

Original Article

Comparison of Three Methods to Estimate Heparin Loading Dose for Cardiopulmonary Bypass

T. Dale Clark, RPh, CCP; Jodie M. Ecklund, BS, CCP; Mary M. McCall, BSN, CCP; Dennis R. Wolk, BSRN, CCP; Jeffrey B. Riley, BA, CCP

Medical University of South Carolina, Program in Extracorporeal Circulation Technology, Charleston, South Carolina

Presented as a poster at the 31st International Conference of the American Society of Extra-Corporeal Technology, Dallas, Texas, February 26-March 1, 1993

Keywords: cardiopulmonary bypass, activated clotting time, heparin loading dose, RX/DX, HMS

ABSTRACT

Three available methods used to determine heparin loading dose were studied to determine the most reliable method for reaching a target pre-bypass activated clotting time (ACT) of 510 seconds. One hundred and seven patients were randomly assigned to one of three treatment methods: A) 300 units/kg; B) Hemostasis Management System (HMS); C) RX/DX. Five different lots of heparin were assigned to Groups A and B, and Group C had one heparin lot. Different lots were used to account for possible variations in heparin activity.

Post-skin incision ACTs, post-heparin pre-bypass ACTs, and heparin loading doses were compared. The mean and standard deviation of the post-heparin pre-bypass ACTs were used to determine which method was most reliable to obtain a desired ACT.

There was no statistical difference between different heparin lots. There was no difference in the post-heparin ACTs for the three methods (A:487±135 vs. B:474±105 vs. C:474±111 sec). There was a statistically significant difference between the standard deviation for the HMS and 300 u/kg standard deviations ($p<0.05$). The HMS has the smallest deviation which makes it the most reliable predictor of heparin loading doses to reach a target ACT for cardiopulmonary bypass.

Address correspondence to:
Jodie M. Ecklund, BS, CCP
Program in Extracorporeal Circulation Technology
101 Doughty St., 2nd Floor
Charleston, SC 29401

INTRODUCTION

The definitive test for monitoring anticoagulation and coagulability in cardiac surgery has been the activated clotting time (ACT). Several studies have suggested that the standard target ACT for initiating cardiopulmonary bypass (CPB) be greater than 480 seconds using a loading dose of 300-400 units of heparin per kilogram body weight (1). Optimal heparin management and extracorporeal circuit anticoagulation are often difficult to control when using the ACT alone due to variation in the patient's response, assigned heparin units of activity, and ACT reliability (1).

According to Gravlee et al., the advantage to selecting the ACT for monitoring adequate anticoagulation during CPB is that other coagulation studies, i.e., activated partial thromboplastin time (APTT) and thrombin time (TT), become highly variable at heparin concentrations routinely used during CPB (about 2.0-4.0 u/ml) (2). However, the ACT measurement carries a certain degree of variability itself. This may be due to hemodilution, hypothermia, and a non-linear relationship of ACTs greater than 600 seconds (1,3). Furthermore, the ACT variability doubles at the heparin doses needed to initiate bypass (2).

Testing variability and patient individuality can lead to other sources of error as well. Some factors which come into play include estimating the patient's circulating blood volume, pre-operative coagulation status (platelet dysfunction, low fibrinogen levels, or decreased clotting factors), age, and abnormal anti-thrombin III (AT-III) levels (4).

Potential variability between different preparations of heparin and assigned units of activity is a possible source of error. A clinical study comparing two brands of beef lung heparin with the same assigned units of activity exhibited different levels of anticoagulation. Twenty-five percent more of one heparin brand was required to reach a desired ACT than was necessary with the other heparin. USP assigned units of activity did not result in clinical equivalence between the two brands of heparin (5). A study by Walton and coworkers reported finding greater differences among heparins from different tissues within a species than among those obtained from the same tissue of different species (6). This may explain why heparin lots derived from the same source with the same assigned units of activity may not be clinically equivalent.

Based on our experience, a heparin loading dose of 300 units/kg may be inappropriate for all patients in attaining a target ACT of 510 seconds (approximately 4-10% at our institution). For this reason, alternate methods for achieving the target ACT should be studied. Many clinicians have recommended CPB anticoagulation techniques that combine ACT measurement

and heparin blood concentration assay (1). The three methods tested included: A) 300 units/kg heparin loading dose B) the Hemostasis Management System (HMS)^a and C) RX/DX^b. These three methods were tested and compared in attempt to test the null hypothesis that there was no difference between methods to determine a heparin loading dose needed to achieve an ACT of 510 seconds.

METHODS AND MATERIALS

One hundred and seven adult patients weighing > 45 kg were randomly assigned to one of the three methods: A) 300 units/kg (n=34), B) HMS (n=38), and C) RX/DX (n=35). Furthermore, patients in Groups A and B were randomly assigned to five lots of heparin in order to avoid potential variability between units of assigned heparin activity. Group C patients received RX/DX heparin per manufacturer protocol. These three techniques were employed in this study to determine the ideal method to reach the target ACT which was set at 510 seconds. The ACT of 510 seconds was selected based on the nomogram provided by the RX/DX slide rule and the RX/DX automated slide rule. The patient weight criteria was assigned by the RX/DX protocol.

Pre- and post-skin incision ACTs were drawn, as well as a baseline hematocrit (pre-bypass). Once the sternum was separated, the heparin loading dose was calculated for each patient (if assigned to Groups B or C) and further assigned to a heparin lot.

Group A, the control group, was administered a 300 units/kg loading dose using one of the heparin lots listed in Table 1. A post-heparin ACT was measured using either the Hemochron^b 400 or 801 machine with CA510 Hemochron tubes^b.

Group B loading doses were determined via the Hemotec HMS System. A HMS heparin dose response was performed which measures the ACT at three different heparin concentrations (0.0 u/ml, 1.5 u/ml, and 2.5 u/ml) to create the heparin dose response curve to estimate the actual loading dose of heparin required to reach the target ACT.

Group C incorporated matched RX/DX heparin to two Hemochron tubes containing known amounts of anhydrous heparin (3.0 u/ml and 0.0 u/ml). A heparin response time (HRT)

Table 1: The brands and lot numbers of heparin utilized in this study

Brand	Lot number (1000 u/ml)
Organon beef lung ^c	#150029801
Lyphomed beef lung ^d	#110152
Lyphomed beef lung ^d	#100737
Organon beef lung ^c	#1490191801
Upjohn beef lung ^e	#499FY
RX/DX Group ^a	#110409 matched heparin

- a Medtronic Hemotec Inc., Englewood, CO 80112
- b International Technidyne Corp., Edison, NJ 08820
- c Organon Inc., West Orange, NJ 07052
- d Fujisawa USA, Inc., Deerfield, IL 60015
- e Upjohn Co., Kalamazoo, MI 49001

Table 2: The means and standard deviations for variables studied. Group A = 300 u/kg, Group B = HMS, Group C = RX/DX

Variable	Group A	Group B	Group C	p value
Post-heparin loading dose ACT (sec)	487 ± 135	474 ± 105	474 ± 111	NS
Post-skin incision pre-bypass ACT (sec)	125 ± 23	117 ± 18	117 ± 17	NS
Circulating blood volume (ml)	4934 ± 1011	5434 ± 1252	5421 ± 1024	NS
Heparin loading dose (units)	23529 ± 3933	23281 ± 5356	26814 ± 6299	NS
Priming volume (ml)	1767 ± 73	1813 ± 81	1822 ± 168	NS

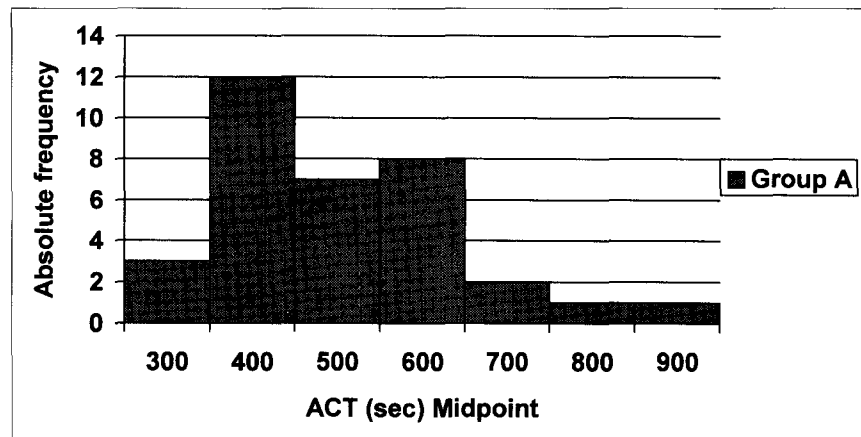
value was derived based upon the patient's post-skin incision response to the heparinized tube. Once this HRT value was obtained, the baseline ACT, patient weight and height were used in conjunction with a provided RX/DX slide rule or automated slide rule to determine the heparin loading dose. After heparinization, an ACT was run to determine adequate anticoagulation for CPB (>400 seconds). The mean ACTs post-heparinization were compared using a Minitab^f statistics package with one-way ANOVA. The standard deviations of the three groups' post-heparinization ACTs were compared by Bartlett's F test. The effect of heparin lot was compared by comparing heparin lot mean ACTs ± the standard deviations between methods. A p value less than 0.05 was considered significant.

RESULTS

Table 2 lists the means and standard deviations for the variables studied. There was no statistically significant difference between the mean activated clotting times for the three methods used to determine heparin loading doses. Bartlett's F test performed on the standard deviations of the post-heparin ACTs resulted in no difference between the RX/DX and HMS HDR groups. The HMS group had the smallest standard deviation among the three methods and was statistically different from the 300 u/kg group. Based on the difference between the standard deviations of the mean post-heparin ACTs between the HMS and 300 u/kg group, HMS is a more predictable method for determining heparin loading doses.

DISCUSSION

There are many methods of anticoagulation control available for use during CPB. This study compared three of those currently available methods to see which is the most reliable

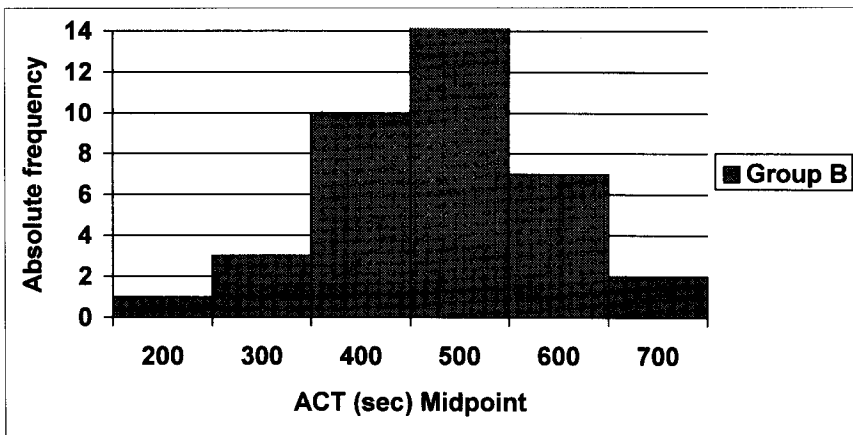
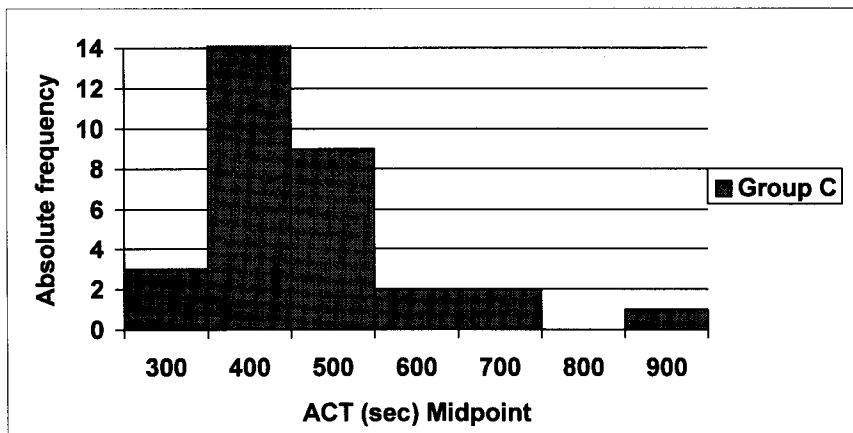
Figure 1: The distribution of post-heparin ACTs in Group A (300 u/kg). n = 34

method for estimating heparin loading doses. There was no difference in the heparin loading dose required to obtain a target ACT among the three groups. The standard deviations of the post-heparin ACTs indicated the HMS group to be the most reliable method.

The 300 u/kg group does not utilize an in vitro analysis of heparin dose response and may result in underdosing in heparin resistant patients and overdosing in heparin sensitive patients. This proved to be true for this group as seen by the large standard deviation. As shown in Figures 1-3, the frequency distribution plots of ACTs around the target ACT was closer in the RX/DX and HMS groups than in the 300 u/kg group. The wide distribution in the 300 u/kg group was expected since this group was empirical and did not utilize HDR analysis.

The HMS and RX/DX methods for predicting loading dose both use in vitro analysis of heparin dose response. The HMS uses two observations at the three heparin concentrations to draw a heparin dose response line. The RX/DX method uses two observations to plot the heparin dose response. The RX/DX method matches heparin lot to heparin loading dose to avoid variability between brands of heparin. In this study, the HMS and RX/DX

^f Minitab Statistics Package, State College, PA 16801

Figure 2: The distribution of post-heparin ACTs in Group B (HMS HDR). n = 38**Figure 3: The distribution of post-heparin ACTs in Group C (RX/DX). n = 35**

exhibited no statistical difference in estimating heparin loading doses as determined from the standard deviations of the post-heparin ACTs. The RX/DX group had a standard deviation of 111 seconds compared to 105 seconds for the HMS group. The HMS and RX/DX groups were expected to be more predictable than the empiric 300 u/kg group since both methods utilize in vitro heparin dose response.

The effects of different lots of heparin did not appear to be statistically significant in attaining a desirable ACT for bypass. The Lyphomed heparin (lot 110152) had a much lower mean ACT (394 seconds) in the 300 u/kg group. Further examination revealed that only four data points in the 300 u/kg group were collected using lot 110152 heparin and one of these points appeared to be a case of heparin resistance. There were no other significant differences among the ACTs obtained from the different lots of heparin in the three groups.

CONCLUSIONS

1. There was no statistical difference between the three methods in obtaining a target ACT of 510 seconds.

2. The HMS HDR method had the smallest standard deviation among post-heparin ACTs and appears to be the most reliable method for predicting heparin loading doses.

3. The RX/DX method had a smaller standard deviation than the 300 u/kg method. The RX/DX appears to be similar to the HMS group and more predictable than the 300 u/kg group in predicting heparin loading doses.

4. The 300 u/kg group uses empirical dosing and based on the wide distribution of post-heparin ACTs is the least effective method to determine heparin loading doses.

REFERENCES

1. Bull BS, Huse WM, Korpman RA. Heparin therapy during extracorporeal circulation: II. The use of a dose response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg.* 1975; 69: 685-689.
2. Gravlee GP, Case LD, Angert KC, Rogers AT, Miller GS. Variability of the activated coagulation time. *Anesth Analg.* 1988; 67: 469-472.
3. Cohen EJ, Camerlengo LJ, Dearing JP. Activated clotting times and cardiopulmonary bypass I: The effect of hemodilution and hypothermia upon activated clotting time. *J Extra-Corpor Technol.* 1980;12(6):139-141.
4. Esposito RA, Culliford AT, Colvin SB, Thomas SJ. The role of the activated clotting time in heparin administration and neutralization for cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1983; 83: 174-185.
5. Stewart SR, Gaich PA. Clinical comparison of two brands of heparin for use in cardiopulmonary bypass. *J Extra-Corpor Technol.* 1980;12:29-33.
6. Novak E, Sekhar NC, Dunham NW, Coleman LL. A comparison of the effect of lung and gut heparins on platelet aggregation and protamine neutralization in man. *Clin Med.* 1972; July: 22-27.