Reports of Investigation

Heparin and protamine titration do not improve haemostasis in cardiac surgical patients

Linda Shore-Lesserson MD,
David L. Reich MD,
Marietta DePerio RN

Purpose: Weight-based heparin and protamine dosing strategies for cardiopulmonary bypass (CPB) do not take into account interpatient variability in drug sensitivity and may result in bleeding complications. We compared the Hemochron® RxDx heparin and protamine titration system with standard weight based management with regard to heparin dose, protamine dose, and perioperative bleeding.

Methods: One hundred and thirty-five cardiac surgical patients were randomised into four groups. Group 1 received standard heparin and protamine management: Group 2 received heparin and protamine by *in vitro* titration. Group 3 had the heparin dose titrated, and group 4 had the protamine dose titrated. Coagulation tests, bleeding, and transfusion requirements were measured.

Results: The initial heparin bolus predicted by the titration was <300 U·kg^{-1} in all patients. Group 2 received a lower heparin bolus for the initiation of bypass but total heparin doses were not different among groups (group 1 = 365 ± 43, group 2= 348 ± 73 U·kg^{-1}, group 3= 394 ± 86 U·kg^{-1}, group 4= 376 ± 60; $P = 0.06$). Groups 2 and 4 received a lower initial and a lower total protamine dose (total dose group 1 = 4.03 ± 0.65 mg·kg^{-1}, group 2 = 3.56 ± 1.11 mg·kg^{-1}, group 3= 4.22 ± 0.90 mg·kg^{-1} , group 4= 3.38 ± 0.98 mg·kg^{-1}, $P = 0.001$). The incidences of incomplete heparin neutralisation ($P = 0.14$) and heparin rebound ($P = 0.1$) were not different among groups. Postoperative bleeding and transfusion requirements did not differ.

Conclusion: In cardiac surgical patients, heparin and protamine titration did predict a lower protamine dose but did not result in a measurable improvement in haemostasis during the perioperative period.

Objectif : Au cours de la circulation extracorporelle (CEC), la façon d'administrer l'héparine et de la protamine selon le poids du sujet ne tient pas compte des différences interindividuelles de sensibilité pour les médications et peut provoquer des complications hémorragiques. Nous avons comparé les doses d'héparine et de protamine et l'importance du saignement postopératoire lorsqu'une des deux méthodes suivantes était utilisée : le système Hemochron® RxDx pour le titrage de l'héparine et de la protamine, et la méthode usuelle basée sur le poids.

Méthodes : L'étude regroupait 135 opérés cardiaques répartis aléatoirement en quatre groupes. Au groupe 1, on appliquait la méthode standard d'administration de l'héparine et de la protamine ; le groupe 2 recevait l'héparine et la protamine conformément au titrage *in vitro*. Pour le groupe 3, on titrait l'héparine et pour le groupe 4, on titrait la protamine. Le bilan hémostatique, le saignement et les besoins transfusionnels étaient évalués.

Résultats : Le bolus initial prédit par titrage était inférieur à 300 U·kg^{-1} chez tous les patients. Le groupe 2 a reçu un bolus d'héparine moins important pour la mise en marche de la CEC mais les doses totales d'héparine n'ont pas différé entre les groupes. (groupe 1 = 365 ± 43 U·kg^{-1}, groupe 2 = 348 ± 73 U·kg^{-1}, groupe 3 = 394 ± 86 U·kg^{-1}, groupe 4 = 376 ± 60 U·kg^{-1}, $P = 0,06$). Les groupes 2 et 4 ont reçu une dose initiale et totale de protamine moins importante (dose totale groupe 1 = 4,03 ± 0,65 mg·kg^{-1}, groupe 2 = 3,56 ± 1,11 mg·kg^{-1}, groupe 3 = 4,22 ± 0,90 mg·kg^{-1}, groupe 4 = 3,38 ± 0,98 mg·kg^{-1}, $P = 0,001$). L'incidence de neutralisation héparinique incomplète ($P = 0,14$) et le rebond héparinique ($P = 0,1$) ne différaient pas entre les groupes.

Conclusion : En chirurgie cardiaque, le titrage de l'héparine et de la protamine permet de prédire une dose moins importante de protamine mais n'améliore pas de façon tangible l'hémostate postopératoire.

From the Department of Anesthesiology, Mount Sinai Medical Center, One Gustave L. Levy Place, Box 1010, New York, NY 10029.
Address correspondence to: Linda Shore-Lesserson MD;
Phone: 212-241-7467; Fax: 212-876-3906; E-mail: linda_shore@SMTPLINK.MSSM.EDU
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SURGICAL procedures requiring cardiopulmonary bypass (CPB) have been successfully conducted for decades as a result of systemic anticoagulation using heparin. Heparin has features of an ideal anticoagulant in that its activity is rapid in onset, is readily reversed with protamine sulfate, and is conveniently measured using the activated coagulation time (ACT). Heparin is a heterogeneous compound composed of carbohydrates that vary in biological activity,[1] molecular weight, and susceptibility to protamine antagonism. The response to heparin varies greatly among patients and is dependent upon such factors as patient age, sex, body surface area, heparin source, and anti-thrombin III concentration.[2] Higher heparin concentrations may allow for reduced activation of the coagulation cascade,[3] but have also been shown to result in increased mediastinal tube bleeding postoperatively.[4]

Protamine administration has been associated with a spectrum of adverse effects. These include histamine-related hypotension, mild to severe anaphylactoid reactions, frank hypersensitivity, and catastrophic pulmonary arterial hypertension.[5] Protamine has anticoagulant effects when given alone or in excess of heparin;[6] thus its dose should be carefully calculated.[7]

Young *et al.*, in 1978, determined that an ACT ≥400 sec was needed to inhibit production of fibrin monomer during CPB in a primate model.[8] It is current practice in many institutions, including ours, to administer a single bolus of heparin (300 $U \cdot kg^{-1}$) in order to achieve the therapeutic ACT. The protamine dose is then calculated based on the heparin dose given or by a protamine titration assay. Dosing schema for heparin and protamine that are based on patient weight do not account for interpatient variability and may result in a relative overdose or underdose of either or both drugs. In a prospective randomised trial, we examined the utility and value of an *in vitro* system designed to titrate the heparin and protamine dose. Secondly, we compared our standard weight-based management with the *in vitro* titration method to determine if the latter offered any advantages with respect to heparin dose, protamine dose, and bleeding and transfusion requirements in the perioperative period.

Methods

The protocol was approved by the Institutional Review Board and all patients gave written informed consent to participate. Patients undergoing elective primary cardiac surgery were assigned to groups according to a computer generated table of random numbers. Patients receiving preoperative heparin infusions for >24 hr were included and were randomised separately in order to ensure equal distribution among the groups. Patients were excluded if they were undergoing repeat sternotomy, or if they had hepatic, renal, or coagulation system dysfunction as determined by preoperative laboratory testing. Hepatic disease was defined as alanine amino transferase (ALT) or gamma glutamyl transferase (GGT) >twice the normal value. Renal dysfunction was defined as creatinine >2.0 $mg \cdot dl^{-1}$, and coagulation system dysfunction was defined as platelet count <100,000·μl^{-1}, prothrombin time (PT) >1.3 times control, or activated partial thromboplastin time (aPTT) greater than 1.3 times control in the absence of heparin therapy. Also excluded were patients with residual warfarin effect and those undergoing procedures requiring deep hypothermic circulatory arrest.

Randomisation of the first 30 patients was into one of two study groups (group 1 = control and group 2 = titration), in order to assess the safety and efficacy of the *in vitro* titration. The remaining 105 patients were randomised into one of four groups. (Table I).

Preoperative laboratory testing included PT, aPTT, platelet count, and fibrinogen concentration. In all patients, the heparin response test (HRT®) and protamine response test (PRT®, International Technidyne Corp., Edison, NJ) were measured, regardless of whether or not the test was used to guide anticoagulation management. All patients

TABLE I Group assignments

	Group 1 (Control)	*Group 2*	*Group 3*	*Group 4*
Number (phase 1) safety/efficacy	18	12	–	–
Number (phase 2)	35	24	18	28
Heparin management	300 $U \cdot kg^{-1}$ via right atrium	Hemochron® HRT titration via central line	Hemochron® HRT titration via central line	300 $U \cdot kg^{-1}$ via right atrium
Protamine management	1 mg·100 U^{-1} total heparin dose	Titration by Hemochron® PRT	1 mg·100 U^{-1} total heparin dose	Titration by Hemochron® PRT

HRT= Heparin response test; PRT= Protamine response test

received the Hemochron RxDx® (International Technidyne Corp., Edison, NJ) brand of bovine lung heparin (1000 U·ml^{-1}) and protamine (10 mg·ml^{-1}), the same lot of drug used in the *in vitro* titrations. The Hemochron® ACT was measured at baseline, five minutes after the administration of heparin and every 30 min thereafter until protamine was given. The ACT was maintained at >400 sec by the addition of 50 U·kg^{-1} of RxDx® heparin as necessary. The baseline ACT and HRT were measured after sternotomy as suggested by Gravlee *et al.*[9] The PRT was measured during the final warming phase of CPB. Fifteen minutes after the neutralisation of heparin by protamine, an ACT, a Hemochron® thrombin time (TT) and heparin neutralised thrombin time (HNTT) were measured to detect residual heparinisation. If the ACT was 20% above baseline and the TT exceeded the HNTT by >25 sec,[10] then an additional 25–50 mg protamine was given. Further tests were ordered at the discretion of the attending anaesthetist.

In all patients, intraoperative transfusion of packed red blood cells (PRBCs) was performed in the presence of hypovolaemia (pulmonary artery diastolic pressure <20% baseline) and a haematocrit <25%. During CPB, the transfusion trigger was a haematocrit <20% when the oxygenator volume was low. After CPB, transfusion guidelines were as follows: The transfusion of fresh frozen plasma (FFP), platelet concentrates and cryoprecipitate occurred only if bleeding was excessive (>100 ml in 10 min) and there was documented laboratory evidence of coagulopathy. (PT/PT control >1.5, platelet count <100,000·µl^{-1}, and fibrinogen level <100 mg·dl^{-1}, respectively) The anaesthetists and surgeons ordering transfusions for the patient intraoperatively were blinded to the group assignment of each patient.

Anaesthesia consisted of oxygen 100%, 25–75 µg·kg^{-1} fentanyl, 0.1–0.2 mg·kg^{-1} midazolam, and isoflurane. Pancuronium was used to facilitate muscle relaxation. Cardiopulmonary bypass was conducted using a reverse-phase hollow fibre membrane oxygenator, and moderate systemic hypothermia to 25°–28°C. The extracorporeal circuit was primed with Plasmalyte A® (Baxter Corp., Deerfield, IL), dextrose 5%, 250 ml albumin 5%, and 3000 U RxDx® heparin. Separation from CPB was performed when the patient was fully rewarmed and inotropic support was instituted at the discretion of the anaesthetist.

On arrival to the cardiothoracic intensive care unit (ICU), routine coagulation studies (PT, aPTT, and platelet count) and the TT and HNTT were measured. Additional protamine was given based on the TT-HNTT difference in conjunction with clinical bleeding in all patients regardless of group assignment. This was to ensure that protamine administration in the first postoperative hour was based upon a specific heparin assay (HNTT) and was strictly controlled in all patients. Transfusion decisions after the first postoperative hour were made at the discretion of the physicians in the ICU who were blinded to the patient's group assignment. The same group of three ICU physicians care for all cardiac surgical patients and they have similar transfusion practices. Thus it was felt unnecessary and impractical to attempt to control transfusion in the ICU by an algorithm. Mediastinal tube drainage that occurred over the first eight postoperative hours was transfused to the patient if the total volume exceeded 100 ml. This volume is termed "autologous reinfusion." Mediastinal tube drainage from 8–24 hr after surgery was not reinfused and was referred to as "mediastinal tube drainage."

Coagulation monitoring

The HRT measures an individual patient's heparin sensitivity (sec(ACT)·U^{-1}·ml^{-1}) using a two-point *in vitro* evaluation. The HRT test tube contains diatomaceous earth activator, stabilisers, buffers, plus six units heparin. Similar to the ACT, a 2 ml sample of whole blood is dispensed into the HRT test tube, agitated, inserted into the appropriate Hemochron® 800/801 or 400/401 test well, and the time to fibrin formation is measured. After a baseline diatomaceous earth ACT and HRT are performed, a heparin dose response curve is generated, which in conjunction with the patient's estimated blood volume, is used to calculate the individual patient's heparin requirement to achieve an ACT = 480 sec.

The PRT is an *in vitro* protamine titration used to determine the dose of protamine necessary to reverse the circulating heparin. The PRT test tube contains 40 µg protamine sulfate, diatomaceous earth activator, stabilisers, and buffers. The test is performed using 2 ml whole blood in a manner identical to that of the ACT and HRT described above. Once an ACT and PRT are performed, a two-point protamine dose-response curve is constructed for the individual patient, and the dose of protamine needed to return the patient's ACT to baseline is calculated using protamine sensitivity and estimated blood volume.

The Hemochron® TT is a measure of the time required for fibrin formation when a lyophilised preparation of human thrombin, calcium salts, stabilisers, and buffers are added to whole blood. The TT is susceptible to prolongation by hypofibrinogenaemia, dysfibrinogenaemia, or residual heparin effect. The HNTT is the TT plus a concentration of protamine sulfate that is sufficient to neutralise the effects of heparin up to a con-

centration of 1.6 U·ml^{-1}. Residual heparin effect is detected by prolongation of the TT in the absence of HNTT prolongation. Both of the above tests are performed using test tubes that require prehydration and prewarming in the Hemochron® instrument after which one ml of whole blood is dispensed into the tube. Normal values for unheparinised TT = 45.9 ± 3.9 sec (range 39–53 sec) and for HNTT = 43.7 ± 5.4 sec (range 33–58 sec).[11]

Statistical methods

An initial power analysis was conducted using mediastinal tube drainage values of patients undergoing primary cardiac surgery that were obtained from our existing database. The power analysis was performed in order to determine the sample size in each of groups 1 and 2, needed to rule out a significant effect of the *in vitro* titration on mediastinal tube drainage. In order to achieve a 200 ml reduction in mean 24 hr postoperative blood loss (750 ± 300 ml to 550 ± 300 ml) with two-tailed significance set at $\alpha = 0.05$, with 80% power, 36 patients in each arm would be required. The power analysis was performed in order to detect a significant difference in blood loss due to the use of the RxDx titration (groups 1 and 2). In the event that a significant difference was found, groups 3 and 4 would be analysed in order to isolate the difference as due to heparin management, protamine management, or both.

All values are reported as the mean ± SD, unless otherwise stated. In order to exclude the possibility of a temporal bias, the patients enrolled in the safety and efficacy protocol were compared with patients within their respective groups who were subsequently enrolled in the four group model. Groups were combined to assess the effect of heparin titration on heparin dose since heparin dose is independent of protamine dose. Thus, groups 1 and 4 who had heparin administered by weight calculations, were combined and compared with Groups 2 and 3 who had heparin administered by the *in vitro* titration. When groups were combined, unpaired Student's t test was used to assess statistical significance between groups. Intra- and inter-group differences among the four groups with respect to heparin and protamine doses were compared using two-way ANOVA. Coagulation data were compared using one-way ANOVA or repeated measures ANOVA, where appropriate. When statistical significance was achieved with ANOVA, post hoc analyses were determined using Tukey's protected t tests. Mediastinal tube drainage (non-parametric data) was analysed using the Mann-Whitney-U test (group 1 *vs* 2) and similarly with a correction for multiple comparisons when the four groups were compared. Spearman's rank correlation was used to test the relationship between heparin dose, protamine dose, CPB duration, and postoperative mediastinal drainage volumes. Chi square analysis was used to interpret categorical data. Statistical significance was assumed at $P < 0.05$ and all analyses were two tailed.

Results

A total of 143 patients were enrolled and 135 completed the protocol. Thirty patients were enrolled into groups 1 and 2 under the initial safety and efficacy protocol, and the remaining 113 were enrolled after the protocol was changed to a four group model. There were no temporal differences in demographic parameters, cardiopulmonary bypass variables, mediastinal tube drainage, or transfusion requirements between patients enrolled into the safety and efficacy protocol and those enrolled subsequently. Three patients (two in group 2, one in group 4) required reoperation for bleeding and these patients' data were excluded from the analysis. In all three patients a surgical source of bleeding was found. Four patients (one in group 2, two in group 3, one in group 4) received prophylactic tranexamic acid prior to CPB as requested by the surgeon and these patients' data were excluded from the analysis. An additional patient was excluded when the heparin dose was inadvertently administered in violation of the protocol.

See Table II for a summary of the demographics of the patients in each group.

Heparin and protamine doses

The heparin dose for each patient was calculated by both weight (300 U·kg^{-1}) and *in vitro* titration by the Hemochron® HRT test. Overall, the initial heparin dose calculated by *in vitro* titration was lower (274 ± 73 U·kg^{-1} *vs* 300 ± 2 U·kg^{-1}, $P = 0.0001$). There were no intergroup differences in the heparin sensitivity among the patients in each of the four groups. (Table III) Additionally, the heparin sensitivity was not different in the preoperative heparin therapy group (n = 35) compared with the group that did not receive heparin preoperatively (n = 100). (142 ± 22 sec·U^{-1}·ml^{-1} *vs* 148 ± 23 sec·U^{-1}·ml^{-1}, $P = 0.2$).

The heparin dose required for the initiation of CPB in groups 2+3 (277 ± 72U·kg^{-1}) was lower than that for groups 1+4 (300 ± 2 U·kg^{-1}, $P < 0.006$). All patients had an initial ACT > 400 sec in response to the heparin bolus. The total heparin dose in groups 2+3 (363 ± 80 U·kg^{-1}) was not different from that in groups 1+4 (369 ± 50 U·kg^{-1}, $P = 0.6$) (Table III) The heparin to protamine dose ratio (H:P) was calculated as Units total heparin per mg total protamine.

TABLE II Demographic data

Variable	*Group 1 (n = 53)*	*Group 2 (n = 36)*	*Group 3 (n = 18)*	*Group 4 (n = 28)*
CABG n (%)	44 (83)	25 (69)	15 (83)	21(75)
Single valve n (%)	5 (9)	6 (17)	0 (0)	4 (14)
Combined procedure n (%)	4 (8)	5 (14)	3 (17)	3 (11)
Male/Female	31/22	20/16	11/7	19/9
Weight (kg)	78 ± 15	74 ± 18	76 ± 11	71 ± 12
Height (cm)	168 ± 10	166 ± 10	166 ± 9	162 ± 8
Preoperative Heparin n (%)	11 (21)	8 (22)	7 (39)	9 (32)
Preoperative Nitroglycerin n (%)	13 (25)	9 (25)	7 (39)	11 (39)
Lowest CPB core temp °C	27.4 ± 1.5	27.0 ± 1.3	27.0 ± 1.9	27.0 ± 2.1
CPB time (min)	105 ± 23	111 ± 30	109 ± 38	116 ± 24
Cross-clamp time (min)	72 ± 18	76 ± 23	78 ± 33	81 ± 20

CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; temp = temperature
No significant difference among groups in any variable

TABLE III Anti-coagulation testing and coagulation management

Variable	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*P value*
Heparin sensitivity ($sec \cdot U^{-1} \cdot ml^{-1}$)	145 ± 23	147 ± 22	135 ± 22	140 ± 22	0.2
Calculated† heparin dose ($U \cdot kg^{-1}$)	271 ± 76	263 ± 62	305 ± 84	292 ± 83	0.1
Actual heparin dose ($U \cdot kg^{-1}$)	300 ± 2	263 ± 62*	305 ± 84	299 ± 3	0.0004
Total heparin dose ($U \cdot kg^{-1}$)	365 ± 43	348 ± 73	394 ± 86	376 ± 60	0.06
Baseline ACT (sec)	152 ± 19	152 ± 19	156 ± 44	154 ± 20	0.9
Post-heparin ACT (sec)	693 ± 116	623 ± 118*	692 ± 101	667 ± 120	0.04
Post-protamine ACT (sec)	148 ± 11	145 ± 12	135 ± 6*	143 ± 6	0.04
Calculated† protamine ($mg \cdot kg^{-1}$)	2.94 ± 1.0	3.08 ± 0.83	3.24 ± 1.17	3.15 ± 0.91	0.6
Fixed ratio protamine ($mg \cdot kg^{-1}$)	3.67 ± 0.48	3.47 ± 0.73	3.94 ± 0.87	3.76 ± 0.60	0.08
Initial protamine dose ($mg \cdot kg^{-1}$)	3.67 ± 0.48	3.08 ± 0.83*	3.94 ± 0.87	3.15 ± 0.92*	<0.0001
Total protamine dose ($mg \cdot kg^{-1}$)	4.03 ± 0.65	3.56 ± 1.10*	4.22 ± 0.90	3.38 ± 0.98*	0.001
Heparin/protamine‡ ratio	91.6 ± 11.1	105.3 ± 31.8*	93.6 ± 9.0	121.5 ± 45.3*	‡
n TT-HNTT >25 sec post-protamine	5/53 (9%)	1/36 (3%)	0/18 (0%)	0/28 (0%)	0.14
n TT-HNTT >25 sec in ICU	7/53 (13%)	10/36 (28%)§	2/18 (11%)	2/28 (7%)	0.1

ACT = activated clotting time; TT = thrombin time; HNTT = heparin neutralized thrombin time; ICU = intensive care unit; Pts. = patients
*significant difference ($P < 0.05$)
†calculated = based on *in vitro* titration
‡$P < 0.01$ for 4 *vs* 1,3; $P < 0.05$ for 2 *vs* 4, 1
§$P = 0.003$ *vs* post-protamine value

The baseline, post-heparin, and post-protamine ACT values are shown in Table III. In all four groups, the post-protamine ACT was not significantly different from the baseline ACT.

The TT-HNTT difference, both in the operating room and upon arrival to the ICU, was not different among the four groups, nor was the incidence of administration of additional protamine. (Table III) The incidence of a TT-HNTT difference >25 sec was higher in the ICU than it was in the operating room in group 2 (heparin and protamine titrated), $P = 0.003$.

Coagulation data

Compared with pre-CPB values, analysis of variance revealed that the haematocrit was lower at the end of CPB and at 24 hr postoperatively ($P < 0.01$) in each of four groups, and that there were no differences among the groups. There were no differences among groups in PT, PTT, or fibrinogen at any time. (Table IV)

There were no differences in autologous reinfusion volume or mediastinal tube drainage among the four groups. Exclusion of patients receiving preoperative heparin therapy yielded an analysis in 100 patients which also revealed no differences among groups. (Table V).

The lack of a statistical difference in mediastinal tube drainage due to the RxDx intervention prompted a power analysis using the data from groups 1 (n = 53) and 2 (n = 36). The statistical power of the study to detect a bleeding difference of 200 ml between these groups was 90%. Therefore, if the RxDx titration did reduce mediastinal tube drainage postoperatively, it did so by a volume <200 ml in 24 hr.

TABLE IV Coagulation test results

Coagulation variable	*Group 1*	*Group 2*	*Group 3*	*Group 4*	*among groups "P"*
Platelets-pre ($\times10^3 \cdot \mu L^{-1}$)	245 ± 70	253 ± 61	265 ± 39*	246 ± 46	<0.01
Platelets-end CPB ($\times10^3 \cdot \mu L^{-1}$)	136 ± 47	136 ± 36	153 ± 27*	134 ± 34	<0.05
Platelets-24 hour postop ($\times10^3 \cdot \mu L^{-1}$)	154 ± 52	150 ± 35	168 ± 33*	157 ± 34	<0.05
Haematocrit-pre (%)	39 ± 6	39.8 ± 3	40 ± 2.2	38.3 ± 4.4	NS
Haematocrit-end CPB (%)	32.3 ± 4.3	31.7 ± 3.3	34 ± 2.3	32.2 ± 4.3	NS
Haematocrit-24 hr postop (%)	30.2 ± 3.9	30.4 ± 2.9	32 ± 2.5	31.1 ± 3.4	NS
PT/PT control-pre (sec)	1.05 ± 0.08	1.04 ± 0.07	1.08 ± 0.12	1.01 ± 0.12	NS
PT/PT control-post-CPB (sec)	1.24 ± 0.11	1.18 ± 0.20	1.24 ± 0.08	1.22 ± 0.11	NS
Fibrinogen-pre ($mg \cdot dl^{-1}$)	345 ± 88	325 ± 81	353 ± 111	328 ± 88	NS
Fibrinogen-end CPB ($mg \cdot dl^{-1}$)	227 ± 62	195 ± 55	224 ± 72	214 ± 52	NS

*statistically significant among groups
CPB = cardiopulmonary bypass
PT = prothrombin time

TABLE V Mediastinal tube drainage

	Group 1 n = 53	*Group 2 n = 36*	*Group 3 n = 18*	*Group 4 n = 28*	*P value*
8 hr autologous reinfusion* (ml) median (range)	300(0–1100)	315(0–1300)	300(0–710)	215(0–850)	0.37
8–24 hr mediastinal tube drainage (ml)	681 ± 274	742 ± 459	680 ± 241	619 ± 431	0.36
No preoperative heparin therapy:	Group 1 n = 42	Group 2 n = 28	Group 3 n = 11	Group 4 n = 19	
8 hr autologous reinfusion* (ml) median (range)	300(0–1100)	315(0–1300)	400(0–710)	275(0–850)	NS
8–24 hr mediastinal tube drainage (ml)	713 ± 111	763 ± 135	690 ± 48	730 ± 124	NS

all values are mean ± SD unless otherwise noted
*non-parametric statistics used

TABLE VI Transfusion requirements

	Group 1	*Group 2*	*Group 3*	*Group 4*	*P value*
Red blood cells (ml)	500 (0–1500)	500 (0–2500)	0 (0–1000)	0 (0–2500)	0.7
FFP (ml)	0 (0–800)	0 (0–1200)	0 (0–0)	0 (0–600)	0.9
Platelets (ml)	0 (0–400)	0 (0–400)	0 (0–0)	0 (0–200)	0.9
Number of patients transfused	28/53 (53%)	23/36 (64%)	7/18 (39%)	14/28 (50%)	0.35
Exposures/patient transfused (Units)	4.2	4.1	3.1	5.1	0.3

all transfusion volumes are median (range)

In the entire cohort of patients, autologous drainage and mediastinal tube drainage did not correlate with heparin dose, protamine dose, or time on CPB. However, there was a correlation between autologous reinfusion volume and the H:P dose ratio (Spearman R = –0.30, $P = 0.0005$) and between 24 hr mediastinal tube drainage and the H:P dose ratio (Spearman R = –0.23, $P < 0.007$).

There were no differences in the mean (or median) transfused volume of PRBCs, FFP, or platelets among the four groups. The mean volume of PRBCs transfused was 389 ± 424 ml in group 1, 483 ± 540 ml in group 2, 306 ± 407 ml in group 3, and 410 ± 613 ml in group 4, $P = 0.6$. (Table VI).

Discussion

Heparin and protamine doses are process variables that have been suggested to affect the outcomes of postoperative bleeding and transfusion requirements.[3] A number of different heparin and protamine management strategies have been reported to result in reduced perioperative bleeding, but the contributions of heparin dose and protamine dose, separately, to the successful outcome, have not been established.[12,13]

Using the RxDx system, we measured the heparin sensitivity and constructed individualised dose response curves for each patient. Heparin sensitivity was not different among the four patient groups, and

the calculated dose of heparin using the titration was not different among the four groups. In patients in groups 2 and 3, whose heparin dose was based on the *in vitro* titration, the ACT achieved after administration of heparin exceeded the projected level of 480 sec. This *in vivo* accentuation of the *in vitro* heparin response has been reported previously.[12]

The heparin dose administered for the initiation of CPB was lower in group 2 than the standard 300 $U \cdot kg^{-1}$ dose used in groups 1 and 4. Despite the lower initial heparin dose, the additional doses of heparin required to maintain ACT >400 sec equalised the total heparin doses in the four groups ($P = 0.06$). It seems likely that the additional heparin administered to patients in group 2 was related to a lower post-heparin ACT (Table III). Due to heparin consumption, the ACT in group 2 was more likely to decrease below the 400 sec threshold during CPB, necessitating the administration of additional heparin.

Using the protamine response test via the RxDx system, titration predicted lower protamine doses than the fixed ratio dose in all groups. Thus groups 2 and 4 received lower protamine doses in the operating room than did groups 1 and 3; titration allowed the administration of less protamine, regardless of the method of heparin management. Laboratory evidence of heparin rebound upon admission to the ICU did not differ among the four groups, and the administration of additional protamine in the ICU after the first postoperative hour was not different among the groups. Thus, the lower total protamine doses in groups 2 and 4 were a result of the strict operating room management using the *in vitro* titration. Despite differences among groups in the protamine dose and the H:P dose ratio, mediastinal tube drainage and autologous reinfusion volumes were not different among the groups in the current study.

Jobes *et al.*[12] compared a control group with a group that had the doses of heparin and protamine titrated using the Hemochron® RxDx system. No mention is made of the initial heparin dose comparison between the two groups. Total heparin dose was higher in the intervention group, though it is unclear if this is a result of higher initial heparin doses or the administration of more supplemental heparin on CPB. Protamine doses (initial and total) were lower in the intervention group and mediastinal tube drainage and transfusions were also reduced. The fact that the initial protamine dose was lower in the intervention group suggests a definite protamine sparing effect of the *in vitro* dose calculation. However, the study and control groups had different protamine management strategies after CPB which could have contributed to differences in total protamine doses and even to differences in postoperative bleeding. Additionally, no attempt was made to adhere to a transfusion algorithm or to evaluate different dosing strategies for heparin and protamine independently. Lower protamine doses have been successfully used by others to neutralise heparin after CPB[14,15] and have been associated with reduced bleeding and transfusion requirements.[12,16]

Despotis *et al.*[13] demonstrated a marginally significant reduction in postoperative bleeding and reduced transfusion of non-red blood cell components using Hepcon® (Medtronic Hemotec, Parker, CO) heparin management with a transfusion algorithm. The Hepcon differs from Hemochron® RxDx instrument in that the former measures ACT and heparin concentration via an automated protamine titration technique and calculates the heparin dose required to maintain a stable heparin concentration. Maintenance of the heparin concentration rather than a predetermined ACT results in the administration of higher doses of heparin during CPB because ACT increases during haemodilution and hypothermia. Although the measure of heparin concentration has been shown to better correlate with the anti factor Xa activity on CPB than the ACT,[17] the level of agreement of heparin concentration and anti factor Xa activity has recently been challenged.[18] The postulated haemostatic advantage in maintaining higher heparin concentrations is that it may preserve coagulation better, minimise subclinical fibrin formation, and blunt the consumptive coagulopathy that occurs with microvascular coagulation.[3,19] However, the maintenance of such high heparin levels has been shown by others to result in increased bleeding possibly due to heparin rebound[20] or to platelet dysfunction.[4,21-23]

Another potential reason that Despotis *et al.*[13] were able to demonstrate a haemostatic advantage in maintaining higher heparin concentrations may be the long CPB times and high incidence of transfusion in their patient population. They also reported a correlation between a high H:P ratio (higher heparin and lower protamine doses) and improved haemostasis, however, the high H:P ratio was obtained due to higher heparin doses without any reduction in the protamine dose. The heparin doses they employed were nearly two times the doses reported in the current protocol. Another confounding factor is that heparin and protamine management strategies were not studied independently.

A potential advantage of the RxDx titration is the ability to measure heparin sensitivity and to predict the heparin dose needed to achieve a therapeutic ACT for CPB. The system was successful in this regard as confirmed by the presence of a therapeutic ACT in all

patients. This system may be specifically useful in patients receiving preoperative heparin therapy who traditionally require larger heparin doses to achieve a given level of anticoagulation when that anticoagulation is measured by the ACT.[24] Heparin sensitivity is diminished in these patients due to reductions in antithrombin III, activation of platelets, or other postulated mechanisms. In our protocol, however, patients receiving preoperative heparin infusions did not exhibit heparin resistance, as assessed by the HRT. Therefore, the impact of the RxDx titration system in patients with heparin resistance could not be evaluated. Another potential advantage was the reduction in the protamine dose. Successful neutralisation of heparin was confirmed by a return of ACT to baseline values and no increased incidence of heparin rebound. The incidence of protamine-related adverse events was not specifically addressed in this protocol. The cost of the HRT and PRT tubes are $240/box of 40 tubes with the advantage that they can be used in any Hemochron instrument.

The titration did not result in any measurable differences in bleeding or transfusion requirements in our population of patients. Bleeding after CPB is multifactorial in origin and is not always accompanied by an increase in transfusion of allogeneic blood products. Increased postoperative blood loss has been associated with certain preoperative demographic variables, increased time on CPB, degree of hypothermia, low initial heparin dose, higher protamine dose, and abnormalities of coagulation tests while on CPB.[3,25] The prophylactic use of antifibrinolytic agents has also been shown to reduce bleeding and transfusions associated with CPB. When risk factors for bleeding are not present in the preoperative or perioperative demographic profile, and careful attention is paid to intraoperative haemostasis, differences in transfusion incidence and volumes are difficult to elicit.[26] Attempts to reduce risk factors for bleeding seem to be a logical approach to the overall reduction of transfusion of blood products, assuming that the cost of such measures is not prohibitive.

In conclusion, the use of the Hemochron® point of care assay to individualise heparin and protamine dosing yielded a therapeutic heparin dose for the initiation of CPB and a lower protamine dose for heparin reversal. The PRT is a simple and convenient test that may be used to calculate the minimal protamine dose needed for heparin neutralisation, however, no demonstrable improvements in haemostasis were found when compared with weight based fixed ratio management strategies. We were unable to detect a difference in mediastinal tube drainage due to the point of care assay and we had 90% power to detect a 200 ml reduction. In primary cardiac surgical patients the introduction of the HRT and PRT appears to offer no haemostatic advantage over current dosing methods.

Hemochron® RxDx heparin and protamine, and HRT, PRT, TT, and HNTT test tubes were provided by International Technidyne Corp., Edison, NJ.

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