% to 30% of normal adult values (9). Schmidt and coworkers reported lower AT-III levels in a group of neonates with either moderate or severe respiratory distress syndrome (10). In addition, low levels of AT-III in congenital heart disease (CHD) patients undergoing Fontan procedures, repair of large atrioventricular (AVSD) or ventricular septal defects (VSD) were seen preoperatively by Turner-Gomes and coworkers. They noted further decreases during CPB and throughout the early postoperative period (5). As reported by Kern and coworkers, some researchers believe that a reduced hepatic synthetic capacity may result in diminished coagulation factors (11). Hepatic maturation in neonates continues throughout the first 2 to 3 weeks of life. In neonates with complex cardiac defects, however, hepatic development may be delayed or impaired by poor organ perfusion or severe cyanosis.

Hashimoto and coworkers found decreased AT-III levels and elevated fibrinopeptide A (FPA) levels in eight pediatric control patients, compared to six pediatric patients that were administered AT-III supplement prebypass (3). Subclinical plasma coagulation is associated with elevated FPA levels, perhaps resulting in clinical problems such as increased postoperative blood loss and subsequent blood product administration.

At this institution, AT-III concentrate was given prophylactically to supplement AT-III levels. It is estimated that each international unit per kilogram body weight administered will raise the plasma activity level by 2% to 2.5% of normal (12). Although AT-III concentrate is prepared from pooled human plasma, it has been heat-treated in solution at 60°C ± 0.5°C which appears to be successful at inactivating hepatitis B and human immunodeficiency viruses (13).

The purpose of this retrospective study was to characterize the age, weight, and disease process of the pediatric patient who required AT-III injectate prior to the initiation of CPB. In addition, this study evaluated the effect of AT-III concentrate administration on postoperative bleeding, blood product administration, and AT-III levels. The above stated outcome measurements will also be compared to the pediatric patient population who had AT-III levels drawn, but were not given AT-III concentrate.

MATERIALS AND METHODS

After Internal Review Board approval, a retrospective chart review of 149 pediatric patients undergoing cardiopulmonary bypass (CPB) at the Medical University of South Carolina between August 1994 and August 1995 was done. AT-III concentrate was given to patients with AT-III levels less than 80 percent prior to heparinization according to physician protocol.

The AT-III concentrate dosage given for the treated group corrects the AT-III level to 120%. The manufacturer formula for AT-III correction is as follows:

[((Desired AT-III – Baseline AT-III)/1.4) * weight in kgs] = AT-III dosage in units

The corresponding calculated dose was either given by anesthesia before the institution of CPB or added to the heart-lung bypass machine.

All cases were performed using a standard roller pump[a], one of four membrane oxygenators[b,c,d,e], a filtered cardiotomy reservoir[b,f], a custom non-heparin coated tubing pack[g,h], and an arterial line filter[b,i], which were individually selected according

a Shiley, Inc., Irvine, CA 92714
b Medtronic, Inc., Anaheim, CA 92807
c Terumo, Tokyo 151, Japan
d Cobe Cardiovascular, Inc., Arvada, CO 80004-3599
e 3M Health Care, Ann Arbor, MI 48103
f Bard Cardiopulmonary Division, Billerica, MA 01822
g Gish Biomedical, Inc., Irvine, CA 92714-5821
h Baxter Healthcare Corp., Chicago, IL 60015
i Pall Biomedical, Inc. Fajardo, PR 00648

to patient size. Most cases employed a hemoconcentrator[j]. The prime consisted of Plasmalyte A[k] solution supplemented with sodium bicarbonate and heparin. Diuretics, aprotinin[l], steroids, antibiotics and vasodilators may be included, according to physician protocol. The decision to add homologous red blood cells to the prime was made by calculating post-dilutional hematocrit and relating this value to the severity of the lesion. Hemic prime solutions were used in the majority of neonatal patients, and fresh frozen plasma (FFP) was included as needed to maintain the estimated post-dilutional fibrinogen concentration greater than 100 mg/dL along with maintenance of a post-dilutional colloid oncotic pressure greater than 15 mmHg by the addition of 25% salt-poor albumin.

Bleeding was assessed by measuring the chest tube drainage in each 6 hour period up to 24 hours postoperatively as well as total chest tube drainage. The blood product requirement intraoperatively and postoperatively, days in ICU, rate of reoperation and patient mortality were recorded. All data was obtained from the anesthesia, perfusion, and nursing report sheets.

Data was placed into a spreadsheet[m] and analyzed with a statistical package[n] where descriptive statistics, two sample t-tests, Mann-Whitney, correlation, analysis of covariance, and chi-square tests were performed. A p value of 0.05 or less was considered significant.

RESULTS

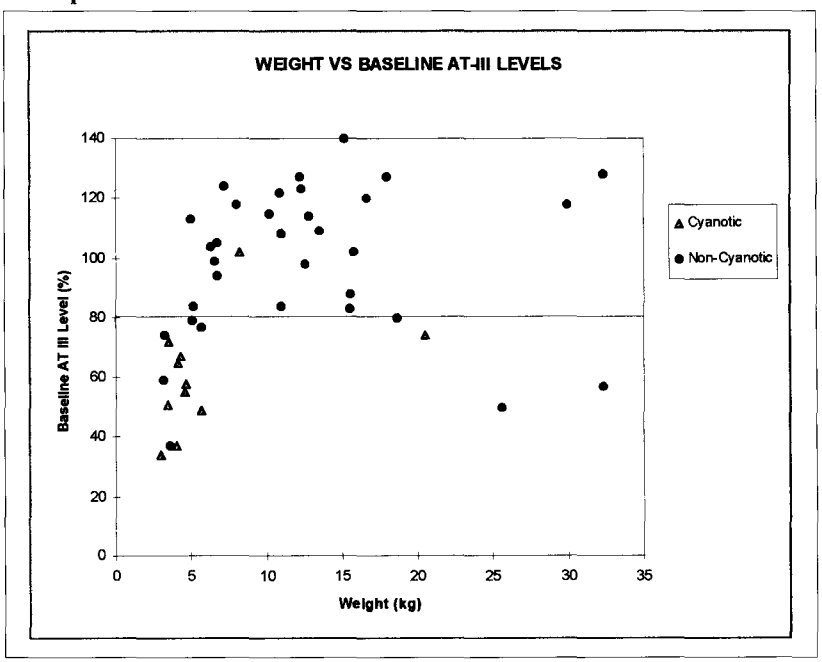
The findings from the comparison of those patients receiving AT-III concentrate (n=31) with those patients not receiving AT-III concentrate (n=118) are summarized in Table 1. The age, weight, and body surface area (BSA) of patients receiving AT-III concentrate tended to be lower than those patients not receiving AT-III concentrate, although no significant differences were seen. Patient sex, a history of a prior sternotomy, and the use of platelet altering medication preoperatively were equally distributed between the two groups (p=NS). Preoperative cyanosis, defined as arterial oxygen saturations less than 85% revealed a highly significant difference between the two groups (p=0.001). Cyanotic patients had a tendency to weigh less and have lower AT-III levels than the non-cyanotic patient (Figure 1).

Each patient's disease process was classified as either a simple or complex congenital lesion. Simple shunts or obstructive lesions were generally classified as simple congenital lesions; the coexistence of a simple shunt and an obstructive lesion was classified as complex. The type of cardiac surgery the patient had was also classified as simple or complex. Patch re-

Table 1: Patient demographics and intraoperative data. All data are mean ± standard deviation. Abbreviations: BSA=body surface area; NS=not significant; AT-III=antithrombin III; CPB=cardiopulmonary bypass; CA=circulatory arrest

	AT-III Concentrate	No AT-III Concentrate	P Value
Demographics	(n=31)	(n=118)	
Age (years)	1.2 ± 2.4	2.1 ± 2.9	0.089
Weight (kg)	7.7 ± 7.5	10.5 ± 9.7	0.088
BSA (m^2)	0.36 ± 0.25	0.45 ± 0.28	0.067
Cyanotic (% of patients)	81%	47%	0.001
Complex Lesion (% of patients)	100%	84%	0.017
Complex Repair (% of patients)	100%	82%	0.011
Prior Sternotomy (% of patients)	29%	19%	NS
Intraoperative			
Dilution (mL)	815 ± 179	847 ± 217	NS
CPB Time (min)	135 ± 42.1	115 ± 50.1	0.031
CA Time (min)	17.5 ± 23.5	8.0 ± 20.4	0.047
Temp (°C)	24.6 ± 4.4	26.4 ± 3.8	0.040

Figure 1: Scattergram of weight and pre-operative AT-III level in cyanotic and non-cyanotic patients



j Minntech Corp., Minneapolis, MN 55447
k Baxter Healthcare Corp., Deefield, IL 60015
l Miles, Inc., West Haven, CT 06516
m Microsoft Corp., Redmond, WA 98052-6399
n Minitab Inc., State College, PA 16801-2756

pairs comprised the simple surgery classification, all others being complex. Significantly, all patients receiving AT-III injectate had a complex congenital lesion (p=0.017) in addition to undergoing complex cardiac surgery (p=0.011) by the same surgeon (p=0.013).

Increased circulatory arrest time (p=0.047) and the amount of time spent on CPB (p=0.031) along with increased AT-III levels on bypass (p=0.0001) were found in the treated group. Conversely, temperatures on CPB (p=0.040) and baseline AT-III levels (p<0.0001) were significantly lower for the AT-III treated group, as illustrated in Table 1. Figure 2 shows the difference in the preoperative and intraoperative AT-III level between the two groups (p<0.0001). No significant differences were discovered in patient hemodilution, the amount of ultrafiltrate or modified ultrafiltrate removed, aprotinin or aminocaproic acid given, and the time cross clamped on bypass between the groups (p=NS).

Table 2 depicts the routine laboratory measurements taken at different time intervals throughout the patient's hospital course. Baseline values were not different between the groups (p=NS).

Prime constituents did not reveal any significant differences with the exception of FFP. More FFP was given to patients who received supplemental AT-III (223±99) than controls (163±121) (p=0.0062). When adjusted for covariates, no significant difference was found between the groups in the amount of blood products administered during CPB, by anesthesia, in the ICU, and total products administered (p=NS). Figure 3 illustrates the amount of blood products given between the two groups. Figure 4 shows blood product administration in a subgroup of patients with preoperative AT-III levels below 80%. Figure 5 shows that AT-III supplemented patients received a greater total number of donor exposures than the non-treated patients. However, when adjusted for relevant covariates, this difference did not prove to be significant.

Chest tube drainage in the treated group was elevated 6 and 12 hours postoperatively. However, the patients who received AT-III had lower total chest tube output than the non-treated group (Table 2). After adjust-

Figure 2: Comparison of preoperative and intraoperative AT-III levels of both the AT-III supplemented group and the non-supplemented group of patients. All data is mean ± standard deviation. * indicates a significant difference (p<0.0001)

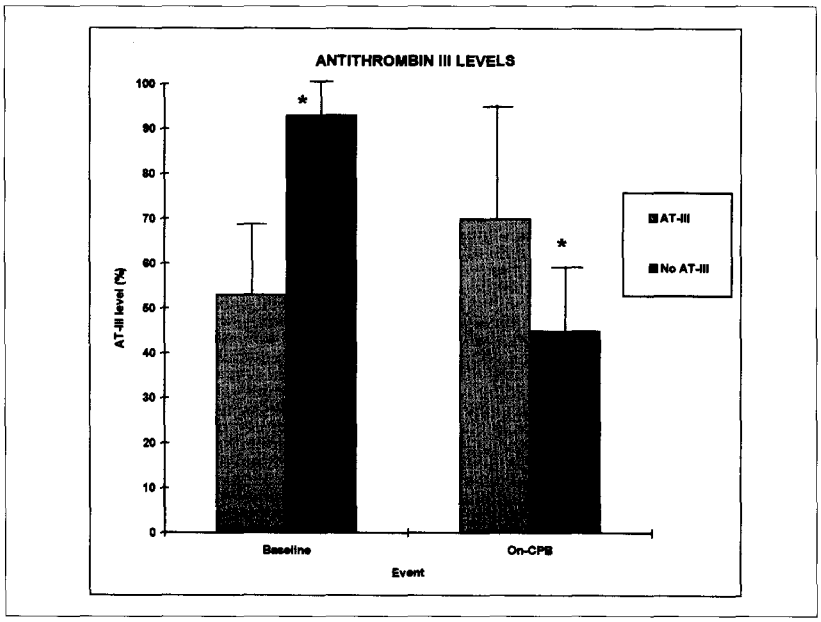


Table 2: Lab measurements and chest tube drainage obtained at various events. All data is shown mean ± standard deviation. * indicates a significant difference between groups (p<0.005). Abbreviations: ICU=intensive care unit; NS=not significant; NA=not applicable

	Time of Measurement						
Measurement Group	Baseline	CPB	ICU	6 hrs ICU	12 hrs ICU	24 hrs ICU	Total
Hematocrit (%)							
AT-III	38 ± 7	37 ± 8	43 ± 8	47 ± 8	46 ± 8	44 ± 7	NA
No AT-III	36 ± 7	33 ± 7	39 ± 8	41 ± 8	41 ± 7	41 ± 7	NA
p Value	NS	0.009	0.019	0.001	0.009	0.0065	NA
Platelets (10^3)							
AT-III	263 ± 117	71 ± 68	206 ± 82*	222 ± 79	221 ± 60	105 ± 41	NA
No AT-III	293 ± 109	63 ± 5	152 ± 73*	208 ± 101	172 ± 69	142 ± 64	NA
p Value	NS	NS	0.002	NS	0.020	NS	NA
Fibrinogen (mg/dL)							
AT-III	205 ± 58	136 ± 49*	186 ± 32	185 ± 40	227 ± 72	112 ± 39	NA
No AT-III	216 ± 43	114 ± 35*	169 ± 61	207 ± 90	191 ± 77	210 ± 24	NA
p Value	NS	0.031	NS	NS	NS	NS	NA
Chest Tube Drainage (mL/kg)							
AT-III				19 ± 23	24 ±27	29 ± 29	53 ± 49
No AT-III				13 ± 18	18 ± 22	26 ± 25	72 ± 116
p Value				NS	NS	NS	NS
Subgroup of Low Preoperative AT-III Patients							
Chest Tube Drainage (mL/kg)							
AT-III				19 ± 24	23 ± 28	27 ± 29	52 ± 52
No AT-III				11 ± 13	18 ± 19	26 ± 27	84 ± 103
p Value				0.033*	0.023*	0.051	NS

ing for covariates, chest tube output did not prove to be significantly different between the groups at any time period (p=NS).

There were no significant differences between groups in the total ICU stay, rate of reoperation, or patient mortality. The AT-III supplemented group remained in the ICU a median of 6 days (3 hrs – 49 days) whereas the control group had a median ICU stay of 5 days (3 hrs – 59 days). Four patients in the treated group went back for reoperation, while 11 patients in the control group went back to the operating room. There were 6 deaths in the AT-III group and 14 deaths in the control group. No deaths were attributed to the use of Antithrombin III injectate.

Figure 3: Comparison of blood product administration per kilogram body weight of the AT-III treated group to control group at each event. All data mean ± standard deviation. Abbreviations: NS=not significant

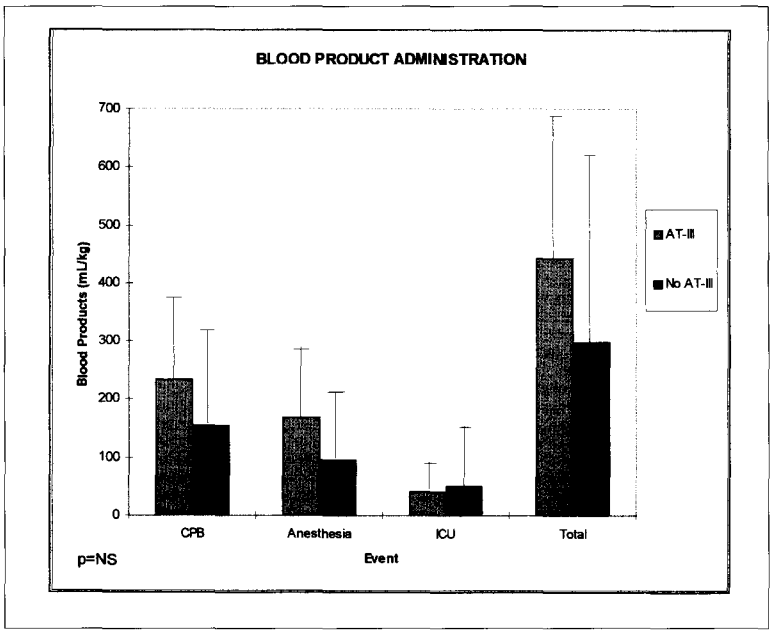
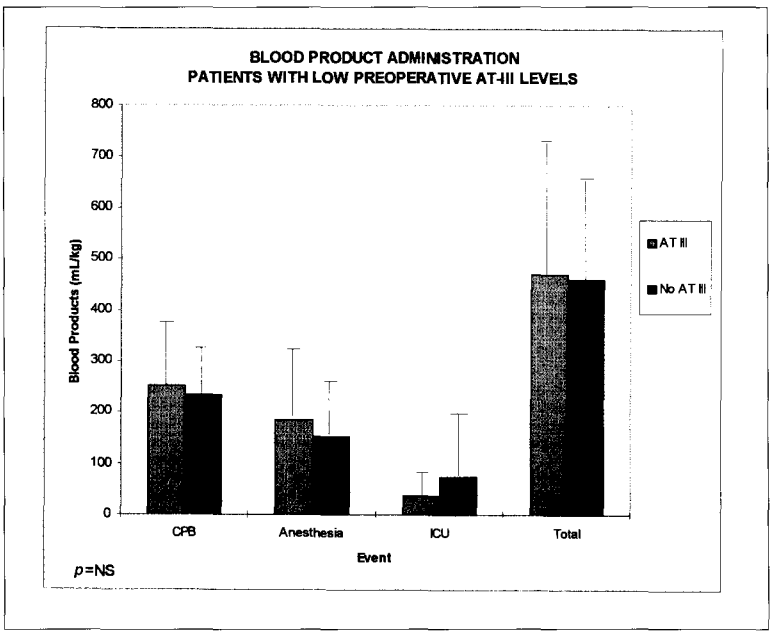


Figure 4: Comparison at each event of blood product administration per kilogram body weight in the subgroup of patients with low preoperative AT-III levels; AT-III supplemented group vs. non-treated group. All data mean ± standard deviation. Abbreviations: NS=not significant



DISCUSSION

The analyses of clinical outcomes are important because of the ability to portray the complete representation of a patient's recovery. A change in a laboratory value may not reflect external variables such as surgeon protocols, blood product and medication administration, or the employment of adjunct procedures. Moreover, risks versus benefits and cost-effectiveness of a procedure may be easier to analyze when scrutinizing the outcome.

Hashimoto and coworkers found that prebypass administration of AT-III to the pediatric patient prevented decreases in serum AT-III levels and elevated FPA levels before and after bypass. Elevated FPA levels are associated with subclinical plasma coagulation, perhaps resulting in increased postoperative blood loss (3). The study by Hashimoto and coworkers did not evaluate whether supplementing AT-III levels affected clinically measurable outcome variables. In this retrospective study of 149 patients, we found no difference in the postoperative chest tube drainage and amount of blood products given in the patients who received the AT-III supplement.

Patients in this study with low preoperative plasma AT-III levels were smaller, more likely cyanotic, and had more complex cardiac lesions than patients with normal AT-III levels. Patients with pre-existing cyanosis have frequently demonstrated decreased plasma factor levels, thrombocytopenia, polycythemia, defective clot retraction, platelet dysfunction, and disseminated intravascular coagulation (DIC) (11). Polycythemia often occurs in conjunction with cyanosis in the attempt to compensate for desaturated hemoglobin (14). It has been postulated that sludging in the microvascu-

lature secondary to the polycythemia promotes generalized coagulation, subsequently consuming clotting factors to the point that functional coagulation is unattainable (14). Moreover, evidence of hemostatic system activation in cyanotic children with congenital heart disease has been reflected by elevated FPA levels (15). Previous studies have shown a correlation between increased hematocrit and fibrin degradation products (16). Therefore, the observation of elevated FPA levels by Hashimoto and coworkers may have been due to cyanosis and DIC, not decreased AT-III levels and decreased heparinization.

Poor microcirculation due to polycythemia has been associated with decreased production of AT-III and other coagulation factors that are produced in the liver. The deficient synthesis of the procoagulants may have resulted from poor organ perfusion and immature hepatic development (17). This may explain why these patients had decreased AT-III levels. We also observed higher mean prothrombin time (PT) and partial thromboplastin time (PTT) in the treated group (p=0.026). This may be attributed to the presence of cyanosis or decreased liver perfusion which may be associated with a reduction in factors that are reflected by these tests. Furthermore, elevated levels of consumption factors have been found in young cyanotic children in whom polycythemia has not yet developed, resulting in a hypercoagulable state which depletes the supply of clotting factors (18). Because cyanosis in the pediatric patient is associated with an altered coagulation system, the physiologic stresses that accompany CPB (exposure of blood to a foreign surface, hemodilution, deep hypothermic temperatures, circulatory arrest) in conjunction with pre-existing coagulation abnormalities contribute to post-CPB bleeding dyscrasias (19,20).

Surgeon protocols for complex cardiac repair at our institution include a higher postoperative hematocrit. When performing statistical analysis, it is important to adjust for the co-variables when evaluating blood and blood products given because of the abundance of confounding variables affecting hemostasis and surgeon variation relative to transfusion trigger points.

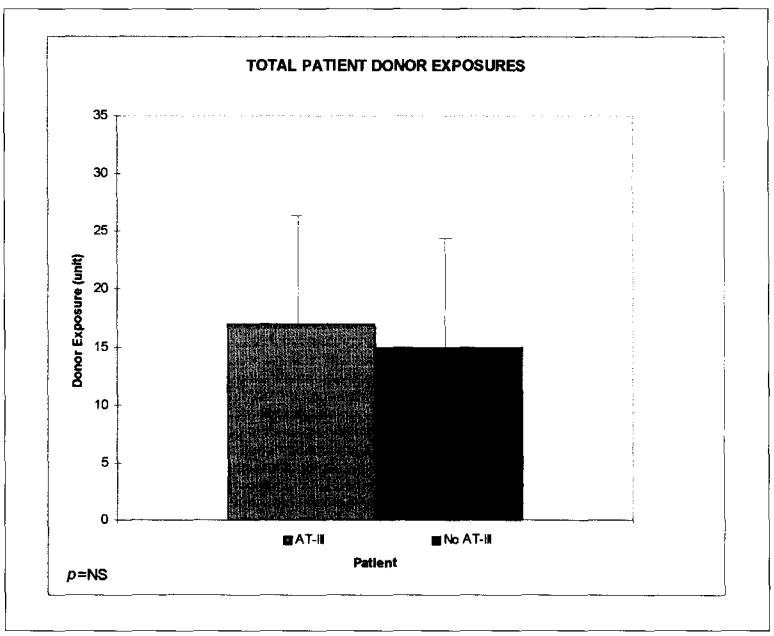
As shown in Figure 3, no significant differences were found between the groups in the amount of blood products administered during bypass, by anesthesia, in the ICU or in the total products given. Surgeon protocols for complex cardiac repair at our institution include a higher postoperative hematocrit, which may reflect the increased blood product administration on bypass in the treated group. Circulatory arrest patients received FFP, cryoprecipitate and platelets from anesthesia, which may account for the elevated blood product administration by anesthesia in the AT-III supplemented patients (p=NS). Chest tube drainage in the treated group was elevated 6 and 12 hours after surgery (Table 2). This group did go on to have a lower total chest tube drainage than the untreated group. However, none of these difficulties proved significant when adjusted for covariates.

We further subdivided and evaluated the efficacy of AT-III by comparing patients with AT-III levels below 80% who received the injectate with those who also had low AT-III levels but did not receive supplementation. This would exclude the effect of the outcome of those patients who had normal AT-III levels on the total average of all patients. No significant difference was found between the subgroups in the amount of blood product administration at any event (Figure 4). Immediate postoperative bleeding was significantly increased in the subgroup of patients who received AT-III, as reflected by the 6 and 12 hour chest tube drainage (Table 2). Total chest tube drainage was lower, but not significantly different (p=NS).

The retrospective nature of this study imposes certain limitations on the interpretation of our findings; in particular, incomplete data recording at the time of patient care. We did not measure intraoperative bleeding which may have changed the outcomes reflected in this study. If we had looked at FPA levels in this study, we may have found lower levels than Hashimoto and coworkers saw because we run higher heparin concentrations (3.5 u/ml) on bypass than they do (1.3–1.8 u/ml) to maintain the activated clotting times (ACT).

In conclusion, AT-III concentrate has been shown to raise the circulating AT-III plasma level during CPB. We found no difference in postoperative chest tube drainage and amount of blood products given in the patients who received the AT-III

Figure 5: Comparison of the total number of patient donor exposures received associated with the current surgery between the AT-III treated group and the non-treated group. All data mean ± standard deviation. Abbreviations NS=not significant



supplement. Therefore, there appears to be no clinical benefit in giving supplemental AT-III in the effort to raise a clinically low plasma concentration in pediatric patients undergoing cardiac surgery.

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