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Original Article

Impact of Low-Dose Heparin on Accurate Anticoagulation during Cardiopulmonary Bypass and Postoperative Blood Loss in Cardiac Surgery

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ABSTRACT

Background: Activated clotting time (ACT) is most commonly measured for monitoring the anticoagulation effect of heparin during cardiopulmonary bypass (CPB). The aim of this study was to compare the standard heparin dose (300 IU/kg) with lower doses to achieve ACT of 480 sec during CPB.

Methods: In this prospective, randomized, double-blind clinical trial, 120 patients (40/group) who underwent first-time elective coronary artery bypass grafting were randomized into 3 groups A, B, and C receiving an initial heparin dose of 200, 250, and 300 IU/kg. Extra incremental heparin (50 IU/kg) was added if required to achieve a target ACT of 480 sec before initiating CPB. Postoperative blood loss was measured from the time of heparin reversal until the chest drains were removed 48 h after operation in the intensive care unit.

Results: The study groups were similar in demographic data. Target ACT was achieved in 32.5%, 50%, and 65% of the patients in groups A, B, and C — respectively — after the initial dose of heparin (P=0.051). The postoperative mean blood loss in the 2 groups of B and C (13.14±1.07 and 12.5±0.79 mL/kg, respectively) was lower than that in group A (15.97±1.31 mL/kg) (P=0.58). However, this difference between the 3 groups was not statically significant. The mean total dose of heparin in groups A and B was lower than that in group C (P=0.002).

Conclusions: The patients receiving lower doses of heparin to achieve the target ACT did not have lower postoperative blood loss. An initial heparin dose of 300 IU/kg was most often sufficient to reach the target ACT with the lowest incremental dose of heparin.***(Iranian Heart Journal 2015; 16(3): 11-15)***

Keywords: ■Heparin ■Cardiopulmonary bypass ■Activated clotting time ■Blood loss

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Safe cardiopulmonary bypass (CPB) cannot be accomplished without the anticoagulation of the blood in preparation for contact with the extracorporeal circuit because the non-physiological stimulus of CPB causes the massive activation of the hemostatic system. Roller pumps are the standard modality for driving the blood though the CPB circuit.[1] An ideal anticoagulant should be easy to administer, rapid in onset, titratable, predictable, measurable in timely fashion, and reversible. Heparin use during CPB has been continued until the present time — most probably due to its rapid onset, ease of measurement, and ease of reversibility. Decades of the use of heparin are a testament to its effectiveness. Heparin acts by binding and activating antithrombin III (AT III) as well as heparin cofactor II2. Activated coagulation time (ACT) is most commonly measured for monitoring the anticoagulation effect of unfractionated heparin during CPB.[3] Heparin dosing in patients undergoing open heart surgical procedures has moved from the practice of empiric dosing (300 IU/kg)[4] to one of a structured approach of ACT monitoring. With this approach, a considerable reduction in the total heparin dose is witnessed in most patients. The current practice is to measure ACT at half-hourly intervals and maintain it at > 400 sec or > 480 sec throughout the conduct of CPB.[5] Given that systemic heparinization with empiric dosing (300 IU/kg) may carry the risk of increased postoperative bleeding and need for transfusion, we sought to achieve a considerable reduction in the total heparin dose based on ACT monitoring.

METHODS

This study was conducted on 120 adult patients of either sex who underwent elective isolated primary coronary artery bypass graft surgery (CABG) in Seyed Al-Shohada Hospital, Urmia, Iran.

Randomization was done by picking a sealed envelope with a group designation. The study population was divided into 3 groups of A, B, and C to receive an initial heparin dose of 200, 250, and 300 IU/kg, respectively. Patients with a history of bleeding disorders or liver disease as well as those receiving preoperative heparin were excluded. The other exclusion criteria included re-exploration for surgical bleeding and use of aprotinin or tranexamic acid intraoperatively. The operating surgeon and intensive care clinician were blinded to the dose of heparin used. All the data were systematically collected by one of the authors and analyzed at the conclusion of the study.

Heparin was given through the central venous line as a bolus after the internal thoracic artery harvest and before cannulation. Thereafter, ACT was measured in duplicates, using the Hemochron Response System, 2 minutes after each heparin administration. We used an ACT of 480 sec as target ACT following our unit protocol, which was based on the recommendations of most pump manufacturers. If the target ACT was not achieved, additional heparin was given in 50 IU/kg increments.

The different groups were analyzed for the total heparin needed to achieve the target ACT and the degree by which the target ACT was exceeded after the initial dose. The postoperative blood loss in mL/kg was evaluated in each group from the time of heparin reversal until the chest drains were removed 48 h later in the intensive care unit (ICU).

The data were analyzed using regression analysis, and a P value < 0.05 was considered significant.

RESULTS

Complete data were collected in 120 patients. The patients' characteristics and demographic data were not different significantly.

The target ACT was achieved in 32.5%, 50%, and 65% of the patients in groups A, B, and C after the initial dose of heparin, and the additional dose in the groups that had received a greater initial dose was less than that in the groups with a less initial dose (C>B>A). Although this difference was not significant, it was borderline (P=0.05). The average of the additional dose of heparin was 48.75±6.8 SE (200→248) in group A, 32.4±6.08 SE (250→282) in group B, and 18.75±4.3 SE (300→318) in group C. The analysis of the data showed that the difference constituted statistical significance between the 3 groups (P=0.002).

The amount of total blood loss in the 3 groups was 13.3 mL/kg in group A, 15.3 mL/kg in group B, and 12.3 mL/kg in group C — without significant differences between them (P=0.058). Based on these results, despite the increase in need to an additional dose of heparin in group A, after 24 h, blood loss in group B was more than that in the other groups. However, there were no significant differences between the patients in terms of the first ACT (preoperative), off ACT, and pump time.

Table 1. Patients' characteristics and demographics

Variables	Groups (N)	A(40)	B(40)	C(40)	P Value
Sex (M/F)	%	27/13	24/16	29/11	0.49
Age	Mean	61.48±9.37	60.08±9.45	60.05±10.24	0.75
Weight	Mean	73.40±10.38	73.38±13.44	70.65±11.83	0.49
CPB time	Mean	135.28±3.126	136.03±37.03	138.63±30.48	0.89
First ACT	Mean	136.68±25.29	118.13±13.98	126.05±18.57	0.1
Off ACT	Mean	153.02±31.26	143.57±18.38	147.18±33.15	03.4

Abbreviations: CPB, Cardiopulmonary bypass; ACT, Activated clotting time

The need for additional heparin to achieve the target ACT of 480 sec between the 3 groups was nearly significant (P=0.05).

Table 2. Number and percentage of the patients from of each group requiring different amounts of extra heparin to achieve the target activate clotting time of 480 sec

Groups	0 IU/kg	50 IU/kg	100 IU /kg	150 IU/kg	Total
A (200 IU/kg)	16 (40%)	17 (42.5%)	5 (12%)	2 (5%)	40 (100%)
B (250 IU/kg)	20 (50%)	15 (37.5%)	4 (10%)	1 (2.5%)	40 (100%)
C (300 IU/kg)	18 (45%)	18 (45%)	4 (10%)	0 (0%)	40 (100%)

Table 3. Mean additional heparin dose to achieve the target activated clotting time of 480 sec and the amount of bleeding in the 3 groups

Groups (N)	Additional dose (IU/kg)	Bleeding (mL/kg)
A(200 IU/kg)	48.75±6.81	13.14±1.07
B(250 IU/kg)	32.50±6.08	15.97±1.31
C(300 IU/kg)	18.75±4.27	12. 50±0.79

All the values are expressed as mean ± standard error (SE).

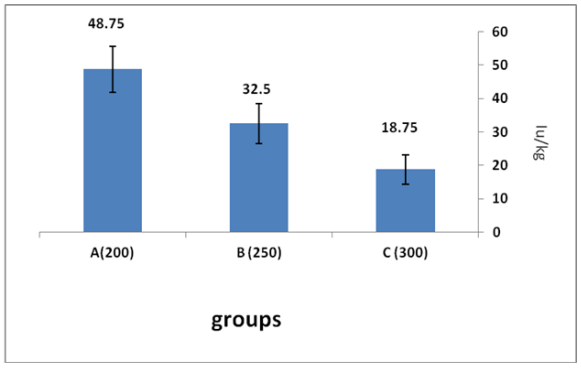

Figure 1. Mean additional heparin dose to achieve the target activated clotting time of 480 sec in the 3 groups is illustrated here.

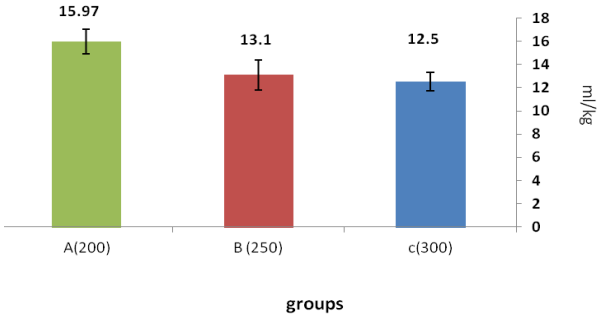

Figure 2. Mean postoperative blood loss in the 3 groups is depicted here.

DISCUSSION

CPB involves the exposure of the blood to foreign surfaces with the consequent activation of humoral and cellular defense mechanisms, leading to a whole-body inflammatory response. Unaltered, the immediate consequence of the activation would be widespread coagulation with the clotting of the bypass equipment and thromboembolism. Presently, this is avoided with high-dose heparin, which disarms the coagulation cascade. The current practice of using 300 IU/kg of heparin to achieve the target ACT to go on CPB has little evidence in the literature. Our study demonstrated that 65% of the patients that received the standard dose of heparin achieved the target or more-than-the-target ACT before the initiation of CPB and that 35% of them required extra heparin supplementation to achieve the target ACT. These results are not consistent with those reported by some previous studies.[5,6]

We hypothesized that the ideal dose would need to have the following criteria: a high percentage of the patients reaching the target ACT with the initial dose and a low percentage of the patients needing an incremental dose to achieve the target ACT. We also expected that a lower dose of heparin would correlate with less blood loss postoperatively.[6,7] It became apparent that a starting lower dose of heparin at 250 IU/kg and one 50 IU/kg increment if needed achieved the set ACT target in 87.5% of the patients and 91.5% after a second increment. Starting with a much lower heparin dose (i.e., 200 IU/kg) needed several incremental doses of heparin to achieve the target ACT. As a result, in this group, the target ACT was achieved within a longer time because we had to wait for 2 min before we could start ACT. Every regimen would, thus, add at least between 8 and 9 min. It would be fair to assume that no cardiac surgeon in practice would be prepared to wait 25 to 35 min to achieve the target ACT.

Despite our expectation and in contrast to the results of some other previous research,[6] in the present study, blood loss was not decreased by a reduction in the initial heparin dose. The amount of blood loss in group C was less than that in the other groups; nevertheless, this difference was not statistically significant between the 3 groups. Particularly, this difference was worthless between group C and group B. This finding may be the consequence of the influence of some other factors in addition to the heparin dose.

The limitation of this study was the effect of the compounding factors such as heparin resistance and anti-thrombin activity. Nonetheless, these variables were not pre-identified and should affect the study and standard dosage equally. We also believe that the risk of under heparinization was cancelled out in the study design since we changed neither the desired target ACT nor any of our intra- or postoperative practices. It is also

worth bearing in mind that the heparin dose response is not predictable.

Although blood loss in the patients who received 250 IU/kg of heparin was slightly more than that in the patients who received the standard dose (without significant differences), the total dose of heparin in this group was less than that in the standard dose group (285 IU/kg vs. 318 IU/kg). This led us to adapt the 250 IU/kg initial dose of heparin and if necessary to administer further increments of 50 IU/kg to achieve the target ACT. With this protocol, we succeeded in having more patients requiring less heparin to achieve the target ACT without compromising practicality.

CONCLUSIONS

The patients receiving lower doses of heparin to achieve the target ACT did not have lower postoperative blood loss. The initial heparin dose of 300 IU/kg was most often sufficient to reach the target ACT with lowest incremental dose of heparin. Further studies with a larger number of cases are necessary to assess the other potential advantages such as reduction in postoperative blood loss and transfusion requirement.

REFERENCES

1. Khuri SF, Valeri CR, Loscalzo J, , Weinstein MJ, Birjiniuk V, Healey NA, et al. Heparin causes plaetlet dysfunction and induces fibrinolysis before cardiopulmonary bypass. Ann Thorac Surg1995:60;1008.
2. Spiess BD, Silvay G. Overview of myocardial outcome: the interrelationships among coagulation, inflammation, and endothelium. J Cardiothorac Vasc Anesth 2000;14;2–5.
3. Despotis GJ, Joist JH. Anticoagulation and anticoagulation reversal with cardiac surgery involving cardiopulmonary bypass: an update. J Cardiothorac Vasc Anesth 1999;13:18–29.
4. Doty DB, Knot HW, Hoyt JI, Koepke JA. Heparin dose for accurate anticoagulation in cardiac surgery. J Cardiovasc Surg 1979;20: 597–604.
5. Lesserson LS, Gravlee GP. Anticoagulation for cardiopulmonary bypass, in Gravlee GP (ed). Cardiopulmonary bypass Principles and Practice, Philadelphia, PA, Lippincott Williams and Wilkins2000, pp 435–72.
6. Shuhaibar MN, Hargrove M, Millat MH, O'Donnell A, Aherne T How much heparin do we really need to go on pump? A rethink of current practices. Eur J Cardiothorac Surg. 2004 Nov;26(5):947-50.
7. Despotis GJ, Joist JH, Hogue Jr. CW, Alsoufiev A, Kater K, Goodnough LT, et al. The impact of heparin concentration and activated clotting time monitoring on blood conservation: a prospective, randomized evaluation in patients undergoing cardiac operation. J Thorac Cardiovasc Surg 1995;110(1):46–54.