Activated Clotting Times versus Protocol Anticoagulation Management

James P. Dearing, David M. Bartles, Martha R. Stroud, and Robert M. Sade
The Extracorporeal Circulation Technology Program
College of Allied Health Sciences

The Division of Cardiothoracic Surgery
Medical University of South Carolina
Charleston, SC 29425

Abstract

This study compares the management of heparin and protamine administration during cardiopulmonary bypass by a protocol assuming a constant heparin degradation rate with management by an activated coagulation time dose-response method.

The charts of 648 adult patients operated on between January 1975 and December 31, 1980, were reviewed. In Group I patients, heparin was administered at a dosage of 2.5 mg/kg of body weight and supplemented by 50% of the loading dose at 2 hours and 25% each hour thereafter. Protamine was administered on a 1:1 basis according to an assumed heparin degradation rate of 0.4% per minute. In Group II patients, heparin and protamine doses were based upon activated coagulation time dose-response curves.

Data extracted from the charts included blood loss and replacement data, heparin and protamine doses, and coagulation profiles. The data from the two groups were compared and analyzed.

Group II patients received more heparin, but less protamine, had more complete heparin reversal, less post-operative bleeding, and required less blood or blood product replacement.

Address correspondence to: James P. Dearing, B.S., C.C.P., College of Allied Health Sciences, Extracorporeal Circulation Technology Program, 171 Ashley Avenue, Charleston, SC 29425.

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Introduction

The controversy over the best management protocol for heparin-protamine administration during cardiopulmonary bypass (CPB) is yet to be resolved.[1] Empirical doses of both heparin and protamine, based on an assumed heparin degradation rate, are still advocated in the literature[2,3] while activated clotting times (ACT)[4], automated ACT[5] and automated protamine titration[6] devices are recommended by others.

In our institution, two distinct periods of heparin management can be identified; 1975–76 when we managed heparin empirically, and 1978–80 when we used an ACT dose-response method.[7] Recognizing the hazards in a retrospective study over an extended period of time with differing surgical teams and a changing patient population, we feel, nevertheless, that any differences between the two groups should be reported, for they reinforce our conviction that ACT dose-response curve management of heparin-protamine dosage has significantly improved the management of the patient undergoing CPB.

Methods and Materials

The hospital records of 187 adult patients operated between January 1975 and June 1976 and of 461 operated between January 1978 and December 31, 1980, were reviewed. The time period July 1976 to December 1978 was excluded because this

was a period of experimentation and refinement of the ACT method. Twenty-eight percent of the patients had valve replacements, 55%-coronary artery by-pass, 3%-combined valve and by-pass procedures, 5%-correction of congenital anomalies and 9%-other procedures. In all patients, the priming volume and constituents were the same: two liters of Lactated Ringer's solution, 500 ml of 6% hydroxyethyl starch in 0.9% saline,[a] and 1500 units of beef lung heparin.[b]

A variety of oxygenators including both membrane and bubble types were used throughout the study periods. A standard protocol for management of CPB was followed: blood flow 2.2–2.4 L/min/m^2 at normothermia, 1.5–2.0 at moderate hypothermia (28–30°C); blood pressure maintained between 50–70 mmHg with neosynephrine, nitroprusside, or nitroglycerin as needed. After CPB, all patients received two units of fresh frozen plasma as protamine was administered.

In the earlier group of patients, heparin was administered at an initial dosage of 2.5 mg/kg of body weight, supplemented by 50% of the loading dose 2 hours later, and 25% each hour thereafter. The reversing dose of protamine was the same as the residual amount of heparin, calculated with an assumed heparin degradation rate of 0.4% per min.

The initial dose of heparin in the latter group was 3 mg/kg; subsequent doses were determined on the basis of an ACT dose-response curve.[9] This curve was also used to estimate the protamine requirement.

From each patient's chart, the following data were recorded: patient age and weight, duration of CPB, blood loss over first 24 hours after surgery, the amount of blood transfused in units, the amount of heparin and protamine administered, hemoglobin and hematocrit values, prothrombin time, partial thromboplastin time, thrombin time, fibrinogen concentration, and platelet count. It was also noted whether the patient required reexploration for postoperative bleeding. Data from the two groups were compared and analyzed using Student's "t" test.

Results

Several significant differences between the two groups were found (Table 1). Although the ACT group received more total heparin than the earlier group, they received less protamine. The ACT group had lower post CPB thrombin times in the face of similar fibrinogen concentrations. Despite the fact that CPB times were longer in the ACT

[a] Hespan, American Critical Care, McGraw Park, Ill. 60085.
[b] Upjohn, Kalamazoo, Michigan.

TABLE I

VARIABLE	1975 - JUNE 1976	1978-1980	P. VALUE
Age (Yrs)	46.7 ± .9	51.4 ± .6	<.0001
Weight (Kg)	70 ± 1	75 ± 1	<.0001
Pump Time (hrs)	1.9 ± .1	2.3 ± .04	<.0001
Heparin Given (Mg)	233 ± 5	283 ± 3	<.0001
Protamine Given (Mg)	205 ± 4	185 ± 3	<.0001
Blood Loss (ML)	861 ± 73	437 ± 21	<.0001
Blood Given (U)	5.99 ± .41	2.87 ± .13	<.0001
Colloid Given (L)	1.56 ± .09	1.10 ± .04	<.0001
PT PRE-POST	3.5 ± .8	3.2 ± .1	<.51
PTT PRE-POST	4.0 ± 1.0	5.3 ± .4	<.15
Fibrinogen PRE-POST	148 ± 7	148 ± 4	<.96
TT POST	24.9 ± 1.7	21.6 ± .7	<.03
RE-OP	11 (5.9%)	9 (1.95%)	<.025

ALL VALUES = MEAN ± SEM

Comparative Results for Groups 1 and 2

group and that the patients were older and larger, the later patients required less blood, had significantly less post-operative blood loss, and a lower incidence of post-operative bleeding requiring re-exploration.

Discussion

The objective of anticoagulation management during cardiopulmonary bypass is to prevent the formation of thrombus and the consumption of clotting factors during CPB. If this objective is achieved, post-perfusion coagulation should be nearly normal.

Until July 1976, heparin administration and reversal was managed by a standard protocol in all patients. This protocol assumed that heparin exerted the same anticoagulant effect in all patients and that heparin disappeared from the circulatory system of all patients at substantially the same rate, 0.4% per minute. These assumptions are probably not valid.

Individualization of the heparin-protamine management using an ACT dose-response method described previously[8] has significantly improved the results in terms of post-operative bleeding and laboratory values. The blood loss and replacement were cut nearly in half. Heparin was more effectively neutralized in the ACT group, as suggested by the lower thrombin time with similar fibrinogen concentrations even though less protamine was given.

The ACT dose-response curve has been very useful in our hands. The precision of the hand-tilted ACT method has been documented.[9,10] Published studies that have found poor correlation between heparin levels and ACT dose-response curves invariably have used an automated ACT device.[c,11,12] At heparin levels commonly used during bypass, the manufacturer warns of the loss of precision of the instrument and recommends that it *not* be used for such purposes.

The objective of protamine titration, whether hand tilted or automated, is to estimate the true heparin concentration in the patient's blood. It should be noted, however, that protamine titration gives little information on the coagulability of the blood. For example, patients with anti-thrombin III deficiency may exhibit a "normal" protamine titration and yet not have the expected prolongation of the coagulation time needed for safe cardiopulmonary bypass.

The validity of our conclusions is compromised by the retrospective, uncontrolled nature of this study. The groups were dissimilar in many variables and differences due to changes over time of surgical technique, surgical staff, models of oxygenator, pharmacologic management and the like, may have influenced the variables measured. Within these recognized limitations, however, we showed that the ACT and the dose-response curve are effective in managing anticoagulation during CPB. The ACT provided a more precise protamine dose estimation which led to a lowered protamine requirement. The ACT method was associated with a substantial reduction in postoperative blood loss and blood or blood product requirement.

[c] Hemochron, International Technidyne Corporation, Metuchen, NJ 08840.

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