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Should the postoperative ACT value be higher or lower than the preoperative value in cardiac surgery?

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ABSTRACT

Aims: The aim of this study was to compare the activated clotting time (ACT) values after heparin neutralization with the values before heparin in patients undergoing cardiac surgery and to investigate the relationship with postoperative outcomes.

Methods: Between 2022 and 2023, a total of 726 patients (518 males; mean age 58.2±11.5 years) who underwent cardiac surgery were evaluated. The patients were initially divided into two groups. Group A (n=401): Patients whose ACT values before heparinization were lower than the ACT values after neutralization, and group B (n=325): Patients whose ACT values before heparinization were equal to or higher than the ACT values after neutralization.

Results: There were no differences between the groups in terms of bleeding amount and blood product use. However, the need for postoperative exploration and subxiphoid decompression was higher in group B than in group A (p=0.001 and p=0.008, respectively). Hospital stay did not differ between the groups. Intubation time and intensive care unit stay were longer in group B compared to group A (p=0.003 and p=0.04, respectively). Additionally, the mortality rate was higher in group B than in group A (p=0.02).

Conclusion: In cardiac surgery, we found no difference in bleeding amounts and blood product use between patients with post-neutralization ACT values higher than pre-heparin ACT values and those with lower ACT values. However, we observed higher postoperative exploration and mortality rates, as well as longer intubation times.

Keywords: Activated clotting time, heparin, protamine sulfate, cardiac surgery, bleeding

INTRODUCTION

Cardiopulmonary bypass (CPB), first designed by John Gibbon in 1953, has enabled many cardiac operations to be performed successfully.[1] To use CPB, anticoagulation is often achieved using heparin, which is then neutralized with protamine sulfate. The anticoagulant activity of heparin is monitored using activated clotting time (ACT). Recommended ACT values range between 300 and 600 seconds, depending on the ACT measurement method.[2]

Bleeding and subsequent postoperative exploration after cardiac surgery are among the most important causes of morbidity and mortality. The overall incidence of exploration due to bleeding ranges between 2.3% and 6%.[3] One of the most important causes of bleeding is coagulopathy. Therefore, preoperative and postoperative ACT values are important in terms of bleeding. The appropriate protamine dose for heparin neutralization is a topic of debate. It is suggested that protamine should be given at a 1:1 ratio with heparin to minimize bleeding, and that this ratio should not be exceeded initially to avoid potential protamine overdose and increased perioperative bleeding.[2] In a prospective study by Taneja et al.,[4] it was reported that a protamine:heparin ratio of 0.3 was sufficient for some patients to neutralize heparin, while a ratio of 0.5 was sufficient for most patients. It is also controversial what the ACT value should be after neutralization with protamine. In the study by Yamamoto et al.,[5] it was shown that there was no residual heparin in the blood after 1:1 protamine, but ACT values were longer, and clotting factors were lower. In the study by Wang et al.,[6] it was reported that postoperative ACT values shortened operative time, decreased bleeding, and reduced need for blood transfusion.

There are not enough studies to make a definitive decision on comparing the ACT values after neutralization with protamine with the ACT values before heparinization. The aim of this study was to compare the ACT values after heparin neutralization with the values before heparin in patients undergoing cardiac surgery and to investigate the relationship with postoperative outcomes.

METHODS

This study has been approved by the Clinical Researches Ethics Committee of Başakşehir Çam and Sakura City Hospital (Date: 23.10.2023, Decision No: 2023-443). All

procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a retrospective single-center observational study with a total of 726 patients. All patients over the age of 18 who underwent cardiac surgery at the Cardiovascular Surgery Clinic of Başakşehir Çam and Sakura City Hospital between February 2022 and July 2023 were included in the study. Patients who underwent surgery due to aortic dissection and those who used extracorporeal membrane oxygenation or intraaortic balloon pumps in the perioperative period were excluded from the study. The patients were first divided into two groups. Group A (n=401): Patients whose ACT values before heparinization were lower than the ACT values after neutralization, and group B (n=325): Patients whose ACT values before heparinization were equal to or higher than the ACT values after neutralization.

All patients' basic demographic characteristics, medical history, preoperative and first-week postoperative laboratory parameters, surgical procedure details, and postoperative complications (postoperative exploration, subxiphoid decompression, cerebrovascular accident (CVA), continuous renal replacement therapy (CRRT), postoperative atrial fibrillation (POAF), deep sternal wound infection (DSWI), intubation time, intensive care unit stay, hospital stay and mortality) were recorded by reviewing their medical records. Then, preoperative and perioperative data and postoperative complications were compared between the groups. Afterward, patients who received dual antiplatelet therapy in the preoperative period were excluded from both groups. Subgroups were obtained as group C (n=325) and group D (n=269), respectively. In the second stage, group C and group D were compared in terms of postoperative parameters.

In our clinic, all patients who have undergone CABG are taken into surgery without stopping acetylsalicylic acid. For patients who have recently undergone percutaneous intervention, the decision of whether or not dual antiplatelet therapy will be continued is made by the primary surgeon, depending on the status of coronary artery lesions. Intravenous heparin (Poliparin, Polifarma, İstanbul, Turkiye) is administered to all patients who underwent cardiac surgery using CPB at a dose of 3 mg/kg to reach the target value of 480 sec ACT before starting CPB. ACT values are tested with Hemochron® Signature Elite (International Technidyne Corporation, Edison, NJ, USA). Preoperative ACT is tested after anesthesia induction. Following heparin administration, control ACT values are checked 3 minutes later, and then control values are checked every 30 minutes during CPB. Additional doses of heparin are administered when necessary. Protamine sulfate (Promin, Vem, Turkiye) is used for neutralization at a ratio of 1:1. After protamine, the ACT value is checked 5 minutes later. In patients with serious bleeding diathesis, if the ACT values are higher than the pre-heparin value after neutralization, additional protamine is administered.

Statistical Analysis

Data were analyzed by using SPSS software version 27.0 (IBM, USA). Continuous variables in the study were presented as minimum, maximum, median, and interquartile range. Categorical variables were expressed as numbers and percentages. The normality of distribution was assessed by the Kolmogorov–Smirnov test. For numerical variables, differences between patients and controls were tested using t test for parametric data or the Mann–Whitney U test for non-parametric data. Categorical variables were analyzed using the Pearson $\chi 2$ test and Fisher's exact test. The level of statistical significance was set at $p<0.05$.

RESULTS

The comparison of patient demographics, comorbidities, and laboratory parameters between group A and group B is presented in **Table 1**. The mean age was 58.2±11.5 years and 518 (71.3%) of the patients were male. The mean follow-up period was 245±126 days, (median: 279, 0–535 days). There were no significant differences between groups A and B in terms of basic demographic characteristics, except for the median age values, which were higher in group B (p=0.03). Comorbidities showed no difference between the two groups. Additionally, there were no significant differences between group A and group B in terms of preoperative and postoperative 1st-week laboratory parameters, except for the median preoperative and postoperative creatinine values, which were higher in group B than in group A (p<0.001 and p=0.004, respectively).

The comparison of operative data between group A and group B is presented in **Table 2**. No differences were found between the groups in terms of emergency operation rates and types of operations performed. Similarly, no differences were found between the groups in terms of cross-clamp (XCL) times and CPB times.

A comparison of blood product, bleeding data, and medication data between Group A and Group B is presented in **Table 3**. No differences were found between the groups in terms of intraoperative red blood cells (RBCs), fresh frozen plasma (FFP), and platelet suspension. Similarly, no differences were found in terms of postoperative RBCs and platelet suspension. Only in group B, postoperative FFP usage was more common than in group A (p=0.01). No difference was found between the groups in terms of postoperative bleeding amounts. The rates of being operated on under dual antiplatelet therapy were higher in group B than in group A (p=0.01). Preoperative and postoperative acetylsalicylic acid use, postoperative oral anticoagulant use, and postoperative dual antiplatelet use were also similar between the groups. Preoperative median ACT values of group A were higher than in group B (150 sec and 124 sec, respectively, p<0.001). After the operation, the median ACT values of group A were lower than group B (123 sec and 143 sec, respectively, p<0.001). No difference was found between group A and group B in terms of heparin, protamine sulfate, and fibrinogen doses used during the operation. Higher doses of tranexamic acid were used in group B compared to group A (p=0.03).

The comparison of postoperative data between group A and group B is presented in **Table 4**. There was no difference between the groups in terms of the incidence of CVA, CRRT, POAF, and DSWI. The need for postoperative exploration and subxiphoid decompression was higher in group B than in group A (46 (%14.2) vs. 27 (%6.7), p=0.001 and 8 (%2.5)

Table 1. Comparison of patient demographics, comorbidities, and laboratory parameters between group A and group B

	Group A (n=401)			Group B (n=325)			
	Min-max or n (%)	Median	IQR	Min-max or n (%)	Median	IQR	p
Demographic data							
Gender male	298 (74.3)			220 (67.7)			0.05
Age (years)	19-86	59	14	18-90	60	14	0.03
Height (cm)	142-196	169	54	140-190	169	12	0.33
Weight (kg)	42-130	78	20	39-150	80	19	0.39
Body surface area (kg/m^2)	1.33-2.42	1.89	0.24	1.22-2.6	1.89	0.23	0.90
Body-mass index (m^2)	15.9-55.6	27.6	6.6	15.6-46.2	27.8	6.4	0.04
Comorbid diseases							
Diabetes mellitus	159 (39.7)			126 (38.8)			0.80
Hypertension	199 (49.6)			170 (52.3)			0.47
Chronic obstructive pulmonary disease	36 (9)			31 (9.5)			0.79
Cerebrovascular accident	29 (7.2)			33 (10.2)			0.16
Chronic renal failure	15 (3.7)			19 (5.8)			0.18
Malignancy	20 (5)			14 (4.3)			0.66
Ejection fraction (%)	22-65	60	10	15-65	55	10	0.39
Preop atrial fibrillation	30 (7.5)			29 (8.9)			0.48
Preop laboratory parameters							
White blood cells (10^9/L)	1.9-19.9	8.1	3	3.5-92	8.1	3	0.74
Hematocrit (%)	22-51.9	40.6	6.8	20.5-58.7	40	7.8	0.44
Platelets (10^9/L)	63-563	235	87	59-688	250	102.5	0.39
Urea (mg/dl)	7.8-272	33.4	15.9	13.8-138	35.2	18.5	0.01
Creatinine (mg/dl)	0.07-10.9	0.90	0.27	0.48-5.4	0.96	0.3	<0.001
Sodium (mEq/L)	122-147	139	4	120-149	139	4	0.74
Potassium (mEq/L)	2.2-5.9	4.3	0.56	3.2-5.8	4.4	0.59	0.29
Alanine aminotransferase (IU/L)	1-301	18	13	3-338	18	12	0.85
Aspartate aminotransferase (IU/L)	4-431	20	10	9-321	20	10.5	0.87
C-reactive protein (mg/dl)	0.2-195	3.8	7.5	1-162	3.7	9.2	0.79
Hba1c (mmol/mol)	2.9-13.5	6	1.5	4.4-14.3	5.9	1.3	0.057
Postop laboratory parameters							
White blood cells (10^9/L)	4.6-44.2	16.1	8.3	5.2-72	16	8.7	0.99
Hematocrit (%)	12.9-46.5	28.7	5.7	14-47.1	28.5	5.8	0.56
Platelets (10^9/L)	32.9-480	169	79.5	48-496	175	86	0.36
Urea (mg/dl)	13.5-200	41.3	18	14.5-129	41.3	18.9	0.68
Creatinine (mg/dl)	0.08-7.8	1.18	0.42	0.49-6.1	1.24	0.49	0.004
Sodium (mEq/L)	126-163	142	4	133-163	142	4	0.42
Potassium (mEq/L)	2.9-8.9	4.2	0.59	2.6-5.7	4.1	0.78	0.13
Alanine aminotransferase (IU/L)	4-302	23	18	2-850	22	17	0.58
Aspartate aminotransferase (IU/L)	13-912	59	41.5	8-2512	61	45	0.87
C-reactive protein (mg/dl)	2.9-315	38.4	28.3	4.6-276	36.4	25.7	0.13

Min: Minimum, Max: Maximum, IQR: Interquartile range

vs. 1 (%0.2), p=0.008, respectively). There was no difference between the groups in terms of hospital stay. However, the intubation time and intensive care unit (ICU) stay were longer in group B than in group A (median 12 hours vs. 10 hours, p=0.003, 3 days, and 2 days, p=0.04, respectively). The mortality rate was higher in group B than in group A (32 (9.8%) and 22 (5.5%), respectively, p=0.02).

After excluding patients who underwent surgery without stopping dual antiplatelet drugs, the remaining patients in both groups were compared based on postoperative data, as presented in **Table 5**. There were no differences between group C and group D in terms of CVA, POAF, DSWI, ICU stay, and hospital stay. However, the need for postoperative exploration and subxiphoid decompression was higher in group D compared to group C (36 (13.4%) vs. 22 (6.8%), respectively, p=0.007, and 7 (2.6%) vs. 1 (0.3%), p=0.01). Additionally, intubation time and mortality rate were longer in group D than in group C (p=0.004 and p=0.04, respectively).

Table 2. Comparison of operative data between group A and group B

	Group A (n=401)			Group B (n=325)			
	Min-max or n (%)	Median	IQR	Min-max or n (%)	Median	IQR	p
Emergency surgery	18 (4.5)			16 (4.9)			0.78
Infective endocarditis	16 (4)			11 (3.4)			0.66
Thoracic surgery	26 (6.5)			28 (8.6)			0.27
Aortic valve replacement	77 (19.2)			65 (20)			0.78
Aortic root enlargement	3 (0.7)			4 (1.2)			0.38
Mitral valve replacement	65 (16.2)			57 (17.5)			0.63
Mitral ring annuloplasty	11 (2.7)			10 (3.1)			0.79
Tricuspid valve replacement	8 (2)			8 (2.5)			0.67
Tricuspid ring annuloplasty	22 (5.5)			18 (5.5)			0.97
Pulmonary valve replacement	3 (0.7)			0			0.16
Ablation	13 (3.2)			9 (2.7)			0.71
Atrial septal defect	23 (5.7)			14 (4.3)			0.38
Morrow	0			3 (0.9)			0.08
Coronary artery bypass graft	269 (67.1)			211 (64.9)			0.54
Beating heart	14 (3.5)			17 (5.2)			0.24
Endarterectomy	12 (3)			7 (2.2)			0.48
The number of grafts	0-7	2	3	0-5	2	3	0.44
Left ventricular assist device	2 (0.5)			4 (1.2)			0.25
Commando procedure	1 (0.2)			1 (0.3)			0.69
Redo	28 (7)			18 (5.5)			0.42
Cross-clamp time (minute)	0-321	87	64	0-323	90	66	0.48
Cardiopulmonary bypass time (minute)	0-444	135	64	0-515	136	71	0.39

Min: Minimum, Max: Maximum, IQR: Interquartile range

Table 3. Comparison of blood product, bleeding data and medication data between group A and group B

	Group A (n=401)			Group B (n=325)			
	Min-max or n (%)	Median	IQR	Min-max or n (%)	Median	IQR	p
Blood product and bleeding data							
Intraop RBC using	0-10	0	2	0-7	0	2	0.38
Intraop FFP using	0-4	0	0	0-4	0	0	0.33
Intraop platelet suspensions	0-6	0	0	0-6	0	0	0.16
Postop RBC using	0-13	0	1	0-24	0	2	0.055
Postop FFP using	0-12	0	1	0-9	0	2	0.01
Postop platelet suspensions	0-5	0	0	0-9	0	0	0.06
Postop 1st day amount of bleeding (ml)	50-4200	400	290	50-3000	400	300	0.37
Postop 2nd day amount of bleeding (ml)	0-1700	250	240	0-2200	250	250	0.75
Preop medication data							
Preop acetylsalicylic acid	288 (71.8)			226 (69.5)			0.50
Operation without stopping dual antiplatelet therapy	5 (1.2)			14 (4.3)			0.01
Postop oral anticoagulant	143 (35.6)			130 (40)			0.23
Postop acetylsalicylic acid	299 (74.5)			246 (75.6)			0.72
Postop dual antiplatelet	199 (49.6)			143 (44)			0.13
Intraop medication data							
Preop ACT (second)	101-357	150	36	56-201	124	25	<0.001
Dose of heparin administered (IU)	5000-50000	30000	5000	5000-65000	30000	5000	0.40
Dose of protamine administered (IU)	0-50000	30000	5000	0-60000	30000	5000	0.44
ACT after protamine (second)	57-228	123	23	89-339	143	29	<0.001
Dose of tranexamic acid (mg)	0-3000	1000	1500	0-6000	1000	1500	0.03
Dose of fibrinogen concentrate (mg)	0-4000	0	1000	0-4000	0	1000	0.56

Min: Minimum, Max: Maximum, IQR: Interquartile range, ACT: Activated clotting time, RBC: Red blood cells, FFP: Fresh frozen plasma, Intraop: Intraoperative, Postop: Postoperative, Preop: Preoperative

Table 4. Comparison of postoperative data between group A and group B

	Group A (n=401)			Group B (n=325)			
	Min-max or n (%)	Median	IQR	Min-max or n (%)	Median	IQR	p
Postop exploration	27 (6.7)			46 (14.2)			0.001
Subxiphoid decompression	1 (0.2)			8 (2.5)			0.008
Cerebrovascular accident	8 (2)			3 (0.9)			0.19
Continuous renal replacement therapy	20 (5)			9 (2.8)			0.12
Postop atrial fibrillation	92 (22.9)			82 (25.2)			0.47
Deep sternal wound infection	8 (2)			12 (3.7)			0.16
Intubation time (hour)	1-1145	10	8	2-672	12	8	0.003
Intensive care unit stay (days)	1-120	2	1	1-28	3	2	0.04
Hospital stay (days)	1-124	7	4	1-111	7	5	0.38
Mortality	22 (5.5)			32 (9.8)			0.02

Min: Minimum, Max: Maximum, IQR: Interquartile range

Table 5. Comparison of postoperative data between group C and group D

	Group C (n=325)			Group D (n=269)			
	Min-max or n (%)	Median	IQR	Min-max or n (%)	Median	IQR	p
Postoperative exploration	22 (6.8)			36 (13.4)			0.007
Subxiphoid decompression	1 (0.3)			7 (2.6)			0.01
Cerebrovascular accident	7 (2.2)			3 (1,1)			0.25
Continuous renal replacement therapy	18 (5.5)			5 (1.9)			0.02
Postop atrial fibrillation	79 (24.3)			68 (25.3)			0.78
Deep sternal wound infection	6 (1.8)			10 (3.7)			0.16
Intubation time (hour)	1-1145	10	9	2-672	11	8	0.004
Intensive care unit stay (days)	1-120	2	1	1-28	3	2	0.09
Hospital stay (days)	1-120	7	4	1-111	7	5	0.50
Mortality	19 (5.8)			27 (10)			0.04

Min: Minimum, Max: Maximum, IQR: Interquartile range

DISCUSSION

Despite numerous advancements, such as advanced technology, modern equipment, and surgical techniques that do not require stopping the heart, CPB is still commonly utilized in cardiac surgery today. One of the major challenges associated with CPB is the need for effective anticoagulation. Unfractionated heparin is considered the gold standard for anticoagulation during CPB due to its quick onset of action, reliability, and rapid reversal with protamine sulfate.[7] However, even if neutralization is achieved, postoperative bleeding continues to be a significant cause of morbidity and mortality due to many factors, such as the high bleeding risk of cardiac surgery, factors related to the operation, and coagulopathy caused by CPB.[8] One way to prevent this is to completely neutralize the anticoagulant effect of heparin. The dosage of protamine sulfate used for this purpose has not been determined.[2,4,9,10] While the dose of protamine sulfate that should be administered is important, another important point is the target ACT value. After the heparin dose is compensated, additional protamine administration may cause protamine overdose and consequent bleeding.[11] Therefore, it is important to obtain the ACT value after the planned dose of protamine sulfate has been administered. This ACT value may be below, above, or similar to the preoperative value. There is no definitive consensus on how much this value should be reduced after the operation. High postoperative ACT values (especially ACT ≥140 sec) are associated with an increased risk of bleeding and transfusion.[12] However, due to the risk of increased bleeding due to protamine overdose, the target ACT value is not certain. Therefore, in this study, we aimed to investigate the relationship between postoperative complications and whether the postoperative ACT value was reduced below the preoperative ACT value.

There are many risk factors for postoperative bleeding, such as patient factors, comorbid diseases, medications used, operation type, CPB, and XCL times. However, the most important point in our study is that the basic characteristics of the patient groups are similar. We did not detect any significant differences in terms of basic demographic characteristics, comorbid diseases, laboratory parameters, operation type and types, XCL and CPB times, and medications used. The most important difference between the groups is the rate of being taken to surgery under dual antiplatelet therapy. This was found to be higher in group B than in group A. Therefore, to eliminate the effect of this risk factor, these patients were excluded from the study and subgroups were obtained as group C and group D, and the comparison was made again in terms of postoperative results. However, in both comparisons between the groups, in the groups where postoperative ACT values were above preoperative values, postoperative exploration, need for subxiphoid decompression, and mortality rates were higher,

and the intubation time was longer. In the study by Wang et al.,[6] it was reported that lower postoperative ACT values than ACT values before heparin administration were associated with lower operative time, bleeding, and blood transfusion. However, this study was conducted only on CABG patients and with relatively fewer patients (n=398) than our study. Zahid et al.[13] reported similar intraoperative and postoperative results in a study comparing 101 patients whose ACT values were within and outside 10% of the initial value after protamine. One of the important points of our study is that it was conducted with a larger number of patients compared to similar studies on this subject and included other types of operations in cardiac surgery. Despite a complicated patient group and the high number of concomitant procedures, probably due to the larger number of patients, the basic characteristics and types of operations were similar between the groups. Moreover, CPB and XCL times, among the most important risk factors for bleeding, were also similar between the groups.

We did not find any difference in intraoperative blood product usage between group A and group B. There were no differences in postoperative RBCs and platelet suspension, while only FFP usage was higher in group B compared to group A. Interestingly, we did not find any difference in postoperative bleeding amounts between group A and group B. However, the need for postoperative exploration was higher in group B and group D. While the median ACT after neutralization was 123 sec in group A, it was 143 sec in group B. The higher postoperative exploration rates in group B may be related to the higher ACT value compared to group A. Indeed, it has been shown that an ACT value >140 sec is associated with bleeding, which supports this result.[12] However, considering that the postoperative bleeding amounts are similar, it would not be correct to say that ACT is the only reason for this. Considering that the need for postoperative exploration and subxiphoid decompression can occur at any time after the operation and that the median follow-up period of our study was 245±126 days, other factors than early ACT elevation also play a role in this. Heparin rebound may be an important factor in this. Heparin rebound has been defined as the return of heparin to circulation in the postoperative period despite apparently sufficient neutralization with protamine.[14] According to one review, the incidence of heparin rebound in cardiac surgery is approximately 40%.[15] Such a frequent occurrence may have increased the need for postoperative exploration in the group that already had higher ACT values. However, as we mentioned in the limitations of our study, we could not compare ACT values during postoperative follow-up hours between the groups. It would be useful to investigate this in future studies.

Another point to consider is the comparison of the drugs used. Preoperative and postoperative acetylsalicylic acid use, postoperative oral anticoagulant use, and postoperative dual antiplatelet use were similar between groups A and B. Even though there was no significant difference in the early postoperative period, the efficacy levels of the drugs may have differed, especially in discharged patients, due to irregular oral anticoagulant use. The data regarding the international normalized ratio (INR) follow-up between the groups could not be compared. In addition, bleeding may occur due to the procoagulant effect after overdose of protamine sulfate. However, there was no difference in the doses of heparin and protamine sulfate administered between the groups.

We did not find any difference between the groups in terms of CVA, CRRT, POAF, and DSWI. In addition, we did not find any difference in the length of hospital stay between all groups. ICU time and intubation time were longer in group B than in group A. Intubation time was longer in group D than in group C. We think that these were due to more postoperative exploration, as expected. Similarly, the mortality rate was higher, probably due to more exploration. These results support that postoperative ACT values above the preoperative values are associated with higher bleeding-related adverse events, morbidity, and mortality than those below. However, future studies are needed to give a definitive idea about how much ACT should be reduced. It is also essential to avoid unnecessary protamine use due to the procoagulant effect of excessive protamine sulfate. Prolonged ACT, poor clot structure, and platelet dysfunction occur, especially with protamine administration at a ratio greater than 1:1.3.[16] In addition, hypotension, pulmonary vasoconstriction, allergic reactions, pulmonary hypertension, bronchoconstriction, and anaphylactic reactions may develop with protamine administration.[17] Therefore, caution should be exercised when administering additional doses of protamine, the target ACT value should be carefully determined, and most importantly, the patient should be carefully evaluated in terms of bleeding risk. In patients who are considered to have a high risk of bleeding during surgery, administering an additional dose of protamine sulfate to keep the target ACT value below 140 will be beneficial in reducing bleeding-related complications.

Limitations

The most important limitation of the study is that it is retrospective. Secondly, ACT values were measured only as a single value preoperatively, intraoperatively, and postoperatively. ACT values in the following hours could not be accessed and therefore this analysis could not be performed. Frequently seen conditions such as heparin rebound could not be evaluated for this reason. Thirdly, the patient group was heterogeneous. Only isolated CABG patients were not included. A data group including complex patients with multiple concomitant procedures was evaluated. Another point is that the drug types of patients receiving dual antiplatelet could not be separated. Drugs containing different active ingredients may have affected the results. Finally, data regarding INR monitoring in the postoperative period could not be evaluated, especially for patients receiving oral anticoagulants. In addition, in a very labile measurement method such as INR, sudden increases and decreases may be observed at any time during the follow-up period. It does not seem possible to evaluate this clearly.

CONCLUSION

In cardiac surgery, we found no difference in bleeding amounts and blood product use in patients with post-neutralization ACT values higher than pre-heparin ACT values compared to patients with lower ACT values. However, we observed higher postoperative exploration and mortality rates and longer intubation times. Patients should be carefully evaluated for bleeding risk. In patients with high bleeding risk, additional doses of protamine sulfate, which will reduce

the target ACT value to 140 seconds, may reduce bleeding-related complications.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Clinical Researches Ethics Committee of Başakşehir Çam and Sakura City Hospital (Date: 23.10.2023, Decision No: 2023-443).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

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