




Titrated *versus* conventional anticoagulation management for thrombin generation in cardiac surgery: a randomized controlled trial

Gestion de l'anticoagulation par titrage *versus* conventionnelle pour la génération de thrombine en chirurgie cardiaque : une étude randomisée contrôlée

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Abstract

Purpose Optimal heparin titration during cardiopulmonary bypass (CPB) may reduce coagulation system activation and preserve hemostatic function post-CPB. Our objective was to assess if the Heparin Management System (HMS) Plus improves heparin titration, thereby leading to higher thrombin generation post-CPB compared with activated clotting time (ACT)-guided management.

Methods We conducted a randomized controlled trial of 100 patients undergoing cardiac surgery with CPB at a

single center. A total of 50 patients were randomized to conventional ACT-guided management, and 50 to the HMS Plus system. The primary outcome was change in thrombin generation post-CPB compared with baseline, as assessed by calibrated automated thrombography. Secondary outcomes included intraoperative blood loss, chest drain output up to 72 hr, and transfusions. In an exploratory analysis, we compared the quintile of patients with the highest average heparin concentration on CPB ($\geq 4.0 \text{ mg}\cdot\text{kg}^{-1}$) with the rest of the cohort.

Results A total of 100 patients were included in an intent-to-treat analysis. We observed no difference in post-CPB thrombin generation or secondary outcomes. However, patients in the HMS Plus group had higher average heparin concentrations while on CPB than patients in the conventional management group did (mean difference,

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-0.21; 95% confidence interval, -0.42 to -0.01). The quintile of patients with the highest average heparin concentration ($4.0 \text{ mg}\cdot\text{kg}^{-1}$) had higher thrombin generation post-CPB than the rest of the cohort did.

Conclusions The HMS Plus system did not show significant benefits in thrombin generation, bleeding outcomes, or transfusion in patients undergoing cardiac surgery with CPB. Higher average heparin concentrations on CPB were associated with higher post-CPB thrombin generation.

Study registration www.ClinicalTrials.gov (NCT03347201); first submitted 12 October 2017.

Résumé

Objectif Un titrage optimal de l'héparine pendant la circulation extracorporelle (CEC) peut réduire l'activation du système de coagulation et préserver la fonction hémostatique après la CEC. Notre objectif était d'évaluer si le système de gestion de l'héparine HMS Plus améliorait le titrage de l'héparine, entraînant ainsi une génération de thrombine plus élevée après la CEC par rapport à la gestion guidée par le temps de coagulation activé (ACT).

Méthode Nous avons réalisé une étude randomisée contrôlée de 100 patients bénéficiant d'une chirurgie cardiaque sous CEC dans un seul établissement. Au total, 50 patients ont été randomisés à une gestion conventionnelle guidée par l'ACT et 50 à une gestion guidée par le système HMS Plus. Le critère d'évaluation principal était la variation de la génération de thrombine post-CEC par rapport aux valeurs de base, telles qu'évaluées par thrombographie calibrée automatisée. Les critères secondaires comprenaient les pertes sanguines peropératoires, le drainage thoracique jusqu'à 72 heures et les transfusions. Dans une analyse exploratoire, nous avons comparé le quintile de patients ayant la concentration moyenne d'héparine la plus élevée sous CEC ($\geq 4,0 \text{ mg}\cdot\text{kg}^{-1}$) au reste de la cohorte.

Résultats Au total, 100 patients ont été inclus dans une analyse en intention de traiter. Nous n'avons observé aucune différence dans la génération de thrombine post-CEC ou dans nos critères d'évaluation secondaires. Cependant, les patients du groupe HMS Plus présentaient des concentrations moyennes d'héparine plus élevées sous CEC que les patients du groupe de gestion conventionnelle (différence moyenne, -0,21; intervalle de confiance à 95 %, -0,42 à -0,01). Le quintile de patients ayant la concentration moyenne d'héparine la plus élevée ($4,0 \text{ mg}\cdot\text{kg}^{-1}$) avaient une génération de thrombine post-CEC plus élevée que le reste de la cohorte.

Conclusion Le système HMS Plus n'a pas montré d'avantages significatifs dans la génération de thrombine, les issues hémorragiques ou la transfusion chez les patients bénéficiant d'une chirurgie cardiaque sous CEC. Des

concentrations moyennes d'héparine plus élevées sous CEC ont été associées à une génération de thrombine post-CEC plus élevée.

Enregistrement de l'étude www.ClinicalTrials.gov (NCT03347201); soumis pour la première fois le 12 octobre 2017.

Keywords anticoagulation · cardiac surgical procedures · thrombin

Coagulopathy and bleeding are common complications of cardiac surgery with cardiopulmonary bypass (CPB).^{1–3} While the causes of coagulopathy are multifactorial, impaired thrombin generation plays a central role.¹ Heparin-coated CPB circuits and high levels of systemic heparin anticoagulation are used to prevent hemostatic system activation and thrombin generation during CPB.⁴ Nevertheless, activation of the extrinsic and intrinsic hemostatic systems on bypass circuit components can continue, resulting in consumptive coagulopathy.²

Conventional heparin management using weight-based heparin dosing and activated clotting time (ACT) monitoring has been the historical mainstream practice for suppression of thrombin generation during CPB.⁵ Nevertheless, there are a number of reasons to question the reliability of ACT-guided heparin management. Firstly, nonspecific prolongations of the ACT are common and may be caused by patient or CPB-related factors independent of the achieved heparin concentration.^{6,7} Secondly, there is poor agreement between different ACT devices, which may lead to important differences in heparin and protamine dosing.^{8,9} Lastly, variation in individual responses to heparin limits the effectiveness and safety of weight-based heparin dosing.¹⁰

The Heparin Management System (HMS) Plus hemostasis system (Medtronic, Inc., Minneapolis, MN, USA) was developed to address the limitations of ACT-guided heparin management. It allows for personalized anticoagulation by assessing a patient's individual heparin dose–response curve, and uses heparin–protamine titration (HPT) to measure heparin concentration and dose protamine. Heparin concentrations assessed with HMS Plus show better correlation with plasma heparin levels^{11–13} during CPB than ACT measurements do. Additionally, the HMS Plus system may improve post-CPB protamine management.^{14–16} A technology capable of assessing thrombin generation is calibrated automated thrombography (CAT), which provides a more accurate reflection of hemostatic potential related to thrombin generation than conventional tests of hemostasis do.^{1,17–20}

If the HMS Plus system prevents thrombin generation more effectively during CPB by personalizing heparin dosing, it may be more effective at preserving thrombin generation potential post-CPB, thereby reducing coagulopathy and transfusion, along with their associated effects on morbidity and mortality. The primary aim of this study was to determine if heparin management using the HMS Plus system improves post-CPB thrombin generation as assessed by CAT parameters. The secondary aim was to assess if HMS Plus use is associated with improvements in clinical bleeding outcomes, including blood loss and transfusion rates 24 hr after CPB. Our hypothesis was that reliably higher heparin concentrations while on CPB would improve post-CPB thrombin generation.

Methods

Study design

This was a single-center, parallel-group prospective randomized controlled trial (www.ClinicalTrials.gov; identifier NCT03347201; first submitted on 12 October 2017) of 100 patients randomized 1:1 in randomly permuted blocks to titrated heparin and protamine dosing based on HMS Plus management (intervention group), or conventional ACT-guided management (control group). Research ethics board approval was obtained from the University Health Network (Toronto, ON, Canada; REB ID 15-9761). Eligible patients were those undergoing nonemergent coronary artery bypass grafting, valve repair or replacement (with or without ascending aortic replacement), or a combination of these procedures requiring the use of CPB. Exclusions included an inability to provide informed consent, age less than 19 yr, liver dysfunction (defined as liver enzymes > two-fold higher than upper limit of normal), planned use of deep hypothermic circulatory arrest or brief circulatory arrest, highly complex cases (left ventricular device insertion or explant, heart transplant, or complex congenital repairs), pre-existing coagulopathy (international normalized ratio > 1.5, partial thromboplastin time > 45 sec, fibrinogen < 1.0 g·L⁻¹, platelet count < 100 × 10⁹·L⁻¹), use of long-acting oral anticoagulants that had not been appropriately discontinued, preoperative use of heparin infusion, major hemoglobinopathies, thalassemia or iron storage diseases, and a previous diagnosis of heparin-induced thrombocytopenia. Results are reported according to the Consolidated Standards of Reporting Trials guidelines.²¹

Heparin management

INTERVENTION GROUP

In the HMS Plus group, the initial heparin bolus before CPB was determined by HMS Plus calculation to achieve a theoretic target ACT point (480 sec) on the heparin dose responsiveness (HDR) curve of each patient or to achieve a target heparin concentration of 4 mg·kg⁻¹, whichever required a higher dose of heparin. The calculation was based on the HMS Plus-estimated patient plasma volume and a HDR curve generated with the HDR cartridge (304-20POR, Medtronic, Inc., Minneapolis, MN, USA) containing known heparin concentrations of 0.0, 1.7, and 2.84 U·mL⁻¹ performed before skin incision. Heparin concentration was then measured by the HMS Plus HPT cartridge four minutes after the initial heparin loading dose, then at ten minutes and every 30 min after commencing CPB. Concurrently, ACTs were measured by the HemochronTM Signature Elite system (Werfen, Bedford, MA, USA). If ACT values by the Hemochron Signature Elite system were above 480 sec, further doses of heparin were given as dictated by HMS Plus to target a heparin concentration of 4 mg·kg⁻¹ until the end of CPB. If the ACT fell below 480 sec, an additional heparin bolus was given as indicated by HMS Plus or independent of HMS Plus (based on individual perfusionist judgment) if the calculated additional heparin amount was zero. The initial protamine dose was determined by HMS Plus based on the last heparin concentration on CPB. Four minutes after protamine administration, residual heparin was measured and additional protamine was given as calculated by HMS Plus until none was detected.

CONTROL GROUP

In the control group, patients underwent heparin anticoagulation using a weight-based initial dose of 400 U·kg⁻¹, aiming for an ACT of > 480 sec with the Hemochron Signature Elite system as per conventional management at our institution. Heparin-protamine titration measurements for heparin concentration were performed concurrently at the same time points as selected for the HMS Plus group. Further heparin doses (5,000 to 10,000 units) were to be given only when the ACT by the Hemochron Signature Elite system fell below 480 sec. After the cessation of CPB, heparin was reversed with protamine based on the initial heparin loading dose given pre bypass, using a ratio of 1 mg of protamine for every 100 units of heparin.

Clinical management

No changes were made to usual anesthetic or surgical care. Cardiopulmonary bypass circuits comprised a Cortiva coated Fusion[®] integrated oxygenator, Balance[™] coated tubing, and Balance coated Affinity[™] centrifugal pump (all, Medtronic, Inc., Minneapolis, MN, USA). Standard nonpulsatile CPB with moderate hypothermia aiming for a core temperature of 34–36°C was used. The CPB circuit was primed with 1,000 mL of PLASMA-LYTE A solution (Baxter Corporation, Mississauga, ON, Canada), 25 g of mannitol, and 5,000 units of heparin. Patients received tranexamic acid as per institutional practice.²² Transfusion was managed in both groups according to departmental protocol, consistent with current guidelines.²³ The red blood cell transfusion trigger was generally a hemoglobin level ≤ 70 g·dL⁻¹ during CPB, ≤ 80 g·dL⁻¹ in the post-CPB period, and ≤ 90 g·dL⁻¹ for bleeding or unstable patients. Additional blood components (plasma, platelets, cryoprecipitate, fibrinogen concentrate) were transfused as per departmental protocol.^{24,25}

Outcome measurements

The primary outcome of interest was the difference in thrombin generation potential post-CPB compared with baseline, as assessed through CAT. Plasma samples were taken before heparinization for a baseline reading and ten minutes after reversal of heparin with protamine. All samples were obtained from preoperatively placed arterial lines discarding the first 10 mL of blood. Specimens were collected in sodium citrate tubes (0.13 M, 9 parts blood, 1 part sodium citrate) containing corn trypsin inhibitor (20 μ g·mL⁻¹) and centrifuged twice at 2,900 g for ten minutes at room temperature. Platelet-poor plasma was collected from the upper three quarters of the supernatant. Samples were prepared within 30 min of sampling and frozen for later batch analysis. Calibrated automated thrombography was performed as described by Hemker *et al.*¹⁷ with the standardization of reagents suggested by Dargaud *et al.*²⁶ Calibrated automated thrombography assays were performed using a Thrombinoscope (Maastricht, The Netherlands) system based on a Fluoroskan Ascent[®] fluorometer (Thermo Fisher Scientific, Waltham, MA, USA). Citrated plasma samples (80 μ L) were combined in wells of 96-well plates with 20 μ L of trigger solution (Thrombinoscope PPP or PPP-low reagent; Stago Canada, Mississauga, ON, Canada) containing phospholipids (~ 4 pM) and tissue factor (TF) (~ 5 and ~ 1 pM TF, respectively).^{27–30} The plate was then moved to the fluorometer and 20 μ L of FluCa solution added containing the fluorogenic substrate Z-Gly-Gly-Arg-AMC and CaCl₂. The outcome of the thrombin generation

reaction was observed by monitoring a thrombin-specific fluorogenic substrate.³¹

Rotational thromboelastometry (ROTEM[®]) was performed on the ROTEM delta instrument (Werfen, Bedford, MA, USA) using 300 μ L citrated whole blood as previously described.³² Rotational thromboelastometry assays used were contact factor activation, contact factor activation with heparinase to neutralize the heparin effect, TF activation, and TF activation with platelet inhibition to assess fibrinogen status. These were performed at two time points—when the patient was rewarmed to 36°C during CPB and ten minutes after the reversal of heparin with protamine following cessation of CPB. Platelet function analysis was performed with Plateletworks[™] (Helena Laboratories, Beaumont, TX, USA) as per standard clinical practice in our institution as part of a blood transfusion algorithm that has been previously described.²⁴

Secondary outcomes included intraoperative blood loss, chest drain output up to 72 hr, and transfusions. Intraoperative blood loss was recorded by subtracting inputs (irrigation volume, cell salvage anticoagulant) from losses (cell salvage volume collection, wet volume - dry volume sponges, suction canister volumes), which gave the total blood loss at the end of surgery. Postoperative blood loss for the first 24 hr was calculated from the chest drain output. Intraoperative transfusion of packed red cells, pooled platelets, plasma, cryoprecipitate, prothrombin concentrate, and fibrinogen concentrate intraoperatively and postoperatively was recorded.

Sample size

As noted in the above paragraph, our primary outcome of interest was the difference in thrombin generation post-CPB compared with baseline. Bosch *et al.* observed a change in mean (standard deviation [SD]) peak thrombin from 321 (63) nM pre CPB to 241 (36) nM post-CPB.³³ Assuming a decrease in peak thrombin generation post-CPB of half (50%) the decrease observed in the control group in patients undergoing HMS Plus-based heparin management, to achieve a power of 0.80 with a two-sided alpha of 0.05, our approximate sample size was 50 patients per group, giving a total number of 100 patients.

Analysis

We utilized an intention-to-treat analysis approach. Continuous outcomes were compared between groups using Student's *t* test for normally distributed variables and the Wilcoxon rank sum test for non-normally distributed variables. Categorical variables were compared using Fisher's exact test for cell count values of 5 or less or the Chi square test otherwise.

We conducted additional exploratory analyses to better understand the impact of higher heparin concentrations on thrombin generation post-CPB. To better understand whether higher CPB heparin concentrations are associated with improved post-CPB thrombin generation regardless of study group, we stratified data based on quintiles of heparin concentration level maintained during CPB, with quintile 5 (the approximately 20% of patients with the highest average heparin concentrations during the first 120 min of CPB) maintaining an average heparin concentration on bypass of $4 \text{ mg}\cdot\text{kg}^{-1}$. We considered two-sided P values < 0.05 significant for the primary endpoint and two-sided P values < 0.001 for secondary comparisons. SAS University Edition (SAS Institute Inc., Cary, NC, USA) was used for analysis.

Results

All randomized patients were eligible for inclusion in the final analysis (Figure). The date of study initiation was 2 October 2017, with the first randomized patient sample collected on 16 October 2017. The final date of data collection for the primary endpoint was on 5 March 2019. There were no important differences in baseline characteristics between the intervention and control groups (Table 1).

In terms of the primary outcome, we observed no differences in thrombin generation parameters between the HMS Plus group and the control group. While all measures of thrombin generation showed significant changes post-CPB indicating a profound global impairment in thrombin generation (significant increases in the lag time and time to peak, with significant decreases in the endogenous thrombin potential [ETP] and peak thrombin), thrombin generation parameters post-CPB were not better in the HMS Plus group (Table 2). Similarly, we found no between-group differences with respect to other measures of hemostasis, including any ROTEM parameters (see Electronic Supplementary Material [ESM] eTable 1) or absolute platelet number or function (ESM eTable 2).

Although heparin concentrations were generally below the prespecified target threshold of $4 \text{ mg}\cdot\text{kg}^{-1}$, the HMS Plus group had significantly higher heparin dosing ($P < 0.001$), and maintained a higher average heparin concentration during CPB than the control group did (mean difference, -0.21 ; 95% confidence interval [CI], -0.42 to -0.01) (Table 3). Despite a significantly higher heparin level in the HMS Plus group before termination of CPB, the total protamine use and the protamine-to-heparin ratio in the HMS Plus group was lower than in the control group (Table 3), while both groups showed similar postprotamine heparin levels (Table 4).

Further analysis of heparin concentrations and ACT measurements during CPB (Table 4) showed that serial ACT measurements did not reflect the significant differences in heparin concentrations between the two groups, whose values were comparable in both groups at all time points. The discordance between ACT and heparin concentration was especially noticeable at 120 min of CPB, when the control group had a heparin concentration which was lower than the HMS Plus group by a mean difference of $1.1 \text{ mg}\cdot\text{kg}^{-1}$ (95% CI, -2.2 to 0.1), while the ACT values tended to be higher (Table 4).

With respect to secondary outcomes, at the time of patient arrival in the intensive care unit, both groups had significant reductions in hemoglobin level and absolute platelet count, and elevations in the prothrombin time and activated partial thromboplastin time compared with baseline, with no significant between-group differences (ESM eTable 2). There were no differences between the two groups in estimated blood loss, chest drain output up to 72 hr postoperatively (Table 2), or in transfusion of individual blood components (ESM eTable 3).

In the control group, heparin overdosing (where additional heparin was given with an ACT > 480 sec outside of the study protocol) occurred in 34% of participants ten minutes after initiation of CPB. Conversely, in the HMS Plus group, less than 6% of patients were overdosed or underdosed at any time (ESM eTable 4). In our exploratory analysis where patients were divided into quintiles of average heparin concentration achieved during the first 120 min of CPB, regardless of assigned study group, the quintile with the highest concentration consisted of 18 patients with a mean (SD) heparin concentration of 4.0 (0.3) $\text{mg}\cdot\text{kg}^{-1}$ (Table 5, ESM eTable 5). Examining thrombin generation parameters as measured by CAT using 5 pM of TF as a reagent, this group had significantly higher absolute ETP and peak thrombin generation, and shorter lag time and time to peak values than the remainder of the cohort did. A similar pattern was also observed under low TF conditions (1 pM), but no statistical significance was detected. We observed no differences in the estimated blood loss, chest drain output up to 72 hr postoperatively or in rates of transfusion compared with patients with lower heparin concentrations during CPB (Table 5).

Discussion

In the setting of cardiac surgery requiring CPB, maintaining a stable therapeutic heparin concentration is critical for effective inhibition of coagulation factor and thrombin consumption.^{34–36} Targeting a higher heparin concentration is advocated by several studies for its dose-

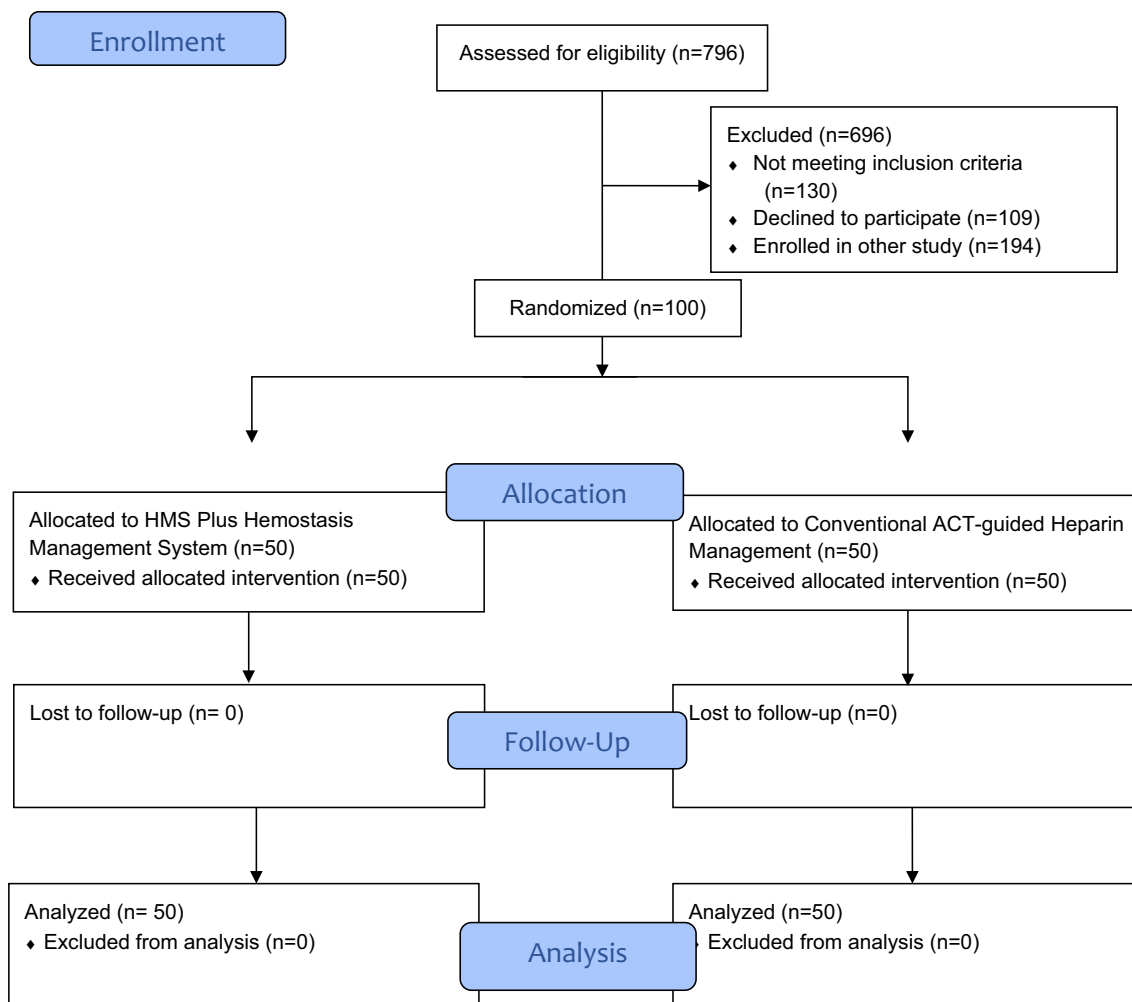


Figure CONSORT Flow diagram of patient screening, eligibility, and retention throughout the original randomized controlled trial^{21,48}

related antithrombin activity^{35,36} and platelet inhibition during CPB.^{37,38} In this study, the HMS Plus group had significantly higher and more stable average heparin concentrations while on CPB. Nevertheless, our study was limited by a high rate of protocol violations in the control group (additional heparin boluses despite an ACT > 480 sec), which led to higher average heparin concentration while on CPB for the control group than our protocol would dictate. This would have minimized between-group differences in average heparin concentrations, and may partly explain why no major differences in outcomes were seen in the HMS Plus group compared with the conventional management group. Our data suggests that when used per-protocol, the HMS Plus system offers advantages over conventional ACT-guided management, particularly in relation to the stability of the average heparin concentration achieved while on CPB.

The protamine-to-heparin ratio is an important factor associated with postoperative bleeding and transfusion.³⁹ In prior studies, a two-fold decrease in the protamine-to-

heparin ratio was associated with significant improvements in platelet function.⁴⁰ The majority of prior work showing favorable outcomes with HMS Plus-based management had significantly reduced protamine-to-heparin ratios, with a range of 0.6–0.7 in the HMS Plus group compared with 0.9–1.2 in the control group.^{13,14,41–43} The protamine-to-heparin ratio in our study was reduced to 0.6 in the HMS Plus group with no observed increase in bleeding or transfusion requirements. This suggests that the proper application of the HMS Plus system allows finer titration of protamine dosing, which may avoid the adverse effects associated with excessive protamine. Nevertheless, our control group protamine-to-heparin ratio of 0.7 is lower than that of the control groups in previously published studies, which may contribute to a smaller observed difference between the HMS Plus and control groups in our study. Additionally, our study was not powered to detect a difference in clinical bleeding or transfusion. Hence, while we did not observe a difference, a clinically relevant effect cannot be entirely excluded.

Table 1 Patient baseline characteristics and clinical data

Parameter	Control <i>N</i> = 50	HMS Plus <i>N</i> = 50	SMD
Age (yr), median [IQR]	67 [54–73]	65 [54–73]	-0.06
BMI (kg·m ⁻²), median [IQR]	27 [24–30]	28 [25–32]	0.26
Males, <i>n</i> /total <i>N</i> (%)	34/50 (68%)	35/50 (70%)	0.05
Height (cm), median [IQR]	172 [164–179]	171 [162–180]	-0.07
Weight (kg), median [IQR]	81 [71–92]	86 [68–98]	0.17
Hypertension, <i>n</i> /total <i>N</i> (%)	34/50 (68%)	35/50 (70%)	0.05
Dyslipidemia, <i>n</i> /total <i>N</i> (%)	26/50 (52%)	31/50 (62%)	0.20
Diabetes, <i>n</i> /total <i>N</i> (%)	9/50 (18%)	13/50 (26%)	0.19
Obstructive pulmonary disease, <i>n</i> /total <i>N</i> (%)	3/50 (6%)	5/50 (10%)	0.15
MI, <i>n</i> /total <i>N</i> (%)	2/50 (4%)	5/50 (10%)	0.24
Renal disease	79 [71–92]	75 [65–86]	-0.20
• eGFR (mL·min ⁻¹ /1.73 m ⁻²), median [IQR]			
Arrhythmia, <i>n</i> /total <i>N</i> (%)	25/50 (50%)	24/50 (48%)	-0.04
Ejection fraction (%), median [IQR]	60 [55–65]	60 [55–65]	-0.05
Preoperative antiplatelet agents	23/50 (46%)	24/50 (48%)	0.04
• Acetylsalicylic acid, <i>n</i> /total <i>N</i> (%)	3/50 (6%)	4/50 (8%)	0.08
• Clopidogrel, <i>n</i> /total <i>N</i> (%)			
Preoperative anticoagulant	2/50 (4%)	1/50 (2%)	-0.12
• Warfarin, <i>n</i> /total <i>N</i> (%)			
Preoperative laboratory parameters, median [IQR]			
• Hemoglobin (g·L ⁻¹)	140 [129–149]	141 [127–152]	0.08
• Platelet count (x10 ⁹ ·L ⁻¹)	218 [184–257]	207 [178–246]	-0.04
• PT (sec)	12 [11–12]	12 [11–12]	-0.18
• INR	1.0 [0.9–1.0]	1.0 [1.0–1.0]	-0.21
• aPTT (sec)	24 [23–26]	24 [23–25]	-0.32
• Fibrinogen (g·L ⁻¹)	3.4 [2.8–3.8]	3.3 [3.0–3.9]	0.28

Standardized mean differences were calculated with the difference in means or proportions divided by the pooled standard deviation

aPTT = activated partial thromboplastin time; BMI = body mass index; eGFR = estimated glomerular filtration rate; HMS = Heparin Management System; INR = international normalized ratio; IQR = interquartile range; MI = myocardial infarction; PT = prothrombin time; SMD = standardized mean difference

To better examine our hypothesis of whether higher heparin concentrations during CPB are associated with improved thrombin generation post-CPB, we conducted an exploratory analysis examining the quintile of patients (*N* = 18) with the highest heparin concentrations while on CPB, and compared them with the rest of the cohort. These patients had a median heparin concentration of 4.0 mg·kg⁻¹ while on CPB, precisely the target heparin concentration of our original study protocol. In this group compared with the rest of the cohort, there was evidence of less impairment in thrombin generation post-CPB. This preservation of hemostatic function with higher heparin concentrations may be due to enhanced heparin

antithrombin activity via antithrombin III, as well as enhanced TF pathway inhibition, which may play a larger role as CPB time is prolonged and antithrombin III is consumed.⁴⁴

These results suggest that preventing thrombin generation while on CPB through more accurate heparin concentration maintenance can improve hemostasis and clinical bleeding outcomes post-CPB. Prior studies have suggested that HMS Plus reduces thrombin generation while on CPB,^{14,15} improves platelet preservation,^{14,40} and reduces blood product use.¹³ Nevertheless, these findings are not consistent, nor has the application of HMS Plus across studies been uniform. Individualized heparin target

Table 2 Thrombin generation and functional platelet parameters between groups

	Control N = 50	HMS Plus N = 50	P value	
Post-CPB thrombin generation parameters (% change from baseline)				
<i>Tissue factor concentration 1 pM</i>				
Lag time	+82% [48–118]	+73% [48–117]	0.84	
TTP	+79% [47–102]	+68% [43–105]	0.98	
ETP	-52% [-82 to -32]	-58% [-83 to -25]	0.82	
Peak thrombin	-74% [-90 to -51]	-72% [-92 to -45]	0.74	
Post-CPB thrombin generation parameters (% change from baseline)				
<i>Tissue factor concentration 5 pM</i>				
Lag time	+55% [36–83]	+51% [33–73]	0.64	
TTP	+44% [22–75]	+43% [22–77]	0.81	
ETP	-29% [-42 to -14]	-27% [-47 to -15]	0.96	
Peak thrombin	-44% [-65 to -33]	-42% [-66 to -29]	0.75	
Post-CPB platelet parameters at rewarming				
Absolute platelet count ($\times 10^9 \cdot L^{-1}$)	155 [124–173]	160 [140–176]	0.33	
Functional platelets ($\times 10^9 \cdot L^{-1}$)	133 [97–150]	126 [98–146]	0.91	
• % dysfunctional platelets	17 [9–25]	22 [10–29]	0.42	
Intraoperative Blood Loss, mL				
Estimated blood loss, mL	1300 [600–1600]	1350 [1000–1600]	0.45	
Postoperative chest drain output, mL				
Time	Number (%)			
1 hr	90 (90%)	70 [45–115]	65 [50–140]	0.87
4 hr	84 (84%)	168 [123–210]	180 [120–283]	0.62
24 hr	96 (96%)	415 [323–563]	440 [358–705]	0.21
48 hr	35 (35%)	655 [485–980]	600 [530–1150]	0.99
72 hr	11 (11%)	690 [620–1175]	835 [605–1820]	0.93

Values are expressed as medians [interquartile ranges]. The Mann–Whitney test was used for between-group comparisons. Estimated blood loss was derived by subtracting irrigation volume and cell salvage anticoagulant from losses.

CPB = cardiopulmonary bypass; ETP = endogenous thrombin potential; HMS = Heparin Management System; ICU = intensive care unit; TTP = time to peak

concentrations and dosing based on a HDR curve have potential benefits; however, inadequate anticoagulation using this approach has also been reported.^{45–47} To minimize these potential limitations, our study set a heparin target concentration of $4.0 \text{ mg} \cdot \text{kg}^{-1}$ when programming HMS Plus settings for heparin dose calculation. Having this particular setup, this study reported median heparin concentrations in the HMS Plus group as $3.5 \text{ mg} \cdot \text{kg}^{-1}$ for the majority of time points. Nevertheless, it is worth noting that subsequent heparin concentration measurements were conducted 30 min after additional heparin doses and immediately before subsequent heparin doses if required. Given the half-life of heparin, it is unsurprising that recorded measurements may have been lower than $4.0 \text{ mg} \cdot \text{kg}^{-1}$. In addition, the HPT cartridge used in this study has a measurement

resolution of $0.5 \text{ mg} \cdot \text{kg}^{-1}$, with a maximum display value of $4.0 \text{ mg} \cdot \text{kg}^{-1}$. This may also contribute to the perceived lower than expected median heparin levels in the HMS Plus group. Despite the limitations of HMS Plus, this modified application of the HMS Plus system allowed for more reliable, improved heparin concentration management, with fewer fluctuations in heparin levels, thereby reducing the risk of inadequate anticoagulation.

Although our results indicate that the HMS Plus system may offer a better management strategy over ACT-guided management, the optimal heparin concentration to preserve thrombin function while on CPB is yet to be established. Few published studies comparing HMS Plus with conventional management have reported the heparin concentration levels maintained on CPB, and future studies establishing an evidence-based target heparin

Table 3 Cardiopulmonary bypass characteristics and management values by group

Parameter	Control N = 50	HMS Plus N = 50	P value
Before cardiopulmonary bypass			
Total cardiopulmonary bypass time (min)	80 [70–103]	89 [66–124]	0.49
Baseline ACT (sec)	105 [101–115]	108 [100–114]	0.90
Heparin loading dose (units)	35,000 [30,000–40,000]	35,000 [30,000–42,000]	0.20
During cardiopulmonary bypass			
Additional heparin on cardiopulmonary bypass (units)	10,000 [5000– 15,000]	18,750 [15,000–25,600]	< 0.001
Heparin concentration on CPB (mg·kg ⁻¹)	3.0 [2.6–3.5]	3.3 [3.1–3.5]	0.03
Last heparin concentration on CPB (mg·kg ⁻¹)	3.0 [2.5–3.5]	3.5 [3.5–4.0]	< 0.001
Total heparin dose (units)	50,000 [40,000–55,000]	58,300 [50,000–67,000]	< 0.001
Total protamine dose (mg)	350 [300–400]	318 [260–393]	0.28
Protamine-to-heparin loading dose ratio	1.0 [0.9–1.0]	0.9 [0.7–1.0]	< 0.001
Protamine-to-total heparin dose ratio	0.7 [0.6–0.8]	0.6 [0.5–0.6]	< 0.001

Values are expressed as medians [interquartile ranges]. Wilcoxon two-sample *P* values are shown for continuous or ordinal data. Two-sided *P* values < 0.001 were considered significant.

ACT = activated clotting time; CPB = cardiopulmonary bypass; HMS = Heparin Management System

Table 4 Comparison of anticoagulation monitoring during cardiopulmonary bypass

Time points during cardiopulmonary bypass	Control	<i>n</i>	HMS Plus	<i>n</i>	<i>P</i> value
ACT (sec)					
Before cardiopulmonary bypass initiation					
Post heparin Loading dose	694 [556–917]	50	632 [528–782]	50	0.28
After cardiopulmonary bypass initiation					
+30 min	572 [532–671]	49	544 [494–650]	49	0.04
+60 min	628 [52–748]	47	635 [557–837]	48	0.17
+90 min	552 [506–771]	23	622 [572–762]	28	0.14
+120 min	631 [600–717]	6	572 [519–846]	16	0.66
Post protamine	113 [104–121]	50	115 [108–125]	50	0.28
Heparin concentration (mg·kg ⁻¹)					
Before cardiopulmonary bypass initiation					
Post heparin loading dose	3.5 [3.3–4.0]	48	4.0 [3.5–4.0]	50	0.07
After cardiopulmonary bypass initiation					
+30 min	3.0 [2.5–3.5]	48	3.0 [2.5–3.5]	48	0.38
+60 min	3.0 [2.5–3.5]	47	3.5 [3.0–4.0]	50	0.001
+90 min	3.0 [2.5–3.5]	23	3.5 [3.5–3.5]	29	0.01
+120 min	2.0 [2.0–2.5]	5	3.5 [3.5–3.5]	17	0.04
Post protamine	0 [0–0]	50	0 [0–0]	50	0.99

Values are expressed as medians [interquartile ranges]. Wilcoxon two-sample *P* values are shown for continuous or ordinal data. Two-sided *P* values < 0.001 were considered significant

ACT = activated clotting time; HMS = Heparin Management System

concentration range are warranted. Importantly, improvements in thrombin generation parameters and other laboratory measures of coagulation should be

studied in relation to potential improvements in patient clinical outcomes.

Table 5 Thrombin generation and functional platelet parameters between quintiles of average heparin concentration achieved on cardiopulmonary bypass

	Heparin concentration quintiles 1–4 <i>N</i> = 82	Heparin concentration quintile 5 <i>N</i> = 18	<i>P</i> value	
Heparin concentration during first 120 min on CPB (mg·kg ⁻¹), mean (SD)	3.1 (0.39)	4.0 (0.3)	< 0.001	
Heparin concentration during first 120 min on CPB (mg·kg ⁻¹)	3.2 [2.8–3.3]	4.0 [4.0–4.0]	< 0.001	
Post-CPB thrombin generation parameters (% change from baseline)				
<i>Tissue factor concentration 1 pM</i>				
Lag time	+78% [54–118]	+65% [38–116]	0.35	
TTP	+74% [44–104]	+61% [40–115]	0.63	
ETP	-59% [-84 to -32]	-38% [-76 to -16]	0.09	
Peak thrombin	-73% [-92 to -51]	-64% [-88 to 36]	0.18	
Post-CPB thrombin generation parameters (% change from baseline)				
<i>Tissue factor concentration 5 pM</i>				
Lag time	+55% [40–79]	+36% [24–59]	0.04	
TTP	+45% [25–83]	+27% [15–67]	0.05	
ETP	-30% [-48 to -17]	-18% [-29 to 0]	0.02	
Peak thrombin	-46% [-67 to -33]	-38% [-52 to -19]	0.05	
Post-CPB platelet parameters at rewarming				
Absolute platelet count (x10 ⁹ /L ⁻¹)	160 [136–173]	153 [122–183]	0.89	
Functional platelets (x10 ⁹ ·L ⁻¹)	133 [100–148]	125 [86–146]	0.57	
% dysfunctional platelets	17 [9–27]	23 [15–39]	0.16	
Intraoperative Blood Loss (mL)				
Estimated blood loss, mL	1300 [800–1600]	1200 [700–1600]	0.67	
Postoperative chest drain output (mL)				
Time	Number (%)			
1 hr	90 (90%)	70 [45–115]	65 [50–140]	0.86
4 hr	84 (84%)	168 [123–210]	180 [120–283]	0.62
24 hr	96 (96%)	415 [323–563]	440 [358–705]	0.21
48 hr	35 (35%)	655 [485–980]	600 [530–1150]	0.99
72 hr	11 (11%)	690 [620–1175]	835 [605–1820]	0.93

Values are expressed as medians [interquartile ranges] unless otherwise stated. Wilcoxon two-sample *P* values are shown for continuous or ordinal data. Estimated blood loss was derived by subtracting irrigation volume and cell salvage anticoagulant from losses. Two-sided *P* values < 0.001 were considered significant

CPB = cardiopulmonary bypass; ETP = endogenous thrombin potential; HMS = Heparin Management System; IQR = interquartile range; SD = standard deviation; TTP = time to peak

Conclusion

Although HMS Plus-based anticoagulation management did not show significant benefits over conventional management in terms of reducing clinical bleeding, the modified use of the HMS Plus system in this study was more effective for achieving a stable heparin concentration during CPB and appropriate protamine dosing. Our results suggest higher heparin concentrations of 4 mg·kg⁻¹ during CPB are associated with improved thrombin generation capacity after CPB, highlighting the potential benefits of using a targeted heparin concentration range to help

preserve thrombin generation during cardiac surgical procedures.

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