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# Heparin Dose and Postoperative Bleeding in Patients Undergoing Cardiopulmonary Bypass

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**Abstract:** Heparin is the most widely used anticoagulant for cardiopulmonary bypass (CPB). Several authors suggest that lower doses of heparin during CPB would produce lower postoperative chest tube losses and fewer transfusion events. In the present study, a heparin dose–response (HDR) test was used to determine the heparin dose for each patient. We hypothesize that higher doses of heparin do not cause increased postoperative bleeding and transfusion events in postoperative patients undergoing CPB when the heparin dose is determined by a HDR test. This prospective observational study followed 66 patients undergoing CPB-supported primary coronary artery bypass grafting. Patients were placed in one of two groups, sensitive (n = 37) or resistant (n = 29) based on the result of a HDR test slope. Data on patient characteristics, secondary outcomes, transfusion, and the primary outcome, chest tube losses, were collected. Patient characteristics differed in the baseline activated coagulation time (ACT) and thromboelastograph G parameter as well as number of patients with hypercholesterolemia. The resistant group had lower postheparin and postprotamine ACTs and heparin sensitivity index. Initial heparin dose, total heparin dose, heparin dose per kilogram, HDR, and protamine dose were higher in the heparin-resistant group. The primary outcome, postoperative chest tube loss volume, was collected at four time points and the two groups were then compared. The heparin-resistant group was noninferior to the sensitive group and had clinically fewer transfused patients and transfusion events. The resistant group was noninferior to the sensitive group with respect to chest tube losses at all measured time points. Higher doses of heparin determined by a HDR test do not cause increased postoperative chest tube losses or increased transfusion events. **Keywords:** cardiopulmonary bypass, heparin, bleeding. *JECT. 2013;45:228–234*

Patients requiring cardiopulmonary bypass (CPB) to support surgery such as coronary artery bypass grafting (CABG) must be anticoagulated for the period they are supported by the heart–lung machine. Unfractionated heparin is the most commonly used anticoagulant for this surgery. Heparin dosing for such procedures may be based on patient weight or heparin concentration. A common theme in the literature suggests that higher doses of heparin result in increased postoperative bleeding (1–3). Furthermore, patients who are resistant to heparin may receive more heparin to achieve therapeutic effect (4–7). Heparin resistance has been defined as failure to reach a desired target activated clotting time (ACT) such as 480 seconds (8,9). Clinically, the concern with not achieving a desired ACT is that anticoagulation for CPB is subtherapeutic and may result in factor consumption and postoperative bleeding (8). We sought to determine if patients who are found to be resistant to heparin and needing a higher dose bleed more post operatively on comparison to heparin-sensitive patients. This prospective observational study seeks to determine if higher doses of heparin, determined by a heparin dose–response (HDR) test, causes increased postoperative bleeding, defined by excessive chest tube losses (CTL) and transfusion events in the postoperative patients undergoing CPB.

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## MATERIALS AND METHODS

Ethics approval was sought and received from University of Saskatchewan Research Ethics Board (approval given

on January 16, 2012 [Bio# 12-37]) and the University of Nebraska Medical Center Institutional Review Board (approval given on April 9, 2012 12 [IRB#105-12-ET]). The clinicaltrials.gov identifier is NCT01574105. Consents were obtained from each study participant before the date of surgery.

Study patients were first identified in a preadmission clinic or on the ward. They were enrolled in the study (May 1, 2012, to January 15, 2013) if they met the inclusion criteria and signed the informed consent. Inclusion criteria included: adult patients presenting for primary CABG, weighing more than 75 kg, and presenting a preoperative hemoglobin of 110 g/L or greater. Exclusion criteria included: renal failure (serum creatinine greater 200 μmol/L or urine output less than 10 mL/h), liver dysfunction, baseline international normalized ratio >1.5, clotting factor deficiencies, intra-aortic balloon pump therapy, emergency surgery, pregnancy, ejection fraction less than 50%, age younger than 18 years, pulmonary hypertension (pulmonary artery systolic pressure greater than 60 mmHg), infectious endocarditis, and a history of heparin-induced thrombocytopenia.

We then completed participant enrolment, baseline data recording, and data sampling. Blood samples for this study were taken before heparinization for CPB in the operating room and at the same intervals as routine samples in the intensive care unit (ICU). ICU sampling intervals are immediately on arrival in the ICU and 6 hours after arrival.

During surgery, a Sorin heart–lung machine (S3 or S5; Sorin, Munich, Germany) roller pump was used with flows of 2.4–2.6 L/min/$m^2$ in the nonpulsatile setting. An Affinity oxygenator with Trillium (polymer with heparin) coating with a Trillium-coated affinity 20-μm arterial line filter (Medtronic, Minneapolis, MN) was used. The extracorporeal circuit tubing used was Sorin S5 with Physio (phosphorylcholine) (Sorin, Mirandola, Italy) coating. Circuits were flushed with carbon dioxide before priming. Prime consisted of Plasma-Lyte A (Baxter, Mississauga, Canada), Voluven (Fresenius Kabi, Bad Homburg, Germany), sodium bicarbonate (50 mEq), mannitol (2.5 g/kg), and heparin (10,000 IU). Patients were cooled to 32°centigrade (C) and then rewarmed to 37.0°C centigrade toward the end of the CPB run. Cardioplegia was delivered through the Quest MPS2 pump (Quest Medical, Allen, TX) with microplegia settings. Cardiac arrest was achieved with an initial dose of warm cardioplegia followed by cold intermittent doses through antegrade and retrograde routes. A warm terminal dose of cardioplegia with 2 g of magnesium sulphate was delivered before crossclamp removal.

The first blood sample was drawn before heparinization. This sample was analyzed for baseline activated clotting time (ACT) (ACT Plus; Medtronic), HDR, thromboelastograph (TEG 5000 Thromboelastograph Hemostasis Analyzer System; Haemonetics Corporation Braintree, MA) (TEG, R, reaction time; K, time from R to 20 mm; angle, kinetics of clot development; MA, maximum amplitude; LY30, percent lysis 30 minutes after MA), and hemoglobin. Patients were grouped by their sensitivity and resistance to heparin using an analyzer, The Heparin Management System (HMS) (Medtronic), which performs a HDR test. In this test, a patient's whole blood sample is mixed with increasing amounts of heparin to determine the required heparin dose to achieve a predetermined level of anticoagulation. At this time, the patient's heparin sensitivity or resistance was determined by HDR slope. The following HDR slope values determined to which of the two study groups the patient would be assigned: sensitive to heparin: at or above 90 seconds/IU/mL; or resistant to heparin: below 89 seconds/IU/mL.

The terms sensitive and resistant are used to identify each group based on their HDR slope and do not necessarily indicate an overt resistance or sensitivity to heparin. This slope value of 90 seconds/IU/mL was decided upon as the separation point between the two groups because it is our institution's 2-year average for HDR slope.

Heparin dose is derived from the HDR result. If the calculated heparin dose from the HMS is below 300 IU/kg, the minimum remains 300 IU/kg. An additional 100 IU/kg of heparin was always added to the HMS-recommended heparin dose so as to ensure an ACT above 480 seconds at the onset of CPB. Intravenous tranexamic acid (20–30 g/kg) (Pfizer Canada, Kirkland, Quebec, Canada) was administered just after the initial heparin (Sandoz Canada, Boucherville, Quebec, Canada) bolus. Approximately 5 minutes after heparin administration, a blood sample for an ACT was taken. ACT and a heparin protamine titration (HPT), using the HMS, were performed to ensure the ACT is above 480 seconds and the HPT was at or above the calculated level. CPB was initiated after the ACT had reached 480 seconds. ACTs were measured no more than every 30 minutes while on CPB. Heparin bolus doses during CPB were in increments of 10,000 IU as required. Before weaning from CPB, an HPT assay was done to calculate a post-CPB protamine (Sandoz Canada) dose. Approximately 5 minutes after protamine administration, a blood sample for a TEG, ACT, and a HPT determination was taken to confirm a return to baseline for the ACT and zero heparin concentration for the HPT. Additional protamine was given if indicated by the HPT. Topical tranexamic acid (2 g in 50 mL warm .9% sodium chloride) was poured into the chest wound (10,11) during chest closure and later suctioned out of the chest tubes before connection to the chest tube drainage reservoir.

Other than the perfusionist performing the HDR test, no other member of the operating room nor ICU staff was made aware of which study group patients were in. No guidelines were provided to direct therapy. Patients in the operating room were given nonred blood cell products to treat bleeding in the surgical field deemed to be coagulopathic in etiology. Red blood cells transfused in the operating room were administered for low hemoglobin determinations while on CPB and not for post-CPB bleeding.

CTL were recorded at departure from the operating room (OR), upon arrival in the ICU, after 6 hours in the ICU and after chest tube removal. Transfusion events such as that of red blood cells, plasma, and platelets were recorded while the patient was in the OR and ICU. Activated partial thromboplastin time (aPTT), international normalized ratio, platelets, and hemoglobin were measured and recorded on ICU arrival and 6 hours thereafter. Additional protamine doses in the ICU were also recorded as were time spent on the ventilator in ICU and ICU length of stay in hours.

## STATISTICS

PASS Number Cruncher Statistical Systems (Kaysville, UT) was used for the power analysis calculation. Sample sizes of 26 in the heparin-resistant group and 26 in the heparin-sensitive group achieve 90% power at the .025 level of significance to detect a noninferiority using a one-sided two-sample *t* test assuming a noninferiority margin is 200 mL in the postoperative CTL and an estimated standard deviation is 217. Clinical difference for patients transfused was set at 7.5% because this would represent a difference of five patients determined in a pilot study group of a similar size. In reviewing this result, one must keep in mind that the test remains to find that the resistant group is at least equivalent or not worse than the sensitive group. The reason there are 66 patients, 29 resistant and 37 sensitive, is that we continued to enroll patients to ensure there was a minimum of 26 values in all data fields.

SAS Version 9.2 (SAS Institute, Inc., Cary, NC) was used for analyses of patient characteristics and primary and secondary outcomes. For the analyses of the patient characteristics, Wilcoxon, $\chi^{2,}$ and Fisher's exact tests were used. An upper bound of a two-sided 95% confidence interval of the mean difference between resistant and sensitive groups for all values of CTL was computed by analyses of covariance (ANCOVA) and compared with prespecified noninferiority limits. Covariates in the ANCOVA model included patient characteristics differing between two groups with a $p$ value $< .1$.

## RESULTS

Comparison between the two groups' patient characteristics data indicates baseline ACT, baseline TEG G (clot firmness as shear elastic modulus) (12), and patients with hypercholesterolemia were statistically different. These values were used in the ANCOVA model for the analyses of CTL. Although time since heparin was stopped was significantly different between the groups, this possible confounder was not added later to the outcomes analyses as a result of only patients on preoperative heparin would have this value among patient characteristics.

The resistant group was off heparin for a shorter period of time and no resistant patients had been on low-molecular-weight heparin (LMWH) for the previous 48 hours. The resistant group demonstrated lower ACTs at all time points. Although not clinically different, the resistant group had a higher TEG G of 13.2 Kd/sec, at the top end of the normal range (Table 1).

For all analyses, the sensitive group were used as the control. The resistant group was then compared with the sensitive group using predetermined clinical limits of equivalence (noninferiority). ANCOVA, the analysis of covariance, was used for all CTL values (Table 2). As determined from a previous pilot study, the "a" or noninferiority limit was set at 200 mL for total CTL. Shorter time periods were given appropriate volume loss limits. The first four are CTL values taken from the drainage reservoirs; CTL/kg is total CTL divided by patient weight in kilograms. Total heparin dose in units divided by total milliliters of CTL indicates that 101.5 IU of heparin relates to 1 mL of CTL in the resistant group and 84.4 IU of heparin relates to 1 mL of CTL in the sensitive group. This calculation is to determine how many units of heparin relate to 1 mL of CTL. ANCOVA suggests that only heparin IU divided by CTL may be not equivalent. In all other values, including CTL per kilogram body weight and CTL at all time points, the resistant group is equivalent to the sensitive group.

First of the secondary outcomes to consider are the laboratory values from the time of patient arrival in the ICU and values from after 6 hours in the ICU. ICU aPTT values for the sensitive group remain approximately the same (29.9 seconds arrival and 28.6 seconds at 6 hours) and the aPTT from the resistant group rises approximately 4 seconds during the arrival to 6 hours in ICU time interval (28.77 seconds and 32.72 seconds). One patient in the resistant group returned to the OR for bleeding for which a surgical cause was found.

In this noninferiority study, our study hypothesis states that the resistant group would not be inferior to the sensitive group. Clinically, the resistant group of 29 patients had four patients transfused for a transfusion rate of 13.8%. The sensitive group of 37 patients had 16 patients

**Table 1.** Patient characteristics.

| Patient Characteristics | Resistant (n = 29) Mean ± SD, No. (%) | Sensitive (n = 37) mean ± SD, No. (%) | *p* Value |
|---|---|---|---|
| CABG, graft number | 4.24 ± .91 | 4.3 ± 1.15 | .74 |
| Age (years) | 67.45 ± 9.82 | 67.78 ± 9.38 | .88 |
| Height (cm) | 174.22 ± 7.98 | 172.49 ± 8.03 | .29 |
| Weight (kg) | 91.32 ± 13.11 | 89.52 ± 13.41 | .35 |
| Body surface area ($m^2$) | 2.08 ± .18 | 2.04 ± .17 | .40 |
| Body mass index ($kg/m^2$) | 30.22 ± 3.53 | 30.22 ± 4.12 | .81 |
| CPB time (minutes) | 111.31 ± 17.77 | 119.46 ± 28.46 | .12 |
| Crossclamp time (minutes) | 94.28 ± 16.57 | 98.51 ± 25.45 | .30 |
| Euroscore (%) | 1.41 ± .76 | 1.32 ± .66 | .76 |
| Ejection fraction (%) | 61.23 ± 5.23 | 60.64 ± 4.15 | .40 |
| Preoperative hemoglobin (g/L) | 144.69 ± 12.24 | 142.11 ± 12.38 | .68 |
| Preoperative platelets (10e9/L) | 229.07 ± 48.28 | 209.68 ± 64.74 | .13 |
| Preoperative INR | .97 ± .08 | .98 ± .12 | .97 |
| Preoperative aPTT (seconds) | 40.48 ± 18.55 | 37.54 ± 14.87 | .64 |
| Baseline hemoglobin (g/L) | 134.9 ± 11.75 | 129.54 ± 13.03 | .17 |
| Baseline activated coagulation time (seconds) | 129.9 ± 10.67 | 141.22 ± 15.05 | .002* |
| Baseline TEG R (minutes) | 6.38 ± 2.23 | 6.8 ± 2.06 | .27 |
| Baseline TEG K (minutes) | 1.94 ± .73 | 1.91 ± .68 | .83 |
| Baseline TEG angle (degrees) | 64.7 ± 7.39 | 64.44 ± 7.37 | .96 |
| Baseline TEG MA (mm) | 71.84 ± 4.08 | 69.57 ± 5.59 | .10 |
| Baseline TEG G (d/sec) | 13.21 ± 2.79 | 11.63 ± 3.25 | .057* |
| Baseline TEG LY30 (%) | .47 ± .79 | .6 ± .83 | .15 |
| Female sex | 3 (10.34) | 5 (13.51) | .99 |
| Heparin (unfractionated and LMWH) | 13 (44.83) | 11 (29.73) | .21 |
| LMWH | 0 (0%) | 4 (10.81%) | .13 |
| Heparin, hours since stopped | 4.58 ± 2.22 | 14.5 ± 13.4 | .007* |
| Plavix | 14 (48.28%) | 14 (37.84%) | .39 |
| Plavix, days since last dose | 3.86 ± 2.14 | 3.36 ± 1.91 | .50 |
| ASA | 28 (96.55%) | 32 (86.49%) | .22 |
| ASA, days since last dose | 2.97 ± 1.91 | 3.16 ± 2.09 | .77 |
| Warfarin | 0 (0%) | 1 (2.7%) | .99 |
| Previous myocardial infarction | 14 (48.28%) | 15 (40.54%) | .53 |
| Diabetes | 11 (37.93%) | 14 (37.84%) | .99 |
| Hypertension | 24 (82.76%) | 34 (91.89%) | .29 |
| Hypercholesterolemia | 18 (62.07%) | 31 (83.78%) | .045* |
| Tranexamic acid IV | 26 (89.66%) | 34 (91.89%) | .99 |
| Tranexamic acid topical | 28 (96.55%) | 37 (100%) | .44 |

SD, standard deviation; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; INR, international normalized ratio; aPTT, activated partial thromboplastin time; TEG, thromboelastograph; R, reaction time for initial clot development; K, kinetic time denoting rate of clot growth; MA, absolute clot strength; G, clot shear elastic modulus strength; LY30, percent lysis 30 minutes after maximum amplitude; LMWH, low-molecular-weight heparin; ASA, acetylsalicylic acid; IV, intravenous.
*Statistical difference between the two values.

**Table 2.** Chest tube losses.

| | | | LS Mean Difference | | | | |
|---|---|---|---|---|---|---|---|
| End Point | Sensitive Group | Resistant Group | Mean Difference | Upper Bound of 95% CI | Noninferiority Limit | *p* Value | |
| Total CTL (mL) | 750.9 | 682.1 | –68.76 | 108.44 | 200 | .002 | Noninferior |
| Departure CTL (mL) | 50.55 | 49.46 | –1.09 | 24.86 | 30 | .01 | Noninferior |
| Arrival ICU CTL (mL) | 76.72 | 71.3 | –5.42 | 29.62 | 30 | .02 | Noninferior |
| ICU 6 hours CTL (mL) | 429.02 | 373.54 | –55.47 | 68.42 | 100 | .007 | Noninferior |
| Total CTL/kg | 8.33 | 7.67 | –.66 | 1.26 | 2 | .004 | Noninferior |
| Total heparin IU/CTL | 84.43 | 101.48 | 17.05 | 38.36 | 30 | .11 | Cannot reject inferior |

LS, least squares; CI, confidence interval; CTL, chest tube losses; ICU, intensive care unit.

transfused for a transfusion rate of 43.2%. Clinically, the resistant group has a better result. Statistically the resistant group is not inferior or not worse than the sensitive group with respect to transfusion events. When broken down for further analyses, the numbers for transfusion events are too small for statistical analysis (Table 3).

For the following secondary outcomes, differences were expected. The HDR slope is the value used to place

**Table 3.** Transfusion.

| Variables | Resistant (n = 29) | Sensitive (n = 37) |
|---|---|---|
| Patients transfused, no. (%) | 4 (13.79) | 16 (43.24) |

Multiple logistic regression

| End Point | Odds Ratio | | Noninferiority Odds Ratio Limit | *p* Value | |
|---|---|---|---|---|---|
| | Odds Ratio | 95% CI | | | |
| Patients transfused | .11 | (.02–.58) | 1.35 | .003 | Noninferior |

Transfused units

| Group | OR RBC | OR FP | OR Plt | ICU RBC | ICU FP | ICU Plt | Units TxFx | Pts TxFx | Prot |
|---|---|---|---|---|---|---|---|---|---|
| Resistant | 6 | 0 | 0 | 1 | 0 | 1 | 8 | 4 | 4 |
| Sensitive | 9 | 8 | 4 | 2 | 2 | 1 | 26 | 16 | 5 |

CI, confidence interval; ICU, intensive care unit; OR, operating room; RBC, red blood cells; FP, frozen plasma; Plt, platelet (1 unit is one adult dose/5 donors); TxFx, total units transfused; Prot, patients given protamine in the ICU.

patients into each study group. The heparin sensitivity index (ACT after initial heparin dose minus baseline ACT divided by the initial heparin dose in IU/kg) (4), initial heparin dose, total heparin dose, and heparin dose in IU/kg are different as a result of higher amounts of heparin being administered to the resistant group. The postheparin ACT is lower and the protamine dose is higher in the resistant group, although postprotamine ACT is not different. No patient received antithrombin or plasma to treat a low ACT after heparinization.

Two additional outcomes, time on the ventilator in ICU and ICU length of stay, were not statistically different between the two groups (Table 4).

## DISCUSSION

Heparin resistance has been described by not reaching an ACT of 480 seconds after the initial dose of heparin (6,8,9). The present study used an HDR test to calculate a heparin dose to achieve an ACT of at least 480 seconds. A definition of heparin resistance as failure to reach an ACT of 480 or another similar value may not apply here. The HDR test allows for anticipation of heparin resistance and an adjustment in dose. Because the heparin dose was determined by an HDR, an ACT of 480 seconds was achieved and as such, heparin resistance was not identified by a failure to reach this ACT value. ACT values at all time points were lower in the resistant group than the sensitive group, although the resistant postprotamine ACT was statistically equivalent.

Preoperative exposure to heparin was found to be equivalent between the two groups, although the resistant patients had been off heparin for a shorter period of time and the resistant group had no patients on LMWH preoperatively. Higher TEG G and the lower ACTs may suggest a robust coagulation state in the resistant patients. We suggest that in the resistant group, an upregulation or a mechanism to improve clot firmness/stability is at work. This is a possible explanation for the higher rate of transfused patients and transfusion events in the sensitive group. It is notable that the resistant group did not receive plasma or platelets in the operating room, presumably because it was clinically determined they did not require these items. The resistant group was found to be statistically equivalent (not worse than) to the sensitive group with respect to transfusions.

The increase in aPTT at 6 hours in the resistant group may be attributed to the heparin rebound or heparin leak phenomena, although these values are within the normal range. This should be kept in mind when reviewing the CTL results.

The only post-CPB TEG determination showing statistical significance between the resistant and sensitive groups is the R or reaction time, the onset of measureable clot strength. This difference would not be clinically different. The longer R is likely caused by dilution during the perioperative phase rather than through a heparin effect.

Because neither antithrombin nor antifactor Xa activity was measured in this study, their roles cannot be determined. The variables examined in this study are standard and routine clinical and laboratory values, which the clinicians in our institution would have at their disposal on any given day. No guidance was given to those clinicians making transfusion decisions. Patients selected for this study met narrow inclusion and exclusion criteria in an attempt to control for transfusion events for reasons other than bleeding. For this reason, reoperations and valve

**Table 4.** Secondary outcomes.

| | Least Squares Mean of Sensitive Group | Least Squares Mean of Resistant Group | Mean Difference | | Equivalence Limit | *p* Value | |
|---|---|---|---|---|---|---|---|
| | | | Mean Difference | 95% CI | | | |
| HDR slope (sec/IU/mL) | 103.27 | 76.36 | –26.9 | (–34.47 to –19.33) | ±20 | .96 | Not equivalent |
| Heparin sensitivity index | 1.42 | 1.03 | –.39 | (–.61 to –.18) | ±.3 | .8 | Not equivalent |
| Initial heparin dose (IU) | 35,806.3 | 44,492.4 | 8686.1 | (5076.3–12,296) | ±5000 | .98 | Not equivalent |
| Total heparin dose (IU) | 55,389.7 | 62,942.3 | 7552.6 | (1258.1–13,847) | ±5000 | .79 | Not equivalent |
| ACT after heparin (seconds) | 697.79 | 649.62 | –48.17 | (–138.5 to 42.16) | ±100 | .13 | Not equivalent |
| Total protamine (mg) | 417.48 | 442.2 | 24.72 | (–34.61 to 84.05) | ±50 | .2 | Not equivalent |
| Heparin dose (IU/kg) | 621.9 | 700.8 | 78.9 | (11.82–145.97) | ±50 | .8 | Not equivalent |
| Postprotamine ACT (seconds) | 131.14 | 124.63 | –6.51 | (–13.26 to .25) | ±20 | .0001 | Equivalent |
| Postprotamine TEG R (minutes) | 8.6 | 9.04 | .44 | (–2.08 to 2.97) | ±2 | .11 | Not equivalent |
| Postprotamine TEG K (minutes) | 2.15 | 2.41 | .26 | (–.5 to 1.00) | ±1 | .03 | Equivalent |
| Postprotamine TEG angle (degrees) | 62.72 | 61.49 | –1.23 | (–6.88 to 4.42) | ±10 | .001 | Equivalent |
| Postprotamine TEG MA (mm) | 61.49 | 63.59 | 2.09 | (–.96 to 5.14) | ±10 | < .0001 | Equivalent |
| Postprotamine TEG G (d/sec) | 8.32 | 9.13 | .81 | (–.34 to 1.97) | ±4 | < .0001 | Equivalent |
| Postprotamine TEG LY30 (%) | .36 | .34 | –.02 | (–.39 to .35) | ±.075 | < .0001 | Equivalent |
| Arrival ICU hemoglobin (g/L) | 113.01 | 120.96 | 7.95 | (2.1–13.8) | ±20 | < .0001 | Equivalent |
| Arrival ICU platelets (10e9/L) | 143.47 | 156.55 | 13.09 | (–10.34 to 36.52) | ±50 | .001 | Equivalent |
| Arrival ICU INR | 1.225 | 1.219 | –.006 | (–.087 to .075) | ±.1 | .01 | Equivalent |
| Arrival ICU aPTT (seconds) | 29.9 | 28.77 | –1.13 | (–2.62 to .35) | ±5 | < .0001 | Equivalent |
| 6 hours ICU hemoglobin (g/L) | 119.53 | 128.6 | 9.07 | (–.34 to 18.48) | ±20 | .01 | Equivalent |
| 6 hours ICU platelets (10e9/L) | 156.11 | 164.33 | 8.22 | (–16.78 to 33.23) | ±50 | .0007 | Equivalent |
| 6 hours ICU INR | 1.08 | 1.077 | –.0036 | (–.063 to .056) | ±.1 | .001 | Equivalent |
| 6 hours ICU aPTT (seconds) | 28.61 | 32.72 | 4.11 | (–2.81 to 11.03) | ±5 | .4 | Not equivalent |
| Ventilator time ICU (hours) | 8.09 | 8.62 | .53 | (–2.04 to 2.09) | ±4 | .004 | Equivalent |
| ICU length of stay (hours) | 19.71 | 21.88 | 2.17 | (–.91 to 5.25) | ±8 | .0002 | Equivalent |

CI, confidence interval; HDR, heparin dose–response; ACT, activated clotting time; TEG, thromboelastograph; R, reaction time for initial clot development; K, kinetic time denoting rate of clot growth; MA, absolute clot strength; G, clot shear elastic modulus strength; LY30, percent lysis 30 minutes after maximum amplitude; ICU, intensive care unit; INR, international normalized ratio; aPTT, activated partial thromboplastin time.

replacement surgeries were not included and our results may not apply to such patients.

Finally, the resistant group was not inferior to the sensitive group in the primary outcome of CTL at all time points. Because the post-CPB ACT had returned to baseline, the HPT indicated no heparin concentration; the TEG R indicated no heparin effect and the ICU arrival and 6-hour aPTT were within normal limits, postoperative CTL should not be related to the presence of heparin. In this study, the value heparin units per milliliter of CTL for the resistant group is higher, meaning that resistant patients require more heparin to create the same volume of chest tube blood loss. These findings suggest that when heparin-resistant patients receive a higher heparin dose, they do not bleed more nor are they exposed to more transfusions than heparin-sensitive patients receiving a lower heparin dose as determined by an HDR assay.

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