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Original Article

A Blinded Randomized Trial Comparing Standard Activated Clotting Time Heparin Management to High Target Active Clotting Time and Individualized Hepcon HMS Heparin Management in Cardiopulmonary Bypass Cardiac Surgical Patients

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Purpose: High-dose heparin has been suggested to reduce consumption coagulopathy.
Materials and Methods: In a randomized, blinded, prospective trial of patients undergoing elective, complex cardiac surgery with cardiopulmonary bypass, patients were randomized to one of three groups: 1) high-dose heparin (HH) receiving an initial heparin dose of 450 u/kg, 2) heparin concentration monitoring (HC) with Hepcon Hemostasis Management System (HMS; Medtronic, Minneapolis, MN, USA) monitoring, or 3) a control group (C) receiving a standard heparin dose of 300 u/kg. Primary outcome measures were blood loss and transfusion requirements.
Results: There were 269 patients block randomized based on primary versus redo sternotomy to one of the three groups from August 2001 to August 2003. There was no difference in operative bleeding between the groups. Chest tube drainage did not differ between treatment groups at 8 hours (median [25th percentile, 75th percentile] for control group was 321 [211, 490] compared to 340 [210, 443] and 327 [250, 545], p = 0.998 and p = 0.540, for HH and HC treatment groups, respectively). The percentage of patients receiving transfusion was not different among the groups.
Conclusion: Higher heparin dosing accomplished by either activated clot time or HC monitoring did not reduce 24-hour intensive care unit blood loss or transfusion requirements.

Keywords: Hepcon HMS, bleeding, anticoagulation

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Introduction

For over 45 years, heparin has been the anticoagulant of choice for cardiopulmonary bypass (CPB), yet the optimal dosing of heparin is still controversial.[1,2] In an effort to reduce thrombin activation with resultant consumption coagulopathy and excessive bleeding, high-dose heparin therapy has been suggested.[3] Dosing of heparin based upon an automated heparin dose–response assay with the Hepcon Hemostasis Management System (HMS; Medtronic, Minneapolis, MN, USA) results in individualized heparin and protamine dosing management, and has been reported to result in higher heparin doses during CPB.[3–5] The use of the Hepcon HMS may or may not reduce post-CPB blood transfusions.[3–9] The use of higher dose heparin during CPB has also shown mixed results for biomarkers of thrombin generation, fibrinolysis, and platelet function.[5,10,11] Further, it is unclear whether the benefits of heparin concentration-guided anticoagulation are purely due to higher dosing of heparin or if higher heparin dosing can be achieved simply by using a higher target activated clotting time (ACT) during CPB.[12,13]

Excessive bleeding following cardiac surgery occurs in 6%–50% of patients,[14–16] and worsens early and late patient prognosis.[17–20] It is associated with transfusion of blood and reoperation for bleeding.[21] It is also associated with prolonged intensive care unit (ICU) stay, hospitalization duration and mechanical ventilation duration, increased stroke, low cardiac output, greater transfusion of all blood products, and increased 30-day mortality.[22] The impact of excessive bleeding on increased patient care costs has been demonstrated repeatedly.[23] Several interventions to reduce bleeding have been recommended with the most recent guidelines suggesting increased heparin dosing.[4]

Given the above studies, we hypothesized that increased heparin dosing either by increasing heparin dosing or the use of the Hepcon HMS would be associated with reduced chest tube bleeding following cardiac surgery. Reduced consumption of coagulation factors would be the mechanism for this reduced bleeding. We designed a randomized prospective blinded trial between three different strategies of anticoagulation management for patients undergoing CPB and cardiac surgery that consisted of heparin concentration management with automated heparin dose–response assay, higher heparin dosing with higher ACT target value for anticoagulation, and a control group of standard heparin management.

Materials and Methods

Study protocol

Following institutional review board approval and written informed consent, 302 patients above 18 or below 90 years of age scheduled for elective cardiac surgery requiring CPB were screened for enrollment from August 2001 to August 2003. Exclusion criteria included emergency surgery, circulatory arrest, combined non-cardiac procedures such as carotid endarterectomy, congenital heart repair, history of bleeding or clotting disorder, thrombolytic therapy, severe hepatic disease, cooling <28°C during CPB, dialysis-dependent renal failure, and platelet receptor glycoprotein IIIa/IIb antagonists medication received within 48 hours of surgery. Patients who did not receive tranexamic acid (TA) intraoperatively were excluded, since it was our practice to not use TA in patients thought to need a very short CPB duration. Patients who have received aspirin, heparin, or warfarin were not excluded.

Patients were placed into one of the three treatment groups using blocked stratified randomization in a blinded fashion. The stratification was based on previous sternotomy (redo) or not (primary). Given that there were three treatment groups and they were stratified as redo versus primary, the block size was six.

The control group (C) received standard porcine heparin in a dose of 300 u/kg prior to arterial cannulation for CPB. A celite ACT obtained with a Hemochron 801 (International Technidyne, Inc., Edison, NJ) was used to manage anticoagulation for group C. An ACT was obtained 5 minutes after the initial bolus of heparin. If the ACT was not >480 seconds, 5000 u of heparin was given and an ACT repeated; additional heparin was administered until the ACT was >480 seconds. An additional 5000 u of heparin was given if the ACT fell below 480 seconds anytime during CPB and the ACT was repeated. An ACT was obtained during CPB a minimum of every 30 minutes. Following separation of CPB, heparin was neutralized with 1.3 mg of protamine per 100 u of heparin. An ACT was obtained 10 minutes after protamine was given. Adequate heparin neutralization for group C was defined by an ACT value within 10% of the pre-CPB baseline ACT or <140 seconds if there was heparin infusing preoperatively. A heparinase ACT was also obtained in addition to the standard ACT to help detect heparin rebound at the end of surgery. A heparinase and standard ACT was performed 30 minutes after arrival in the ICU to detect heparin "rebound" in all groups.

The second group, high-dose heparin (HH), received an initial porcine heparin dose of 450 u/kg prior to arterial cannulation for CPB. A celite ACT obtained with the Hemochron 801 was utilized to assess anticoagulation. An ACT was obtained 5 minutes after heparin administration. An additional 5000 u of heparin was given if the ACT was <600 seconds anytime during CPB followed by a repeat ACT to ensure that the ACT was >600 seconds. During CPB, an ACT was obtained at least every 30 minutes. Heparin was neutralized with 1.3 mg of protamine per 100 u of heparin followed by an ACT 10 minutes after protamine. The dose of protamine used in this study is our standard protamine dose to reverse heparin. For the group HH, adequate heparin neutralization was determined by an ACT value that was within 10% of the pre-CPB baseline ACT or <140 seconds if the patient had been receiving heparin infusion. An ACT was also obtained after the closure of the sternum and 30 minutes after arrival in the ICU. A heparinase ACT was performed in addition to the standard ACT to detect heparin rebound. The heparinase ACT was also performed again 30 minutes after arrival in the ICU.

The third group, heparin concentration monitoring (HC), had anticoagulation during CPB monitored with the Hepcon Hemostasis Management System (HMS; Medtronic, Minneapolis, MN, USA). The initial heparin dose for the HC group was derived from the heparin dose response (HDR) test. The HDR tests were determined from a blood sample prior to heparinization, the heparin concentration (u/ml) to obtain a kaolin ACT of at least 480 seconds. During CPB, the heparin concentration was determined by the heparin assay or heparin protamine titration (HPT) cartridge. Additional heparin doses were given if the heparin concentration was less than the initially measured reference heparin concentration or if the kaolin ACT was <480 seconds. Heparin neutralization in the HC group was based on the most recent heparin concentration measurement before discontinuation of CPB. The amount of protamine to use for neutralization of heparin was determined by the Hepcon. Adequacy of heparin neutralization was validated according to a difference of less than 10% between the post-protamine kaolin ACT and heparinase-treated kaolin ACT. A final heparin concentration, standard ACT, and heparinase ACT were performed prior to leaving the operating room (OR) and again 30 minutes after arrival in the ICU.

The Hepcon HMS works differently from the ACT in that it estimates the free plasma heparin concentration from a whole-blood sample. The HDR test is done first to determine the patients' individual response to heparin prior to heparin administration. There are six channels in the HDR cartridge with two chambers with no heparin to determine baseline ACT, two chambers with 1.5 u/ml heparin, and two chambers that have 2.5 u/ml of heparin. The machine adds 0.4 ml of un-heparinized whole blood into each chamber from a syringe and measures the clotting time for each chamber. The results are plotted and the slope of the graphs is used to determine the patient's individual HDR. This is used to calculate the dose of heparin for the patient. During CPB, the heparin assay cartridge is used to determine the patient's individual heparin concentration using HPT and the need for additional heparin administration. Following CPB, the protamine dose to reverse circulating heparin is reported. The use of the Hepcon HMS allows heparin and protamine dosing to be individualized for each patient.

Patients were maintained on their current preoperative medications until they arrived in the OR. All patients received the institutional standardized balanced anesthetic regimen. Routine monitoring for cardiac surgery included an indwelling arterial catheter and a central venous catheter. CPB was conducted with a membrane oxygenator (Terumo Capiox SX25; Terumo Cardiovascular Systems Corporation, Ashland, MA, USA) at a flow of 2.0–2.4 l/min/m^2. The CPB circuit was primed with 1.5 L plasmaLyte, 10 mEq sodium bicarbonate, and 12.5 g mannitol. Mean perfusion pressure during CPB was maintained between 50 and 90 mmHg.

The cardiothoracic surgeons and anesthesiologists were blinded to the patient's type of heparin management. The anesthesiologist and certified registered nurse anesthetist (CRNA) or resident anesthesiologist was temporarily replaced by another CRNA prior to administration of heparin. The study physician investigators managed anticoagulation beginning with the initial administration of heparin until protamine had been administered and any residual heparinization had been corrected. Additional protamine was given only for evidence of residual heparin according to the findings of one of the three tests: thromboelastogram (TEG), Hepcon, or heparinase ACT. A maximum of 50 mg of additional protamine was administered in response to incomplete heparin neutralization. The original caregivers returned to manage all aspects of the patient until admission to the ICU. The study investigators did not participate in any transfusion-related decisions. The study was discontinued if the cardiac surgeon or the anesthesiologist believed the patient's best interests

necessitated the blinding be stopped and the patient was removed from the study.

Ten minutes after heparin neutralization, the surgical field was classified as dry, moderate, or wet by the surgeon and the anesthesiologist. If there was no identifiable surgical source for a "wet" surgical field, microvascular bleeding was considered present. The algorithm for transfusion of blood products described in **Fig. 1A** and **1B** subsequently guided the diagnosis and treatment in all three anticoagulation groups. These coagulation tests were obtained in patients identified as having a "wet" surgical field: prothrombin time (PT), activated partial thromboplastin time (APTT), TEG, platelet count (PLT), and fibrinogen (FIB). All the blood for the coagulation tests was obtained from the indwelling arterial catheter after 6 dead space volumes of blood were removed. Subsequently, the blood was returned to the patient immediately after the draw was complete. PLT results were available within 10 minutes from the clinical laboratory. The PT and APTT results were available in 20–30 minutes and the complete TEG in 30 minutes. Packed red blood cells (PRBCs) were given for a hemoglobin (Hgb) <9.0 g/dl or if clinical conditions such as ischemia, hypotension, or rapid blood loss merited PRBC transfusion. Albumin 5% and lactated Ringer's but not hetastarch or low molecular weight dextran were given for volume expansion.

Intraoperative blood loss was assessed by the volume of cell salvage blood collected after separation from CPB until the end of anesthesia. The volume of salvaged blood collected was recorded. The collected blood was processed and a hematocrit (HCT) obtained and recorded. Subsequently, the salvaged red blood cells were made available to the patient as autologous blood units that were administered to the patient for an Hgb <13.0 g/dl. Most of the blood left in the venous reservoir of the extracorporeal circuit (EC) was transfused to the patient prior to all the protamine given.

Upon arrival in the ICU, mediastinal chest tube drainage (MCTD) was recorded hourly for the duration of the first 24 hours in the ICU. Shed mediastinal blood was infused into the patient until such time that the volume exceeds 500 ml or reinfusion had been ongoing for 6 hours at which point it was discontinued. One additional dose of protamine was an option to be given in the ICU if the APTT was >1.5 times baseline, MCTD was >2 cc/kg/h, or TEG R value was >30 mm. Excessive bleeding was defined as MCTD >2 cc/kg/h. The cause of excessive bleeding in the ICU was determined by obtaining APTT, PT, and PLT. The ICU transfusion algorithm (**Fig. 1A** and **1B**) guided transfusion of blood products.

These variables were recorded: age; sex; height; weight; body surface area; operative procedures; CPB and aortic cross-clamp duration; time to surgical closure; ICU and hospital duration; lowest temperature during CPB; average temperature during CPB; lowest temperature during the post-CPB period; coagulation test results; initial heparin dose; total heparin dose; protamine dose; ACT values; total amount of fluid given during CPB; heparin concentration values; perioperative blood products; albumin 5% (ml); lactated Ringers (ml); autologous blood; HCT of collected blood; MCTD at 4, 8, and 24 hours; re-exploration for excessive bleeding; cardiovascular complications; tamponade; inotropic

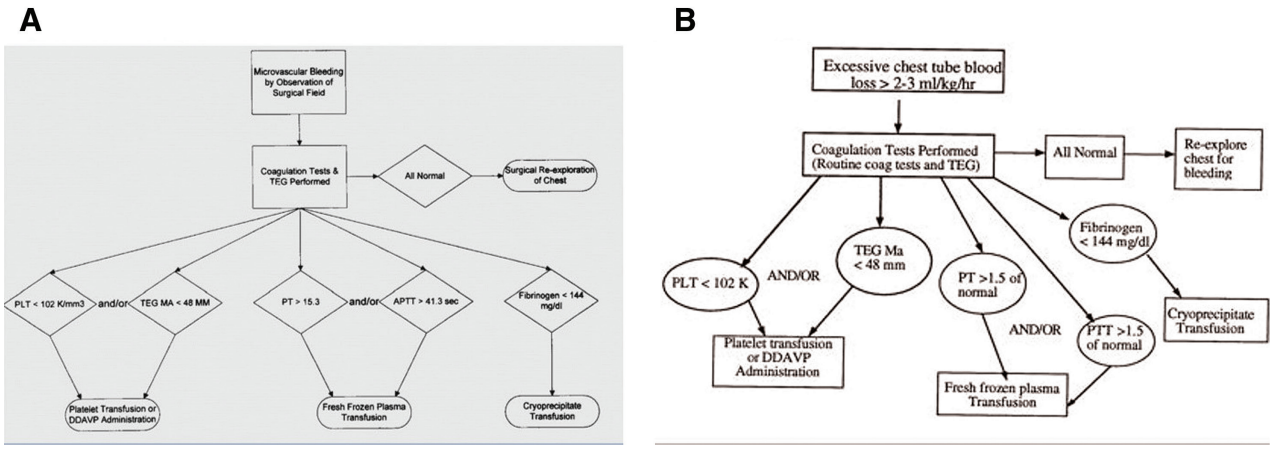

Fig. 1 (**A**) Algorithm for intraoperative microvascular bleeding. (**B**) Transfusion algorithm for postoperative ICU bleeding. PLT: platelet count; PT: prothrombin time; MA: maximum amplitude; TEG: thromboelastogram; APTT: activated partial thromboplastin time; DDAVP: desmopressin; ICU: intensive care unit

support; use of fibrin glue; and desmopressin. The medications that were recorded included preoperative anticoagulation drugs (aspirin, heparin, warfarin) and any other anti-platelet medications.

Statistical analysis

The goal was to enroll 55 primary and 35 redo patients into each of the three treatment groups: C, HH, and HC. The primary endpoint was the amount of postoperative blood loss (MCTD) in the ICU during an 8-hour period. Katsaros et al.[24] have demonstrated an expected mean and standard deviation (SD) of about 270 (160) ml of postoperative blood loss during 8 hours in patients receiving TA. Assuming a two-sided t-test at the alpha-0.05 significance level, an SD of 160 ml in each group, and a sample size of 50 in each group, there was 87% power to detect a difference of 100 ml in postoperative blood loss. The value of 100 ml in postoperative blood loss was chosen to demonstrate a clinically significant difference between groups. The primary comparisons of interest were the pairwise treatment comparisons in the non-redo group of patients. Assuming, for redo patients, the SD was 50% greater (240 ml) with 30 patients per group, there was 89% power to detect a 200 ml difference in postoperative blood loss.

Patients were placed into one of the three treatment groups (C, HH, or HC) using blocked stratified randomization. The stratification was based on previous sternotomy (redo patients) or not (primary patients). The block size was six. All primary and secondary analyses were separated for redo and primary patients. The primary analyses were pairwise treatment comparisons of 8-hour postoperative blood loss for the primary patients. Secondary analyses included pairwise comparisons of 8-hour postoperative blood loss for the redo patients and analysis of blood loss at other time points (16 and 24 hours) and transfusion requirements. Continuous outcomes (e.g. amount of blood loss and amount of transfusion) were analyzed using two-sample t-tests with logarithmic transformations where necessary. Dichotomous outcomes (e.g. whether transfusion was required) were analyzed using chi-square tests and Fisher's exact tests. Tertiary analyses included adjustment for covariates in primary and secondary analyses, pooled analysis of primary and redo patients, and longitudinal analysis of blood loss measurements over time. In all cases, two-sided tests were used and $p < 0.05$ defined statistical significance. As each of the pairwise comparisons was a separate question, no adjustment was made for multiple comparisons in order to control the per-comparison error rate.

Results

There were 302 patients screened but 32 patients were not randomized resulting in 269 patients enrolled from August 2001 to August 2003. The causes for not randomizing the patients once enrolled were: received aprotinin (5), the operation started too late (6), new onset neurologic changes (2), surgical complications during sternotomy (2), a surgery not needed (2), PLT too high (2), clopidogrel use (2), a change in surgeon (1), determined to use off pump (1), a concern for pulmonary embolism history found (1), the surgeon did not want intraoperative autologous transfusion (1), the use of hemodilution (1), personnel unavailable (1), the possible gastrointestinal (GI) bleed (1), polycythemia (1), the procedure changed (1), a change in patient consent (1), and hepatitis B (1). There were 90 patients in group C, 88 in group HH, and 91 in group HC. There were no differences between the groups regarding demographics (**Table 1**). The incidence of previous sternotomy was 12%, 10%, and 12% in the control, HH, and HC groups ($p = 0.91$), respectively. There was no difference in the surgical characteristics (aortic cross clamp, CPB, and surgical duration) (**Table 1**) except for the significant differences in the amount of heparin and protamine administered. Total heparin administered was significantly greater in groups HH (59334 ± 18669 u) and HC (62436 ± 15101 u) compared to group C (44428 ± 14556 u; $p < 0.001$). Total protamine was significantly greater for group HC (418 ± 99 mg) than group C (334 ± 67 mg; $p < 0.001$).

There was no difference in the classification of surgical bleeding between the groups (**Table 1**). **Figure 2** shows the MCTD for the three groups at 4, 8, and 24 hours. Chest tube drainage did not differ between treatment groups and control at 8 hours (median [25th percentile, 75th percentile] for control group was 321 [211, 490] compared to 340 [210, 443] and 327 [250, 545], $p = 0.998$ and $p = 0.540$, for HH and HC treatment groups, respectively). The percentage of patients who received transfusion is displayed in **Table 2**. There were no differences in intraoperative and ICU blood transfusions between groups except that the HC group had a higher rate of cryoprecipitate transfusion in the 24 hours after ICU admission compared to the control group (1.1% vs 7.8%, $p = 0.034$). The incidence of surgical

Table 1 Demographics and surgical characteristics

	Control (n = 90)	High heparin (n = 88)	Hepcon (n = 91)	p value
Demographics				
Age, years	66.0 (13.4)	63.3 (15.0)	66.1 (14.7)	0.34
Body surface area, m^2	2.0 (0.2)	2.0 (0.2)	2.0 (0.2)	0.30
Gender, female	29 (32%)	18 (20%)	24 (26%)	0.21
Race, white	88 (98%)	84 (95%)	89 (98%)	0.91
Previous sternotomy	11 (12%)	9 (10%)	11 (12%)	0.91
Preoperative medications				
Insulin	8 (9%)	5 (6%)	8 (9%)	0.72
Aspirin	50 (56%)	47 (53%)	45 (49%)	0.71
Coumadin	12 (13%)	11 (13%)	9 (10%)	0.77
Heparin	11 (12%)	10 (11%)	15 (16%)	0.61
Surgical characteristics				
Surgical procedures				0.84
Valve only	43 (48%)	46 (52%)	39 (43%)	
CABG only	30 (33%)	27 (31%)	31 (34%)	
CABG + valve	16 (18%)	13 (15%)	20 (22%)	
Other	1 (1%)	2 (2%)	1 (1%)	
CPB duration, minutes	84 (48)	81 (36)	86 (33)	0.73
AXC duration, minutes (n = 268)	53 (25)	54 (25)	61 (26)	0.08
Operation time, minutes	242 (88)	246 (71)	257 (75)	0.40
Anesthesia duration, minutes	298 (89)	301 (75)	310 (77)	0.59
Low CPB temperature, °C	33.5 (2.3)	33.6 (2.9)	33.5 (2.4)	0.96
Ultrafiltration duration, minutes (n = 265)	1670 (567)	1774 (701)	1713 (711)	0.58
Inotropic support	33 (37%)	36 (41%)	37 (41%)	0.82
Total heparin (units × 1000)	44.4 (14.6)	59.3 (18.7)	62.4 (15.1)	<.001
Total protamine (mg)	334 (67)	353 (74)	418 (99)	<.001
Reoperation for bleed	7 (8%)	4 (5%)	1 (1%)	0.08
Post CPB bleeding				0.46
None/minimal	60 (67%)	64 (73%)	65 (71%)	
Microvascular	29 (32%)	23 (26%)	22 (24%)	
Surgical	1 (1%)	1 (1%)	4 (4%)	
Reinstate CPB	2 (2%)	1 (1%)	3 (3%)	0.87
Balloon pump (n = 268)	3 (3%)	2 (2%)	4 (4%)	0.91
Fibrin glue (n = 267)	0 (0%)	1 (1%)	0 (0%)	0.33

Values are mean (SD) for continuous variables and number (percentage) for categorical variables. p-values are from Fisher's exact tests for categorical variables and ANOVA for continuous variables. Continuous variables are summarized as mean (SD) and compared using ANOVA. Categorical variables are summarized as number (percentage) and compared using Fisher's exact tests. ANOVA: analysis of variance; CPB: cardiopulmonary bypass; AXC: aortic cross clamp; CABG: coronary artery bypass grafting; SD: standard deviation; post CPB bleeding: extent of bleeding noted by observation of the surgical field

re-exploration for bleeding for groups C, HH, and HC was 8%, 5%, and 1%, respectively (p = 0.08).

The baseline median ACT for group HC (138 seconds) was significantly shorter than that for the control group ACT (152 seconds) but not clinically significant (p <0.001) (**Fig. 3**). After heparin bolus, median ACT values for both HH and HC were significantly longer than those for group C (p <0.001). After initiation of CPB, ACT values for only group HH were significantly longer than those for group C (p <0.01). There was no difference in ACT values between the groups following protamine. There were no differences regarding Hgb, APTT, PT, and PLT values among the groups intraoperatively or during the initial 24 hours in the ICU (**Supplemental Table 1; available online**) except for the APTT upon arrival in the ICU. The median APTT upon arrival to the ICU was significantly longer for group HH (40 seconds) than that for group C (38 seconds, p = 0.031) but not clinically significant.

The duration of mechanical ventilation, ICU, and hospital stay was not different between the groups (**Table 1**). There was no difference in the incidence of cardiac

arrest, renal dysfunction/failure, stroke, myocardial infarction, cardiac tamponade, and clotted coronary artery grafts between groups. There was no difference in the number of patients who died: 3 (3%), 1 (1%), and 2 (2%) for groups C, HH, and HC, respectively.

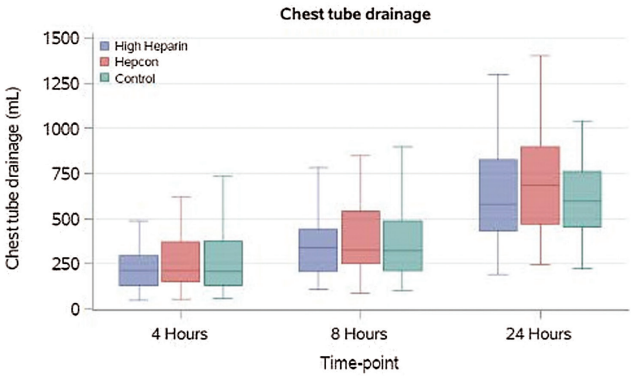

Fig. 2 MCTD. Time points are measured after the patient arrived in the ICU. All values are represented as median and interquartile values. MCTD: mediastinal chest tube drainage; ICU: intensive care unit

Discussion

In a blinded, prospective, randomized trial, we found the same amount of bleeding and blood product transfusion with the use of standard dose heparin therapy, high-dose heparin therapy, and heparin concentration management with the Hepcon HMS. This shows that heparin has a very wide dose safety profile for cardiac surgery with CPB. The heparin doses were considerably different between HH and HC groups and the CC group as were the ACT values during CPB. There were no clinically significant differences in other coagulation test values between the groups.

The optimal management of anticoagulation for CPB and cardiac surgery continues to evolve with new technologies.[4] Heparin remains the most common drug to provide anticoagulation during CPB, but the optimal dosing to minimize thrombin generation from contact of blood and the CPB circuit is not defined. The ACT is employed most commonly to assess heparin anticoagulation and ensure adequate heparin dosing for CPB and

Table 2 Blood transfusions during CPB and in ICU*

Transfusion product	Control (n = 90)	High heparin (n = 88)	Hepcon (n = 91)	p-values†		
	n (%)	n (%)	n (%)	HH vs C	HC vs C	Overall
RBCs						
Any RBC transfusion	49 (54.4)	45 (51.1)	51 (56.0)	0.764	0.882	0.812
CPB	26 (28.9)	21 (23.9)	29 (31.9)	0.498	0.747	0.500
Post-CPB	23 (25.6)	21 (23.9)	19 (20.9)	0.863	0.485	0.762
ICU (24 hours)	26 (28.9)	25 (28.4)	28 (30.8)	1.00	0.871	0.942
Non-RBCs						
Any non-RBC transfusion	23 (25.6)	20 (22.7)	21 (23.1)	0.727	0.731	0.904
Cryoprecipitate						
Any cryoprecipitate	8 (8.9)	3 (3.4)	2 (2.2)	0.212	0.058	0.126
Post-CPB	1 (1.1)	1 (1.1)	1 (1.1)	1.00	1.00	1.00
ICU (24 hours)	7 (7.8)	2 (2.3)	1 (1.1)	0.169	0.034	0.068
Plasma						
Any plasma	17 (18.9)	17 (19.3)	18 (19.8)	1.00	1.00	1.00
CPB	2 (2.2)	1 (1.1)	0 (0)	1.00	0.246	0.435
Post-CPB	8 (8.9)	10 (11.4)	14 (15.4)	0.627	0.255	0.419
ICU (24 hours)	11 (12.2)	9 (10.2)	8 (8.8)	0.813	0.478	0.748
Platelets						
Any platelets	22 (24.4)	18 (20.5)	18 (19.8)	0.592	0.478	0.737
Post-CPB	16 (17.8)	9 (10.2)	11 (12.1)	0.196	0.304	0.332
ICU (24 hours)	11 (12.2)	11 (12.5)	9 (9.9)	1.00	0.644	0.863

* Data are number (percent) requiring the given transfusion products. Transfusions given on bypass (CPB), post bypass to the ICU environment, and in the first 24-hours in the ICU are summarized

† p-values are from Fisher's exact tests. High heparin and Hepcon groups are compared to the control group. In addition, all three groups are tested for simultaneous equality (Overall)

RBC: red blood cells; CPB: cardiopulmonary bypass; ICU: intensive care unit; HH: high-dose heparin; HC: heparin concentration monitoring

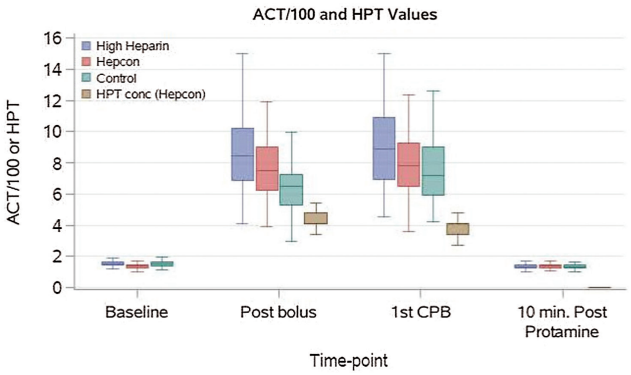

Fig. 3 ACT results divided by 100 and Hepcon HPT results over time. All values are median and interquartile. Post bolus: value after heparin administration for CPB. ACT: activated clotting time; CPB: cardiopulmonary bypass; HPT: heparin protamine titration

protamine dosing following CPB, though other heparin monitoring and management technologies have been developed including the Hepcon HMS.[25] The safe or optimal range for ACT dates back to the 1970s when Bull et al.[2] demonstrated no clot development in the oxygenator or CPB circuit when the ACT was maintained above 300 seconds. Young et al.[12] noted that fibrin formation occurred in CPB circuits with a minimum ACT value of 300 seconds and suggested a target threshold of 400 seconds. To reduce the risk of under-dosing heparin, many institutions a minister heparin to attain and maintain an ACT value greater than 480 seconds for CPB.

In 1994, Despotis et al. found that whole-blood heparin measurements with the Hepcon HMS correlated quite well with anti-Xa measurements during bypass, whereas the correlation with ACT was poor.[26] This led to a study by Despotis et al.[3] who found significantly less transfusion of platelets with heparin concentration monitoring via the Hepcon HMS compared to ACT during cardiac surgery with CPB in 254 randomized patients without antifibrinolytic therapy. More importantly, the incidence of hemostatic transfusion perioperatively with the heparin concentration management group during cardiac surgery was only 17% compared to 33% in the control group ($p < 0.005$). The study pointed to better anticoagulation with 25% higher heparin dosing resulting in less thrombin activation and consumption during CPB leading to more bleeding. However, the study failed to determine if it was purely the higher heparin dose that resulted in the improvement. In our study, we constructed three groups to assess the impact of higher heparin dosing with the ACT compared to Hepcon management and a control with normal ACT parameters for anticoagulation. We had significantly greater heparin dosing compared to the control, but there was minimal difference between Hepcon and HH. More importantly, there were no significant differences in the transfusion of blood products aside from the HC group that had a higher rate of cryoprecipitate transfusion in 24 hours after ICU admission compared to the control group (**Table 1**). Otherwise, unlike Despotis et al.,[3] there was no evidence of better hemostatic status during CPB compared to the control ACT.

A recent prospective randomized trial by Lax et al.[5] compared high-dose heparin 600 u/kg and ACT greater than 600 seconds to standard dose heparin 300 u/kg and ACT greater than 400 seconds for CPB in 63 consecutive primary coronary artery bypass grafting (CABG) patients. They found no differences in blood loss up to 18 hours postoperatively and no differences in blood transfusions between the groups. There were differences in median total heparin administered and median factor Xa levels between the groups. There were no differences in multiple electrode aggregometry and rotational thromboelastography results between the groups.

Another recent prospective randomized trial by Braatz et al.[27] compared high-dose heparin with goal ACT greater than 680 seconds to standard dose heparin with goal ACT greater than 480 seconds for CPB in 29 primary CABG patients. The high-dose heparin group received greater amounts of heparin and protamine than the standard dose heparin group. They found no differences in intraoperative blood loss, but median chest tube blood loss was higher in the high-dose heparin group compared to the standard heparin dose group ($p = 0.029$). Blood transfusion data were not reported. There were no differences between the groups in the measure of inflammatory markers interleukin-6 and tumor necrosis factor-α. Smaller, prospective randomized trials of heparin dosing found mixed results of increased heparin dosing on bleeding and blood transfusion.[6–8,28] Also like Lax, the use of higher dose heparin during CPB has shown mixed results for biomarkers of thrombin generation, fibrinolysis, and platelet function.[5,10,11]

To determine if protamine titration using the Hepcon HMS was associated with less bleeding after CPB, Wang et al.[9] performed a meta-analysis of four prospective randomized trial with 507 patients, which primally underwent CABG procedures. The majority of the patients were in the study by Despotis et al.[3] In the

study arm, the protamine dosing was determined using the Hepcon HMS. Blood loss and transfusion requirements were lower in the study arm. They concluded that titrated heparin and protamine dosing was more effective than standard dosing for reducing postoperative blood loss.

Limitations

The data presented in this study are old. The principal investigator of this study, Dr. William C. Oliver, Jr, delayed analyzing the data after it was collected and then died. This delayed publication of the results of this study since the data had to be found, verified, and analyzed. Since that time, surgical and coagulation management techniques and technology have somewhat changed, thus potentially limiting the impact of this study. Our study contained a wide range of patients and surgeries including complex surgeries. It could be, as discussed above, primary sternotomy and less complex surgery patients would benefit from the Hepcon HMS and/or higher dose heparin management for CPB. Our goal was to enroll 55 primary and 35 redo patients into each of the three treatment groups, but our ratios enrolled were about 80 primary and 10 redo patients in each group (**Table 1**). Further in **Table 1**, the dose of protamine appears low compared to the total heparin dose given. The dosing of protamine was based on the initial heparin dose; what is reported in **Table 1** is the total heparin administered including the subsequent heparin doses during CPB. There evidence of residual heparin following protamine administration in the heparin monitoring group as demonstrated by some patients is having HPT heparin levels greater than zero and increased APTT upon ICU arrival. Our hypothesis was that increased heparin dosing would result in greater inhibition of thrombin activity. We did not measure thrombin generation and coagulopathy in this study. Therefore, if we found differences between the groups, we are unable to test a mechanism for these differences such as greater heparin being associated with greater inhibition of thrombin activity or differences in coagulation coagulopathy between the groups. Of note, there were no clinically significant differences in standard coagulation tests between groups in the intraoperative or 24 hours in the ICU. Finally, we found a higher incidence of reoperation for bleeding in the control group that was not statistically significant but could be considered clinically significant.

Conclusion

Higher heparin dosing accomplished by either ACT or heparin concentration monitoring did not reduce 24-hour ICU blood loss or transfusion requirements when personnel were blinded to the anticoagulation regimen.

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Disclosure Statement

The authors declare no competing interests.

Supplementary Information

Coagulation test results.

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