

Method to Calculate the Protamine Dose Necessary for Reversal of Heparin as a Function of Activated Clotting Time in Patients Undergoing Cardiac Surgery

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Abstract: Activated clotting time (ACT) has been used to monitor coagulation and guide management of anticoagulation control in patients undergoing cardiac surgery for decades. However, reversal of heparin with protamine is typically empirically based on total heparin administered. Dose-related adverse effects of protamine are well described. The aim of this study was to evaluate a heparin reversal strategy based on calculation of the protamine dose based on ACT measurements. We present a method using a mathematical formula based on the dose–response line (1). To check the formula, we performed a retrospective observational cohort study of 177 patients undergoing cardiac surgery with cardiopulmonary bypass (CPB). The study group of 80 patients was administered the dose of protamine obtained using our formula, and the control group of 97 patients was administered the empirically calculated dose. The ACT

returned to normal values in patients who were given doses of protamine that were calculated using our formula; all but two had a final ACT of 141. The application of the formula resulted in a significant reduction in the dose of protamine ($p < .023$). The formula we present is a valid method for calculating the dose of protamine necessary to neutralize heparin. This same method can be used working with a target ACT to adjust the dose of heparin. As a result of its functionality, it allows application on a daily basis standardizing the process. We believe that the formula we developed can be applied in all those procedures in which it is necessary to anticoagulate patients with heparin and later neutralization (cardiac surgery with or without CPB, vascular surgery, procedures of interventional cardiology, and extracorporeal deputation procedures). **Keywords:** cardiopulmonary bypass, heparin, protamine, ACT. *JECT. 2013;45:235–241*

In 1966, Hattersley (2) described the activated clotting time (ACT). This test is the most economic and common method for coagulation and anticoagulation control of patients during cardiac surgery (3–6). Later, in 1975, Bull et al. established that each patient responded differently to the anticoagulation level reached with a dose of heparin (1,7). Using a coordinate chart, we observe this response (Figure 1). Bull et al. also proposed the individualization of the doses of heparin and protamine in accordance with the dose–response curve (1,7,8). Since then, several publications have coincided with the desirability of adjusting the dose of these drugs (5,9–17). However, the most widespread practice consists of administering a standard dose of 3 mg heparin per kilogram of

patient weight without establishing the dose–response curve (5) but rather by confirming anticoagulation with the ACT greater than 400 seconds (5,8,9,15). With respect to protamine administration, there have been various proposals over the years (1,3–5,7–15,18–22). These range from the proposal put forward by Castaneda (1966), which consists of not administering protamine and allowing the coagulation to spontaneously return to normal to the administration of four times the total dose of heparin (1,3–5,7–14,18). Today, the current practice consists of administering between 1 and 1.5 mg protamine for each milligram of heparin given or, using graph paper to draw the line proposed by Bull (1,7), to calculate empirically the milligrams per kilogram of circulating heparin, and thus administer the dose of protamine accordingly. Finally, in many cases, this calculation is performed based only on the experience of the professional, estimating the dose as they consider appropriate, both for convenience and not to waste time with the sole aim of returning the ACT to normal values (5).

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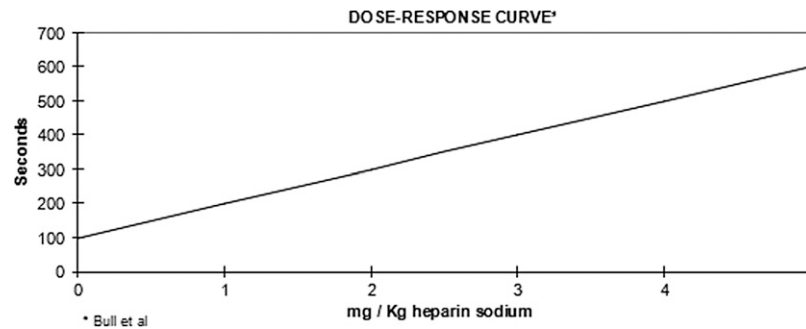


Figure 1. Dose-response curve.

The administration of protamine has been associated with different side effects such as anaphylactic reaction, hypotension, and pulmonary hypertension (21–23). Protamine is well known as an anticlotting agent (5,10–12,14,15,17,21,22). For this and other reasons, different publications (5,10–17,19,20) agree about convenience of an accurate dose adjustment, because a nonappropriated administration, either a shortage or excess, is related to a higher incidence of adverse events in the postoperative period. High doses of protamine lead to platelet dysfunction with subsequent anticoagulant action (5,9–17,19,20), especially if more than 1.3 mg protamine, per each milligram of heparin administrated, is given (14). In addition, several publications point out that dose reduction is correlated with more satisfactory results (5,9–17,19,20), although other authors do not confirm this (21).

The selection of the dose of protamine to be used is verified by the value of the ACT, which must, again, be within normal parameters (100–140 seconds) or, in any case, at the basal values observed before surgery (1,3,4,8,18,24).

Currently there are different devices available on the market such as the Hemochron RxDx system (International Technidyne Corp., Edison, NJ) or the HMS (Hemostasis Management System; Medtronic Inc., Minneapolis, MN) that predict the required doses of these drugs. The dose of protamine obtained using these devices is lower than with other methods and consequently achieves less bleeding and transfusions in postoperative period (13,16,25–27). In recent years, other thromboelastography tests have become available that measure several aspects related to coagulation (23). They can report on heparin levels in blood, several coagulation parameters, and even if there is a shortage of platelets. Even so, the determination of the ACT as coagulation proof is practical, quick, cheap, and can be used in the operating room itself, although it continues to be imprecise and can vary by up to 10–12% between both HemoTec channels (9,24).

The ACT remains the most widespread test in clinical practice at an international level (6,15,22,23).

In this study we intend to establish a standard and objective method for calculating the protamine dose to be administrated, based on the ACT, through a daily basis with patients undergoing heart surgery and treated with heparin as an anticlotting agent.

Our main objective is to demonstrate that the proposed method achieves the reversal of the ACT to normal levels. Secondary objectives are to analyze the amount of postoperative bleeding, the transfusion needs, and the reoperations resulting from bleeding.

MATERIAL AND METHODS

We performed a retrospective observational cohort study of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) during the period 2007–2010. We selected systematically all patients treated during this period at the hospital to avoid bias. Only those patients with incomplete clinical records regarding variables studied were excluded.

The daily anticlotting protocol for cardiac surgery at our hospital is control of the ACT: Medtronic ACT II (Medtronic Inc.) with cartridges of high-range Medtronic HR-ACT with kaolin reagent at .75%, .0025M CaCl₂ HEPES buffer, and sodium azide (24). We consider the normal range to be between 100 and 140 seconds. The extracorporeal circuit used is Maquet with Bioline coating and a set of HLM tubes. The rigid venous cardiomy reservoir used is VHK 2001. The oxygenator is Quadrox-i. We use a quart of blood filter. We carry out the measurement of basal ACT when the patient arrives to the operating room, after piercing the radial artery for monitoring, having previously discarded the first few milliliters (24). We administer an initial dose of 3 mg heparin per kilogram maintaining the ACT values above 400 seconds during the CPB. Before and after the CPB, blood samples for ACT measurements are collected from the introducer catheter, which does not contain any heparin, having previously discarded 20 mL. During CPB, blood samples are extracted from the extracorporeal circuit. Heparin is

not added to the prime. We measure basal ACT, post-heparinization, and final levels in normothermic conditions. For all measurements, to release the catalyst, the ACT cartridge is shaken after previous preheating, according to the manufacturer's instructions (24).

At our hospital, the surgical team is formed by the same surgeons, anesthesiologists, and perfusionists. The perfusionist is the one in charge of determining the dose of protamine. After developing the formula, the lead researcher decided to apply it systematically to all his patients, thereby constituting the study group. The control group was formed by patients attended by other two perfusionists who also belong to the research team and who continued following the usual method at the hospital to calculate the dose of protamine. The control group calculation was based on Bull's curve (1), bearing in mind the measurements of basal ACT, heparin postbolus ACT, and ACT before the administration of protamine. They assumed that 1 mg heparin neutralizes 1 mg protamine but without using any mathematical method or graph paper.

The following parameters were collected for both groups from clinical records: sex, date of birth, height, weight, body surface area, type of surgical procedure (myocardial revascularization surgery or other), scheduled or emergency procedure, if it was the first cardiac surgery or successive, type of extracorporeal circulation used: conventional or minimal extracorporeal circulation system (MECCs), CPB duration, aortic cross-clamp duration, minimum temperature reached during the CPB, basal ACT, initial heparin in bolus, post-heparinization ACT, total heparin administered, ACT levels along the CPB, estimated protamine dose using the proposed formula, protamine dose administered, and final ACT.

We collected the following information from our cardiac surgery database: total bleeding from the chest drains, need for transfusion in the intensive care unit, and need for reoperation resulting from bleeding in the immediate postoperative period (24 hours).

We performed a descriptive analysis of the main study variables, calculating averages and standard deviations for numeric variables and frequencies and percentages for categorical variables. We used the Student's *t* test for independent samples and related samples for the bivariate analysis according to requirements as well as their confidence intervals. For the distribution of the quantitative variables, we assumed normality for large samples from $n = 30$ according to the central limit theorem. For the association between categorical variables, we use χ^2 . We consider statistically significant when a *p* value is $< .05$. We used the computer program SPSS® release 15.0 (SPSS Inc., Chicago, IL) for management and statistical analysis of the data.

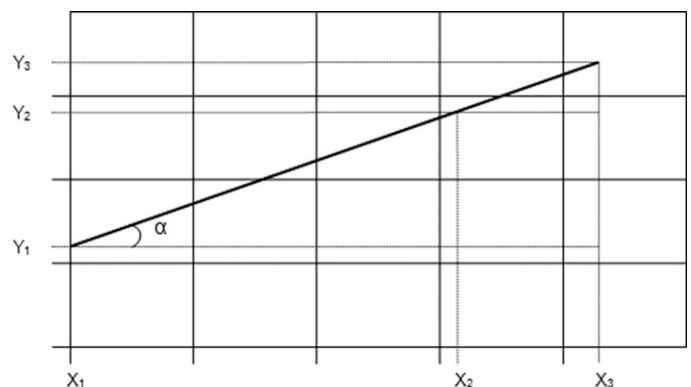
The present study has received favorable judgment from the Clinical Ethics Committee for Clinical Research of Galicia on December 9, 2010, and was classified by the Spanish Agency for Drugs and Health Products from the Ministry of Health, Social and Equality Policy on March 28, 2011. The international rules of good practice for trials with humans were followed (Helsinki Declaration, CONSORT, Oviedo Convention) as well as applicable law (Biomedical Research Law 14/2007, Act for the Protection of Personal Data).

Description of the Proposed Method: Calculation of the Dose of Protamine Using a Mathematical Formula

The following mathematical formula is based on the linear relationship (individual for each patient) that is the initial anticoagulative response to a first dose of heparin: dose-response line (1,7) and assumes that 1 mg protamine neutralizes 1 mg heparin. Starting from this basis, we sought a mathematical relationship, which is found in the equation of a straight line passing through two points (Figure 2). Thus, we may determine that:

$$\frac{X_3 - X_1}{X_2 - X_1} = \frac{Y_3 - Y_1}{Y_2 - Y_1}$$

With the current ACT, or before protamine administration, we intend to get a real-time estimation of



- Y₁ = Basal ACT
- Y₂ = Post-initial heparin bolus ACT
- Y₃ = Pre-Protamine ACT
- X₁ = 0
- X₂ = Initial heparin bolus / Weight (Usually 3)
- X₃ = mg / Kg of circulating heparin

Figure 2. Equation of a straight line passing through two points.

circulating heparin. Because 1 mg protamine neutralizes 1 mg heparin, if we calculate the amount of circulating heparin, we may calculate the amount of protamine to administer.

$$\frac{X_3 - X_1}{X_2 - X_1} = \frac{Y_3 - Y_1}{Y_2 - Y_1} \quad X_3 - X_1 = \frac{Y_3 - Y_1}{Y_2 - Y_1} \times (X_2 - X_1)$$

X₁ = 0; so:

$$X_3 = \frac{Y_3 - Y_1}{Y_2 - Y_1} \times X_2$$

mg/Kg of circulating heparin

$$= \frac{\text{Preprotamine ACT} - \text{Basal ACT}}{\text{post initial heparin} - \text{Basal ACT bolus ACT}} \times \frac{\text{Initial heparin bolus}}{\text{Weight}}$$

Finally, by multiplying milligrams of circulating heparin by weight of the patient, we obtain:

Protamine to administer

$$= \frac{\text{Preprotamine ACT} - \text{Basal ACT}}{\text{post initial heparin} - \text{Basal ACT bolus ACT}} \times \text{Initial heparin bolus}$$

The Bull proposal (1) is to determine the basal ACT, administer 2 mg/kg heparin, thus obtaining the Bull dose-response curve. Later we must extrapolate a target ACT of 480 seconds from the curve to determine the second dose of heparin required to achieve the total anticoagulation of the patient. The proposed formula can also be used for this purpose

mg/Kg of heparin

required for target ACT : 480

$$= \frac{\text{Target ACT : 480} - \text{Basal ACT}}{\text{ACT post initial} - \text{Basal ACT heparin bolus}} \times \frac{\text{Initial heparin bolus/Weight or mg/Kg of initial heparin administered 2 :}}{\text{mg/Kg of initial heparin administered 2 :}}$$

RESULTS

Table 1 shows characteristics for both groups. Populations were homogeneous, although it should be noted that all of the patients in the control group were undergoing cardiac surgery for the first time. In the study group, a statistically significant proportion (*p* = .003) had previously undergone heart surgery.

Table 1. Characteristics of the study population.

Variable	Cases (n = 80)	Control Subjects (n = 97)	<i>p</i> Value
Male, no. (%)	63 (78.8)	75 (77.3)	.819
Type of surgery:	36 (45.0)	48 (49.5)	.552
coronary, no. (%)			
Programming:	79 (98.8)	97 (100.0)	.269
scheduled, no. (%)			
Reoperation no., no. (%)	73 (91.3)	97 (100.0)	.003
Type of extracorporeal circulation: CPB	71 (88.8)	79 (81.4)	.178
conventional, no. (%)			
Reoperation resulting from bleeding: yes, no. (%)	0 (.0)	3 (3.1)	.113
Concentrated erythrocytes, no. (%)	Cases (n = 67)	Control Subjects (n = 82)	
0 units	45 (67.2)	49 (59.8)	1
1 unit	7 (10.4)	9 (11.0)	.760
2 units	8 (11.9)	13 (15.9)	.416
3 units	1 (1.5)	4 (4.9)	.228
More than 3 units	6 (9.0)	7 (8.5)	.907
Plasma, no. (%)	Cases (n = 71)	Control Subjects (n = 91)	
Yes	8 (11.2)	13 (14.3)	.904
Platelets, no. (%)	Cases (n = 72)	Control Subjects (n = 91)	
Yes	13 (18.1)	17 (18.7)	.425

CPB, cardiopulmonary bypass.

In the study group (Table 2), calculated protamine was 242.50 mg and administered 243.88 mg, giving a ratio of 1:1.006 (correlation coefficient of .995). In the study group, two patients had final ACT values over 140 seconds, both

Table 2. Quantitative variables of the study population.

Variable	Cases (n = 80) Mean ± SD	Control Subject (n = 97) Mean ± SD	<i>p</i> Value
Age (years)	70.58 ± 8.09	70.13 ± 8.97	.734
BSA (m ²)	1.80 ± .15	1.80 ± .16	.927
CPB time (minutes)	163.60 ± 49.69	163.71 ± 54.78	.989
Aortic cross clamp time (minutes)	137.90 ± 43.36	134.14 ± 45.22	.576
Minimum temperature (°C)	34.06 ± .65	34.32 ± .77	.018
Basal ACT (seconds)	127.88 ± 16.86	125.43 ± 16.32	.330
Heparin (initial bolus) (milligrams)	252.06 ± 35.10	240.00 ± 38.73	.330
Postheparin ACT (seconds)	492.53 ± 108.36	497.66 ± 101.83	.746
Planned protamine (milligrams)	242.50 ± 72.29	226.50 ± 62.34	.116
Protamine (milligrams)	243.88 ± 71.49	266.91 ± 60.02	.023
Final ACT (seconds)	118.75 ± 12.55	119.18 ± 10.91	.810
Total heparin (milligrams)	398.31 ± 86.91	418.71 ± 135.00	.226
Total bleeding at chest drainage (milliliters)	1089.19 ± 803.89	1340.34 ± 1009.721	.087
Hct (ICU) (%)	28.06 ± 3.60	27.31 ± 3.70	.191
Hb (ICU) (grams per deciliter)	9.53 ± 1.26	9.42 ± 1.87	.671

SD, standard deviation; BSA, body surface area; CPB, cardiopulmonary bypass; ACT, activated clotting time; Hct, hematocrit; ICU, intensive care unit.

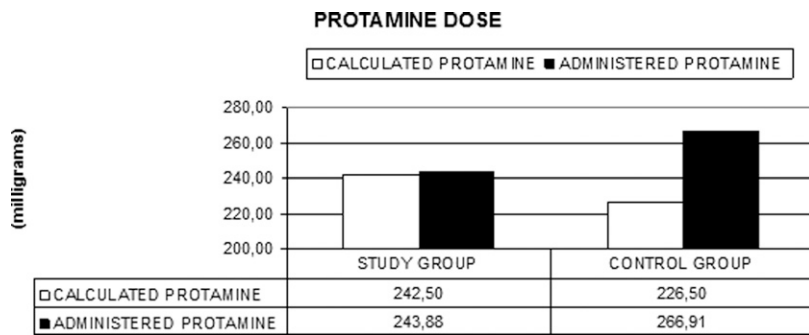


Figure 3. Average doses of protamine.

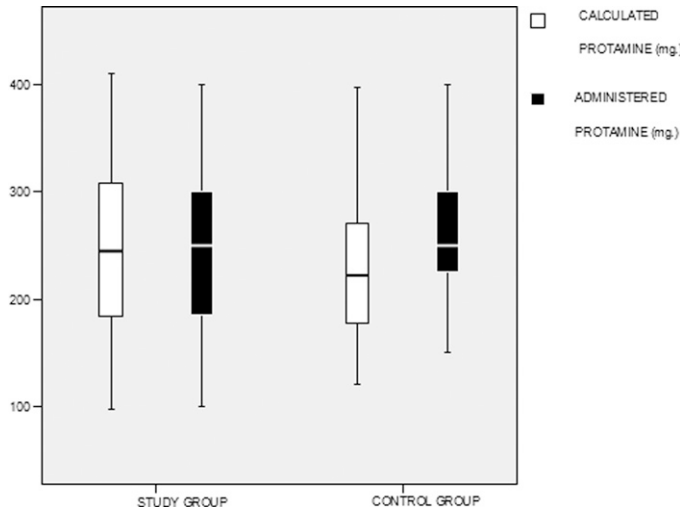


Figure 4. Protamine dose range.

of 141. In all other cases, the ACT returned to normal values and did not require further doses.

We gave the control group an average of 266.91 mg protamine. This amounts to a ratio of 1:1.178 (correlation coefficient of .704). Using the data from the clinical records, we calculated the protamine dose for the control group. If we had used the formula, the protamine calculation would have been 226.50 mg. So, 40.41 mg extra was administered to the control group (17.84%). Three patients had a final ACT over 140 seconds. This value was exactly 141. We did not administer extra protamine doses. (Figures 3 and 4).

Regarding total bleeding during postoperative draining, it has been observed (Table 2) that there an increase of bleeding situations in the control group but it was

without statistical significance (an average of 251.15 mL, $p = .087$) (Figure 5).

DISCUSSION

The ACT is the most common and economic control method for coagulation and anticoagulation in patients undergoing cardiac surgery. There are different methods to calculate the required dose of protamine sulphate to reverse heparin sodium administered on the basis of this test. Through the use of graph paper, estimating it empirically, or through any other method, the fact remains that the calculation of this dose is not standardized.

Our formula accurately calculates the dose of protamine sulphate necessary to neutralize the heparin sodium given. It is a valid method for the calculation of the doses of protamine, because on administering the amount given by the formula, the ACT returns to normal values. The patients in the study group were given a significantly ($p = .023$) lower dose of protamine than those of the control group. Despite this, the postoperative results stayed the same. The formula avoids the need to use graph paper to calculate this dose and it also has the advantage of being fast, simple, objective, and functional. It avoids subjective variability in the calculation and thus unreasonably high or low doses, thereby reducing the adverse effects of inaccurate and thus inadequate protamine doses. One milligram of protamine is enough to neutralize 1 mg heparin. This method can also be used to work with a target ACT, also adjusting the heparin dose. This can be particularly useful in cases of resistance to heparin.

Using the formula leads to a statistically significant reduction in the dose of protamine. Table 3 shows that if

Table 3. Test of related samples (control group).

	Related Differences					
	Mean	Standard Deviation	95% Confidence Intervals for the Difference		T	Significance (bilateral)
			Lower	Upper		
Calculated protamine – protamine administered	-40.41	47.09	-49.90	-30.91	-8.451	< .0001

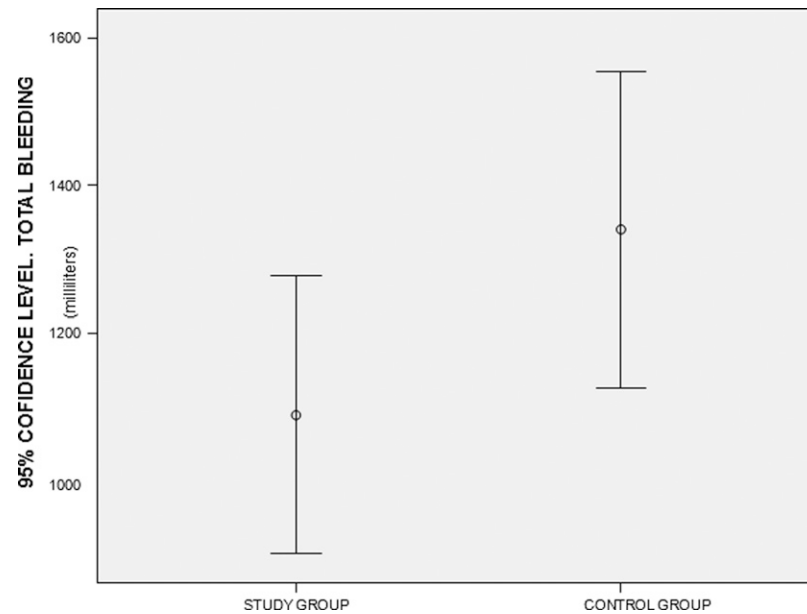


Figure 5. Total bleeding at chest drainage.

we have applied the formula to calculate the dose for patients in the control group, we would have reduced the dose 40.41 mg less ($p < .0001$).

We believe that our formula can be applied in all those procedures where it is necessary to anticoagulate patients with heparin sodium and later neutralize the heparin with protamine sulphate such as cardiac surgery with or without CPB, vascular surgery, procedures of interventional cardiology, and extracorporeal deputation procedures.

We describe a simple method of determining protamine dosage based on ACT that resulted in a smaller doses of protamine. For hospitals in which, like ours, only ACT is available in the operating room to control clotting and the anticlotting process, this formula will provide an easy method for calculating the dose of protamine necessary to neutralize heparin standardizing and simplifying the process.

LIMITATIONS

In the control of anticoagulation with the ACT, we should bear in mind constraints that it presents. However, in the absence of another cause that justifies the anticoagulation, the value of the ACT should be a reflection of heparin level circulating in blood. In addition, the curve of Bull (1) can be shifted as a result of different causes such as hemodilution or hypothermia among other causes of coagulopathy (15,22,23). To apply the method, the patient should be in normothermia.

Because the data collection procedure was retrospective, we should note that, in our cardiac surgical database, we found that 16 patients had no records of bleeding and

transfusion needs during the postoperative period. This in the total sample is equivalent to 9% of missing values.

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