Original Article

Antithrombin III in Cardiac Surgery: An Outcome Study

James C. Conley, BS, CCP; Patrick F. Plunkett, PhD

Maine Medical Center, Portland, Maine, and Northeastern University, Boston, Massachusetts

Keywords: cardiopulmonary bypass, antithrombin III, patient outcome, heparin resistance

Presented at the American Society of Extra-Corporeal Technology 36th International Conference, March 12-14, 1998, Philadelphia, Pennsylvania

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 post-operative 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.

Address correspondence to:
James Conley, BS, CCP
Maine Medical Center
22 Bramhall Street
Portland, ME 04102

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 Unpublished raw data, National Center for Health Statistics, Hyattsville, MD. 1997).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.

Table 1: Anthropomorphic, Perioperative, and CPB Variables Collected

Age	Diabetic	Pump Time
BSA	Pre-Op IV Heparin	Lowest N/P Temp.
Height	Pre-Op IV Nitroglycerine	Total Protamine Given
Weight	Pre-Op Aspirin	Heparin Loading Dose
Gender	Cell Saver Volume	Total Heparin Given
Pre-Operative Hct	Last CPB Hct	Time CPB Initiated
Pre-Operative Platelets	Lowest ACT	Time ATIII Administered

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.

Table 3. Anthropomorphic, Perioperative, and CPB Variables

Variable	Group 1	Group 2	Group 3	P-value
Number of patients (n)	110	101	99	
Age (years)	64.84 ± 9.85	64.99 ± 9.87	67.70 ± 10.51	NS
BSA (m^2)	1.94 ± .20	1.97 ± .16	1.92 ± .19	2>3
Height (cm)	170.2 ± 10	169.7 ± 9	167.6 ± 10	1>3
Weight (kg)	81.9 ± 14	86.1 ± 13	82.7 ± 13.5	2>1
Gender (male/female)	85/25	67/34	72/27	NS
Preoperative Hct (%)	39.2 ± 3.9	39.3 ± 4.1	40.6 ± 4.4	3>1,2
Preoperative Platelets (10^3)	224 ± 68	237 ± 61	228 ± 65	NS
Diabetic (yes/no)	33/73	40/60	28/71	NS
Preoperative I.V. Heparin (yes/no)	67/43	84/17	29/70	1-2 SIG 1-3 SIG 2-3 SIG
Preoperative I.V. Nitroglycerine (yes/no)	18/92	28/73	6/93	1-2 SIG 1-3 SIG 2-3 SIG
Pre-Op Aspirin (yes/no)	35/73	34/53	34/53	NS
Cell Saver Volume (ml)	645 ± 201	718 ± 233	674 ± 185	NS
Last CPB Hct (%)	24.6 ± 3.2	24.7 ± 3.4	24.3 ± 3.6	NS
Lowest ACT (sec)	398 ± 42	385 ± 42	451 ± 68	3>1,2
Cardiopulmonary Artery Bypass Time (min)	96 ± 27	106 ± 29	88 ± 23	1>3 2>3,1
Lowest NP Temp (C°)	34 ± 1	34 ± 1	34 ± 1	NS
Total Protamine Dose (mg)	340 ± 75	384 ± 92	280 ± 80	1>3 2>3,1
Heparin Loading Dose (mg)	32 ± 7.9	36.3 ± 8.5	26.6 ± 6.5	1>3 2>3,1
Total Heparin given (mg)	54 ± 12	59 ± 11	32 ± 8	1>3 2>3,1

Data are mean ± SD. NS = not significant. Group 1 = Heparin resistant treated with Heparin. Group 2 = Heparin resistant treated with ATIII. Group 3 = Non heparin resistant control group.

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.

Table 4: Outcome Variables

Variable	Group 1	Group 2	Group 3	P-value
Number of patients (n)	110	101	99	
24 Hour CTD (ml)	783 ± 361	769 ± 567	767 ± 408	NS
Reoperation For Bleeding (yes/no)	0/110	5/95	0/99	1-2 SIG 2-3 SIG
Post-Op Coagulopathy (yes/no)	0/110	6/95	0/99	1-2 SIG 2-3 SIG
ICU LOS (hours)	22 ± 8	23 ± 9	22 ± 8	NS
PRBCs transfused (units)	1.19 ± 1.94	1.53 ± 2.70	.88 ±1.36	2>3
Total FFP transfused (units)	.18 ± .87	.32 ± 1.22	.09 ± .45	NS
Total Cryoprecipitate transfused (units)	0	.51 ± 2.68	.20 ± 1.41	2>1
Total Platelets transfused (units)	.49 ± 1.89	1.16 ± 3.49	.49 ± 2.12	NS

Data are mean ± SD.NS = not significant. SIG = significant. CTD = chest tube drainage. ICU LOS = Intensive Care Unit length of stay. PRBC's = packed red blood cells. FFP = fresh frozen plasma. Cryo = cryoprecipitate.

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

Outcome Variables	Group 1	Group 201	Group 211	Group 200	Group 210	Group 3	Significance
Number of patients (n)	110	40	41	12	8	99	
24 Hour CTD (ml)	782.7 ± 360.9	873.8 ± 681.8	776.9 ± 534.2	621.3 ± 278.3	419.3 ± 72.9	766.7 ± 407.6	1,201,3,211> 210
Reop Bleeding (yes/no)	0	2/40	3/41	0	0	0	NS
Post-Op Coagulopathy (yes/no)	0	3/40	3/41	0	0	0	NS
ICU LOS (hours)	22.2 ± 7.7	21.4 ± 5.2	26.1 ± 11.2	19.9 ± 4.5	22.5 ± 12.7	22.3 ± 7.9	211> 1,201,3
PRBCs (units)	1.19 ± 1.94	1.42 ± 2.78	1.51 ± 2.86	2.5 ± 2.65	.75 ± 1.04	.88 ± 1.36	200> 1,3
FFP (units)	.18 ± .86	.45 ± 1.5	.29 ± 1.14	.17 ± .58	0	.09 ± .45	201>3
Cryo (units)	0	.3 ± 1.89	.98 ± 3.74	0	0	.2 ± 1.41	211>1,3
Platelets (units)	.49 ± 1.89	1.5 ± 4.1	.8 ± 2.9	2.2 ± 4	0	.49 ± 2.1	201,200>1,3

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 twenty 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 use; but also, the time at which ATIII was delivered. The results are listed in Table 5.

The subset of Group 2 patients, who received aminocaproic acid and early ATIII, had the lowest 24-hour CTD of any group. This group's CTD was statistically significantly lower than all other groups except group 2 patients who did not receive aminocaproic acid but received early AT III. This group had the second lowest 24-hour CTD. Three of the 40 patients who received no aminocaproic acid and late ATIII developed a postoperative coagulopathy and required re-exploration for bleeding. Also, three of the 41 patients who received aminocaproic acid and late ATIII developed a coagulopathy and required re-exploration for bleeding. None of the Group 1, Group 3 or early ATIII Group 2 patients developed a coagulopathy or required re-exploration for bleeding. Group 2 patients who received aminocaproic acid and late ATIII had SCU LOS which were significantly longer than Group 2 patients who did not receive aminocaproic acid, but received ATIII early, Group 1 and the control patients. The Group 2 patients who did not receive aminocaproic acid, but received early ATIII 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 ATIII required significantly more FFP and platelets than the control group or Group 1. The Group 2 patients who received aminocaproic acid and late ATIII 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 alone was 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 subpopulation of Group 2. These findings support the notion that administration of ATIII 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 ATIII 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 ATIII 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

1. Society of Thoracic Surgeons National Cardiac Surgery Database -Incidence of complications summary first-op CAB only patients [Electronic database]. Chicago, IL: Society of Thoracic Surgeons [Producer and Distributor]. 1996.
2. Fedoruk, L.M., Stewart, K.M., Hayden, R.I. 1993. The cardiac surgery program at Royal Columbian Hospital: Review of the first fiscal year. Can J Surg. 1993; 36:541-545.
3. Magovern, G.J. Sr., Magovern G.J. Jr. A model for predicting transfusion after coronary artery surgery grafting. Ann Thorac Surg.1996; 61: 27-32.
4. Lacritz, E.M., Satten, G.A., Aberle-Grasse, J., Dodd, R.Y., Raimond, V.P., Janssen, R.S., Lewis, W. F., Notari, E.P., Petersen, L.R.. Estimated risk of transmission of the human immunodeficiency virus by screened blood in the United States. N Engl J Med. 1995; 333: 1721-1725.
5. Shahian, D.M., Weiner, N.J., Kurtz, S.R. Anti JKb delayed hemolytic transfusion reactions after cardiopulmonary bypass. Panminerva Med. 1995; 37: 95-97
6. Vamvakas, E.C., Moore, S. B. Blood transfusion and postoperative septic complications. Transfusion,1994; 34: 714-727.
7. Harker, L.F. Bleeding after cardiopulmonary bypass. N Engl J of Med. 1986; 314: 1446-1448.
8. Zilla, P., Fasol, R., Groscurth, P., Klepetko, W., Reichenspunuer, H., Wolner, E. Blood platelets in cardiopulmonary bypass operations. J Thorac Cardiovasc Surg. 1989; 97: 379-388.
9. Campbell, F.W. The contribution of platelet dysfunction to postbypass bleeding. J Cardiothorac Vasc Anes. 1991; 5 (Suppl 1): 8-12.
10. Wenger, R.K., Lukasiewicz, H., Mikuta, B.S., Niewiarowski, S., Edmunds, L.H. Loss of platelet fibrinogen receptors during clinical cardioplmonary bypass. J Thorac Cardiovasc Surg. 1989; 97: 235-239.
11. Øvrum, E., Åm Holen E., Tangen, G., Broosstad, F., Abdelnoor, M., Ringdal, M.L., Øystese, R., Istad, R. Completely heparinized cardiopulmonary bypass and reduced systemic heparin: Clinical and hemostatic effects. Ann Thorac Surg. 1995; 60:365-71.
12. van Oeveren, W., Eijsman, L., Roozendaal, K.J., Wildevuur, Ch.R.H. Platelet preservation by aprotinin during cardiopulmonary bypass. Lancet. 1988; 1: 644.
13. Michelson, A.D., Barnard, M.R. Plasmin-induced redistribution of platelet glycoprotein Ib. Blood. 1990; 76: 2005-2010.
14. Cramer, E., Lu, H., Caen, J., Soria, C., Berndt,M. & Tenza, D. Differential redistribution of platelet glycoproteins Ib and Iib-IIIa after plasmin stimulation. Blood.1991; 70: 694-699.
15. Colman, R,W., Marder V.J., Salzman, E.W., Hirsh, J. Overview of hemostasis. In: R.E. Colman, J. Hirsh, V.J. Marder & E.W. Salzman, eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice. Philadelphia, PA: J.B. Lippincott; 1994; 3-18.
16. Silverberg, M., Reddigari, S.R., Kaplan, A.P. . The contact system and its disorders. In: R.I. Handin, S.E. Lux, T.P. Stossel, eds. Blood: Principles and Practice of Hematology. Philadelphia, PA: J.B. Lippincott; 1995; 1140.
17. Boisclair, M.D., Land, D.A., Philippou, H., Esnouf, P., Sheikh, S., Hum, B., & Smith, J. Mechanisms of thrombin generation during surgery and cardiopulmonary bypass. Blood. 1993; 82: 3350-3357.
18. Burman, J.F., Chung, I.P., Lane, D.A., Philippou, H., Adami, A. Role of factor XII in thrombin generation and fibrinolysis during cardiopulmonary bypass. Lancet. 1994; 344: 1192-1193.
19. Heck, H.A., Lutcher, C.L., Falls, D.G. Fatal thrombocytopenic coagulopathy after cardiopulmonary bypass: Clinicopathologic correlations after cardiopulmonary bypass. South Med J. 1994; 87: 789-793.
20. Khuri, S.F., Wolfe, J.A., Josa, M., et al. Hematologic changes during and after cardiopulmonary bypass and their relationship to the bleeding time and nonsurgical blood loss.

J Thorac Cardiovasc Surg. 1992; 104: 94-107.
21. Ogston, D., Murray, K., Crawford, G.P, M. Inhibition of the activated C1s subunit of the first component of complement by antithrombin III in the presence of heparin. Thromb Res.1976; 9: 217-222.
22. Rosenberg, JS., McKenna, P.W., Rosenberg, R.D. Inhibition of human factor IXa by human antithrombin. J Biol Chem.1975; 251: 8883-8888.
23. Stead, N., Kaplan, A.P., Rosenberg, R.D. Inhibition of activated factor XII by antithrombin-heparin cofactor. J Biol Chem.1976; 251: 6481-6488.
24. Venner(d, A.M., Laake, L., Solberg, A.K. Inactivation and binding of human plasma kallikrein by antithrombin III. Thromb Res.1976; 9: 457-466.
25. Cosgriff, T.M., Bishop, D.T., Hershgold, E.J. Familial antithrombin III deficiency: Its natural history, genetics, diagnosis and treatment. Medicine. 1983; 62:209-220.
26. Irani, M.S. Antithrombin concentrates in heparin-resistant cardiopulmonary bypass patients. Clin Appl Thromb Hemost. 1996; 2: 103-106.
27. Zajtchuk, R., Collins, G.J., Schuchmann, G.F., Holley, P.W., Hamaker, W.R. Coagulation abnormalities in patients undergoing myocardial revascularization. J Thorac Cardiovasc Surg. 1978; 75: 168-170.
28. Utley, J.R. Pathophysiology of cardiopulmonary bypass: Current issues. J Card Surg. 1990; 5: 177-189.
29. Cloyd, G.M., D'Ambra, M.N., Akins, C.W. Diminished anticoagulant response to heparin in patients undergoing coronary artery bypass grafting. J. Thorac Cardiovasc Surg. 1987; 94: 535-538.
30. Hashimoto, K., Yamagishi, M., Sasaki, T., Nakano, M., Kurosawa, H. Heparin and antithrombin III levels during cardiopulmonary bypass: Correlation with subclinical plasma coagulation. Ann Thorac Surg. 1994; 58: 799-805.
31. Dietrich, W., Spannagl, M., Schramm, W., Vogt, W., Barankay, A., Richter, J.A. The influence of preoperative anticoagulation on heparin response during cardiopulmonary bypass. J Thorac Cardiovasc Surg. 1991;102: 505-514.
32. Friedenberg, W.R., Myers, W.O., Plotka, E.D. Platelet dysfunction associated with cardiopulmonary bypass. Ann Thorac Surg. 1978; 25: 298-305.
33. Moriau, M., Masure, R., Hurlet, A. Haemostasis disorders in open heart surgery with extracorporeal circulation. Vox Sanguinis. 1977; 32: 41-51.
34 Woodman, R.C., & Harker, L.A. Bleeding complications associated with cardiopulmonary bypass. Blood. 1990; 76: 1680-1697.