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The incidence of heparin resistance in patients undergoing open heart surgery and an evaluation of treatment strategies: a retrospective study

Açık kalp ameliyatı yapılan hastalarda heparin direncinin görülme sıklığı ve tedavi stratejilerinin değerlendirilmesi: Retrospektif bir çalışma

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Background: This study aims to identify the incidence of heparin resistance in patients undergoing open heart surgery and to evaluate treatment strategies.

Methods: January 2010 and December 2010, 1101 consecutive open heart surgery patients were retrospectively analyzed using their anesthetic charts. Demographic data of the patients, activated coagulation time (ACT), administration of additional heparin dose, fresh-frozen plasma, and antithrombin III (AT-III) treatments were recorded. Statistical analysis was performed based on frequency tables and median calculation in all categories.

Results: Of patients, 409 patients (37%) received additional heparin once (n=305) and twice (n=54). Forty-nine patients (4.45%) with normal ACT levels (<450 sec) after second additional heparin dose, received fresh frozen plasma. Antithrombin-III treatment was given to two patients (0.18%). A total of 37% patients needed higher doses of heparin with a 4.45% and 0.18% incidence of fresh frozen plasma and AT-III treatments respectively. The incidence of heparin resistance was 4.6%.

Conclusion: Our study results showed that the most frequently preferred treatment modality was fresh-frozen plasma application in patients with heparin resistance to achieve normal ACT levels.

Key words: Cardiopulmonary bypass; heparin; resistance.

Amaç: Bu çalışmada açık kalp ameliyatı yapılan hastalarda heparin direncinin görülme sıklığı belirlendi ve tedavi stratejileri değerlendirildi.

Çalışma planı: Ocak 2010 - Aralık 2010 tarihleri arasında anestezi dosyaları kullanılarak açık kalp ameliyatı yapılan 1101 ardışık hasta retrospektif olarak incelendi. Hastaların demografik verileri, aktive edilmiş koagülasyon zamanı (ACT), ilave heparin dozu, taze donmuş plazma ve antitrombin III (AT-III) tedavi uygulamaları kaydedildi. İstatistiksel analiz, tüm kategorilerde frekans tabloları ve medyan hesaplamalara göre yapıldı.

Bulgular: Hastaların 409'una (%37) bir kere (n=305) ve iki kere (n=54) ilave heparin verildi. İkinci ilave heparin dozundan sonra ACT düzeyleri normal seyreden (<450 sn.) 49 hastaya (%4.45) taze donmuş plazma verildi. İki hastaya da (%0.18) AT-III tedavisi uygulandı. Hastalarımızın toplam %37'sine, sırasıyla %4.45 taze donmuş plazma ve %0.18 AT-III tedavi insidansı ile daha yüksek heparin dozu gerekti. Heparin direnci insidansı %4.6 idi.

Sonuç: Çalışma bulgularımız, heparin direnci gelişen hastalarda ACT düzeylerini normalleştirmek için en sık tercih edilen tedavi yönteminin taze donmuş plazma uygulaması olduğunu göstermektedir.

Anahtar sözcükler: Kardiyopulmoner baypas; heparin; direnç.

In patients who will undergo heart surgery, anticoagulation, which is achieved with heparin, is essential for cardiopulmonary bypass (CPB). The primary mechanism of action of this drug is the activation of antithrombin (AT) III, which prevents thrombin transformation from prothrombin. Thus, it reduces the production of clots. However, in some cases, despite a standard heparin dose, the intended

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active coagulation time (ACT) cannot be obtained. This condition is known as heparin resistance (HR). For patients undergoing heart surgery, many studies have reported the incidence of HR to be between 4 and 22%,[1-7] with the most frequent causes being AT deficiency, increases in the clearance of heparin the protein that joins with heparin, and high levels of factor 8, fibrinogen, and platelet factor (PF) 4.[8] In addition, HR has also been reported as a result of using medications such as aprotinin and nitroglycerin.[9]

Our goal in this study was to retrospectively determine the incidence of HR in patients who underwent heart surgery at our hospital and evaluate the appropriate treatment strategies.

PATIENTS AND METHODS

After local ethics committee approval, 1,101 patients (mean age, 57.8±27.3; female/male ratio, 781/320) who had undergone open heart surgery at our hospital between January 2010-December 2010 were retrospectively screened, and their intraoperative anesthesia form reports were investigated. Those who had received preoperative heparin, streptokinase, and oral contraceptives as well as those who had coagulation disorder were excluded from the study. We included only patients who had undergone coronary angiography five or more days prior to the surgery, and their demographic characteristics, additional diseases, type of operation, number of reoperations, and times that heparin was given along with their use of fresh frozen plasma (FFP), nitroglycerin infusion, and AT-III were recorded.

For anesthetic premedication, the patients were orally given 5-10 mg of diazepam the night before the operation, and 0.1 mg/kg of morphine was given 30 minutes before the surgery. They were then taken to the operating room. After routine monitoring, arterial blood samples were taken via the arterial route to determine a baseline ACT, and the Hepcon® HMS Plus system (Medtronic, Inc., Minneapolis, MN, USA) was used to obtain the baseline kaolin ACT.

Induction was provided with midazolam, fentanyl, and rocuronium. In addition to the use of oxygen (O_2), fentanyl, dormicum, and rocuronium were utilized to maintain total intravenous anesthesia (TIVA). After tracheal intubation, central venous catheterization (CVC) was provided through the internal jugular vein. Before CPB, heparin was used (3-4 mg/kg) for the purpose of anticoagulation. If the patient's ACT was above 400 seconds, additional therapy was not given, but if it was under 400 seconds, an additional heparin dose of 50 mg was given. After the additional heparin, we obtained one more blood sample and measured the ACT again. If the patient still had not reached the necessary ACT, another 50 mg dose of heparin was given. For these cases, an additional blood sample was taken, and the ACT was measured one more time. If an ACT of above 400 seconds was not obtained at that point, 300 cc (one unit) of FFP was given to the patient intravenously. Intraoperative AT activity could not be measured, so we applied 100 mg AT-III therapy in the cases in which full heparinization was not achieved in spite of the additional heparin and FFP therapy (Figure 1).

Heparin resistance was identified if the ACT was less than 400 seconds after 300 U/kg of heparin (local criteria) or if it was less than 400 seconds after 400 U/kg or more of heparin (stringent criteria). The primary solution for the CPB machine was composed of 1500 ml lactated Ringer's, a 20% mannitol solution calculated by taking into account the patient's body weight, two ampules of vitamin C concentrate, 30 meq of bicarbonate (HCO_3) solution, and heparin added according to patient's weight. The heparin was reversed with protamine in accordance with the first heparin dose.

Statistical analysis was performed in all categories with frequency tables, median calculations, the analysis of variance (ANOVA) table, and a chi-square test.

RESULTS

The incidence rate was 23.6% for diabetes mellitus (DM) and 46.4% for hypertension in our study (Table 1). Coronary artery bypass grafting was performed on 61.7% of the patients. Another 13.7% underwent valve replacement, and 25.6% had other types of surgical procedures. In addition, 29 of the participants underwent

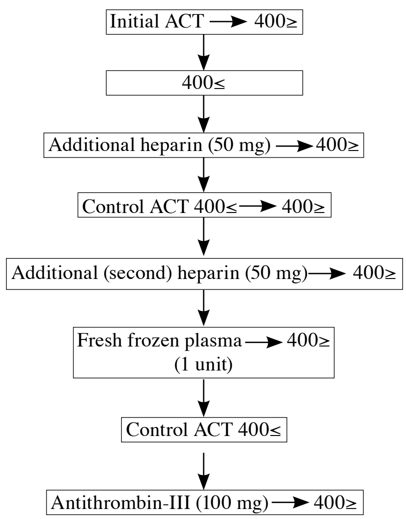

Figure 1. Heparin administration scheme. ACT: Active coagulation time.

Table 1. Demographic data

	n	%	Mean±SD
Age (year)			57.8±27.3
Gender			
Female	781	70.94	
Male	320	29.06	
Diabetes mellitus	260	23.6	
Hypertension	511	46.4	

SD: Standard deviation.

reoperations. Ten of these received additional doses of heparin, and two of the 10 needed FFP. Furthermore, none of the patients who underwent surgery reoperation because of an insufficient response to AT-III achieved the appropriate ACT.

Additional heparin doses were not given to 742 patients (67.4%); however, 305 patients (27.7%) were given heparin once, and 54 patients (4.9%) were given it twice. After the second additional heparin dose, 49 patients (4.5%) who had reached the required ACT (<400 seconds) received FFP. When comparing the group which did not receive additional heparin with the group that did, the statistical FFP intake was found to be significantly more frequent (p<0.000). Two patients (0.18%) were given AT-III treatment, and the frequency of AT-III intake was similar between the two groups of patients (p=0.106). Additionally, there was no statistical difference between the patients who received additional heparin and those who received none with regard to age, gender, DM, hypertension, and type of surgery (Table 2).

Our results showed that 409 patients (37%) needed a higher dose of heparin. In addition, 49 patients (4.45%) were treated with FFP, and two (0.18%) received AT-III.

DISCUSSION

Heparin is a drug that has been available for more than 50 years and is used for anticoagulation. Although it is effective, it has pharmacokinetic, biophysical, and biological limitations. The standard heparin anticoagulant response varies greatly among patients; therefore, before starting treatment, the activated partial thromboplastin time (aPTT) and/or clotting time should be surveyed. Furthermore, treatment should be directed dynamically by titration through the observation of the clinical course and monitorization of the associated parameters. Heparin is used in open heart surgery to provide anticoagulation before entering CPB. After the application, a satisfactory anticoagulation level is maintained with ACT. When sufficient ACT is not obtained, additional heparin is applied. However, if the required ACT is still not obtained, then HR should be

Table 2. Demographic data of patients who received additional heparin doses and those who received no additional heparin

	Additional heparin		No additional heparin	
	n	Mean±SD	n	Mean±SD
Age		59.7±12.4		54.0±15.4
Gender				
Female	117		203	
Male	242		539	
Diabetes mellitus				
Yes	93		167	
No	266		575	
Hypertension				
Yes	195		316	
No	164		426	
Operation type				
Coronary artery bypass surgery	220		459	
Valvular surgery	71		109	
Other	68		174	
Fresh frozen plasma				
Yes	48*		1	
No	311		741	
Antithrombin-III				
Yes	2		0	
No	357		742	

SD: Standard deviation; * p<0.005 (statistically significant).

considered. In cases where HR was observed, when the other intraoperative drugs were evaluated, it was seen that nitroglycerin intake did not differ in the cases where HR did not develop. However, in a previous study in which Kanbak et al.[9] studied the effects of nitroglycerin on coagulation and heparin sensitivity in patients that received nitroglycerin during CPB, they discovered that nitroglycerin had increased HR. On the other hand, in both their in vitro and in vivo studies, Lepor et al.[10] showed that short-term nitroglycerin infusions did not increase HR. Furthermore, Koh et al.[11] reported that the heparin dose was not affected by intravenous nitroglycerin infusion. Similarly, we also observed that nitroglycerin did not affect the heparin response.

Knapik et al.,[12] in their study on the relationship between HR and postoperative complications in cases of open heart surgery determined that 4.3% of their patients obtained an ACT of lower than 400 seconds following 400 IU/kg heparin application. In our study, in spite of giving heparin doses of 400 IU/kg or higher, only 5% of the patients had an ACT of lower than 400 seconds. Assuming that this was a result of HR, we treated the developing situation with FFP (4.5%) and AT-III (0.5%).

Potential risk factors for HR include patients older than 65 years old, a platelet count >300,000 cells/mm^3, recent heparin exposure, and AT deficiency.[13,14] In our study, 32 of the 54 patients who developed HR were 65 years old or older, and 52 of these 54 had a platelet count of 300,000 or over. None of our patients who received preoperative heparin were included in the study since the preoperative AT-III activities of these patients were unknown. Garvin et al.,[14] showed that the preoperative AT-III level did not affect the heparin response but found that preoperative heparin only decreased AT-III activity. However, this decrease did not change the heparin dose response. Researchers have stated that the heparin ACT response is very complex and know that it can be affected by many endogenous factors; hence, it is not the best choice to attest to HR.[15]

In treating patients who develop HR, FFP and AT-III are commonly used. While most patients respond to FFP application, more resistant cases require AT-III. In recent years, different drugs have been used for patients who develop HR. Kikura et al.[16] used nafamostat mesylate (Naf) and determined that the patients reached a satisfactory ACT. Moreover, when evaluating perioperative ischemic stroke, the most important problem associated with the use of this drug, no significant differences were found between the patients who received Naf and those who did not.

This study had important limitations. For example, we did not know the preoperative AT-III concentration. In addition, regardless of how it is used, ACT is unreliable for assessing heparin anticoagulation in the operating room. We also did not include long-term results (ICU length of stay, hospital length of stay, morbidity, and mortality) because we could only conduct our research via the intraoperative anesthesia form reports.

In conclusion we determined incidence of HR 37.2%, 4.6% according to local and stringent criteria respectively. Furthermore, in cases where HR developed, the preferred method of treatment was FFP because it allowed the patients to reach the intended ACT.

Declaration of conflicting interests

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