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Conventional Weight-Based Versus Low-Dose Regimen of Heparin Administration to Achieve Target Activated Clotting Time on Cardiopulmonary Bypass in Pakistani Population

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Author`s Contribution

[1,4] Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work
[2]Final approval of the version to be published
[3]Drafting the work or revising it critically for important intellectual content,

Funding Source: None
Conflict of Interest: None

Received: Oct 05, 2020
Accepted: Mar 19, 2021

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ABSTRACT

Objective: To observe that whether target ACT values are achieved with conventional weight-calculated or low-dose heparin regimen during CPB in Pakistani Population undergoing elective Cardiac Surgery procedures.

Methodology: The cross-sectional comparative study was conducted at Rawalpindi Institute of Cardiology, Department of Cardiac Surgery from 1st January 2019 to 1st January 2020. Three hundred thirty-six patients undergoing elective open-heart surgeries on CPB were included in this study. Patients receiving weight-based heparin dose were placed in Group-A, while those on low-dose heparin were placed in Group-B. ACT was considered to have reached the target value in range of 400-480 seconds, values between 481-1500 seconds were considered excessive, whereas ACT of >1500 was regarded as potentially high-risk for peri-operative bleeding .

Results: 14.1% (n= 28) of Group-A patients achieved target ACT, whereas 58.3% (n=116) exceeded the target of 480. In 25.1% (n=50), ACT values were beyond the measuring capacity of the assay machine i.e. >1500. Only 2.5% (n=5) required additional dosage of heparin. Target ACT in Group B was achieved in 19.7% (n= 27), 55.5% (n=76) had excessive ACT values, whereas in 16.8% (n= 23), it was >1500. 9.5% (n=13) required an additional dosage of Heparin.

Conclusion: In the Pakistani population, a target ACT can be achieved with a significantly lower dose than the conventional weight-based heparin dose. Larger studies, preferably randomized controlled trials are needed to determine the optimal heparin dose calculation for safe anti-coagulation during CPB.

Keywords: Anticoagulation, Clotting Time, Cardiopulmonary, Heparin.

Cite this article as: *Siddiqeh M, Mirza WJ, Iqbal J, Khan I, Mangi AR, Dawood MA, Quershi QA, Mushtaq A. Conventional Weight-Based Versus Low-Dose Regimen of Heparin Administration to Achieve Target Activated Clotting Time on Cardiopulmonary Bypass in Pakistani Population. Ann Pak Inst Med Sci. 2021; 17(1):34-37.doi. 10.48036/apims.v17i1.498*

Introduction

Extra-corporeal circuits of Cardiopulmonary Bypass (CPB) activate the coagulation system of the blood when it comes in contact with non-physiological stimulus, resulting in an increase of perioperative blood loss risk.[1] Open heart surgeries conducted with the help of CPB are associated with increased risk of perioperative bleeding, hence anti-coagulation therapy is initiated prior to CPB in order to prevent formation of thrombi and minimize the activation of Hemostasis.[2,3]

Heparin has been used as an anticoagulant in cardiac surgery procedures for decades, owing to its rapid onset, safety, easy neutralization, and efficacy. The mechanism of action involves binding of heparin with anti-thrombin III thence activation of the latter.[4,5]

On CPB, Heparin administration and its reversal with protamine remains the gold standard anti-coagulation therapy to this day. According to the guidelines of the STS (the Society of Thoracic Surgeons), either a loading dose of heparin (300IU/kg) calculated by weight can be administered for adequate anti-coagulation or, due to varied individual responses, heparin dose can be adjusted in accordance with Activated Clotting Time (ACT) assessment. The dose response curve can be evaluated by measuring the ACT before and after heparin administration. This helps in acquiring a Target ACT of minimum 480 seconds during CPB.[1] This threshold can vary depending on the accuracy and bias of the instrument, so ACT values above 400 are generally accepted as therapeutic.[6] Multiple studies were conducted to establish an initial dose of heparin to achieve target ACT for an effective and safe anti-coagulation during CPB, however no general consensus was made in this regard.[1]

This study aimed to observe that whether target ACT values are achieved with conventional weight-calculated or low-dose heparin regimen during CPB in Pakistani Population undergoing elective Cardiac Surgery procedures.

Methodology

The protocol was approved by the ethical committee at Rawalpindi Institute of Cardiology. Due to observational nature of this study the need for informed consent from each patient was waived off. Patients were selected using non-probability consecutive sampling. Based on a previous study[4] a sample size of 292 was calculated using WHO calculator, with a Confidence interval of 5 and a Confidence level of 95.

336 patients undergoing open heart surgeries on CPB from 1st January 2019 to 1st January 2020 in Cardiac Surgery department of Rawalpindi Institute of Cardiology were included in this study. Patients with a bleeding disorder, liver disease, pre-operative hemoglobin less than 9, on Intra-aortic balloon pump, on anti-platelet therapy, or having prolonged INR were excluded. Patients undergoing minimal, off-pump and emergency cardiac surgeries were also excluded.

The patients in which weight-based heparin dosing (300 IU/Kg) was done were placed in Group A, as for the patients in which low-dose heparin regimen (150IU/Kg) was administered were allocated in Group B. ACT was calculated before and 3 minutes after the administration of heparin as well after every 30-40 minutes during CPB. If target ACT was not achieved additional heparin was given in 50-100 IU/kg increments. CPB machine priming was done with 5000 IU Heparin during all the procedures regardless of initial heparin dose. Both groups were analyzed for the total heparin needed to achieve the target ACT as well as the effect of both methods of heparin administration in ACT surge beyond the target.

Protamine was calculated as per initial dose of Heparin and mean protamine dose of both Groups was recorded.

ACT measurement: ACT was measured twice, using Hemochron® Response system. Values in range of 400-480 seconds were considered Target ACT 6, 7. The machine had the capacity to measure readings as high as 1500, beyond which values could not be calculated due to limitations of the system. In both groups, if ACT values were recorded less than 400, an additional dosage of heparin was administered. Values between 481-1500 seconds were considered excessive, whereas ACT of >1500 was regarded as potentially high-risk for perioperative bleeding.

The data was analyzed using Regression Analysis and Student t Test for means of unequal variants. P value <0.05 was considered significant.

Results

Complete data was collected in 336 patients undergoing elective cardiac surgeries. Patients mean weight, height, Body Mass Index (BMI), and Body Surface Area (BSA), preoperative ACT, CPB time, and cross-clamp time did not differ significantly (Table I).

14.1% (n= 28) of the patients receiving weight based heparin i.e. 300 IU/kg as an initial dose of heparin (group A) achieved target ACT of 400-480 sec, whereas 58.3% (n=116) exceeded the ACT target of 480. It was also observed that in 25.1% (n=50) of these patients, ACT came out beyond the measuring capacity of the assay machine (Table II). Only 2.5% (n=5) required additional dosage of heparin (Table III).

Target ACT in Group B, however, was achieved in 19.7% (n= 27) after the low initial dose of heparin (150 IU/kg), 55.5% (n=76) exceeded the target of ACT almost similarly to Group A, whereas in only 16.8% (n= 23) ACT was observed to be higher than the limits of the testing machine (Table II). 9.5% (n=13) required an additional dosage of Heparin (Table III).

Table 1: Comparison Group of characteristics between two groups

		Group A	Group B	P values
Weight (kg)	Mean	68.68	67.69	0.549
	Mode	71	58	
Height (cm)	Mean	164.79	164.71	0.931
	Mode	165	170	
Body Mass Index	Mean	25.2	24.9	0.522
	SD	±4.9	±4.9	
Body Surface Area	Mean	1.75	1.73	0.627
	SD	±0.21	±0.19	
Baseline ACT (sec) *Activated Clotting Time*	Mean	116.48	120.92	0.078
	SD	±22.97	±22.22	
CPB time (min) *Cardiopulmonary Bypass*	Mean	102.71	106.33	0.528
	SD	±57.97	±40.68	
Cross-clamp time (min)	Mean	71.20	72.34	0.754
	SD	±33.41	±31.79	

Mean ACT achieved in group A was 856.5 ± 414.6 seconds and 769.3 ± 396.1 seconds in group B. Mean protamine administered after CPB for heparin anti-coagulation reversal was 207.5 ± 45.6 in group A and 103.3 ± 26.3 in group B. (Table IV)

Discussion

Since the advent of CPB machine, heparin administration is considered as gold standard for effective anti-coagulation due to its short-half life, efficacy and easy reversibility with protamine. It was being administered as an empirical therapy of initial 300IU/kg based on its dose-dependent half-life.[1,7] However, excessive anti-coagulation with high dose heparin during CPB procedures has been reported to be associated with higher mortality and morbidity due to increased perioperative bleeding. [3,5] There are studies that show reduced incidence of perioperative bleeding, when Heparin administration is monitored with ACT.[8,9] Lower ACT values are associated with high risk of thrombus formation in the extra-corporeal circuit, and higher values may lead to excessive perioperative bleeding.[9,10] It is therefore recommended to achieve safe target ACT, before CPB.

Table III: This shows a significant difference between Group A and Group B in terms of single incremental dose of Heparin on CPB.

	Group A	Group B	P value
Number of patients in which ACT values <400 required a single incremental dosage of heparin	5	13	0.006

Generally, values between 400 and 480 are accepted as optimal or target ACT for safe anti-coagulation.[1,6]

In the present study, it was observed that, Target ACT was achieved in only 14.1% of the patients in which the conventional heparin dose was administered and exceeded the desired ACT in about 58%. In 25.1% of these patients, the high initial dose caused ACT values to topple the maximum measuring capacity of assay machine. Even the group receiving low dose heparin reported around 19.7% cases where ACT of 400-480 was achieved, 55.5% had ACT more than 480 seconds reaching 6-9 folds more than the baseline ACT and in 16.9% cases, it exceeded beyond the assay machines capacity. The mean ACT achieved in both groups was considerably higher compared to as reported in previous studies[2-4] regardless of the initial dosage of Heparin. This raises the question of how much heparin is needed for safe anti-coagulation during CPB in the Pakistani Population as in both groups, the mean ACT with conventional-dose and the low dose was somewhat similar and high, unnecessarily increasing the risks of perioperative bleeding.

As Heparin sensitivity is variable and differs widely, it is often required to optimize the dosage of heparin as per the

Table IV: A comparison between mean initial dosage of heparin, ACT on CPB and Protamine dose reported in both groups.

	Group A (300IU/Kg)	Group B (150IU/Kg)	P value
Mean initial dosage of Heparin	20696 ± 4591 IU	10182 ± 2313 IU	P< 0.0001
Mean ACT on CPB	856.5 ± 414.6	769.3 ± 396.1	0.0546
Mean Protamine administered after CPB	207.5 ± 45.6	103.3 ± 26.3	< 0.0001

patient's response and sensitivity. A study evaluating low dose regimen observed that the optimization of heparin dosage reduces post-operative blood transfusion rates and lesser protamine administration.[11] Similarly a randomized clinical trial conducted to observe effect of different heparin initial dosage proposed that indeed perioperative bleeding is substantially lower when low dose heparin is administered.[5] So for safe anti-coagulation during the procedure, administering low dose initial heparin with ACT monitoring can be a better alternative strategy. This results in maintaining ACT values within the limit and possibly reduces the risk of perioperative bleeding and its complications.[11]

Post-CPB procedure, protamine is calculated as per initial dose of heparin. This way heparin binds with the protamine in blood resulting in its neutralization. This heparin-protamine complex can activate the complement system resulting in systemic inflammatory reaction. Protamine over dosage is also reported to have been associated with serious post-operative bleeding and blood transfusions. Thus, a reduced initial dosage of heparin and reduced protamine dosage could, in turn, reduce the inflammatory response by complement activation as well as lower the risk of post-operative complications.[12,13] However further prospective studies are required in this regard. In the present study, lower dose heparin group had significantly reduced post-CPB protamine administration.

The main limitation of this study was that, quantitative assessment of peri-operative bleeding was not conducted, thence it could not be established that ACT values more than 480, or as observed in some patients to have exceeded the measuring capacity of the machine, cause excessive bleeding.

Conclusion

In the Pakistani population, a target ACT can be achieved with a significantly lower dose than the conventional weight-based heparin dose. Larger studies, preferably randomized controlled trials are needed to determine the optimal heparin dose calculation for safe anti-coagulation during CPB.

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