

Original Article

Utility of In Vitro Heparin and Protamine Titration for Dosing During Cardiopulmonary Bypass Surgery

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ABSTRACT

Methods used to maintain a hemostatic balance during cardiopulmonary bypass surgery include the optimization of heparin and protamine dosing. Higher heparin doses have been associated with increased bleeding, while other studies have attributed reduced blood loss and transfusion requirements to lower protamine doses. We have evaluated the use of an in vitro heparin and protamine titration system and compared it to standard dosing in patients undergoing surgery requiring cardiopulmonary bypass. Based upon the principle of the Hemochron® RxDx® system, Heparin Response Tests (HRT) and Protamine Response Tests (PRT) were performed for 40 patients undergoing cardiac surgery at three hospital centers. The Activated Clotting Time (ACT) was used to monitor adequate heparin dosing prior to placing the patient on bypass, and to monitor heparin reversal after protamine dosing. The efficacy of heparin reversal was determined using the Protamine Dose Assay (PDA-O) test. All centers used standard hospital pharmaceutical preparations of heparin and protamine.

Heparin and protamine RxDx dosing was compared to standard hospital practice for each site. Based on the HRT, the average heparin dose was not different from empirical dosing; however, individual differences were as high as 11,000 units. Only a single patient required a second heparin bolus prior to initiation of bypass. On average, the protamine dose predicted by the PRT was only 67% of the empirical protamine dose. The PDA-O test identified the need for additional protamine in 13% of patients. Patients administered additional protamine at the request of the surgical team, despite the presence of a normal PDA-O test, had no further decrease in ACT.

In summary, the in vitro HRT and PRT system did not alter the initial heparin dose yet significantly decreased the protamine doses administered. Based on prior clinical outcome studies, this reduction is expected to have a beneficial effect on postoperative bleeding and transfusion requirements.

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INTRODUCTION

In 1975, Bull and associates identified the existence of a wide variation in patient response to heparin (1), and recommended the use of a dose-response curve to individualize heparin and protamine dosage during cardiopulmonary bypass (CPB) (2). Since that time, other researchers have confirmed the clinical benefits of close control of heparin and protamine dosing. In 1995, Jobes et al. demonstrated that use of the Hemochron® RxDx®^a system for patient-tailored dosing improved clinical outcome by reducing postoperative blood loss and decreasing transfusions (3).

Early clinical management protocols emphasized the need to deliver sufficient heparin to minimize the likelihood of coagulation activation during CPB (1). These protocols called for a wide range of protamine doses to assure neutralization of the heparin. Minimizing patient exposure to protamine has been shown to be important in improving patient outcome. Both Horrow (4) and Levinson and Ohm (5) documented a range of adverse and significant clinical reactions to protamine, including anaphylaxis, hypotension, myocardial depression, and coronary vasospasm. Therefore, a discernible balance needs to be reached in order to avoid excessive doses of protamine while still ensuring complete heparin reversal.

The RxDx system is one of several *in vitro* methods to optimize heparin and protamine dosage during CPB. It employs the use of ACT^a tests in conjunction with HRT^a and PRT^a assays to individualize heparin requirements for each patient and provide quantitative information to calculate protamine dosing. Studies have demonstrated improved clinical outcome (reduced blood loss, reduced transfusion needs) as well as lower cost, when employing the RxDx system (6). The RxDx system employs identical pharmaceutical preparations of heparin and protamine for patient dosing and diagnostic assay. This eliminates the effects of the varying biologic activity from heparin and protamine obtained from different manufacturing sources. Despite this well characterized variability, the recent reduction in the number of heparin and protamine sources and methods of drug preparation suggest that a RxDx system without matched pharmaceuticals may have similar clinical benefit.

The purpose of this study was to determine the efficacy of employing an unmatched RxDx system in patients undergoing cardiac surgery with CPB. The unmatched RxDx system employs the same Hemochron HRT and PRT diagnostic assays as the matched system, but uses standard hospital pharmaceutical preparations of heparin and protamine for patient dosing. Dosing requirements to achieve a specified ACT level both for heparin and protamine administration using the unmatched RxDx system were compared to empirical dosing guidelines. A secondary evaluation of the utility of the PDA-O^a test to identify

Table 1: Target times and empirical dose protocols

Site	Target ACT (seconds)	Heparin (IU/kg)	Heparin (# lots used)	Protamine (mg/100 IU heparin)	Protamine (# lots used)
Center A	530	400	2	1.6	2
Center B	400	300	2	300 mg/patient	5
Center C	480	300	1	1.0	1

patients in which heparin reversal was incomplete was also included in this study.

MATERIALS AND METHODS

STUDY DESIGN

The study was conducted at the three following hospital centers in the United States (listed with their cardiopulmonary bypass circuitry set-ups): Deborah Heart & Lung Center, Browns Mills, NJ (membrane oxygenator, open venous reservoir system and arterial line filter); Medical Center East, Birmingham, AL (membrane oxygenator, closed venous reservoir system and arterial line filter); and St. Joseph's Medical Center, Joliet, IL (hollow filter oxygenator, open venous reservoir system and arterial line filter). None of the centers routinely used the RxDx system for monitoring and adjustment of heparin or protamine administration.

Patients scheduled for routine cardiac surgery involving CPB were eligible for entry into the study. IRB approval was obtained as required by site. Patients receiving pharmaceutical agents for the purpose of reducing blood loss, such as aprotinin, Σ -aminocaproic acid and tranexamic acid, were not eligible to participate in the study. Patients with elevated baseline ACT (greater than 200 seconds) were also excluded.

PATIENT TREATMENT

For initial heparinization, an HRT-predicted heparin dose was calculated based on patient response characteristics and a specified target ACT time. For reversal of heparinization with protamine, a PRT-predicted protamine dose was calculated. All patients received both protamine and beef lung heparin from the standard hospital pharmacy supply.

CALCULATION OF HEPARIN AND PROTAMINE DOSES

The Hemochron 8000^a instrument was used to measure all ACT, HRT, and PRT levels. Each individual site's target ACT time was used as the target level programmed into the instrument. A response curve was generated using the celite ACT (FTCA510)^a test in conjunction with either a HRT or a PRT to calculate the predicted dose of heparin or protamine.

VERIFICATION OF HEPARIN REVERSAL

After reversal with protamine, the PDA-O assay was used

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in conjunction with an ACT test to determine the presence of residual heparin which would require additional protamine to neutralize. The PDA-O assay tube contains an extremely small amount of protamine, in addition to the celite activator. If the heparin in the patient's blood has not been totally neutralized by protamine in vivo, the protamine in this assay will decrease the clotting time relative to the simultaneous ACT test. If the heparin has been neutralized, the PDA-O time will be equivalent to or greater than the concurrent ACT.

RESULTS

Forty patients were treated using the RxDx unmatched system. Twenty-eight patients (70%) were male. The mean age was 65.8 years (± 10.3), with patients ranging from 45 to 89 years of age. The computed HRT and PRT predicted doses were compared to the empirical doses employed at each institution. The empirical dose protocols, target ACT times and number of hospital lots of heparin and protamine employed in this study are shown in Table 1.

HEPARIN DOSE DETERMINATION

Heparin doses were tailored to the individual patient, based on the patient's response to heparin in the HRT in vitro system. In 90% of the cases, the HRT-calculated dose was administered to the patient. Over the total population, there was no significant difference between bolus doses using standard hospital dosing ($22,855 \pm 8,525$ units) or Hemochron HRT-calculated dosing ($22,008 \pm 7,524$ units). However, for individual patients, HRT-calculated doses ranged from 57% to 185% of the standard empirical dose (Figure 1). Additionally, administration of the HRT-calculated heparin bolus dose to 36 patients allowed immediate initiation of cardiopulmonary bypass in 35 cases (97%).

PROTAMINE DOSE DETERMINATION

Individual protamine doses were calculated by the RxDx system based on in vitro test results in a total of 37 patients. The PRT-calculated dose was administered in 77.5% of all cases. A significant reduction of the protamine dose was observed using the PRT system compared to the empirical dosing (Figure 2). PRT-calculated protamine doses (226 ± 71 mg.) were on average 30% lower than the standard calculated empirical doses (357 ± 121 mg.) (Figure 2b). Of the 31 patients receiving the PRT-calculated prota-

mine doses, the ACT levels returned to baseline in 27 cases.

VERIFICATION OF HEPARIN REVERSAL

Thirty-eight patients were tested for heparin reversal by means of the PDA-O test. Of these, 3 patients' results indicated the need for additional protamine. The calculated additional dose was given to 2 of these patients, and in both cases, the subsequent ACT decreased to below baseline levels.

Four patients for which the PDA-O test detected no residual heparin, also received an additional protamine dose. Subsequent ACT tests showed no reduction from the initial post-protamine

Figure 1: The frequency distribution of the ratio of the bolus dose recommended by the RxDx system to the site-specific empirical dose by patient. Values range from 57% (0.57) to 185% (1.85).

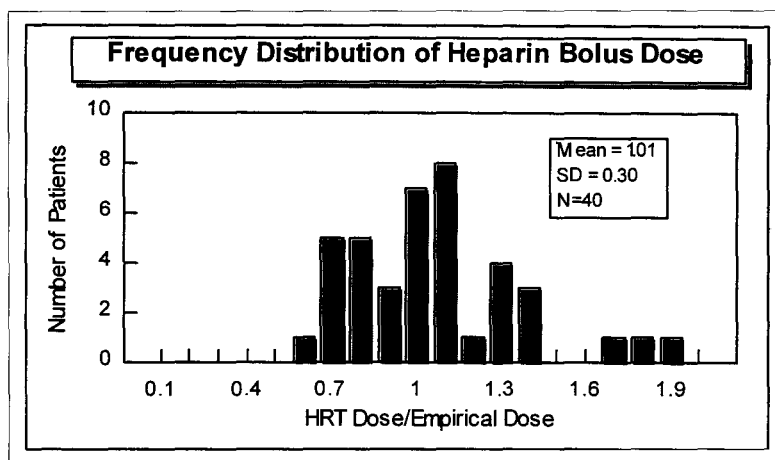


Figure 2: Empirical and RxDx recommended protamine doses are expressed as the ratio of mg protamine per 100 units of heparin given over the entire procedure.

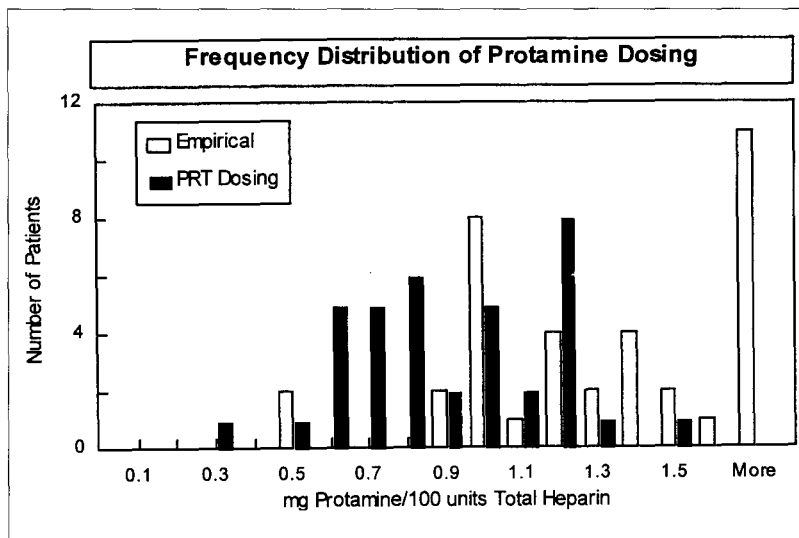
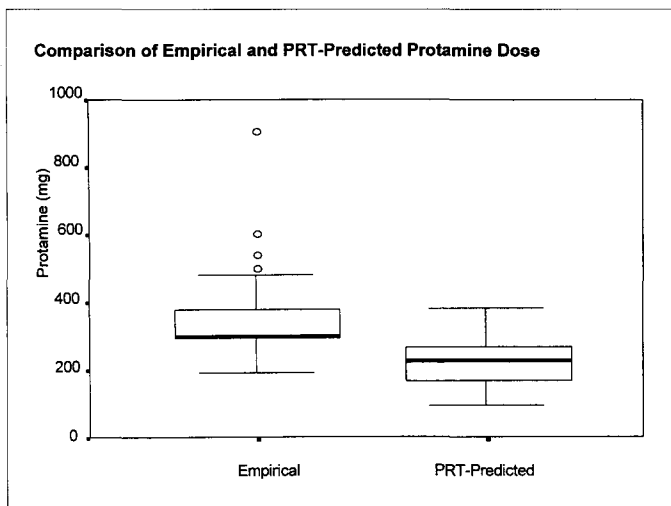


Figure 2b: A comparison of empirical and RxDx recommended protamine dosing ranges (n=37). The mean PRT-calculated protamine dose (226 ± 71 mg) was significantly lower than the mean empirical dose (357 ± 121 mg) ($p < 0.001$). Each box represents the mean 50% of the doses. The line within each box is the median. Outliers noted as circles.



values, suggesting that the PDA-O test was accurate in determining the absence of residual heparin.

DISCUSSION

The utility of monitoring heparin and protamine during cardiovascular surgery has long been recognized (7–9). The use of a matched RxDx system has been shown to accurately predict both heparin and protamine doses (3, 9, 10). Furthermore, both the clinical benefits (10), and the cost-effectiveness (6) of this system have been documented. This study explored the use of a system for monitoring and adjusting heparin and protamine when standard hospital pharmaceutical preparations, rather than preparations specifically matched to the *in vitro* test system, are used.

This study demonstrates the utility of employing the Hemochron RxDx system without the use of matched pharmaceutical preparations to optimize heparin and protamine dose. Mean heparin dosing was not substantially altered by use of the unmatched system. Previous clinical studies differ on the effect of the matched RxDx system on heparin. Jobses and colleagues showed a significant decrease in the heparin dose administered (6), while Nyhan found no mean change from empirical dosing (9). However, individual dose requirements varied substantially from empirical dosing in both studies, as well as in the present study, demonstrating an initial heparin dose tailored to individual patient response characteristics. The underlying variability in patient heparin response (1), and the need to adjust heparin dose in response to this variability (2), have long been recognized.

Despite the use of unmatched pharmaceuticals, the RxDx system allowed all but one patient to be placed on CPB immediately post-bolus. The mean amount of protamine suggested was about 70% of the amount indicated by empirical methods at the study sites, and the maximum protamine dose recommended for the PRT group was less than half the maximum empirical dose. This substantial decrease in protamine dose was previously observed in the matched system (10). Since reducing total protamine exposure is a desirable clinical goal to improve postoperative outcome, the patients dosed with lower protamine doses had a minimized potential for the adverse effects of excess protamine.

After initial protamine infusion, additional protamine doses are frequently requested by surgeons, in an attempt to decrease bleeding of undetermined origin. In this study, the PRT test correctly predicted the amount of protamine required for reversal over 90% of the time. The varying and often subjective practices for administration

of additional protamine after initial reversal emphasize the need for an objective test to identify which patients would benefit from additional protamine. Over 30% of patients received additional protamine; however, according to the results of the PDA-O test, only one-fourth of this group would have benefited from such administration. All patients identified as requiring additional protamine by the PDA-O test that were administered the calculated dose responded with a decreased ACT. Conversely, in patients who did not require additional protamine according to the PDA-O test, additional protamine did not decrease the ACT value. The PDA-O test also identified two patients who did not receive additional protamine, but who may have benefited from its administration.

While it remains to be determined if the unmatched RxDx application can achieve the blood loss and transfusion reduction associated with the matched RxDx system, the control of heparin and protamine dosing parameters obtained with its use appears to be similar to that reported for the matched RxDx system. Although results of this limited study, employing five different heparin and eight different protamine sources, demonstrates the efficacy of an unmatched system, it remains to be determined what result will be observed with a wider panel of drug sources. Studies have shown that the matched system both improves clinical outcome (10) and is cost effective (6). With equal control of these parameters, similar clinical results should be expected with the unmatched system, provided the degree of heparin and protamine biologic variability is not dramatically wide.

This study has demonstrated that an unmatched RxDx system allows accurate prediction of *in vivo* response to heparin and protamine using an *in vitro* assay. The HRT test provided

an excellent in vitro method of predicting the unique patient-specific response to heparin in vivo, while the PRT test was useful in limiting patient exposure to excess and unnecessary protamine. Despite the substantial decrease in protamine dose, return to baseline ACT value after the initial dose was noted in nearly 90% of cases. These results also confirm the value of the PDA-O assay as a verification of heparin reversal. This study provides preliminary data in support of the use of the RxDx system in conjunction with standard hospital heparin and protamine for prediction of required heparin and protamine doses during surgical procedures requiring cardiopulmonary bypass.

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