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Original Article

Comparison of Early Postoperative Outcome Between Intermittent Intravenous Heparin versus Continuous Heparin Infusion after Initial Bolus Dose during Off-Pump Coronary Artery Bypass Surgery

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Key Words : *Heparin, IHD, CABG, Postoperative outcome.*

Abstract

Background: *Heparin is an anticoagulant used invariably in all cardiac surgery. Intermittent heparin dosing after initial bolus dose is widely practiced to maintain ACT level 200- 300 seconds in OPCAB. Fluctuation of ACT level from this range may causes adverse postoperative outcome. This study was aimed to compare early postoperative outcome between intermittent heparin dose and continuous heparin infusion after initial bolus dose during OPCAB.*

Methods: *In this comparative experimental study total 110 patients were enrolled by purposive sampling and divided into 2 groups: group-A where 55 patients received intermittent heparin after initial bolus dose and group-B where 55 patients received continuous heparin infusion after initial bolus dose. Post operative outcomes were compared in both groups.*

Results: *Baseline ACT level of group-A was 87.04±5.51 seconds and group-B was 87.31±5.74 seconds (p = 0.800). After bolus dose of Heparin, ACT level of group-A was 252.02 ± 25.131 seconds and group-B was 259.04 ± 12.645 seconds (p = 0.068). Mean maintenance ACT was 326.34±22.774 seconds in group-A and 258.67±12.285 seconds in group-B patient (p<0.001). Peroperatively 29% from group-A and 11% from group-B developed arrhythmia. Postoperative mean Troponin I level in group-A was 5.78± 1.15 and group-B was 5.32± 1.05 ng/dl (p = 0.030). Postoperative blood loss was significantly higher in group-A than group-B (986.36± 398.31 ml vs 852.73±241.22 ml, p=0.036). There was significantly better reduction of arrhythmia and ischemia in postoperative and on discharge ECG finding in group-B patients (p=0.002). On discharge echocardiography 31% from group-A and 13% from group-B had regional wall motion abnormality (p=0.018). But there was no significant difference in LVEF% (52.65±5.99 vs 53.85±5.77, p = 0.287). There was only one mortality which was from group-A.*

Conclusion: *Early postoperative outcome of continuous heparin infusion is better than intermittent intravenous heparin after initial bolus dose during Off-pump coronary artery bypass surgery. So, during OPCAB use of continuous heparin infusion after bolus dose is eminent time worthy.*

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Introduction

Coronary artery disease (CAD) results from progressive blockage of the coronary arteries by atherothrombotic disease.[1] Coronary artery bypass grafting (CABG) is among the most important surgical procedures in the history of medicine. Arguably, no other operation has prolonged more lives, provided more symptom relief and been more thoroughly investigated.[2]

Off-pump coronary artery bypass grafting (OPCAB) is frequently used to perform coronary artery bypass grafting. The advantages and

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disadvantages of this technique in comparison with the standard operation performed with the arrested heart and cardiopulmonary bypass (CPB) are becoming clearer. Most of the studies involving the general population have shown that a significant reduction of postoperative bleeding and blood product transfusion is observed after OPCAB compared with on-pump operations.[3]

Carrying out OPCAB surgery requires administration of systemic heparin.[4] Sodium heparin is the anticoagulant normally used in heart surgery. Pharmacologically, it allows an adequate control of the anticoagulation and the prevention of thromboembolic events, and is responsible for the great development of surgical techniques. However, an adequate and rigorous control of the levels of anticoagulation is necessary, in order to minimize its adverse effects.[5]

Unfractionated heparin becomes bound to two constitutive plasma serpins, antithrombin formerly called antithrombin III and heparin cofactor II (HC II). Antithrombin inhibits thrombin (IIa) and Xa and, to a lesser degree, IXa, XIa and XIIa. Heparin cofactor II inhibit the action of thrombin.[6] Activated clotting time (ACT) is used as a measure of systemic heparinization.[4] ACT is a nonspecific test affected not only by heparin but also by platelet and temperature. Inconsistent relationship is present between heparin dose, plasma heparin concentration, and clinical effect (as measured by the activated clotting time). So, safe and effective level of heparinization has not been established.[7]

Recently, it was noted that during OPCAB ACT longer than 350 seconds is associated with a significantly higher rate of postoperative myocardial infraction. It is presumed that at a longer ACT there may be platelet activation leading to a detrimental effect, very similar to the situation with percutaneous coronary intervention rather than to that conventional CABG. Longer ACT may lead to postoperative myocardial infarction.[8]

Heparin dose, optimal activated clotting time, and protocol for administering protamine vary from institution to institution. Heparin dose varies from a minimum of 5000 units to full heparinization (3mg/kg).[10,11]

Maintaining low steady ACT is challenging as any further drop in ACT may result in thrombus formation leading to unwanted graft blockage. This is particularly true in prolong procedure. This apprehension of thrombus formation may lead to higher heparin doses resulting in prolong ACT. The conventional method of heparin dosing is initial high bolus dose and followed by intermittent maintenance bolus doses to maintain ACT above a predetermined target value. This practice is mostly derived from conduction of cardiopulmonary bypass where ACT is maintained above 480 seconds. A little higher doses is considered harmless as higher ACT induced bleeding can easily be managed since blood from operative field is returned using cardiotomy suction. Moreover, intermittent bolus doses result in peaks and trough which may be unwanted during OPCAB.[8]

The goal of continuous heparin infusion after initial bolus dose during OPCAB is to maintain a steady low target ACT between 200 to 300 seconds. The objective of which is to assess the effectiveness and safety of heparin infusion by maintaining a steady target ACT level. As per literature review, there is no previous study in Bangladesh on continuous heparin infusion after initial bolus dose during OPCAB. In this study we have compared early postoperative outcome between intermittent intravenous heparin infusion and continuous heparin infusion after initial bolus dose during OPCAB in maintaining target ACT. So, the study is time worthy and quite justified.

Methods:

It was comparative cross-experimental study carried out Department of Cardiac surgery, National Institute of Cardiovascular Diseases (NICVD), Sher-e-Bangla Nagar, Dhaka, Bangladesh during the period of January 2019 to December 2020. Patients who underwent off-pump coronary artery bypass surgery in Department of Cardiac surgery, NICVD with fulfillment of inclusion & exclusion criteria. Total 110 patients were divided into two groups on basis of peroperative heparin administration after initial bolus dose. 55 patients received intermittent intravenous heparin (Group A). 55 patients received continuous heparin infusion (Group B). All patients admitted in the department of cardiac

surgery, NICVD, Dhaka, after fulfilling the inclusion and exclusion criteria enrolled for this study. Meticulous history, detailed clinical examination was performed and recorded in predesigned structured proforma. Demographic data such as age, sex & BMI were recorded. Routine investigations including ECG, Echocardiography, SGPT, Serum creatinine, Platelet count were recorded. A standard anesthetic protocol used throughout the study. All the patients underwent median sternotomy and standard OPCAB was performed. Base line ACT level was measured and recorded before infusion of heparin. All the patients received 200 unit/kg bolus dose and ACT was measured 5 minutes after bolus dose. Then ACT level was monitored hourly. Group-A patients received 50-100 unit/kg intermittent dose of heparin on basis of ACT level aimed to maintain 200-300 seconds. Group-B patients received 40 unit/kg/hour continuous heparin infusion just after bolus dose. Dose was adjusted aiming to maintain ACT level between 200-300 seconds. In all cases we used 5ml vial of sodium heparin containing 5000U/ml, manufactured by Rotexmedica, Germany, Batch-70005, which was available in NICVD. ACT was measured by using Actalyke MINI II Activated Clotting Time test system machine, Model-G5753001, Helena Laboratories, USA, available in NICVD and blood sample was always collected from central venous line. Surgical team was vigilant whether any clot in operative field and the finding was noted. Any arrhythmia during operation was also noted. Total peroperative blood transfusion and number of grafts was recorded. In ICU during postoperative period if any ischemic change or arrhythmia in ECG monitor noticed, a 12 lead ECG was taken. Serum Troponin I level was evaluated after 24 hours postoperatively for every patient. Total postoperative blood loss and 48 hours urine output was recorded. Postoperative platelet count was also evaluated. Others management was done according to the protocol of the institute. All the patients were followed up to 48 hours postoperatively. Finally a 12 leads ECG for any ischemia arrhythmia or MI and Echocardiography to evaluate any regional wall motion abnormality and left ventricular ejection fraction was done at the time of discharge usually at 7th POD. Data were collected pre-designed data collection sheet.

Computer based statistical analysis was carried out with appropriate techniques and systems. All data were recorded systematically in preformed data collection form (questionnaire) and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. 95% confidence limit was took. Data was analyzed by the software statistical program for social science (SPSS 26.0). Probability value <0.05 was considered as level of significance. The association between qualitative variables was measured by Chi-Square test. Student's t test was performed to see the association between quantitative variables.

Results:

Highest percentage of patients from both intermittent and continuous group belongs to 50-59 years (43.64 and 38.18 percent respectively). There had male predominance in both intermittent and continuous group (87% and 82% respectively).

There was no significant difference of preoperative mean baseline ACT level (87.04 ± 5.51 seconds vs 87.31 ± 5.74 seconds, $p = 0.800$) and peroperative mean ACT level after bolus heparin (252.02 ± 25.131 seconds vs 259.04 ± 12.645 seconds, $p = 0.068$) between the groups. But mean maintenance ACT level was significant between the groups (326.34 ± 22.774 seconds vs. 258.67 ± 12.285 seconds, $p < 0.001$). Preoperatively 38% from group-A and 42% from group-B had old MI in ECG findings and the findings was not significant ($p = 0.697$). But peroperative (29% vs 11%, $p = 0.017$), postoperative (15% vs 5%, $p = 0.002$) and on discharge (4% vs 0%, $p = 0.002$) arrhythmia in ECG findings were significant. Preoperative Echocardiography findings of both regional wall motion abnormality and LVEF% ($50.62 \pm 6.39\%$ vs $50.51 \pm 6.04\%$, $p = 0.927$) were insignificant between the groups (p value is >0.05). On discharge regional wall motion abnormality was significant between the groups ($p = 0.018$), but on discharge LVEF% was insignificant between the groups ($52.65 \pm 5.99\%$ vs $53.85 \pm 5.77\%$, $p = 0.287$). Mean peroperative blood transfusion was insignificant between the groups (2.02 ± 0.782 units vs 2.00 ± 0.770 units, $p = 0.902$). But mean

postoperative blood loss was significant between the groups (986.36± 398.31ml vs 852.73±241.22ml, p = 0.036). No clot was found in operative field in both groups. So, this variable could not be computed. There was no significant difference of graft number between the groups (2.93±0.604 vs 2.91±0.617, p = 0.876). There was no significant difference of mean urine output (5871.82± 334.41ml vs 5940.90± 343.47ml, p = 0.288) and ventilator time (9.52± 2.273 hours vs 9.18± 2.098 hours, p = 0.422). There was only one mortality, which was from intermittent group and the result is insignificant (p = 0.315).

Table-I

Demographic characteristics between two groups (N=110).

Characteristics	Group A (n=55) No. (%)	Group B (n=55) No. (%)	p-value
Age (in years)			
30-39 years	2 (3.64)	4 (7.27)	0.853 ^{NS}
40-49 years	18(32.73)	17(30.91)	
50-59 years	24(43.64)	21(38.18)	
60-70 years	10(18.18)	13(23.64)	
70 years and above	1(1.82)	0(0)	
Mean±SD	51.65±7.51	51.95±8.87	
Gender			
Male	48 (87.27)	45 (81.82)	0.429^{NS}
Female	7 (12.73)	10 (18.18)	

Table-II

Comparison of ACT level between the groups (N=110).

ACT (Seconds)	Group A (n=55) Mean±SD	Group B (n=55) Mean±SD	p-value
Preoperative baseline ACT	87.04 ± 5.51	87.31 ± 5.74	0.800^{NS}
ACT after bolus dose	252.02± 25.131	259.04± 12.645	0.068^{NS}
Mean maintenance ACT	326.34± 22.774	258.67± 12.285	<0.001^{S}

Table-III

Comparison of preoperative and on discharge Echocardiography findings between the groups (N=110).

Echocardiography		Group A (n=55) No. (%)	Group B (n=55) No. (%)	p-value
Preoperative Echocardiography	No RWMA	33(60)	30(54.54)	0.563^{NS}
	RWMA	22(40)	25(45.45)	
	LVEF% (Mean±SD)	50.62± 6.39	50.51±6.04	0.927^{NS}
On discharge Echocardiography	No RWMA	37(67.27)	48(87.27)	0.018^{S}
	RWMA	17(30.91)	7(12.73)	
	LVEF% (Mean±SD)	52.65± 5.99	53.85± 5.77	0.287^{NS}

Table-IV

Comparison of peroperative blood transfusion and postoperative blood loss between the groups (N=110).

Variable	Group A (n=55) Mean±SD	Group B (n=55) Mean±SD	p-value
Peroperative blood transfusion (Unit)	2.02±0.782	2.00±0.770	0.902^{NS}
Postoperative blood loss (ml)	986.36± 398.31	852.73±241.22	0.036^{S}

Table-V

Comparison of postoperative Troponin I level between the groups (N=110).

Variable	Group A (n=55) Mean±SD	Group B (n=55) Mean±SD	p-value
Troponin I (ng/ml)	5.78± 1.15	5.32±1.05	0.030^{S}

Table-VI

Comparison of peroperative variables between the groups (N=110).

Variable		Group A (n=55)	Group B (n=55)	Total (N=110)	p-value
Clot in operative field	No clot	55	55	110	-
	Presence of clot	0	0	0	
Number of grafts Mean±SD		2.93±0.604		2.91±0.617	0.876^{NS}

Table-VII

Comparison of postoperative findings between the groups (N=110).

Variable		Group A (n=55)	Group B (n=55)	p-value
Urine output (48 hours) Mean±SD		5871.82± 334.41	5940.90± 343.47	0.288^{NS}
Ventilator time (Mean±SD)		9.52± 2.273	9.18± 2.098	0.422^{NS}
Mortality	No mortality	54	55	0.315^{NS}
	Mortality	1	0	

Discussion:

Majority of the patients from both group-A and group-B belonged to 50-59 years (24 and 21 respectively). Mean±SD age of all patients was 51.80±8.18 years (Table-I). There was male predominance in both group (48% and 45% respectively). There had no significant differences between the two groups of patients regarding age and sex (p value >0.05). These demographic characteristics of our cohort are consistent with different studies across the world[4,5,11] which also reports male predominance along with similar characteristics.

Mean baseline ACT was same in both the groups. In our study ACT level after bolus heparin was 252.02±25.131 seconds in intermittent group and 259.04±12.645 seconds in continuous group (p = 0.068). Filho and colleagues[5] studied over 40 patient found mean ACT 372.2±104.31 seconds after bolus heparin is higher than our study. Heparin responsiveness varies from person to person and also depends on preoperative heparin treatment. Mean maintenance ACT of our study was 326.34±22.774 seconds and 258.67±12.285 seconds respectively in group-A and group-B (p <0.001). These findings correlate with other studies.[4,8]

On preoperative Echocardiography regional wall motion abnormality and mean left ventricular ejection fraction was similar in both gropus. On

discharge echocardiography 17 (30.91%) patients had persisted RWMA of group A and 7 (12.73%) patients had persisted RWMA of group B. RWMA significantly reduced postoperatively in group B (p = 0.018). On discharge mean LVEF was 52.65±5.99% in group A and 53.85±5.77% in group B. Difference of follow up LVEF was not significant (p = 0.287). A study conducted over 199 patients underwent OPCAB having preoperative mean LVEF 56±13% in one group and 53±14% in another group had similar finding to our study.[11]

Mean postoperative Troponin I level of group-A patients was 5.78± 1.15 ng/dl and group-B patients was 5.32± 1.05 ng/dl. Troponin I level of group-A patients was significantly higher than group-B patient (p = 0.030) which indicates ischemic events was higher in group A patient. Several studies conducted over OPCAB patients having similar findings by measuring postoperative CK (MB) and Troponin T level.[4,11]

There was no significant difference between peroperative blood transfusion between group-A and group-B patients. But mean postoperative blood loss was more in group-A patients. Mean peroperative transfusion of group-A patients was 2.02±0.782 unit and group-B patients was 2.00±0.770 unit respectively. Mean postoperative blood loss of group-A patients was 986.36± 398.31 ml and group-B patients was 852.73±241.22 ml. Difference between the group was significant (p = 0.036). Paparella and colleague[12] studied over 31 patients and found mean peroperative blood transfusion 1.3±1.2 unit and mean postoperative blood loss 933.7±382.6 ml in OPCAB group of 15 patients. Peroperative blood transfusion of that study was lower than our study. Peroperative transfusion depends on preoperative anemia, existing loss and expected hemoglobin level and also the study population of their study was very small. But postoperative blood loss had similar findings like our study.[3]

No clot was found in the operative field in all patients of both groups. There was no significant difference in number of grafts in between the groups. Mean graft number in group-A was 2.93±0.604 and in group-B was 2.91±0.617. A study conducted over 201 patients received continuous heparin having similar findings like our study. They also did not find any clot in operative field.[8] Another study conducted over 168 patients had mean graft number 3.3±0.7 similar to our study.[11]

There was no significant difference in postoperative urine output and ventilator time between the groups. Mean 48 hours urine output of group-A patients was 5871.82± 334.41 ml and group-B patients was 5940.90± 343.47 ml. Mean ventilator time of group-A patients was 9.52± 2.273 hours and group-B patients was 9.18± 2.098 hours. There was only one mortality which was from intermittent group. The patient was suffering from critical left main disease and developed postoperative arrhythmia and low cardiac output syndrome. The patient was died on second postoperative day.

The study showed only early postoperative outcome. Long term follow up would be more efficient to differentiate the effect of intermittent versus continuous heparin in OPCAB. But from the findings of this study,s we recommend continuous heparin over intermittent heparin in OPCAB.

Conclusion:

Maintaining a steady target ACT level throughout the period is essential for better postoperative outcome in off-pump coronary artery bypass surgery. Continuous heparin infusion after initial bolus dose is better than conventional intermittent intravenous heparin after initial bolus dose in maintaining ACT level and better postoperative outcome in OPCAB. Maintenance of ACT level 200-300 seconds throughout the period in OPCAB is essential. Further large- scale study in different center is also recommended.

Conflict of Interest - None.

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