Clinical Effects of Different Protamine Doses After Cardiopulmonary Bypass

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ABSTRACT

The optimal dose of protamine needed to reverse the anticoagulant effect of heparin after cardiopulmonary bypass is still not known. In this retrospective cohort study, we investigated 3 different dose regimes in 300 patients undergoing coronary artery bypass grafting. Group A patients (n = 100) were given protamine in the ratio of 1.3 mg to 1 mg heparin, group B patients (n = 100) were given 0.75 mg protamine to 1 mg heparin, and group C patients (n = 100) were given protamine in fractionated doses of 1 mg + 0.15 mg + 0.15 mg to 1 mg heparin. The groups were comparable in all major clinical and operative variables. The heparin dose was almost identical in the groups. The rate of red cell transfusion was significantly higher in group B than in the other groups. A similar but nonsignificant trend was observed in the incidence of resternotomy for postoperative bleeding, mediastinal drainage, and postoperative hemoglobin loss. The study demonstrates that a single bolus dose of 1.3 mg protamine to 1 mg heparin is safe and efficient for neutralizing heparin after cardiopulmonary bypass.

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INTRODUCTION

From the very beginning of heart surgery with cardiopulmonary bypass (CPB), the dosage of heparin required for anticoagulation and the protamine dose for reversing its effect have often been estimated empirically.[1] Bull and associates[2] in 1975 found that both inadequate heparin reversal and excessive protamine administration were common. They devised a technique for individualizing heparin and protamine dosages based on dose-response curves.[3] Since then, several techniques for titrating the protamine dose needed to neutralize circulating heparin in each patient have been developed.[1,4] In routine cardiac surgery, however, individualized protamine/heparin titration is expensive and not necessary. Therefore, standardized doses are very often administered, although little is known about the optimal doses of protamine required after CPB. Furthermore, the consequences of too much or too little protamine remain unclear.

The aim of this study was to investigate the clinical implications of different amounts of protamine given to low-risk patients undergoing coronary bypass. Of particular interest were the effects on postoperative mediastinal drainage, hemoglobin loss during hospital stay, the incidence of resternotomy for bleeding, and the requirement for allogenic blood transfusion.

PATIENTS AND METHODS

Over a period of 22 months, the scheme for protamine administration to neutralize heparin after CPB was

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changed in 3 successive time periods. A retrospective analysis of the first 100 consecutive patients undergoing coronary artery bypass grafting in each period was undertaken. To exclude personal bias, the patients were selected from the experience of a single surgeon and a single anesthetist. In the first cohort, protamine was given in the ratio of 1.3 mg to 1 mg heparin (group A). In the second period, the ratio was 0.75 mg protamine to 1 mg heparin (group B). In the third period, the protamine dose was divided into 3 boluses of 1 mg + 0.15 mg + 0.15 mg to 1 mg heparin (group C) and given after CPB, after retransfusion of the contents of the CPB circuit, and after retransfusion of the autologous blood removed before CPB, respectively.

All patients in the study were first-time candidates for surgery, and most of them were of low operative risk. The patients were selected in close collaboration with a neighboring university department that manages cases of severe renal dysfunction and ventricular aneurysms, as well as patients in need of combined carotid and coronary operations and acute operations after failed angioplasties.

Standard operative procedures included median sternotomy, dissection of the internal mammary artery, and CPB with a two-stage cannula in the right atrium and a cannula in the ascending aorta. CPB was maintained with a pulsatile flow at a rate of 2.4 $L \cdot m^{-2} \cdot min^{-1}$, and mild hypothermia (blood temperature, 32°C to 34°C) was instituted immediately after the start of bypass. The heart-lung machine was primed with 2,000 mL of Ringer's acetate. The aorta was crossclamped and a crystalloid cardioplegic solution (St. Thomas II) infused in the antegrade fashion before distal anastomoses were performed. Venous grafts were attached to the ascending aorta using partial occlusion while rewarming the patient. Cardiotomy suction was used throughout the CPB period.

The activated clotting time (ACT) was measured (Hemo Tec; HemoTec Inc., Englewood, CO, USA) preoperatively, after heparin administration, before CPB, 10 minutes after the start of CPB, every 20 minutes during CPB, after protamine administration, and 2 hours postoperatively. Heparin was given in a bolus dose of 4 $mg \cdot kg^{-1}$ to obtain an ACT above 480 seconds. Additional heparin was given during CPB if ACT was below target level. The administration of supplemental doses of protamine was considered when postoperative ACT exceeded 130 seconds.

The anesthetic technique, designed to permit early extubation, included a combination of diazepam (0 to 0.2 $mg \cdot kg^{-1}$), midazolam hydrochloride (0 to 0.2 $mg \cdot kg^{-1}$), fentanyl (6 to 8 $\mu g \cdot kg^{-1}$), and pancuronium bromide, supplemented with isoflurane and nitrous oxide.

Blood conservation before and after operation was previously described in detail[5,6] and included the removal of autologous blood before bypass for retransfusion after bypass, intra- and postoperative retransfusion of the oxygenator and circuit contents (without any cell processing), and postoperative autotransfusion of shed mediastinal blood up to 18 hours postoperatively. If possible, platelet inhibitors like aspirin were discontinued 7 days preoperatively. Antifibrinolytic or antiinflammatory agents were not given to any patients.

The amount of postoperative bleeding was measured from the time of sternal closure until the drains were removed. The threshold for resternotomy was mediastinal drainage exceeding 250 $mL \cdot h^{-1}$ for 2 hours. Normovolemic anemia was defined as a hematocrit of 0.25 postoperatively, below which allogenic red blood cell transfusion was indicated. Hemoglobin concentration and platelet count were determined preoperatively, at 3 hours and 18 hours postoperatively, and at discharge on the 5th to 7th day.

All patient and laboratory data were recorded prospectively. The groups were compared using the Kruskal-Wallis test for continuous variables. Discrete variables were tested by chi-square, with Yates' correction and Fisher's test when one of the expected cell values was less than 5. Data are expressed as mean ± standard deviation. A p value < 0.05 was considered significant.

RESULTS

The groups were comparable in all major clinical and operative variables, except for a slightly higher mean age in group C, which reflects the fact that patients admitted for coronary bypass are getting older (Table 1).

The doses of heparin were almost identical in all the groups (Table 2). The protamine dose was, according to the protocol, statistically lower in group B, leading to a protamine/heparin ratio of 0.75, compared with 1.3 in groups A and C.

In group B, given the lowest protamine dose, the rate of red cell transfusion was significantly higher compared with the other groups (Table 3). A similar but nonsignificant trend was seen in the incidence of resternotomy for postoperative bleeding (p = 0.09). The amount of mediastinal drainage did not differ significantly, nor did postoperative hemoglobin loss, although a trend could be seen towards higher figures for group B. For all other relevant clinical variables, no significant differences were observed.

DISCUSSION

Although several laboratory techniques for determining more accurate doses of protamine for neutralizing the anticoagulant effect of heparin are available, most cardiac surgical units use standardized doses of protamine after CPB. The most common doses of heparin are 3 to 4 $mg \cdot kg^{-1}$, aiming at an ACT of 400 to 480 seconds,[7] and a protamine/heparin ratio of 0.6–1.8 mg to 1 mg.[8] Within

Table 1. **Demographic and Operative Details**

Parameter	Group A (n = 100)	Group B (n = 100)	Group C (n = 100)	p Value
Age (years)	58.5 ± 8.3	60 ± 8.1	61.1 ± 9.8	0.02
Female (%)	15	22	16	NS
Body surface area (m^3)	1.94 ± 0.15	1.92 ± 0.16	1.92 ± 0.19	NS
Ejection fraction (%)	65.9 ± 12.1	64.7 ± 13.6	65.1 ± 14.2	NS
At least 1 arterial graft (patients)	100	100	99	NS
Number of distal anastomoses	3.8 ± 1.3	3.9 ± 1.3	4.1 ± 1.1	NS
Extracorporeal time (min)	60.1 ± 20	54.8 ± 17.1	57.1 ± 16.8	NS
Ischemic time (min)	28.7 ± 11.9	26.7 ± 9.7	29.8 ± 10.6	NS
Lowest hematocrit on bypass (%)	23.2 ± 2.5	22.4 ± 2.6	22.5 ± 2.1	NS

NS = not significant.

Table 2. **Heparin and Protamine Doses**

Drug	Group A (n = 100)	Group B (n = 100)	Group C (n = 100)	p Value
Heparin (mg)	323 ± 42	318 ± 48	318 ± 52	NS
Protamine (mg)	420 ± 54	240 ± 38	413 ± 52	< 0.0001
Protamine/heparin	1.3	0.75	1.29	< 0.0001

NS = not significant.

Table 3. **Postoperative Data**

Parameter	Group A (n = 100)	Group B (n = 100)	Group C (n = 100)	p Value
Mediastinal drainage (mL)	629 ± 278	693 ± 340	648 ± 241	NS
Autotransfusion (mL)	611 ± 238	666 ± 332	622 ± 216	NS
Red cells and/or plasma transfusion (patients)	1	7	0	0.03
Resternotomy for bleeding (patients)	2	6	1	NS
Preoperative hemoglobin level ($g \cdot L^{-1}$)	146 ± 13	146 ± 11	145 ± 10	NS
Hemoglobin level at discharge ($g \cdot L^{-1}$)	122 ± 14	118 ± 15	120 ± 14	NS
Hemoglobin loss ($g \cdot L^{-1}$)	23.9 ± 1.2	27.6 ± 1.3	24.2 ± 1.1	NS
Postoperative intubation (hours)	1.1 ± 0.6	1.2 ± 0.9	1.1 ± 0.6	NS
Perioperative MI (patients)	2	2	3	NS
Mortality (patients)	0	0	1	NS

MI = myocardial infarction, NS = not significant.

the limitations of a nonrandomized study, the present data clearly show that the dose of 1.3 mg protamine to 1 mg heparin was very effective, causing moderate postoperative mediastinal drainage, few reoperations for bleeding, and a very low incidence of allogenic transfusion. Although a retrospective analysis, the results were obtained under standardized conditions and all the patients underwent identical treatment regimen performed by the same surgeon and the same anesthetist.

There were no significant differences in any of the postoperative variables whether protamine was administered in fractionated doses or in a bolus dose. This is in contrast to the study by Aren and colleagues,[9] who found that a two-dose protocol of protamine administration significantly reduced the level of circulating plasma heparin. A single bolus appears to be the most simple and convenient way of giving protamine, although care should be taken not to infuse the drug too fast as rapid administration may cause arterial hypotension and pulmonary hypertension.[10]

Protamine acts by binding ionically to heparin, which then remains as a stable precipitate. The protamine molecule has 2 active sites: one binds to heparin and the other has a mild anticoagulant effect. This anticoagulant effect was demonstrated in vitro in 1937 by Chargaff and Olson,[11] and it has been suggested that it is due to the inhibition of platelet-induced aggregation.[12] The importance of this effect in vivo is debatable. Administration of very large doses of protamine (600 $mg \cdot kg^{-1}$) to 6 healthy volunteers (without prior heparin administration) was found to cause a mild and transient 30-minute increase in whole blood coagulation time, with no effect on the

partial thromboplastin time.[13] Other studies have shown that protamine has a significant effect as an anticoagulant, but only in nonclinical doses, usually 3 to 5 times the dose normally used to neutralize heparin after CPB.[14,15] This fact indicates that protamine has a large therapeutic window. In this context, it should be noted that the quality of different protamine and heparin preparations is not consistent as the in vitro doses of protamine needed to neutralize heparin are not the same as those shown in vivo.[16] This may also be due to different rates of heparin metabolism.[3,17] Patients' response to heparin varies considerably, depending on various factors such as the body surface, sex, age, and antithrombin III concentration.

In the last 20 years, 4 of the 5 published studies that investigated the effect of a reduced protamine dose on postoperative blood loss or on the need for transfusion showed no benefits of a reduced dose,[1,7,8,18] while one did.[19]

Keeler and associates[8] compared a protamine titration method with an empirical dose protocol for heparinization reversal after CPB in 40 patients. All patients received 3 $mg \cdot kg^{-1}$ heparin, and additional heparin was given as necessary during CPB to maintain the ACT above 400 seconds. The titration group received 2.1 to 7.4 $mg \cdot kg^{-1}$ compared with 5.3 to 9.3 $mg \cdot kg^{-1}$ in the empirical group. Despite a significant reduction in the total protamine dose in the titration group, postoperative bleeding did not decrease.

Shore-Lesserson and colleagues[7] compared both heparin and protamine titration systems to standard weight-based strategies in 135 patients. Although they could predict a lower total protamine dose with the titration technique, this did not result in reduced postoperative bleeding or improved postoperative hemostasis.

Ottesen's group[18] compared an individual heparin dose-response curve technique for protamine dosing to a routine protocol in 20 patients. The dose-response group received 1.18 mg protamine to 1 mg heparin compared to 2 mg in the control group. They did not find any difference in the amount of postoperative bleeding.

In our study, no advantages were observed when the protamine dose was reduced to 0.75 mg to 1 mg heparin. All relevant bleeding variables tended to be negatively affected, and the incidence of allogenic transfusion was significantly higher. In fact, no reasons could be found to reduce the protamine dose to less than 1.3 mg to 1 mg heparin, and it appears safe and convenient to administer protamine in a single bolus dose.

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