
Low Dose Protamine for Heparin Reversal in 40 Consecutive Cardiopulmonary Bypass Patients

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Abstract

(J. Extra-Corpor. Technol. 19[3] p. 348–351 Fall 1987, 13 ref.) Reversal of systemic heparinization in cardiac surgery has been a subject of controversy for some time. For reversal, protamine sulfate (PS) is given in as high a dose as 2:1. We heparinize our patients with 2.0 mg./kg. of beef lung heparin and reverse this with 70% of the total heparin dose. The mean preoperative activated clotting time (ACT) was 148 seconds. The mean ACT on cardiopulmonary bypass (CPB) was 446 seconds. After successfully weaning the patients from CPB at a bladder temperature of 37°C or greater, the 70% dose of PS was given resulting in a mean ACT of 134 seconds post bypass. The mean post-operative blood loss was 695cc (230cc-3120cc) with only 32% (13 patients) requiring platelet administration and 22% (9 patients) requiring fresh frozen plasma (FFP). No patient required re-operation for hemorrhage. There were 33 coronary artery bypass grafts, all of which were on aspirin and persantine, four aortic valve replacements and three atrial septal defects. These data strongly suggest that heparin reversal can be obtained with low dose PS when these patients are weaned from CPB at 37°C bladder temperature.

Introduction

The use of heparin during certain surgical procedures inhibits the formation of clots when blood flow must be ceased in blood vessels or the heart. Systemic heparinization during cardiopulmonary bypass (CPB) allows blood to leave the body and be returned via the extracorporeal circuit (ECC) without thrombus formation. Heparin prevents coagulation by neutralizing

thrombin and inhibiting the action of activated factor IX (plasma thromboplastin antecedent) and factor XI (plasma thromboplastin component). Existing clots are not dissolved but formation of more clots is impeded. Heparin is effective both in vitro and in vivo, but is metabolized rapidly so the duration of its effect is short. The heparin half life of an intravenous injection is one to two hours.¹ The heparin dose in open heart surgery is calculated in mg./kg. and usually ranges from 2.0 mg./kg. to 4.0 mg./kg.² Activated clotting times (ACT) and heparin assays are the two most common methods of determining whether the heparin dose is adequate to prevent thrombus formation.^{3,4} Heparin reversal with protamine sulfate (PS) usually ranges from a ratio of 1:1 to 2:1, but ratios as low as 0.50–0.79:1 have been reported.^{2,5,6,7} Protamine sulfate is a low-molecular weight, strongly basic protein solution which is obtained from the sperm of salmon and certain other mammals and fish. If administered alone, PS is an anticoagulant.^{2,8} However, when it is given in the presence of heparin, a stable and physiologic inert salt is formed, thus neutralizing the anticoagulant activity of both drugs. We reverse our heparin with a low-dose ratio of 0.7:1. This study was carried out to ascertain if this method of heparinization and heparin-reversal will obtain adequate anticoagulation and reversal.

Materials and Methods

Forty consecutive patients including coronary bypass grafts, valve replacements and congenital heart disease were studied prospectively. All coronary artery bypass graft patients received preoperatively persantine 100 mg. PO q 6 h with the last dose at midnight before surgery and 40 mg. of aspirin at 8:00 p.m. the night before surgery. Beef-lung heparin (Organon)^a,

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1,000 units/cc and protamine sulfate (Lilly)^b 10 mg./cc are the drugs used in this study. The ECC consists of tubing by Cobe Laboratories, Inc.^c; Cobe Membrane Lung with Integral Filter; Shiley S-70^d, Pall Arterial Line Filter, EC-3840^e; Bio-medicus 520 pump^f; Cobe Stockard Pump and Sarns Heater-Cooler^g. A Hemochron analyzer^h was used to measure the ACT. Temperature is measured from both the bladder and esophagus by Monotherm monitorsⁱ. Patients were cooled to 28°C bladder temperature and weaned religiously from CPB at 37°C bladder temperature. Heparin was injected into the atrium by the surgeon and protamine (0.7:1) is given for reversal into a peripheral vein. Activated clotting times are drawn at 3 minutes post-heparin injection and 3 minutes post-protamine injection. Activated clotting times were further drawn on CPB every 30 minutes during hypothermia and every 20 minutes after the patient has been rewarmed to 32°C bladder temperature. These 40 patients in addition were compared to the first 40 coronary bypass patients performed at our institution whose data was analyzed retrospectively for a comparison. All comparative data was treated by *t*-test (2-TAIL) and Chi-Square analysis.

Results

The mean preoperative ACT was 148 seconds. The mean ACT on CPB was 446 seconds. After successfully weaning the patients from CPB at a bladder temperature of 37°C or greater, the 70% dose of protamine sulfate was given resulting in a mean ACT of 134 seconds postbypass. The mean postoperative blood loss was 695cc (230cc-3120cc) with only 32% (13 patients) requiring platelet and 22% (9 patients) requiring fresh frozen plasma (FFP). No patient required reoperation for hemorrhage. There were 33 coronary artery bypass grafts, four aortic valve replacements and three atrial septal defects. A comparison of 40 patients done two years earlier is shown in Table 1. These initial patients differed in the use of a roller pump, a bubble oxygenator and no ASA or persantine was given preoperatively.

In the first 40 patients, the mean preoperative ACT was 154 seconds with a mean ACT of 471 seconds on

Data	Group I, 1986	Group II, 1984	P-Value
ACT Pre-Op	148	154	NS
ACT on CPB	446	471	NS
ACT Post-PS	134	139	NS
Blood Loss	695	575	NS (P = .06)
Total PS Dose	138	268	P = .0001
Platelets Given	32%	30%	NS
FFP Given	22%	32%	NS

In a peer-reviewed edition of the Journal, AmSECT ordinarily requires full statistical data. Such completeness is not necessarily featured in the Proceedings articles—Ed.

CPB. Mean postprotamine ACT in this group was 139 seconds. Thirty percent (12 patients) received platelets and 32.5% (13 patients) received FFP (N/S). The mean postoperative blood loss was 575 cc (N/S). There was a statistical difference in the dose of protamine sulfate given. The mean dose in the first 40 patients was 268 mg. as compared to 138 mg. in the low-dose group; 130 mg. per patient less (P = .0001). No neurologic defects nor reoperation for bleeding occurred in either group, but one patient in the low dose group required additional protamine.

Discussion

The absolute goals in giving heparin and reversing it are stated simply: to prevent intraoperative thrombosis and emboli, and with reversal to minimize postoperative bleeding after completion of cardiopulmonary bypass. We feel that the heparin/PS ratio can be so fine tuned that low doses are adequate with very acceptable results. With hemodilution, the clotting factors are diluted and hypothermia decreases the metabolism of the heparin. As patients are warmed to normothermia, ACTs should be monitored closely. The amount of time that the heparin has been in should also be closely monitored. During hypothermia, ACTs are monitored every 30 minutes. Once patients reach 32°C bladder temperature, ACTs are monitored every 20 minutes to insure that the ACT remains above 300 seconds.⁹ Additional heparin is given depending on the ACT and how much longer the patient will be on CPB. Patients are weaned from CPB at 37°C bladder temperature. In our opinion, the reversal of heparin with the patient being normothermic, in addition to the use of albumin and whole blood for volume repletion during warming, reduces residual heparin in the

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e Pall Biomedical Products Corporation, East Hills, NY 11542

f Bio-Medicus, Minneapolis, MN 55344

g Sarns, Inc./3M, Ann Arbor, MI 48106

h Hemochron, International Technidyne Corporation, Edison, NJ 08820

i Monotherm, St. Louis, MO 63101

interstitial tissue and further reduces the incidence of heparin rebound.

Our study clearly indicates that the minimum dose of heparin (2mg./kg.) adequately heparinized each patient as demonstrated by a mean ACT of greater than 400 seconds in each group. In addition, the absence of any intraoperative clotting in the CPB apparatus and no postoperative neurologic sequelae indicates that the first goal of adequate heparinization was reached.¹⁰ Furthermore, with less heparin given initially and throughout the procedure, less protamine is necessary. In view of the numerous complications of protamine and the protamine-heparin complex, a technique that requires less protamine clearly seems warranted. In addition, Velders et al. experimentally reported a 77% acute drop in circulating platelets within 5 minutes after administration of 2:1 dose of protamine to reverse heparin and an 86% drop in platelet function within the same time frame, both of which may account for bleeding with protamine in regard to high doses and why repeated doses do not necessarily help.¹¹ The increased blood loss between Group I and Group II, while not statistically significant, were divergent by 120cc which we feel most likely is accountable by the use of aspirin and persantine in Group I. Most assuredly, the use of preop aspirin and persantine plus a high dose (2:1) protamine reversal should theoretically magnify the postoperative bleeding problem in light of Velders' and Jacques' reports.^{11,12} Finally, this study confirms the fact that a minimal reversing dose is entirely appropriate and effective as demonstrated by a mean ACT postop that is less than preop, extra protamine was necessary in only one patient, and reoperation for bleeding did not occur in any of the patients in this series. Finally, the 695cc mean blood loss despite the preoperative use of aspirin and

persantine is certainly as good as if not better than other reported series.¹³

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Questions from the Audience

Question: Nancy Achorn, San Francisco, CA: What do you accept as your minimum ACTs on bypass?

Response: Minimum ACTs on bypass are usually greater than 400. That is what we accept, but if we are close to coming off bypass, depending on the ACT and the amount of time remaining in the case, we won't treat it. We will not treat a 350 ACT if we're going to be coming off bypass in 10 minutes.

Question: The only point I think I would make is that although most of us use Hemocrons and they are reliable, the company itself will tell you their accuracy can be off as much 20-25%—which means if you're running a patient at 400 it could be easily actually closer to 300. And I think that's why most of us run our ACTs at a higher level, if we're using Hemocrons, in order to give that variance. It also could mean that you're at 500 if your reading 400. But it's always something to keep in mind if you're prone to run them low—that when you're running at 350 at the end of the case you could be down at 250. I'm just making a point that it's something to keep in mind if you're walking on the edge there.

Response: That's a very good point. We heard a phrase earlier stated: "Sometimes we fly by the seat of our pants" when we're doing this work. Very well taken. Thank you, Nancy.

Question—(Unknown): I have a couple of comments. First, though not in relation to what you said, 25% might be a little bit high for Hemocon. But we know that. Let's go with 15. Okay. At any rate, I think, Frank, that the question you haven't pondered is: "What about people who use more heparin than 2 mgs. per kilogram? Low dose worked well here. I agree, a little bit less is better. Do you think that when we start to look at the majority of teams they are using more heparin—that the same extrapolation will be found, namely .7 to 1?"

Response: I do. This reminds me of something that I should have brought out. In our references in this paper one was Veldar et al., done in the Netherlands, and published in 1986 in the *Annals of Thoracic Surgery*. They did a study on platelet dysfunction when 2 to 1 protamine is given. They found a 76% drop in platelet count in the first 5 minutes, when a 2 to 1 dose of protamine is given. And along with that, there was a 86% decrease in platelet function. They attribute this totally to the administration of 2 to 1 protamine to heparin. They did density studies and could not find clumping of platelets, and this is where they derived that.

Question: Mike Wagner, Indianapolis, IN: I notice that all your patients were on aspirin and persantine prebypass and wonder if the effect of that therapy is what maybe gave you the leadway to be able to run with such a low dose heparin. Have you taken a look at some of the microscopic studies and seen whether or not you have any fiber monomer formation or study some of your fibrinogen—fibrin relationship versus the standard or traditional higher dose heparin?

Response: I agree with you about the aspirin and persantine. And yes, we know that it will play an important role and I think that it probably does give our 2 mg. per kilogram a boost. But if you do have a patient on aspirin and persantine then obviously you can get by with that. In answer to your second question, no we have not looked at fibrin formation in any of the patients postop.

Question: Mike Tann, Indianapolis, IN: I know that small number studies can be very misleading. In your overall surgical population, do one-third of your patients routinely get platelets?

Response: From our research in this 40, and looking at the remainder of them, we use very little platelets. Very little fresh frozen in our patients.

Question: I think you misunderstood me. Your study here shows that one third of those patients receive platelets and you're saying your normal surgical caseload in a year does not receive that much platelet concentrate?

Response: I think it probably varies from patient to patient. But in this 40, no, we didn't in our annual caseload—if I'm understanding your question.

Question: I'm just trying to establish if one third of your caseload receives platelets postop.

Response: I would say yes.

Question: I think that is a really generous use of platelets. I'd like to know what your criteria are for giving platelets, and if you could give some indication of what population of those patients receive platelets have a anaphylactoid reaction to that?

Response: I don't have that.

Question: Alan Becker, New York, NY: I'd like to know how you came up with this .7 to 1 number. Why not .6 or .8? What was your basis for .7?

Response: We looked at the more common ways of reversing heparin around the country. I've been in 3 institutions—4 counting the one I'm in and it was usually ranging from 2 to 1 down to 1 to 1. We wanted to try to see if we could get below that 1 to 1. We picked the .7 as the arbitrary constant. Tried it and it worked. Then we tried on one patient .5 and we had to give additional protamine. So it was a figure we looked at to get just below a very commonly used 1 to 1 ratio.