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Comparison of Heparin Administration Using the Rapidpoint™ Coag and Hepcon® HMS

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Abstract: A retrospective chart review was conducted of patients who underwent cardiopulmonary bypass (CPB) to compare the quantities of heparin administered, postoperative blood loss, and homologous blood products transfused during their procedure and subsequent stay in the intensive care unit. The primary purpose of this review was to determine if any difference in heparin administration resulted when two different devices were used for dosing and monitoring heparin. Postoperative blood loss and amount of blood products transfused were also quantified, as any differences would potentially be a result of a difference in administration of heparin. The first group (n = 341) underwent CPB using the Hepcon® HMS, Medtronic Inc., Minneapolis, MN, for heparin dosing and monitoring. The Rapid Point™ Coag, Bayer Healthcare LLC, Tarrytown, NY was used for the second group (n = 345). The two populations were compared for similarity on: age, body surface area (BSA), CPB time (minutes), aortic-cross clamp time (minutes), baseline activated clotting time, and baseline hematocrit. No significant difference was found between the two groups. The second group, using the Rapidpoint™ Coag, received less heparin during CPB than the group using the Hepcon® HMS. In addition, there were decreases in amounts of some blood products transfused as well as mediastinal drainage from the Hepcon® HMS to the Rapidpoint™ Coag group. A summary of the findings can be found in Table 1. A secondary purpose of this study was to determine the influence of hemodilution on the Heparin Management Test (HMT®). Citrated whole blood was diluted to varying degrees at various concentrations to determine whether hemodilution with crystalloid would alter the HMT® measurements. At all heparin levels and degrees of dilution, the HMT® remained stable, with coefficients of variation (CV) of less than 5% at all heparin levels even while incorporating excessive crystalloid dilution (up to 75%). **Keywords:** cardiopulmonary bypass, activated clotting time, heparin-protamine titration, mediastinal drainage, homologous blood products. *JECT. 2004;36:139–144*

Cardiopulmonary bypass (CPB) requires the use of systemic anticoagulation to preserve the extracorporeal circuit and maintain hemostasis in the postoperative period. The anticoagulant most often used is heparin. Activated clotting time (ACT), first described by Hattersley in 1966, has been the preferred method for assessing the coagulation status of the CPB patient since the 1970s (1). Since then, several devices have been developed to monitor heparin levels during CPB.

In 1975, Bull et al. described the prolonging effect of heparin on the ACT. They determined an ACT "safe zone" of 300–600 seconds during CPB, recommending an ACT of 480 seconds as an adequate anticoagulation level (2). In addition, Young et al. noted an absence of fibrin formation when the ACT was maintained above 450 seconds (3). In a concurrent article, Bull et al. cited the additional benefits of using dose–response curves to determine dosing requirements for patients undergoing CPB, caused by variances in patient sensitivities to heparin (4). A dose–response curve allows the determination of an individualized target heparin concentration to reach a desired ACT (usually 480 seconds).

Situations inherently present during CPB, specifically hemodilution and hypothermia, have been shown to cause inaccuracies in ACT measurements (5,6). Consequently, ACTs may not always be indicative of heparin effect, potentially leading to inadequate anticoagulation. Subsequently, heparin–protamine titration was identified as another method for monitoring the heparin concentration in whole blood (7). Some have preferred the additional use of this method for heparin management during CPB, rather than relying on the ACT alone (8,9). However, others have suggested that heparin–protamine titration

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may also be inaccurate during CPB and, therefore, does not provide for better management than use of ACTs alone (10).

Heparin–protamine titration became available in the surgical arena with instruments such as the Hepcon® A-10 and the Hepcon® HMS. Clinicians could compare the measured heparin concentration with the target concentration as determined by a dose–response curve to estimate dosing requirements. The heparin–protamine titration also allowed clinicians to calculate the protamine dose required for heparin neutralization. Although some have cited improved clinical outcomes using this dosing method (11,12), others have not found it to be an improvement over using ACTs alone (13–15).

Given such conflicting data, the debate continues over which methods are most effective for heparin dosing and monitoring. The primary objective of this study was to compare heparin administration when using the Hepcon® HMS versus the Rapidpoint™ Coag/Accent for dosing and monitoring. A secondary purpose was to examine postoperative bleeding and the amounts and types of blood products patients received in each of the two groups as they might directly result from differences in heparin administration. In addition, the influence of crystalloid hemodilution on the Heparin Management Test (HMT®), was examined.

MATERIALS AND METHODS

After Institutional Review Board approval was obtained, a retrospective chart review was conducted of 686 adult patients who underwent relatively routine CPB at Charleston Area Medical Center in Charleston, West Virginia. Patients who experienced aortic dissection, underwent emergent salvage, received plasminogen activators, were diagnosed with heparin-induced thrombocytopenia post operatively, or underwent re-exploration for surgical bleeding were excluded. All patients underwent CPB with a noncoated Terumo extracorporeal circuit with a Capiox® SX-25 oxygenator. Each circuit was primed with a solution of approximately 1800 mL of a balanced electrolyte solution, 1.0 mg/kg of 20% mannitol, and 20,000 units of porcine heparin. To determine if there was a clinical difference potentially resulting from differences in heparin administration between the two groups, the following factors were examined using the Hepcon® Group as the control: total heparin administered, heparin administered during CPB, intra-operative blood salvaged, mediastinal drainage, and number and type of homologous blood products transfused.

Two instruments were used to determine the heparin dose required to maintain adequate anticoagulation during CPB. The first group ($n = 341$) underwent CPB using the Hepcon® HMS (Medtronic Inc., Minneapolis, MN) to determine dosing requirements. The second group ($n = 345$) underwent CPB using the Rapidpoint™ Coag and the Rapidpoint™ Accent (Bayer Diagnostics, Tarrytown, NY) to determine dosing requirements.

For the Hepcon group, the heparin dose-response (HDR), heparin assay (Hepcon®), and ACT cartridges were used with the Hepcon® HMS. The Hepcon® HMS determines the heparin dose requirement based on a comparison of the Hepcon® value with the target heparin concentration. Dosage recommendations given by the Hepcon® HMS were followed. All patients had an HDR performed before initial heparinization to determine the necessary loading dose and target heparin concentration to be maintained throughout CPB. The instrument used an ACT of 480 seconds as the target for heparin dosing. The Hepcon® and ACT were performed after initial heparin dosing and at 30-minute intervals throughout the CPB procedure.

For the RP Coag group, the heparin titration test (HTT) and heparin management test (HMT®) were performed on the Rapidpoint™ Coag before initial heparinization. (The HMT® is a modified ACT that employs a higher activator to blood ratio than traditional systems, although the ratio is undisclosed by the manufacturer.) The results were transmitted automatically to the Rapidpoint™ Accent. Using the HMT® and HTT, the Accent constructs a dose–response curve, which it then uses to determine a patient's heparin loading dose and target heparin concentration. The instrument used an HMT® of 480 seconds as the target for heparin dosing. Dosage recommendations given by the Accent were followed. The HMT® was performed after initial heparin dosing and at 30-minute intervals throughout the CPB procedure.

In addition, as crystalloid hemodilution has been shown to affect ACTs, an in vitro hemodilution experiment was performed to determine if HMT® results are similarly influenced. The experiment was performed using citrated whole blood from a single donor. Heparin was added to the blood to produce the following concentrations of heparin: zero, 1.0, 2.0, 3.0, and 5.0 units/mL. Each sample was then diluted with a balanced electrolyte solution to achieve crystalloid concentrations of zero, 25, 50, and 75%. The diluted samples were then analyzed in triplicate using the HMT® test card and the Rapidpoint™ Coag. The coefficient of variation (CV) for each heparin concentration was calculated using all results for each level of dilution (15 values for each concentration). The CV is the percentage of random variation of an analytical method. The CV is the quotient of the standard deviation divided by the mean multiplied by 100%; thereby, giving the CV units as percentage.

The chosen indicators (total heparin administered, hep-

arin administered during CPB, intra-operative blood salvaged, mediastinal drainage, and number and type of homologous blood products transfused) were compared between the two patient groups with an unpaired *t*-test. A significance level of $p < .05$ was used for all measures.

RESULTS

The two patient groups were clinically similar in age, body surface area (BSA), time on CPB, baseline hematocrit, and baseline ACT (Table 1). The number and types of procedures performed in the two groups were also similar (Table 2). The Hepcon group consisted of 123 females and 218 males. Similarly, the RP Coag group consisted of 132 females and 213 males. Because very few minority races were represented in the patient population, only Caucasian patients were included.

The initial bolus dose of heparin was similar between the groups ($p = .732$) indicating similarity in the heparin dose–response performed by the instruments. However, the amount of heparin administered during CPB significantly decreased ($p < .001$) from 10,000 units in the Hepcon group to 1000 units in the RP Coag group (Table 3). A significant decrease in postoperative bleeding and treatment with blood products was also seen from the Hepcon group to the RP Coag group. This is evident in the significant decreases in mediastinal drainage ($p < .001$), packed red blood cells (PRBC) transfused ($p < .05$), and fresh frozen plasma transfused (FFP) ($p < .01$), illustrated in Table 4. Approximately 50% of patients in both groups received PRBC, FFP and/or albumin. No statistically significant difference was observed for the transfusion of platelets or cryoprecipitate between the groups. However, more than 80% of the patients in each group did not receive either of these interventions.

The amount of protamine administered to the patients was different between the groups ($p < .001$), with the RP Coag group receiving less. There was also a significant difference in both the mean ACT on CPB and the post-protamine ACT ($p < .001$).

The accuracy of the HMT® was confirmed by the in vitro hemodilution experiment, with the variation between all levels of heparin tested being less than five percent. Because the CVs were calculated across the test system, the system was determined to be accurate even with excessive dilution (75%), as illustrated in Table 4.

Table 1. Demographic characteristics (mean ± standard deviation).

Patient Demographics ($n = 686$)	Hepcon Group ($n = 341$)	RP Coag Group ($n = 345$)	*p*-Value (*t*-test)
Age (years)	63 ± 11	63 ± 11	0.49
BSA	1.94 ± 0.24	1.95 ± 0.24	0.49
CPB time (mins)	108 ± 38	104 ± 35	0.08
Hematocrit (%)	36 ± 5	33 ± 4.8	<0.05*
Baseline ACT (seconds)	145 ± 19	149 ± 47	0.05

*Although statistically different, the difference in hematocrit was determined to be clinically insignificant because of assay imprecision between different instruments—GEM premier 3000 (Instrumentation Laboratory, Lexington, MA) was used for the Hepcon Group, and the Rapidpoint 400 (Bayer Diagnostics, Tarrytown, NY) was used for the RP Coag group.

Table 2. Types of procedures.

Procedure ($n = 686$)	Hepcon Group	RP Coag Group
Aortic or mitral valve replacement	16	19
Aortic and mitral valve replacement	2	2
Coronary artery bypass graft (CABG) × 1	5	2
CABG × 2	30	20
CABG × 3	76	76
CABG × 4	102	110
CABG × 5	62	64
CABG × 6	25	22
CABG × 7	2	7
CABG × 8	1	1
CABG/valve combination	15	18
Atrial septal defect repair	1	0
Ascending or descending aortic aneurysm repair	2	2
Left ventricular aneurysm repair	1	1
Pulmonary artery repair	1	0
Atrial myxoma removal	0	1
Total	341	345

DISCUSSION

The mechanism causing the decrease of mediastinal drainage and treatment with blood products between the two groups is difficult to identify. A higher heparin concentration during CPB has been documented as a cause of heparin rebound (16–20). Gravlee et al. indicated that lower heparin concentrations during CPB might result in decreased postoperative bleeding (12). Conversely, subsequent research by Gravlee et al. suggests that higher heparin concentrations may contribute only to heparin rebound without increased clinical bleeding. However, they stated that aggressive treatment of heparin rebound might have prevented clinical bleeding (15). In essence, the incidence and amount of postoperative bleeding as a direct result of heparin dosing is inconclusive. In this retrospective study, it seems that a decrease in the incidence of heparin rebound may be the mechanism responsible for the decrease in postoperative bleeding and subsequent requirement for blood products. This data are inconclusive, however, because they are retrospective in nature and lacking postoperative monitors for heparin rebound such as PTT values, thrombin times, and/or anti-Xa assays.

Although some have observed no increase in postoperative bleeding associated with increased administration of heparin, our results support the initial findings of Grav-

Table 3. Comparison of indicators by group.

Parameter (per Patient)	Hepcon Group (n = 341)	RP Coag Group (n = 345)	% Change	p-Value
Heparin bolus (1000 units)	30 ± 7.3	30 ± 8.4	0.0	p = .732
Total heparin (1000 units)	60 ± 13.6	50 ± 7.9	–17	p < .001
Heparin on CPB (1000 units)	10 ± 9.9	1 ± 2.3	–90	p < .001
ACT on CPB (seconds)	744 ± 144	588 ± 74	–21	p < .001
Total protamine (mg)	407 ± 149	363 ± 164	–11	p < .001
Post-protamine ACT (seconds)	122 ± 14	137 ± 53	12	p < .001
FFP (units)	0.94 ± 2.0	0.55 ± 1.4	–42	p < .01
PRBC (units)	1.75 ± 2.3	1.39 ± 1.9	–21	p < .05
Cryoprecipitate (units)	0.8 ± 3.0	0.8 ± 3.0	0.0	p = .96
Platelets (units)	1.31 ± 3.0	0.99 ± 2.6	–24	p = .13
Albumin (gm)	41 ± 72.5	46 ± 60.6	11	p = .186
Mediastinal drainage (mL)	1083 ± 772	891 ± 522	–18	p < .001

FFP, fresh frozen plasma; PRBC, packed red blood cells.
All data mean ± SD.

lee et al. (12). There was an 18% decrease in mediastinal drainage between the Hepcon group and the RP Coag group. Given the similarity of the patient populations and procedure types, this decrease seems to be a result of the 90% decrease in the amount of heparin administered during CPB from the Hepcon group to the RP Coag group. The decreased blood product use between the two groups reflects decreased postoperative bleeding, as treatment with homologous blood products is not warranted when bleeding is not excessive. It should be noted that perioperative blood loss was similar between the groups (Hepcon = 1060 mL; RP Coag = 1020 mL; p = .11). In addition, the difference in the amount of protamine administered to the RP Coag group seems to be a direct result of lower doses of heparin.

The post-protamine ACTs were also different between the two groups. This variance may simply be assay–assay imprecision because there is only a 15 second difference between the groups at low levels of heparin. However, a much greater difference (166 seconds) was found between the measurements during CPB, indicating there is a greater difference in the two tests at higher levels of heparin. These results indicate the HMT® may not be as falsely elevated by the factors of hemodilution and hypothermia than traditional ACT systems (21–25).

Several authors have similarly reported that dosing recommendations determined by heparin–protamine titration are higher than those of conventional heparin management protocols (9,13,15). However, the preference of some for using heparin–protamine titration for heparin dose determination during CPB remains, predominantly because of the presence of interfering factors (hemodilution and hypothermia) on traditional ACTs (8,9,21). However, the manufacturer of the Hepcon® indicates that the accuracy of the device is affected by hemodilution (22). Furthermore, the device's measurements have been shown to be inconsistent with traditional anti-Xa assays for heparin concentration (10). These questions concerning the accuracy of the test system have led some to reject the technology.

Although most ACT systems are affected to varying degrees by hemodilution, a variable that advocates the additional use of a heparin-protamine titration, the HMT® has been shown to be accurate when blood is diluted with crystalloid solution (23–27). However, it should be noted that dilution with colloids has been shown to cause falsely elevated HMT® results (23). The National Committee for Clinical Laboratory Standards (NCCLS) has determined that a coefficient of variance of less than five percent demonstrates the accuracy of a test system. The HMT® meets this requirement, even in the presence of excessive hemodilution (Table 4). In addition, the HMT® has been shown by others to correlate with anti-Xa activity during cardiovascular surgery (24,28,29). For these reasons, the HMT® seems to measure anticoagulant activity accurately during CPB and is potentially more accurate than the Hepcon®.

Although the influence of hemodilution on the HMT® has been addressed, this study did not attempt to take into account the effects of hypothermia on the HMT®. Although hypothermia has been shown to prolong ACT re-

Table 4. Affect of crystalloid hemodilution on the HMT®.

Heparin	% Dilution with Crystalloid 0%*	25%*	50%*	75%*	Mean ± SD	CV%**
0.0 units/mL	153	163	162	168	161 ± 7.2	4.4
1.0 units/mL	249	245	256	265	253 ± 10.5	4.1
2.0 units/mL	333	351	353	350	347 ± 14.1	4.1
3.0 units/mL	411	404	409	435	413 ± 16.0	3.9
5.0 units/mL	474	483	501	506	490 ± 18.9	3.9

*Mean HMT® result of the three replicates in seconds.
**all replicates included in SD and CV calculations.

sults (6,7,30), the mechanism responsible for this effect remains unknown (6,7). Marcum et al. found heparin-like substances on endothelial surfaces, which possessed anticoagulant activity virtually identical to commercially prepared heparin (31–33). In addition, Paul et al. note the presence of a heparin-like substance circulating in dogs during profound hypothermia (34). Expression of these heparin-like substances during hypothermia may be the cause of elevated ACTs during hypothermia. If so, hypothermia may produce anti-Xa activity rather than interference with the ACT test system.

CONCLUSION

This retrospective comparison of the Hepcon® HMS and the Rapidpoint™ Coag/Accent as means of heparin management during CPB has suggested several conclusions. Use of the Rapidpoint™ Coag and Rapidpoint™ Accent seems to result in the administration of less heparin than using the Hepcon® HMS for heparin management. In addition, the administration of less heparin during CPB may lead to a lower volume of postoperative blood loss and a decreased need for transfusion of blood products. Finally, HMT® measurements do not seem to be influenced by crystalloid hemodilution and may lead to more accurate measures of heparin activity.

Study Limitations

The most significant limitation of this study is its retrospective design. The data for the study were pulled in a nonrandomized patient population and nonblinded. Also, it is possible that differences in operative procedures between surgeons, transfusion practices, and operator variability exist that are difficult to quantify retrospectively. The retrospective nature of this study also notably limited the availability of postoperative heparin rebound tests, the results of which could significantly affect the suggested conclusions of this study. A prospective, randomized study would help clarify the results of this study.

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