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Heparin Therapy during Extracorporeal Circulation: Deriving an Optimal Activated Clotting Time during Cardiopulmonary Bypass for Isolated Coronary Artery Bypass Grafting

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Abstract: Bull's seminal work on heparin therapy during cardiopulmonary bypass (CPB) was carried out over 30 years ago and has not been updated in the modern era. No correlation with postoperative blood loss was performed. The optimal activated clotting time (ACT) with regard to blood loss has not been established for patients undergoing CPB. A minimum ACT of 400 is based on the lack of visible formation of clots in the CPB circuit. The effect of heparin dose, sensitivity, metabolism, patient size, elective/urgent, protamine reversal regime, returned pump blood volume and heparin content, and average ACT during CPB with regard to postoperative blood loss and resternotomy was examined in a consecutive series of patients undergoing isolated coronary artery bypass surgery. One hundred forty-four patients undergoing isolated CABG were studied. Resternotomy was too infrequent an event to analyze. Univariate analysis revealed that an average ACT less than 500 or greater than 700 was associated with significantly increased postoperative blood loss ($p = .001$). Multivariate analyses revealed that body mass index ($p < .0001$) and total loading dose of heparin ($p = .0031$) were also significant factors affecting postoperative blood loss. We extended his work by analyzing postoperative blood loss. An average ACT between 500 and 700 in our series was associated with significantly lower blood loss than an ACT higher or lower. We hypothesize that an ACT below 500 is probably associated with a low-grade coagulopathy but not macroscopic clot formation in the CPB circuit, and above 700 heparin rebound may become important. Each unit should evaluate blood loss and determine the optimal ACT target for their program. **Keywords:** cardiopulmonary bypass (CPB), heparin, bleeding, protamine. *JECT. 2012;44:145–150*

Anticoagulation for cardiac surgery can be divided into four key stages: heparinization, maintenance of anticoagulation, reversal of heparinization, and hemostasis.

Opinion is divided as to whether minimal or liberal use of heparin to achieve an "adequate" activated clotting time (ACT) for cardiopulmonary bypass (CPB) is best (1). Some institutions use minimal heparinization as a result of the perceived reduced incidence of bleeding post-CPB secondary to heparin rebound (2). Other institutions argue that liberal use of heparin is safe and as long as it is reversed adequately, because bleeding may be reduced as a result of the preservation of the coagulation factors (3). Low ACTs and inadequate heparinization during CPB may be associated with a low-grade consumptive coagulopathy and clots appearing in the bypass circuit (4–7). This has resulted in a near universal acceptance that the ACT should be above 400 in uncoated circuits.

We analyzed a single-unit practice based on previously described methodologies (8,9) involving patients undergoing isolated coronary artery bypass grafting (CABG) using uncoated circuits to evaluate factors associated with postoperative blood loss.

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METHODS

Consecutive, prospectively collected data at a single center were analyzed for the effect of ACT on blood loss.

To eliminate operative variance secondary to procedure complexity, only patients undergoing isolated first-time

CABG with clamp times of 30–120 minutes were included. Salvage cases were excluded. All patients received a protamine infusion as previously described (10). Elective and urgent cases were analyzed together and separately. Cases that had undergone resternotomy were analyzed as part of the group and also were removed to account for "surgical bleeding" skewing the data.

To determine a possible mechanism of bleeding postcardiac surgery, the effects of heparin sensitivity, metabolism, patient size, ACT, protamine reversal regime, returned pump blood volume, and heparin content were analyzed. Body mass index (BMI) was calculated by weight (kg) *height $(m)^{-2}$. Body surface area was calculated using the Dubois formula .00718*weight $(kg)^{.425}$*height $(cm)^{.725}$.

The Hemochron-ACT (International Technidyne Corporation, Piscataway, NJ) system was used for all ACT measurements. No kaolin ACT values were used. Aprotinin was not used in any patients; all patients received tranexamic acid. All off-pump cases were excluded.

Heparin sensitivity was defined as the change in ACT (first ACT reading after first dose heparin minus baseline ACT) per unit loading dose of heparin (mg) given (s/mg). Heparin metabolism was defined as change in ACT during bypass per unit time (dimensionless). Patient size was analyzed in two ways: weight and BMI.

ACTIVATED CLOTTING TIME

The distribution of average ACT values for our study population during CPB is shown in Figure 1.

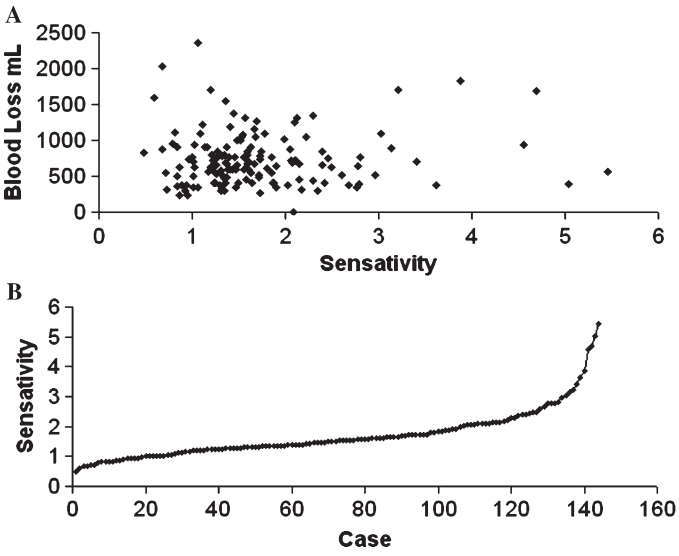

Figure 1. (A) The effect of heparin sensitivity on blood loss, correlation coefficient .06. (B) Heparin sensitivity (s/mg) of patients.

Protamine Reversal Regime

Bull (8,9) described three reversal protocols for protamine dosing: 1:1 total heparin administered, 1:1 total heparin administered to achieve target ACT for CPB, or 1:1 based on estimated heparin level on last ACT value during CPB (Bull back titration method). An Excel program (Microsoft Inc., Redmond, WA) was written to back calculate the estimated heparin level based on the last ACT during CPB. It is available for free download from www.mpoullis.com/act.xls.

Returned Pump Blood Volume and Heparin Content

The volume and total heparin content of the residual pump blood returned to the patient were analyzed.

Confounding Factors

Antiplatelet therapy and surgical causes of bleeding will confound any analysis performed. We have a unit policy of stopping aspirin and clopidogrel in all patients undergoing elective isolated CABG performed on bypass. Urgent patients all received aspirin and have variable adenosine diphosphate antagonist activity. Surgical bleeding usually results in resternotomy. To take account of these confounding factors, patients were subdivided into elective/urgent and resternotomy/no resternotomy, creating a 2×2 matrix for the variables analyzed.

Multivariate Analysis

Multivariate analysis (GraphPad Prism for Windows; GraphPad Software, San Diego, CA; www.graphpad.com), was performed to identify significant factors. Pivot table analysis with Excel was used to subanalyze groups for means and standard deviations.

RESULTS

The cardiac surgery database contained 12,668 patients undergoing isolated CABG. The perfusion database contained 144 patients undergoing isolated CABG who have complete data fields and timings for heparin dosage, and ACT levels, combined with reinfused pump blood volumes and met the inclusion criteria stated in the "Methods" section. (The perfusion database is new to our unit and is based on the JOCAP electronic data acquisition system, Maquet, Wayne, NJ, hence the high disparity in numbers).

Heparin Sensitivity

Heparin sensitivity varied from .49–3.9, average 1.7, standard deviation (SD) .84. The eightfold range is in agreement with previous work (9). Elective and urgent cases had a mean sensitivity of 1.65 and 1.73, respectively ($p = .65$). The range and effect of heparin sensitivity on blood loss is shown in Figure 1. Patients were divided into two groups based on their sensitivity, high or low, based on

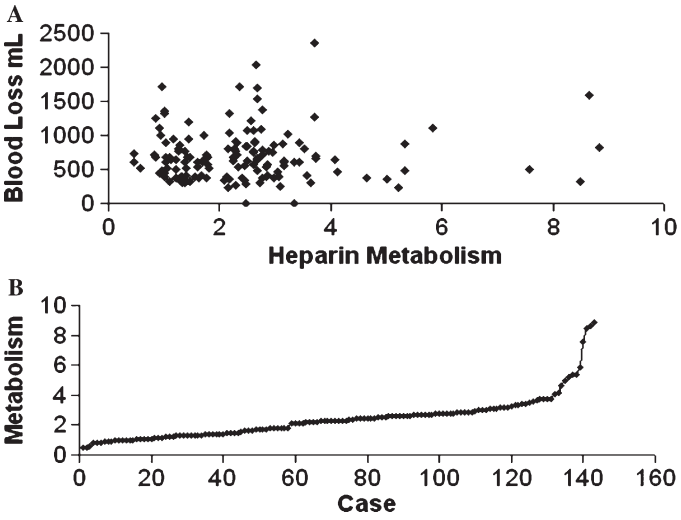

Figure 2. (A) The effect of heparin metabolism on blood loss, correlation coefficient .04. (B) Heparin metabolism of patients.

the mean sensitivity. No correlation was found between these two groups and postoperative blood loss.

Heparin Metabolism

Heparin metabolism varied from .45–8.8, average 2.37, SD 1.39. The 20-fold range is more variable than previously reported (9). Heparin metabolism bore no relationship to resternotomy (p = .87). The range and effect of heparin metabolism on blood loss is shown in Figure 2. Patients were dived into two groups, high metabolizers or low metabolizers, based on the mean of heparin metabolism. No correlation was found between these two groups and postoperative blood loss.

Total Heparin Administered

The effect of total heparin administered on postoperative blood loss in shown in Figure 3. No correlation on univariate analysis existed.

Patient Size

The cardiac surgery database with 12,668 patients undergoing isolated CABG was used to examine the effects of weight and BMI on postoperative blood loss in shown in Figure 4. Body mass index was analyzed to account for

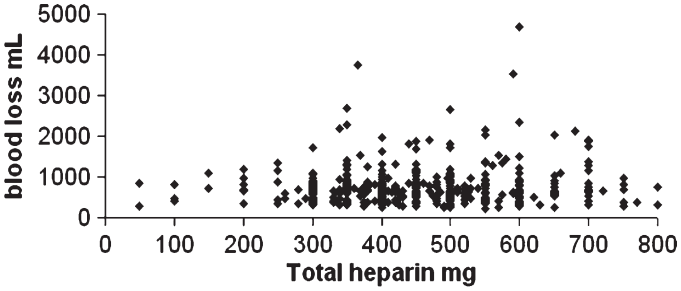

Figure 3. The effect of total heparin administered on blood loss, correlation coefficient –.02.

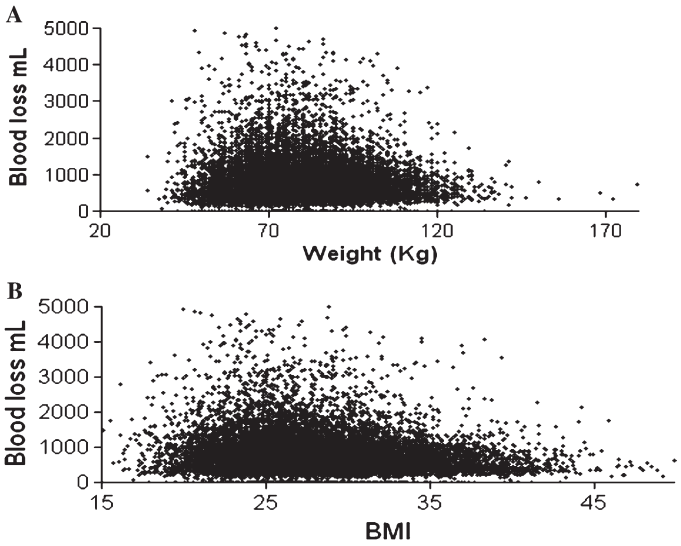

Figure 4. The effect of size (A) weight in kilograms and (B) body mass index (kg/m^2) on blood loss. (Figures show data for the 12,668 patients in the cardiac surgery database. The figures look identical for the 144 cases in the perfusion database.)

body fat that may be involved in heparin rebound (10). No correlation between weight or BMI and blood loss exists; correlation coefficients were –.05 and –.13, respectively.

Activated Clotting Time

The effect of average ACT values versus blood loss for our study population during CPB is shown in Figure 5 (minimum 296, maximum 1500, average 601, SD 220).

The data in Figure 5A is represented differently in Figure 5B. The data are plotted as two series, one in which the average ACT is less than a cutoff and one in which the

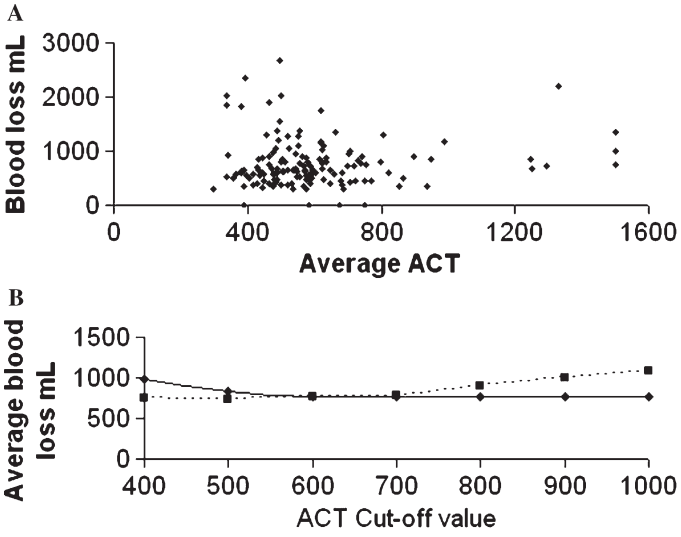

Figure 5. (A) The effect of average activated clotting time (ACT) on blood loss. (B) Average blood loss analyzed by cutoff ACT values. Dotted line demonstrates patients whose average ACT was above the x-axis value, and solid line demonstrates patients whose average ACT was below the x-axis value.

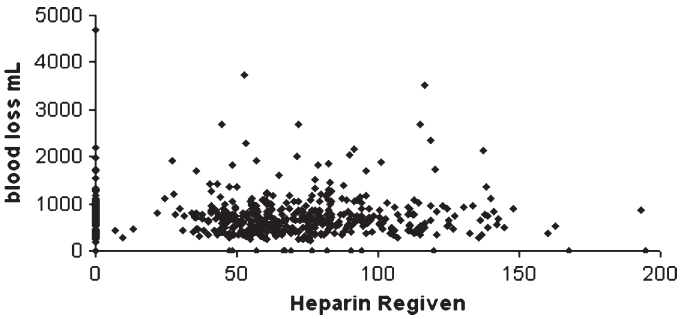

Figure 6. The effect of total dose of heparin regiven in the pump blood after the case on blood loss, correlation coefficient –.02.

average ACT is greater than a cutoff. Analysis of variance was used to calculate significance. It can be seen that patients with an average ACT between 500 and 700 had a significantly reduced blood loss ($p < .0001$).

Returned Pump Blood Volume and Heparin Content

The effect of returned heparin in the form of pump blood is shown in Figure 6. No effect on blood loss can be seen. Further analysis by volume of blood retransfused, total heparin retransfused, stratified by the effect of being a small patient (less than 60 kg), failed to reveal any association with blood loss.

Protamine Reversal Regime

Variation in anesthetic practices exists with regard to protamine dosage. The correlation of protamine administered versus the three different methodologies described by Bull was analyzed (Figure 7). Huge variation existed compared with each possible methodology. No correlation however could be seen when analyzing blood loss compared with protamine dosage. For each methodology, patients were divided into receiving adequate or "potentially excessive" protamine (20% more or less protamine than predicted) based on a 1:1 stoichiometry as dictated by each methodology and then compared with blood loss. When analyzed by Bull's back titration, excessive protamine was significantly ($p = .01$) (Welch test as a result of unequal variance in limbs) associated with excessive blood loss.

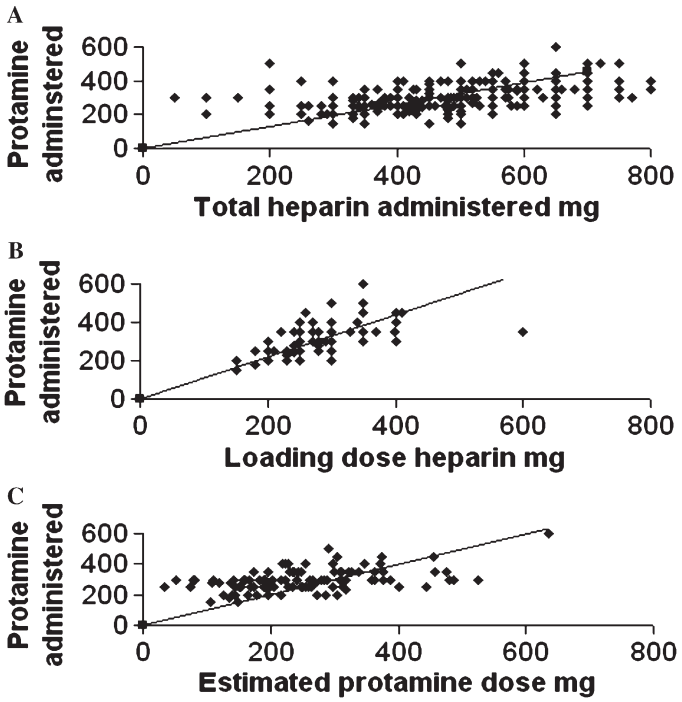

Figure 7. Protamine reversal based on (A) total heparin, (B) loading dose of heparin given to commence cardiopulmonary bypass, and (C) Bull back titration estimation.

Confounding Factors

Urgent patients bleed significantly more than elective cases (733 [SD 436] vs. 883 [SD 465] mL, $p = .049$). Inclusion or exclusion of resternotomy patients did not affect any of these results.

Multivariate Analysis

This revealed that BMI (coefficient –30.6; $p < .0001$) and total heparin loading dose (coefficient 1.7; $p = .003$) were significant factors affecting postoperative blood loss.

CONCLUSION

An average ACT between 500 and 700 in our series was associated with significantly lower blood loss than an ACT higher or lower. BMI and total loading dose of heparin were also significant factors affecting postoperative blood loss on multivariate analysis.

The fact that multivariate analysis failed to identify average ACT as a significant factor may be the result of the U-shaped relationship between average ACT and blood loss (i.e., a nonlinear relationship), a limitation of multivariate linear regression analysis. Residual analysis would be unhelpful in this case because the data set consists of linear and nonlinear components (11).

We hypothesized that an ACT below 400 is probably associated with a low-grade coagulopathy but not macroscopic clot formation in the CPB circuit. The number of 400 was instigated by previous work that looked at the visible formation of clots in the circuit (12). We however found that a cutoff of 500 would seem to be clinically important with regard to postoperative blood loss. The reduction in blood loss with an ACT between 500 and 700 was comparable to the reductions in blood loss previously published that aprotinin or a protamine infusion produces (10,13). Higher heparin levels have been associated with less blood loss and need for transfusion (14,15). We did not analyze clotting factor activation, but blood loss was significantly more the higher the ACT. The confounding effect of heparin rebound is probably nullified

in our series by the routine use of a protamine infusion, as previously described (10). No analysis of clotting factor levels was performed.

Our findings that the sensitivity and metabolism of heparin varied widely have been reported before (8,9). Surprisingly, heparin sensitivity was not associated with urgency of surgery. Heparin sensitivity and metabolism are dependent on different enzyme systems and no correlation existed between them statistically (data not shown). Bull did coagulation assays in his seminal work, but surprisingly did not analyze postoperative blood loss. Multivariate analysis revealed patients who require large doses of heparin to achieve an adequate ACT for CPB, i.e., heparin resistance, have a higher postoperative blood loss.

The majority of resternotomies after cardiac surgery are secondary to surgical bleeding, and the coagulation system is either normal or deranged secondarily to the blood loss. Because these patients can skew the data, analysis was performed with and without resternotomy patients. No significant differences were found (data not shown).

Urgent cases are frequently on dual antiplatelet therapy, which is associated with postoperative bleeding. We confirmed this finding on univariate analysis; however, on multivariate analysis, it was not significant. This might be the result of urgent status cosegregating with heparin resistance, which is why total loading dose (a marker of heparin resistance) was a significant factor.

We were unable to demonstrate any association between the total heparin dose, heparin metabolism, patient size, protamine reversal regime, and returned pump blood volume and heparin content and postoperative blood loss.

Poor reproducibility between different ACT measuring systems exists (16). In addition, variation in circuit technology, set-up, and surgical technique exists. Eight different surgeons with different bypass techniques performed the cardiac surgery, negating surgical technique as a confounding factor in this series. Surgical variation however mirrors real-world practice. As a result of the equipment variation between institutions, different units will have to establish the optimal ACT range for their own patients.

Protamine administration is thought to be a vital step in reversing heparinization. Little agreement seems to exist among units with regard to the dose of protamine to administer. Bull recommended back titration based on the last ACT at the end of CPB; however, no data with regard to blood loss were presented. Our finding that excessive protamine, greater than 20% of the dose predicted by Bull's back titration, is associated with excessive blood loss postoperatively needs to be interpreted with caution. We do not know if extra doses were administered because the chest looked "wet."

We only analyzed patients undergoing isolated first-time CABG. Clamp times between 30 and 120 minutes were chosen to eliminate easy quick cases and long difficult cases so that our results would be applicable to the general CABG population. The set-up and confounding factors of open heart surgery compared with CABG mean further analysis is needed in non-CABG procedures.

In the modern era, we have replicated many of the original finding by Bull with regard to heparin therapy and CPB. We have extended his work by analyzing postoperative blood loss and found an optimal range for average ACT during CPB that may be associated with reduced postoperative blood loss. Correlation by other groups is required.

LIMITATIONS

Our analysis only applies to our unit. Searching for a unique anticoagulation/coagulation reversal guideline may be simplistic as a result of the wide variation of equipment used and surgical techniques and practices, meaning that every unit may have to develop their own ACT range.

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