Comparison of Two Doses of Heparin on Outcome in Off-pump Coronary Artery Bypass Surgery Patients: A Prospective Randomized Control Study

Murali Chakravarthy, Dattatreya Prabhakumar, Patil Thimmannagowda, Jayaprakash Krishnamoorthy, Antony George, Vivek Jawali

From the Department of Anesthesia, Critical Care and Pain Relief, Fortis Hospitals, Bengaluru, Karnataka, India

Abstract

Introduction: While off pump coronary artery bypass surgery is practiced with an intention to reduce the morbidity associated with cardiopulmonary bypass, the resultant 'hypercoagulability' needs to be addressed. Complications such as cavitary thrombus possibly due to the hyper coagulability after off pump coronary artery bypass surgery have been described. Many clinicians use higher doses of heparin - up to 5 mg/kg in order to thwart this fear. Overall, there appears to be no consensus on the dose of heparin in off pump coronary artery bypass surgeries. **Aim of the Study:** The aim of the study was understand the differences in outcome of such as transfusion requirement, myocardial ischemia, and morbidity when two different doses were used for systemic heparinization. **Methods:** Elective patients scheduled for off pump coronary artery bypass surgery were included. Ongoing anti platelet medication was not an exclusion criteria, however, anti platelet medications were ceased about a week prior to surgery when possible. Thoracic epidural anesthesia was administered as an adjunct in patients who qualified for it. By computer generated randomization chart, patients were chosen to receive either 2 or 3 mg/kg of intravenous unfractioned heparin to achieve systemic heparinization with activated clotting time targeted at >240 secs. Intraoperative blood loss, postoperative blood loss, myocardial ischemic episodes, requirement of intraaortic balloon counter pulsation and transfusion requirement were analyzed. **Results:** Sixty two patients participated in the study. There was one conversion to cardiopulmonary bypass. The groups had comparable ACT at baseline (138.8 vs. 146.64 seconds, $P = 0.12$); 3 mg/kg group had significantly higher values after heparin, as expected. But after reversal with protamine, ACT and need for additional protamine was similar among the groups. Intraoperative (685.56 ± 241.42 ml vs. 675.15 ± 251.86 ml, $P = 0.82$) and postoperative blood loss (1906.29 ± 611.87 ml vs 1793.65 ± 663.54 ml , p value 0.49) were similar among the groups [Table 4]. The incidence of ECG changes of ischemia, arrhythmias, conversion to CPB, or need for intra-aortic balloon counter pulsation were not different. **Conclusions:** Use of either 2 or 3 mg/kg heparin for systemic heparinization in patients undergoing OPCAB did not affect the outcome.

Keywords: *Blood loss, heparin, off-pump coronary artery bypass, randomized controlled trial*

Introduction

Off-pump coronary artery bypass (OPCAB) surgery is practiced with an intention to reduce the adverse effects associated with cardiopulmonary bypass (CPB). They are reduced inflammatory response,[1] lesser renal dysfunction,[2,3] decreased the incidence of stroke[4,5] less cognitive problems,[6] lower incidence of coagulopathy, transfusion requirement,[7] lower morbidity, mortality,[5,8,9] and length of intensive care and hospital stay.[10] Carrying out OPCAB surgery requires administration of systemic heparin, the dose of it is not standardized. Many centers use smaller dose (2 mg/kg) for OPCAB in contrast to 3 mg/kg in on pump Coronary artery bypass surgery. However, a few consider OPCAB as a hypercoagulable state and use higher doses of heparin (up to 5 mg/kg), because OPCAB is said to be associated with surgery-related systemic inflammatory response and warm regional myocardial ischemia/reperfusion, jeopardizing the early graft patency.[11] Song *et al*. used activated clotting time (ACT) as a measure of systemic heparinization instead of standardizing the dose of heparin.[12] Tanaka *et al*. studied the effects of varying doses of heparin used for systemic heparinization in patients undergoing OPCAB and concluded that total dose of heparin and protamine required in OPCAB was lower than that of surgery conducted under CPB.[13] Our study consisting of two different doses of heparin was conducted to understand the outcomes of OPCAB such as transfusion requirement, myocardial ischemia, and morbidity.

How to cite this article: Chakravarthy M, Prabhakumar D, Thimmannagowda P, Krishnamoorthy J, George A, Jawali V. Comparison of two doses of heparin on outcome in off-pump coronary artery bypass surgery patients: A prospective randomized control study. Ann Card Anaesth 2017;20:8-13.

Received: August, 2016. **Accepted:** November, 2016.

Address for correspondence:
Dr. Murali Chakravarthy, Department of Anesthesia, Critical Care and Pain Relief, Fortis Hospitals, Bannerughatta Road, Bengaluru - 560 076, Karnataka, India.
E-mail: mailchakravarthy@gmail.com

Access this article online

Website: www.annals.in

DOI: 10.4103/0971-9784.197818

Quick Response Code:

Methods

Hospital Ethical Committee cleared the study protocol. Patients scheduled for OPCAB were chosen. Patients with a history of heparin resistance, prior exposure to heparin in the previous few days, hepatic or renal derangement and requiring emergency surgery, were excluded from this study. Ongoing anti-platelet medications and conversion to CPB were not reasons for exclusion. In a few cases, the surgeon ceased the antiplatelet medication treatment for about a week before surgery. On the day before surgery, thoracic epidural catheter was inserted in patients not contraindicated. The contraindications being, patient refusal, ongoing antiplatelet therapy, trauma or surgery of the spine in the past, and infection at the planned site of epidural catheterization. The epidural catheterization was performed on the eve of surgery in a high dependency area. The patient sat upright, the epidural space was identified in the midline by loss of resistance to saline and about 3 cm of epidural catheter was left indwelling. On the day of surgery, monitoring lines were inserted (arterial and central venous pressure or pulmonary artery pressure monitoring catheters) under local anesthesia as per the institutional protocol. 3 ml of 2% xylocaine with 1 in 200,000 adrenaline was administered as epidural test dose; in the absence of adverse actions, full dose of 10–12 ml of 0.5% of bupicaine was injected. General anesthesia was induced by intravenous administration of suitable doses of propofol, fentanyl, and rocuronium. Patient's trachea was intubated with a suitable sized endotracheal tube and mechanical ventilation was initiated. A basal ACT (Actalyke, Helena Laboratories, Beumonth, TX 77704)was checked. The patients were randomly chosen (using a computer generated randomization chart) to receive either 2 or 3 mg/kg heparin intravenously. Heparin was administered after the harvesting of the left internal mammary artery. ACT was checked at 5 min interval for the first 10 min and 20 min interval for up to 140 min or end of anastomosis, whichever was earlier. ACT of 240 s was deemed necessary. If the ACT was not up to 240 s, the patient was excluded from the study. They, however, underwent OPCAB after further administration of heparin. OPCAB surgery was carried out using Acrobat stabilizer (Maquet Cardiovascular LLC, 45, Barbour Pond Dr, Wayne, NJ 07470, United States) and starfish (Medtronic Limited, 710 Medtronic Parkway, Minneapolis, Minnesota, 55432-5604, USA). After the completion of the anastomoses, residual heparin was reversed by 1 mg of protamine for every mg of heparin used for systemic heparinization. Following protamine administration, ACT was checked 3, 15, and 30 min guided by ACT. The target ACT was. If additional dose of protamine was required, the quantity and resultant ACT were made note of. ACT was performed 10 min after completion of the additional dose of protoamine. Intraoperative events such as arrhythmias requiring treatment, the requirement of intra-aortic balloon counterpulsation and blood loss were noted. After completion of the surgery, the patients were transferred to the intensive care for further care. Postoperative blood loss was recorded for 72 h or till the drainage tube removal, whichever occurred later. Transfusion of packed cells was deemed required when the hematocrit was <24%. Transfusion requirement was made note of. Differences in blood loss and transfusion requirements in patients who received epidural were compared with those who did not. An epidural infusion of 0.125% bupivacaine was set up at rates varying between 3 and 7 ml (depending on the postoperative pain). The epidural catheter was removed before discharge.

Perioperative myocardial infarction was diagnosed using the electrocardiogram (ECG) (ST elevation of more than 1 mm) and enzyme criteria (elevation of creatinine phosphokinase muscle brain fraction and troponin T more than ten times the baseline value).

To identify a difference of 100 ml in the chest drain (assuming a standard deviation of 125 ml) between the groups with an alpha error of 5% and beta error of 20%, the minimum required sample size was 26 in each group. We aimed to recruit about 30 patients considering the possibility of dropouts later.

Statistical methods

Continuous variables were summarized as mean ± standard deviation, and categorical variables as number (%) and were compared across the groups using unpaired *t*-test and Chi-square test, respectively. A $P < 0.05$ was considered statistically significant. SPSS for Windows, (Version 16.0, SPSS Inc., Chicago, IL, USA) was used for analysis.

Results

A total of 62 patients were recruited in the study. There were 32 patients in the 3 mg/kg group and thirty in the 2 mg/kg group. One patient in 2 mg/kg group was converted from OPCAB to CPB, because of technical difficulty. The preoperative characteristics of the patients were comparable and are summarized in Table 1. The groups had comparable ACT at baseline (138.8 vs. 146.64 s, $P = 0.12$); 3 mg/kg group had significantly higher values after heparin, as expected [Table 2 and Figure 1]. However, after reversal with protamine, ACT, and need for additional protamine was similar among the groups [Table 3]. Intraoperative (685.56 ± 241.42 ml vs. 675.15 ± 251.86 ml, $P = 0.82$) and postoperative blood loss (1906.29 ± 611.87 ml vs. 1793.65 ± 663.54 ml, $P = 0.49$) were similar among the groups [Table 4]. The incidence of ECG changes of ischemia, arrhythmias, conversion to CPB, or need for intra-aortic balloon counterpulsation were not different between the groups. The need for blood products was also similar among the groups [Figure 2]. Surprisingly, the mean blood loss in the 3 mg/kg group (1793.65 ± 663.54 ml) was lesser than

Table 1: Comparison of baseline characteristics between groups

	Heparin								
	2 mg/kg (*n*=36)				3 mg/kg (*n*=26)				*P*
	Mean	SD	Count	%	Mean	SD	Count	%	
Age	58.54	8.08			57.52	8.63			0.6
Sex									
Male			33	91.7			22	84.6	
Female			3	8.3			4	15.4	
Weight (kg)	66.97	11.93			67.62	10.40			0.8
Height (cm)	163.81	7.53			165.33	6.37			0.4
Tea									
0			28				24		0.1
1			8				2		
DM									
1			19	52.8			13	50.0	0.8
HTN									
1			27	75.0			16	61.5	0.2
COPD									
1			2	5.6			3	11.5	0.4
Smoking									
1			5	13.9			7	26.9	0.2
Alcohol									
1			5	13.9			5	19.2	0.6
Aspirin									
1			30	83.3			21	80.8	0.8
Clopidogrel									
1	15	41.7%			18	69.2 %			0.053
LMWH									
1	15	41.7%			8	30.8 %			0.38
Hb		13.44	1.75			13.52	1.73		0.87
PltCount		2.2lac	0.75			2.75	0.82		0.02
BT		2.79	0.41			3.16	2.66		0.5
CT		7.60	0.47			8.08	1.07		0.02
INR		1.07	0.11			1.13	0.10		0.02

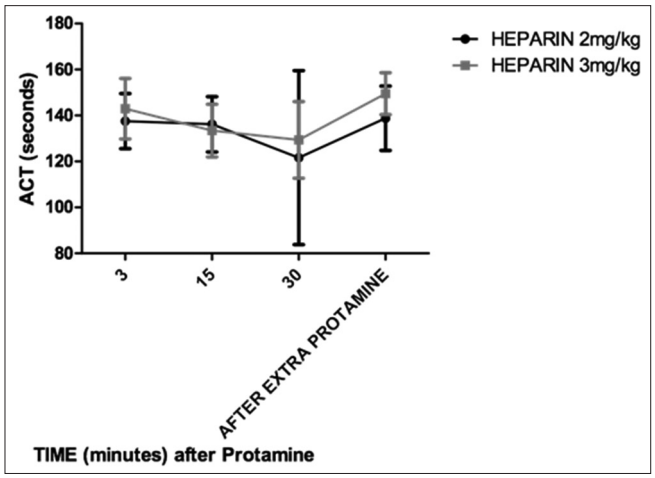

Figure 1: Comparison of activated clotting time over time after portamine

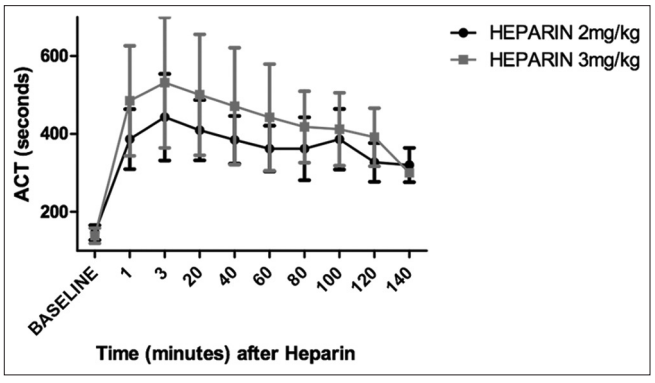

Figure 2: Activated clotting time values over time

the 2 mg/kg group (1906.29 ± 611.87 ml), but this lacked significance (P = 0.49). The blood loss and transfusion requirement were not different when patients with (n = 28) and without epidurals (n = 44) were compared in the two groups. Additionally, it was also not different in our cohort who received antiplatelet medication in contrast to those who did not [Table 5]. There were no re-explorations or exclusions in the cohort. There were no in hospital mortality.

Table 2: Comparison of activated clotting time between the two groups after heparinization

ACT	Heparin				
	2 mg/kg (*n*=36)		3 mg/kg (*n*=26)		*P*
	Mean	SD	Mean	SD	
Baseline	146.64	19.10	138.80	19.66	0.12
ACT after 1 min	386.83	77.15	485.04	141.08	0.002
ACT after 3 min	443.14	111.33	531.92	167.92	0.02
ACT after 20 min	409.77	77.58	500.50	155.31	0.004
ACT after 40 min	384.97	61.26	471.29	149.97	0.004
ACT after 60 min	362.37	58.71	442.52	136.65	0.006
ACT after 80 min	362.00	80.94	418.06	91.68	0.048
ACT after 100 min	386.33	77.80	412.10	93.40	0.441
ACT after 120 min	327.00	49.60	391.86	74.39	0.035
ACT after 140 min	320	44	300	.	0.773
Heparin total	282.84	61.79	314.55	105.64	0.17

ACT: Activated clotting time, SD: Standard deviation

Table 3: Comparison of blood loss between the two groups

Blood loss	Heparin				
	2 mg/kg (*n*=36)		3 mg/kg (*n*=26)		*P*
	Mean	SD	Mean	SD	
Intraoperative	685.56	241.42	671.15	251.86	0.82
First 12 h	451.39	174.54	552.31	291.81	0.12
12-24 h	399.31	233.73	314.42	254.17	0.17
Total blood loss	1906.29	611.87	1793.65	663.54	0.49

SD: Standard deviation

Table 4: Comparison of perioperative events between the groups

	Heparin				
	2 mg/kg (*n*=36)		3 mg/kg (*n*=26)		*P*
	Count	Percentage	Count	Percentage	
ECG changes	3	8.33	1	3.85	0.85
Arrythmias	5	13.88	2	7.7	0.72
Conversion to CPB	1	2.77	0	0	
IABP insertion	2	5.55	0	0	

IABP: Intra-aortic balloon pump, CPB: Cardiopulmonary bypass, ECG: Electrocardiogram

Table 5: Bleeding in patients who received/stopped aspirin/clopidogrel

	Aspirin					Clopidogrel				
	No		Yes		*P*	No		Yes		*P*
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Blood loss OT	639.09	168.55	688.24	257.80	0.55	644.14	241.79	703.12	245.26	0.35
Total blood loss	1530.91	429.75	1930.30	649.03	0.06	1751.96	624.96	1933.44	636.42	0.27

SD: Standard deviation, OT: Operation theatre

Discussion

OPCAB surgery is practiced exploring the possibility to reduce side effects of CPB. To a great extent, clinicians have succeeded in reducing the incidence of strokes, renal dysfunctions, blood loss and requirement of blood products by performing OPCAB.[1-10] However, an apprehension that performing OPCAB surgery might be deny the potential benefits of the coagulopathy (that is inevitable with CPB) may be present in the minds of clinicians. OPCAB, on the other hand, is considered a procoagulant state.[11] We have reported an intra-atrial thrombus which developed *suo moto* in a patient after OPCAB surgery, requiring CPB to retrieve it, supporting the above hypothesis.[14] There are other reports citing instances of thrombosis following smaller doses of heparin used for systemic heparinization.[15] An apprehension on the minds of the clinicians is, whether performing OPAB surgery leads to worse outcomes due to the hyper coagulant state that is associated with OPCAB; such clinicians achieve systemic heparinization with higher

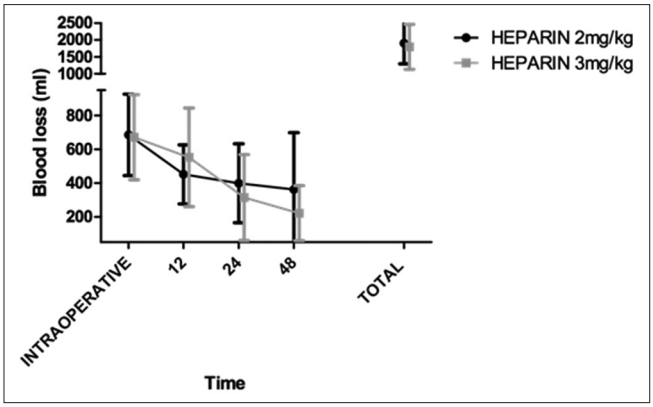

Figure 3: Comparison of blood loss

dose of heparin, up to 5 mg/kg.[12,16] We studied the amount of additional protamine required to achieve the baseline ACT ±, blood loss (intraoperative and postoperative), myocardial ischemic episodes requiring inotropic agents and intra-aortic balloon counterpulsation, perioperative myocardial infarction assessed by electrocardiographic and enzyme criteria. In this study, it was our effort to identify if use of one dose or the other resulted in better or worse outcome. This study showed a lack of superiority/inferiority of one dose over the other. Although the ACT was significantly higher in the 3 mg/kg group (P = 0.12), the postoperative bleeding was paradoxically lower (P = 0.49). It is not possible for this author to comment due to the limited strength of this study. Perhaps a larger better-powered study might offer better explanation on that relationship of heparinization and blood loss [Figure 3].

Blood loss in either group was also not different. In a similar study Chun *et al*. have noted that blood loss, transfusion requirement, and ischemic episodes in the postoperative period does not depend on the dose of heparin, as long as the ACT levels are maintained more than 300 s.[17] In a European survey, Englberger *et al*. showed that the prevailing practice of dosing heparin during OPCAB among the European surgeons varied widely; from 1.5 to 5 mg/kg. There was a tendency to use lower doses among them.[16] In this survey, it was noted that ACT during surgery was accepted to be 200 s by 24%, 250 s by 18% and 300 s by 26% of surgeons. The survey concludes that there is no consensus on the dose of heparin among clinicians of Europe; the value of ACT appears more important than the dose of heparin itself. Rasoli *et al*. commented "Although most technical steps in off-pump revascularization are standardized, it appears that there is inconsistency in intraoperative anticoagulation practice. Surveys conducted in the USA and Europe confirm the lack of uniform policy, with heparin dose ranging between 70 and 500 U/kg and from full-dose protamine to no reversal of anticoagulation. Although the quality of evidence is low, there is a trend for utilization of heparin at 150 U/kg, followed by half-dose protamine reversal, which appears to provide adequate anticoagulation for the safe conduct of anastomoses and thromboprophylaxis without significantly increasing the risk of postoperative bleeding. However, more research is necessary before firm recommendations can be made."[18]

There appears to be paucity of evidence about the optimal dose of heparin and protamine that might provide the best outcome after OPCAB. A multi-centric prospective study on a larger scale is likely to provide the relevant inputs.

Limitations

Our cohort consisted of patients with ongoing antiplatelet medication as well as some in whom it was ceased for about a week. Our study did not go into the patterns of the patients with and without ongoing treatment with antiplatelet medications.

Conclusion

Use of either 2 or 3 mg/kg heparin for systemic heparinization in patients undergoing OPCAB did not affect the outcome.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Edmunds LH Jr. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 1998;66 5 Suppl: S12-6.
2. Ascione R, Lloyd CT, Underwood MJ, Gomes WJ, Angelini GD. On-pump versus off-pump coronary revascularization: Evaluation of renal function. Ann Thorac Surg 1999;68:493-8.
3. Arom KV, Flavin TF, Emery RW, Kshettry VR, Janey PA, Petersen RJ. Safety and efficacy of off-pump coronary artery bypass grafting. Ann Thorac Surg 2000;69:704-10.
4. Brown PP, Mack MJ, Simon AW, Battaglia S, Tarkington L, Horner S, *et al.* Outcomes experience with off-pump coronary artery bypass surgery in women. Ann Thorac Surg 2002;74:2113-9.
5. Sharony R, Bizekis CS, Kanchuger M, Galloway AC, Saunders PC, Applebaum R, *et al.* Off-pump coronary artery bypass grafting reduces mortality and stroke in patients with atheromatous aortas: A case control study. Circulation 2003;108 Suppl 1:II15-20.
6. Taggart DP, Westaby S. Neurological and cognitive disorders after coronary artery bypass grafting. Curr Opin Cardiol 2001;16:271-6.
7. Yadava OP, Prakash A, Kundu A, Yadava M. Coronary artery bypass grafting in women – is OPCAB mandatory? Indian Heart J 2011;63:425-8.
8. Bierbach B, Bomberg H, Pritzer H, Prabhu S, Petzina R, Kempski O, *et al.* Off-pump coronary artery bypass prevents visceral organ damage. Interact Cardiovasc Thorac Surg 2014;18:717-26.
9. Sepehripour AH, Saso S, Harling L, Punjabi P, Ashrafian H,

Athanasiou T. Does off-pump coronary revascularization reduce mortality in re-operative coronary artery surgery? A meta-analysis of observational studies. Perfusion 2013;28:340-9.

10. Bull DA, Neumayer LA, Stringham JC, Meldrum P, Affleck DG, Karwande SV. Coronary artery bypass grafting with cardiopulmonary bypass versus off-pump cardiopulmonary bypass grafting: Does eliminating the pump reduce morbidity and cost? Ann Thorac Surg 2001;71:170-3.
11. MacGillivray TE, Vlahakes GJ. Patency and the pump – The risks and benefits of off-pump CABG. N Engl J Med 2004;350:3-4.
12. Song Y, Song JW, Shim JK, Kwak YL. Optimal anticoagulation during off pump coronary artery bypass in patients recently exposed to clopidogrel. Yonsei Med J 2013;54:1119-26.
13. Tanaka KA, Thourani VH, Williams WH, Duke PG, Levy JH, Guyton RA, *et al.* Heparin anticoagulation in patients undergoing off-pump and on-pump coronary bypass surgery. J Anesth 2007;21:297-303.
14. Chakravarthy M, Jawali V, Patil T. Spontaneous right atrial thrombus after off-pump coronary artery bypass surgery. J Cardiothorac Vasc Anesth 2007;21:564-6.
15. Saha KK, Sangwan DK, Shroff PK, Deval MM, Saha KK, Jacob RV, *et al*. Off-pump coronary artery bypass grafting using continuous heparin infusion. Indian Heart J 2016;68:798-804. [In print, e-published ahead of printing].
16. Englberger L, Streich M, Tevaearai H, Carrel TP. Different anticoagulation strategies in off-pump coronary artery bypass operations: A European survey. Interact Cardiovasc Thorac Surg 2008;7:378-82.
17. Chun DH, Baik SW, Kim SY, Shim JK, Kim JC, Kwak YL. Heparin responsiveness during off-pump coronary artery bypass graft surgery: Predictors and clinical implications. Acta Pharmacol Sin 2011;32:133-8.
18. Rasoli S, Zeinah M, Athanasiou T, Kourliouros A. Optimal intraoperative anticoagulation strategy in patients undergoing off-pump coronary artery bypass. Interact Cardiovasc Thorac Surg 2012;14:629-33.