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Investigation of the Effect of Protamine-heparin Dose Ratio Adjustment on Intraoperative Graft Patency and Postoperative Bleeding

Protamin-heparin Doz Oranının Değiştirilmesinin İntraoperatif Greft Açıklığı ve Postoperatif Kanama Üzerine Etkisinin İncelenmesi

Ferhat Borulu

Atatürk University Faculty of Medicine, Department of Cardiovascular Surgery, Erzurum, Turkey

Abstract

Objective: The use of systemic anticoagulation and protamine is an indispensable issue for cardiopulmonary bypass. We aimed to investigate the effect of protamine administration in different doses on intraoperative graft opening and postoperative bleeding amounts.

Method: Eighty patients scheduled for isolated coronary artery bypass surgery were divided into two equal groups. One group was administered at a ratio of 1:1 (group 1) and the other group (group 2) at doses of 1:0.75 (heparin: protamine). The demographic characteristics of the groups, operative data, and postoperative follow-up parameters were compared. Transit time flow measurement (TTFM) measurements were performed on the grafts used. The amounts of bleeding and transfusion were compared.

Results: Demographic characteristics and operative data of both groups were similar. Pulsatility index value was found to be high in TTFM measurements in the saphenous vein used in one patient in group 1 (thrombus in the saphenous vein). In group 2, a high flow was found in the left internal mammary artery in one patient (vasospasm). Although the erythrocyte suspension transfusion amount was partially higher in group 2, it was not statistically significant (p=0.909). The amount of fresh frozen plasma used in group 2 was significantly higher (p=0.001). Also, there was no significant difference in terms of drainage amounts (p=0.968).

Conclusion: An unnecessary excess of protamine dose does not have a positive effect on bleeding and transfusion amounts. On the contrary, it may facilitate intraoperative graft occlusion. Studies with larger patient numbers are needed for stronger interpretations.

Keywords: Bleeding, coronary bypass, graft patency, protamine

Öz

Amaç: Kardiyopulmoner baypas için sistemik antikoagülasyon vazgeçilmez bir konudur. Bu amaçla kullanılan heparin kadar bu etkiyi ortadan kaldıran protamin de çok önemlidir. Ancak az yapılması kadar fazla yapılması da birtakım yan etkilere neden olabilmektedir. Çalışmamızda farklı dozlarda yapılan protamin uygulamasının intraoperatif greft açıklığı ve postoperatif kanama miktarları üzerine etkisinin araştırılması amaçlanmıştır.

Yöntem: İzole koroner arter baypass cerrahisi yapılması planlanan 80 hasta iki eşit gruba ayrıldı. Bir gruba 1:1 oranında (grup 1) diğer gruba (grup 2) ise 1:0,75 (heparin: protamin) dozlarında uygulama yapıldı. Grupların demografik özellikleri, operatif verileri (baypas süresi, klemp süresi, sıcaklık, aktif pıhtılaşma zamanı değerleri vb.), postoperatif takip parametreleri karşılaştırıldı. Hastalara kullanılan greftlerde transit time flow measurement (TTFM) ölçümleri yapıldı. Kanama miktarları ve transfüzyon miktarları kaydedildi ve karşılaştırıldı.

Bulgular: Gruplar arasında demografik özellikler açısından farklılık görülmedi. Operatif veriler (kardiyopulmoner bypass süresi, klemp süresi, sıcaklık vb.) açısından her iki grubun verileri benzer nitelikteydi. Grup 1'de bir hastada kullanılan safen vendeki TTFM ölçümlerinde pulsatilite indeksi değeri yüksek bulundu (safen vende trombüs). Diğer grupta da bir hastada sol internal meme arterinde akım yüksek bulundu (vazospazm). Eritrosit süspansiyonu transfüzyon miktarları grup 2'de kısmen fazla olmasına rağmen istatistiksel olarak anlamlı değildi (p=0,909). Grup 2'de kullanılan taze donmuş plazma miktarı anlamlı olarak fazla idi (p=0,001). Yine aynı şekilde drenaj miktarları açısından anlamlı bir farklılık yoktu (p=0,968).

Sonuç: Heparin ve protamin kalp cerrahisi için vazgeçilmez iki ilaçtır. Ancak protamin dozunun gereksiz miktarda fazla yapılmasının kanama ve transfüzyon miktarları için olumlu bir katkısı olmamakla beraber aksine intraoperatif greft tıkanıklıkları için kolaylaştırıcı etki yapabilmektedir. Bu konuda daha güçlü yorumlar için daha geniş hasta sayıları ile çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Greft açıklığı, kanama, koroner baypas, protamin

Address for Correspondence: Ferhat Borulu, Atatürk University Faculty of Medicine, Department of Cardiovascular Surgery, Erzurum, Turkey
E-mail: fborulu@gmail.com **ORCID:** orcid.org/0000-0001-9731-9998 **Received:** 11.08.2021 **Accepted:** 30.11.2021

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Introduction

Heparin and protamine are indispensable drugs for open heart surgery. Heparin-protamine balance gains importance in all surgical interventions using a cardiopulmonary bypass (CPB) device. Thanks to the presence of an effective antidote such as protamine sulfate, heparin can be used safely at high doses in cardiac surgery (1). Protamine is widely used to eliminate the effect of heparin after weaning from CPB (2). Like many drugs used, both overdose and low dose administrations may have some unwanted consequences. Although it is actually applied to eliminate the effect of heparin, it can have an anticoagulant effect when applied in large amounts (3,4). There are studies showing that protamine causes dysfunction in platelet functions and thus may cause coagulation disorders (5,6). Since it is a drug with serious side effects, dose adjustment is very important. These side effects are particularly important after a major surgical intervention, such as cardiac surgery, where the risk of bleeding is high and difficulties in hemodynamic stabilization may be experienced. In many centers where cardiac surgery is performed, heparin dose is calculated according to body weight. This may cause high-dose heparin administration, especially in the overweight patient group, and consequently, high-dose protamine after surgery (7). Low activated clotting time (ACT) values that will occur with the effect of high doses of protamine will predispose to thrombus formation and thromboembolic events at different levels, especially in newly anastomosed grafts. In addition, unwanted consequences may occur in patients who already have bleeding potential, as the heparin-protamine balance cannot be fully adjusted.

There are many factors that can cause bleeding in cardiac surgery. Most important of these factors are preoparative drugs, changes in the inflammatory system, the negative effect of the heart-lung machine on the coagulation system, hypothermia, and a decrease in hematocrit levels (8,9). It is very important to reduce the factors that may cause non-surgical leakage bleeding as much as possible.

Another important issue in coronary artery bypass surgery is that the grafts made have good flow. Especially in the early period, technical problems, vascular structures and blockages may occur with thrombotic mechanisms. It is also important to be able to detect graft thrombosis that may occur with overdose of protamine. One of the intraoperative methods that can be used for this purpose is transit time flow measurement (TTFM).

The aim of this study is to investigate the changes in the protamine dose and the amounts of bleeding and transfusion and also to examine the effect of dose adjustment on intraoperative graft patency. This study is the first to examine the effect of protamine dose adjustment on intraoperative graft patency.

Materials and Methods

Method of Study, Patient Selection

A work permit was obtained from the ethics committee of the institution, to which our clinic is affiliated (Atatürk University Clinical Research Ethics Committee. decision no: 18, decision date: 01.10.2020). After getting ethics committee approval, patients who were prospectively planned for isolated coronary artery bypass grafting surgery in our clinic between January 2021 and July 2021 were informed and their consent was obtained. LITA graft was used in both groups. Saphenous vein was used for other grafts (mean 2.9±0.74 grafts were used in group 1 and 2.77±0.69 grafts were used in group 2). Only the perfusionist knew which group the patients would be in, and they were divided into two groups, respectively.

When choosing patients in both groups, the inclusion criteria were determined as that isolated coronary artery bypass grafting operation would be performed under CPB and patients would be at the age of 18-75 years.

On the other hand, using anticoagulants and antiaggregants 48 hours before the operation, receiving dialysis treatment, and needing mechanical support after the operation were determined as the exclusion criteria.

The patients in the first group were administered protamine at a ratio of 1:1 according to the total amount of heparin administered during the CPB period, as in routine practice. Three quarters of the routine protamine dose was administered to the patients in the second group and ACT control was performed. TTFM evaluation was performed on all grafts in all patients after protamine. Demographic data, Euroscore II values, intraoperative and postoperative blood transfusion amounts, pre- and postoperative laboratory values, ACT values (preop, post-protamine, 1st hour in intensive care), TTFM values (after protamine) and follow-up parameters were compared.

ACT Measurement Method

Measurements were made with the Actalyke^{R} MINI (Activated Clotting Time Test System-Helena Laboratories, Beamont, Texas USA, 77704) device in the operating room.

This device uses the 2-point clot detection feature and starts ACT measurement immediately after the ACT Tube is inserted. Celite is used inside the tube (Actalyke® C-ACT).

TTFM Measurement Method

The technique was developed to evaluate graft quality and to measure the blood flow through the graft with its special probe. The device our clinic used is the MediStim VQ1101, MediStim ASA (Oslo, Norway). With this technique, the diastolic filling, mean flow, and pulsatility index (PI) can be measured. The first measurements were made when the anastomoses of the grafts were finished and the heart started to work again (the mean arterial pressure was 50-60 mmHg). Later, second measurements were made after protamine was administered when CPB was terminated. Based on the data from similar studies and recommendations from the manufacturer, we accepted the PI value as the main criterion for flow quality. Intergroup comparisons were made according to the post-protamine data.

Heparin-protamine Applications

ACT was checked before heparin was administered to patients in both groups, as in routine practice. Heparin was administered according to body weight (400 IU/kg). When ACT fell below 480, an additional dose of heparin was administered with the decision of the perfusionist. At the end of the surgical procedure, after weaning from CPB, all of the protamine dose (1:1, ie 1.0 mg/100 IU) calculated for complete neutralization was applied to the first group. In the second group, three-quarters of the full neutralization dose was administered. In the second group, three-quarters of the full neutralization dose was administered based on previous studies (8-10).

As the study endpoints, the primary endpoint was ACT values (200 and above), and the secondary endpoint was the amount of drainage, transfusion amount and bleeding revision.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, in addition to descriptive statistical methods (Average, standard deviation, median, frequency, ratio, minimum, maximum), the distribution of the data was evaluated using the Shapiro-Wilk test. The Mann-Whitney U test was used to compare two groups that did not show normal distribution of quantitative data. The Student's t-test was used to compare the quantitative data between two groups showing normal distribution. The significance was evaluated at the level of $p<0.05$.

Results

Eighty patients, including 40 patients in each group, were included in the study. Two patients were excluded from the study because they were discharged with the help of an intraaortic balloon pump after the operation. There was no difference between the groups in terms of age, gender, body mass index, Euroscore II values, and comorbid factors (Table 1). None of the patients used anticoagulants other than low molecular weight heparin in the preoperative period (last 48 hours). There was no significant difference in the preoperative and postoperative laboratory data of the patients (Table 2). All patients were cooled to 32 degrees (rectal) body temperature during operations and were operated by the same surgical team. There was no difference in intraoperative data (such as CPB duration, cross-clamping time, minimum body temperature, blood gas monitoring) between the groups (Table 3).

Table 1. Demographic data

	Group 1 (n=40)	Group 2 (n=40)	p
Age (years)	64.95±7.7	62.43±9.68	0.200[a]
Gender (M/F)	29 (72.5%)/11 (27.5%)	32 (80%)/8 (20%)	0.599
COPD (n/%)	7 (17.5%)	7 (17.5%)	0.999
Hypertension (n/%)	19 (47.5%)	22 (55%)	0.655
Hyperlipidemia (n/%)	12 (30%)	14 (35%)	0.811
Diabetes mellitus (n/%)	14 (35%)	12 (30%)	0.811
PVD (n/%)	2 (5%)	1 (2.5%)	0.556
BMI (kg/m^2)	30.2±2.84	29.5±2.73	0.264[a]
BSA (m^2)	1.98±0.16	1.95±0.13	0.256[a]
Euroscore II	1.08±0.54	1.19±0.42	0.314[a]

COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, PVD: Peripheral vascular disease, BSA: Body surface area, [a]: Student's t-test

The results of the ACT values that form the basis of the study are given in Table 4. There was no difference in terms of preop ACT values (p=0.114). There was no difference in terms of ACT values measured while CPB was continuing (p=0.412). However, ACT values measured after protamine were high in group 2, which was statistically significant (p=0.001). While the amount of protamine administered in group 1 was 32225±4500 IU on average, it was 26145±3250 IU in group 2. Although there was no statistically significant difference in the TTFM values measured after protamine in the patients, in the higher dose protamine group, a fresh thrombus was detected in the control performed because the saphenous vein graft (circumflex artery) was not flowing well, and the patency was restored with embolectomy. In the other group, low flow was measured in the left internal mammarian artery (LIMA) anastomosis of one patient.

Table 2. Preoperative and postoperative laboratory data

		Group 1 (n=40)	Group 2 (n=40)	p
WBC (K/mm^3)	Preop	7.96±1.87	7.94±1.94	0.977[a]
	Postop 1 day	12.35±2.42	12.07±2.48	0.614[a]
Hgb (g/dL)	Preop	14.02±1.63	13.69±1.27	0.249[b]
	CPB entry	7.34±0.57	7.48±0.62	0.321[a]
	CPB 20 minute	7.27±0.58	7.55±0.64	***0.046[a]**
	CPB output	7.44±0.57	7.61±0.54	0.188[a]
	Postop 1 day	8.77±0.72	8.59±0.54	0.294[b]
Hematocrit (%)	Preop	41.88±5.02	40.37±4.46	0.158[a]
	CPB entry	22.53±1.74	23.03±1.72	0.200[a]
	CPB 20 minutes	21.41±2.61	23.12±1.65	0.346
	CPB output	28.15±2.22	22.84±1.36	0.329[a]
	Postop 1 day	26.87±1.9	26.31±1.67	0.160[a]
Platelet (K/mm^3)	Preop	234±67.53	233.85±67.32	0.992[a]
	Postop 1 day	190.33±32.18	185.95±39.46	0.588[a]
Calcium (mg/dL)	Preop	9.24±0.8	9.43±0.68	0.247[a]
	CPB entry	1.26±0.1	1.28±0.09	0.282[a]
	CPB 20 minutes	1.29±0.09	1.38±0.11	0.321
	CPB output	1.28±0.1	1.3±0.08	0.285[a]
INR	Preop	1.04±0.1	1.07±0.1	0.189[a]
	Postop 1 day	1.11±0.09	1.1±0.08	0.605[a]
aPTT (sec)	Preop	31.3±3.82	34.08±5	****0.007[a]**
	Postop 1 day	29.78±3.86	32.3±5.61	***0.038[b]**

[a]Student's t-test, [b]Mann-Whitney U test, *p<0.05, **p<0.01, WBC: White blood cell, Hgb: Hemoglobin, INR: International normalized ratio, aPTT: Activated partial thromboplastin tim

Table 3. Operative/postoperative data and total drainage amounts

	Group 1 (n=40)	Group 2 (n=40)	p
CPB time (min)	90.93±10.94	89.85±15.28	0.718[a]
X-clamp time (min)	50.13±8.82	52.33±9.77	0.294[a]
Body temperature (°C)	31.87±0.85	31.29±4.63	0.310[b]
Total drainage (mL)	822.63±162.24	820.75±241.06	0.968[a]
Bleeding revision (n/%)	1/2.5%	2/5%	0.624
Extubation time (hour)	7.27±1.5	6.86±1.15	0.180[a]
Red cell suspension transfusion (unit)	2.83±1.06	2.8±0.88	0.909[a]
Fresh frozen plasma (unit)	3.88±0.82	2.58±0.93	****0.001[a]**
Intraoperative FFP (unit)	1.89±0.61	1.93±0.58	0.341[a]

Student's t-test[a], Mann-Whitney U test [b], *p<0.05, **p<0.01, CPB: Cardiopulmonary bypass

Table 4. ACT values of both groups

	Group 1 (n=40)	Group 2 (n=40)	p
ACT preop	132.18±10.27	135.75±9.74	0.114[a]
CPB entry	714.55±157.38	684.58±167.75	0.412[a]
CPB 20 minute	699.1±111.85	706.15±120.39	0.787[a]
CPB output	651.98±66.46	684.15±125.78	0.157[a]
After protamine	136.05±8.66	146.4±8.24	**0.001[a]

[a] Student's t-test, **p<0.01, ACT: Activated clotting time, CPB: Cardio pulmonary bypass

However, this situation was considered due to spasm in LIMA and the problem was solved with local application of papaverine.

There was no difference between the two groups in terms of the amounts of intraoperative and postoperative blood transfusions (erythrocyte suspension, fresh frozen plasma and platelet suspension). Postoperative total drainage amounts were also similar between the groups. One patient from group 1 was revised due to bleeding (bleeding focus was in the saphenous vein branch) at the 5th hour postoperatively. The bleeding was excluded from the study because it was due to surgery.

Discussion

Protamine is an indispensable drug to eliminate the effect of systemic anticoagulation with heparin in cardiac surgery performed with CPB. When protamine is used in an appropriate amount, besides neutralizing the effect of heparin, administration of high doses can increase the amount of bleeding by making an anticoagulation effect with the opposite effect (2). Therefore, the amount of application is very important. In the light of available information, it is recommended that the dose of heparin/protamine be 1/1. However, discussions on this issue are still going on. In this study, we examined the effect of different doses of protamine on postoperative blood transfusion and drainage amounts, as well as intraoperative graft patency.

It has been shown in various studies that if the protamine dose is more than necessary for the neutralization of heparin, it increases the coagulation disorder state rather than improvement in hemostasis (8,9). For the occurrence of this situation, there are studies suggesting that it reduces thrombin formation and inhibits factor V activation (10). In the study conducted by Meesters et al. (8), a significant difference was shown in terms of thrombin levels between the patient groups who received two different doses. It was observed that the amount of blood transfusion due to low thrombin levels increased in the group with excess protamine (8). In our study, no difference was found between the groups in terms of blood transfusion amounts. We did not make a measurement in terms of thrombin levels, but we think that not high protamine dose may be effective in this regard.

Protamine structurally has a peptide structure consisting of 32 amino acids. With its cationic structure, it neutralizes the anionic heparin at a ratio of 1:1 (6). The metabolism and mechanism of action of protamine in the body change with the presence of heparin. While it has a shorter duration of action in the presence of heparin, a longer half-life occurs in the absence of heparin (11). In addition, while the heparin-protamine complex is metabolized from the liver, only protamine is eliminated by the kidneys (12). All this literature information shows that protamine applied above the heparin dose may have different effects than the desired effect. The main hematological side effects are its ability to cause thrombocytopenia (13) and decrease in platelet aggregation via thrombin (14). It has been shown in various studies that these possible side effects are in applications with a protamine/heparin ratio above 1. The absence of an application above this rate in our study suggests that our patients can be protected from these side effects. Even if the thrombotic situation in the saphenous vein graft was not sufficient to make a definite interpretation in a patient in whom the protamine dose was applied exactly, it suggests that the anticoagulant effect may also be at 1:1 doses because some of the heparin made before the pump may lose its effectiveness with the effect of the elapsed time. It is known that there are many factors that are effective in the occurrence of intraoperative or early postoperative graft occlusion in saphenous vein grafts. It should be kept in mind that excessive doses of protamine used to reduce surgical bleeding may contribute to this event.

Besides hematological side effects of protamine, immunological and inflammatory side effects have also been described. These mechanisms include hypotension, bradycardia, pulmonary vasoconstriction, and allergic reactions (15,16). Protamine administration is performed

during the period when CPB is terminated in cardiac surgery. Therefore, most of these side effects can be overlooked since they are associated with the surgery performed. Since the main focus of our study was not side effects, an analysis could not be made in this direction. However, the fact that these side effects have also been shown is important in terms of showing us the drawbacks of overdose of protamine. Particularly, hypotension (17) and pulmonary hypertension (18) side effects are very important as they may lead to unnecessary medical interventions after cardiac surgery (19). In fact, a study by Ocal et al. (20) showed that severe right ventricular failure and pulmonary hypertension developed with the effect of protamine.

The ability of protamine used after cardiac surgery to neutralize heparin is traditionally followed by ACT values. Returning to ACT values before the administration of heparin is considered as the main goal. In our study, where different protamine doses were applied, if ACT values were 20% higher than the first measurement in the measurements made after heparin, although additional doses of protamine were planned, this application was not required in any patient. Although it was higher on average in the low-dose protamine group compared to the other group, this height was not more than 20% in any patient. This situation made us think that adequate neutralization can be achieved even with lower protamine doses because the heparin left from the heparin used in CPB and needing to be neutralized is actually lower than the first dose of heparin.

Postoperative bleeding in cardiac surgery is a very disturbing situation. Surgeons who are afraid of this situation prefer high protamine dose to low. However, the data in the literature show that unnecessary protamine dose has an increasing effect rather than reducing postoperative bleeding. In our study, the fact that there was no difference in the amount of bleeding between the groups with different protamine doses seems to be consistent with this information.

Study Limitations

-Although there are studies showing that ACT alone is not sufficient for protamine dose adjustment, protamine dose adjustment was made by following the ACT value within the routine practice in our clinic.

-Since we do not use a system that determines the effect of heparin remaining from heparin used in CPB, the protamine dose was calculated according to the amount of heparin administered in total. Although this is the traditional approach, there are important studies claiming that this is not enough.

-While TTFM measurements measuring graft patency were performed, other causes that would disrupt the flow were excluded from the scope of the study. This situation made it difficult to interpret the effect of protamine on this issue (because other factors that could affect TTFM measurements were not analyzed in the study). Only problems caused by acute thrombus were included in the evaluation.

Conclusion

Two of the most important points in heart surgery are good graft patency and few bleeding complications. The effect of heparin for anticoagulation in CPB is neutralized by protamine. An excess of protamine dose sufficient to eliminate the effect of heparin does not have a positive additional effect on the amount of postoperative bleeding. In addition, although no analysis has been performed for other parameters that may affect TTFM measurements, we think that low-dose protamine will contribute positively to early intraoperative graft patency. Large randomized studies are needed on this subject.

Ethics

Ethics Committee Approval: A work permit was obtained from the ethics committee of the institution, to which our clinic is affiliated (Atatürk University Clinical Research Ethics Committee. decision no: 18, decision date: 01.10.2020).

Informed Consent: Consent certificate was taken from all patients for the study.

Peer-review: Externally peer-reviewed.

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