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Title page

PROSPECTIVE STUDY TO COMPARE EFFECTIVENESS OF UFH AND LMWH IN PATIENTS RECEIVING IABP UNDERGOING ELECTIVE CABG SURGERY

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Abstract-

Objective- Our study aimed to compare effectiveness and safety of low molecular weight heparin (LMWH) and unfractionated heparin (UFH) in patients undergoing elective coronary artery bypass grafting with prophylactically inserted intra-aortic balloon counterpulsation(IABP).

Material and methods - We included patients scheduled for CABG with ejection fraction less than 40% and prophylactically inserted IABP. Patients were randomized with computer generated sequence to receive LMWH or UFH . 30 patients received UFH (a bolus of injection 70 u/kg immediately after IABP, followed by infusion at a rate of 15 u/Kg/hr) and targeted APT T of 50-70 seconds. Another set of 30 patients received LMWH(subcutaneous injection of 1 mg/kg every 12 hrs). Total of 60 patients were included in study .Major end-points included were thrombotic events and bleeding events. Thrombotic events included arterial thromboembolism and leg-ischemia. Bleeding events included major access and nonaccess site bleeding. Major bleeding was defined by as a

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hemoglobin decrease by >50mg/l or bleeding that caused hemodynamic shock or life threatening or requiring blood transfusion.

Results- Subjects receiving UFH and LMWH were similar in baseline characteristics. Arterial thromboemolism occured in (2/30) patients in UFH group and (1/30) patients in LMWH. Major bleeding occured in 3 and 2 patients in UFH and LMWH groups respectively. Linear Regression analysis indicated no association between ischemia or bleeding with heparin type.

Conclusion- LMWH can reduce complications like ischemia and bleeding, but for statistical significancea larger sample size is needed.

Key-words- IABP- intraaortic balloon counterpulsation LMWH- low molecular weight heparin, UFH- unfractionated heparin, CPB-cardiopulmonary bypass

INTRODUCTION-

In the present era IABP is the most commonly used device for circulatory support during cardiac surgery causing more favorable balance of myocardial supply/ demand in the failing myocardium(1,2). During hospitalizationup to 6-10% patients with ST segment elevation myocardial infarction and about 3% patients with non ST elevation acute coronary syndrome develop cardiogenic shock (3). IABP is indicated in cardiac surgery due to inability to wean the patient from CPB,post operative low cardiac output syndrome, intractable ventricular arrhythmias and as a prophylactic use in patients with unstable symptoms or associated with poor ventricular function (4). To prevent risk of limb ischemia and thrombotic events, unfractionated heparin is most commonly administered after IABP insertion in these patients to maintain aPTT within 50 to 70 seconds(5,6).LMWH inhibits Xa/IIa activity at a ratio of1.5 to 4:1. LMWH has high absorption coefficient upon subcutaneous injection and comparatively less protein binding causing less antithrombotic ability and less impact on aPTT(7). Its use has been increased in PCI and hemodialysis. Studies have even shown that LMWH has comparatively less bleeding andthrombotic risk (8).A Meta -analysis of clinical trial in ACS patients with LMWH versus UFH, has shown a lower rate of major adverse events with Enoxaparin in patients with STEMI(9) .It is also safe in patients receiving hemodialysis (10).Our present study has tried to compare effectiveness and safety of LMWH versus UFH in patients receiving IABP.

Material And Method-

We have conducted our study in accordance with declaration of Helsinki. Patients who underwent coronary artery bypass grafting between Jan20 to Oct 22 and received IABP therapy were analyzed.

Patients who has ejection fraction less than 40% and scheduled for elective CABG were included in the study . IABP was inserted under local anaesthesia in Cardiac ICU 24 hours before the surgery. 30 patients received UFH (a bolus of injection 70 u/kg immediately after IABP, followed by infusion at a rate of 15 u/Kg/hr) and targeted APT T of 50-70 seconds. Another set of 30 patients received LMWH (subcutaneous injection of 1 mg/kg every 12 hrs).Both set of patients were given UFH 3 mg/kg intraoperatively to maintain ACT >300 sec. At the conclusion of procedure, protamine is administered to reverse the anticoagulation of UFH. Maintenance dose of LMWH or UFH was started postoperatively after the bleeding is controlled.Total 60 patients who received prophylactic IABP therapy

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during this period were included in the study. The data was entered prospectively into our database and analyzed retrospectively. IABP used was 7.5F (34 cc ,40 cc) manufactured by Maquet corp., Germany.

Clinical variables and definitions- We have studied clinical variables like age, sex ,diabetes mellitus, hypertension, dyslipidemia, duration of IABP therapy. Hypertension was diagnosed as systolic blood pressure >140mmhg and diastolic blood pressure>90mmhg(12). Diabetes was defined by FBS>126mg/dl or 2 hour plasma glucose>200mg/dl(13). Dyslipidemia was defined by one or more of the following conditions; total cholesterol>200mg/dl, low density lipoprotein cholesterol>100mg/dl,high density lipoprotein cholesterol <40 mg/dl and triglycerides>150mg/dl(14).

Measures of primary interest-The measures of primary interest included ischemic complications and bleeding during IABP. Vascular ultra-sonography was performed to establish arterial thrombosis and embolism in suspected patients. Major bleeding was diagnosed as a hemoglobin decrease by >50mg/l or bleeding that caused hemodynamic shock or life threatening or requiring blood transfusion.

Statistical analysis- Continuous variables are presented as mean+/-standard deviation and analyzed using student t-test. Categorical valuables are presented in percentage and analyzed using chi-square test. Multivariate logistic regression was done to examine association of outcome measures i.e.(major bleeding and ischemia) with the following factors- Heparin type and IABP time. The p-value <0.05 was considered statistically significant.

Result- Baseline characteristics were similar in both groups. There was no significant difference between UFH group and LMWH group (table-1). 2 out of 30 patients receiving UFH developed

ischemic complications. Femoral artery thrombosis in both of them was confirmed by vascular ultrasonography. 1 Out of 30 patients receiving LMWH developed femoral thrombosis. Bleeding events occured in 9 (30%) patients in UFH and 6 (20%) patients in LMWH group (table-2).

Potential factors associated with ischemia- The multivariate logistic regression analysis failed to reveal an association between ischemia and heparin type(UFH and LMWH);P= 0.561 OR;0.483, 95% CI(.041-5.628).Ischemia was not statistically associated with IABP duration(OR; 0.50, 95% CI, 0.818-1.082, p=0.393)(table3).

The association between bleeding and heparin type- Bleeding events (minor) occured in 9(30%) patients in UFH group and 6 (20%)patients in LMWH group. The major bleeding events occured in 3 (10%) patients in UFH and 2 (6.6%) patients in LMWH group. The chi-square test didn't showed the statistical significance between the two groups(p value =0.371 & 0.64)for minor and major bleeding events in UFH and LMWH group respectively (table2). The logistic regression analysis failed to show an association between bleeding and heparin type.**(p = 0.409,OR=0.603 95% CI= 0.181-2.00 for minor bleeding and p = 0.43, OR=0.643, 95% CI= 0.1-4.15 for major bleeding).**

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Table (1)-:-			
Characteristics	UFH	LMWH	p value
Age	60.40 ± 7.82	58.86 ± 6.67	0.418
IABP duration	74.33 ± 9.23	72.83 ± 10.76	0.562
Male	21(53.85)	18(46.15)	0.417
Female	9(42.86)	12(57.14)	0.40
HTN	10(47.62)	11(52.38)	0.787
DM	12(46.15)	14(53.85)	0.602
Dyslipidemia	26(68.42)	12(31.58)	0.001
ischemia	2(66.67)	1(33.33)	0.554
Bleeding	3(60.00)	2(40.00)	0.64
MINOR Bleeding	9(60.00)	6(40.00)	0.371
IABP Time <72	11(44.00)	14(56.00)	0.432
IABP Time ≥ 72	19(54.29)	16(45.71)	

Table(2):-

Characteristics	UFH	LMWH	p value
	N (%)	N (%)	
Ischemia	2(6.67)	1(3.33)	0.554
Bleeding	3(10)	2(6.67)	0.64
MINOR Bleeding	9(30)	6(20)	0.371

Table (3):- Logistic regression analysis of potential factors associated with ischemia			
Characteristics	p value	OR	95% CI
Heparin type	0.561	0.483	0.041-5.628
IABP time (groups <72 h and ≥ 72 h)	0.393	0.501	0.818-1.082
HTN	0.95	0.925	0.079-10.841
DM	0.42	2.75	0.236-32.10

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Dyslipidemia	0.902	1.167	1.00-13.63
Age	0.125	0.901	0.207-1.121
Gender (Male, Female)	0.27	0.25	0.021-2.934

Table (4):- Logistic regression analysis of any bleeding and major bleeding

Characteristics	Any bleeding	Major bleeding
Heparin type	p value = 0.409, OR=0.603, 95% CI= 0.181-2.00	p value = 0.16, OR=1.07, 95% CI= 0.974-1.176
IABP time (groups <72 h and ≥ 72 h)	p value = 0.261, OR=0.965, 95% CI= 0.907-1.027	p value = 0.43, OR=0.643, 95% CI= 0.1-4.15

Discussion - IABP is an effective mean of supporting the failing circulation in patient with poor ventricular function scheduled for surgery. Prophylactic use of IABP in patients with poor ventricular function undergoing surgery has better outcome. Its main effects are reduction of ventricular afterload, improvement of diastolic coronary perfusion and enhancement of subendocardial perfusion(15). In present study, we have compared the clinical complications between use of LMWH & UFH. Use of IABP is associated with certain complications which can be categorized as peripheral ischemia, infection and hematological complications. The incidence of vascular complications reported in literature ranges from 8.7% to 20% (16). In the present study, the rate of ischemia appeared to be lower in patients who received LMWH.(3% vs 6%)for patients receiving UFH. However, the statistical comparison(p= 0.554) and regression analysis failed to reveal significant association between ischemia with heparin type and IABP time. This is similar to finding of Guan et al(17).Jiang et al reported the results of a randomized controlled trial of 153 consecutive patients requiring IABP counterpulsation(18). Here71 patients received anticoagulation with I/v heparin and 82 patients didn't received any heparin. In both groups there was not significant difference between occurrence of limb ischemia.

In our study, the rate of bleeding didn't differ significantly in both groups. However, it was lower in LMWH group (20% vs30%). Regression analysis failed to show any significant association between heparin type and bleeding. However study by Gunan et al had shown that LMWH was associated with less major bleeding(17). A meta analysis also revealed that enoxaparin is associated with reduction in incidence of major bleeding(19). More researchers have considered that enoxaparin can benefit STEMI patient with less bleeding and that nadroparin performs well in preventing venous thromboembolism(20).

New studies are now focusing on the Impella and extracorporeal membrane oxygenator (ECMO) in recent years, but IABP is still first choice for the patient with AMI undergoing surgery because it is easier to use.A recent study had shown that in patients with AMI complicated by cardiogenic shock, IABP and IMPELLA have no significant difference on prognosis(21). Some small size randomized studies had also shown that treatment effect of

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Impella and ECMO was not significantly better in patients with cardiogenic shock compared with IABP (22,23).

Conclusion:-In summary, results of present study show that LMWH can lower the risk of major bleeding and does not increase the risk of ischemia in cardiac surgery patients with IABP support . Small sample size and failure of assessment of D-Dimer and fibrinogen level are some of the limitations of our present study. Further studies with a larger sample size are needed to determine whether LMWH can reduce the mortality and bring more benefits in cardiac surgery patients with IABP support.

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