ORIGINAL ARTICLE

COMPARISON OF ENOXAPARIN AND DALTEPARIN WITH UNFRACTIONATED HEPARIN IN THE TREATMENT OF NON-ST ELEVATED ACUTE CORONARY SYNDROME

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Background: The term non-ST elevated Acute Coronary Syndrome (ACS) encompasses unstable Angina (USA) and non-ST segment elevated Myocardial Infarction (NSTEMI), both of which may end up in death or a fatal/non-fatal Myocardial Infarction (MI). Unfractionated heparin (UFH) has been shown to reduce death and MI in patients with USA and NSTEMI. Of late, there has been a great interest in the role of low molecular weight heparins (LMWHs) in the two conditions and they have been found to be at least as effective as or even more effective than UFH. **Methods:** A total of 90 patients who presented to CCU of Khyber Teaching Hospital, Peshawar with USA or NSTEMI, from June 2008 to June 2009, were enrolled into the study. An equal number of patients were randomly assigned to one of the three arms for 5 days each: Group A received enoxaparin, group B received dalteparin and group C received UFH. The primary end points of the study were all cause mortality, STEMI, refractory USA, recurrent USA or a major bleed. The secondary end point was minor bleeding. **Results:** At the end of the study, there were 2 deaths each in the dalteparin and UFH group, whereas no such event was recorded in the enoxaparin group. Two patients had STEMI in the UFH group but none in the other two groups. **Conclusion:** LMWHs are far more superior to unfractionated heparin.

Keywords: Acute Coronary Syndrome, Coronary Artery Disease, Atherosclerosis, Unstable Angina, Myocardial Infarction, Unfractionated Heparin, low-molecular weight heparin

INTRODUCTION

Although useful in the treatment of non-ST elevated ACS, unfractionated heparin has several limitations. Several clinical trials have served to highlight these limitations.[1–3]

There is a wide variation in anticoagulant effect of unfractionated heparin (UFH). Bioavailability is limited and uncertain,[4] often resulting in too much or too little anticoagulation and necessitating vigilant laboratory monitoring and dose adjustments.[5] Both the antithrombin activity and the anti-factor Xa activity of UFH are neutralised by platelet factor 4 (PF4)[6], which is abundantly expressed by activated platelets.[7] UFH inhibits circulating thrombin but not that bound to fibrin[8] or tissue.[9,10] Ischaemia may recur soon after discontinuation, probably because of accelerated thrombin generation and platelet activation (rebound phenomenon).[11] Hemorrhagic complications may occur that are related not only to an antithrombin effect but also to its effect on platelet function and vascular permeability.[12] Finally it may lead to osteoporosis[13] and heparin-associated thrombocytopenia and thrombosis.[14]

The narrow risk-benefit ratio of unfractionated heparin led to a search for better alternatives. One such treatment emerged through the depolymerization of UFH to low-molecular-weight fragments (LMWHs).[15] LMWHs offer the advantages of a stable and predictable anticoagulant response to a given dose, eliminating the need for laboratory monitoring,[16] and a much simpler subcutaneous route of administration. The decision to use a LMWH would be even more attractive if it were also more efficacious than intravenous UFH, especially in conditions as serious as the acute coronary syndromes (ACS). The aims and objectives of the present study were to evaluate the safety and efficacy of the LMWHs in the local population. Secondly, we wanted to compare the efficacy of the LMWHs and UFH.

MATERIAL AND METHODS

Our study was an unblinded, comparative, randomized trial of 90 consecutive patients who presented with USA or NSTEMI to CCU of Khyber Teaching Hospital, Peshawar from June 2008 to June 2009. All patients aged more than 18yrs, both male and female, were included in the study. The following patients were excluded from the study: patients with acute STEMI, recent Coronary Artery Bypass Graft (CABG) or any major surgery within 2 months, Left Bundle Branch Block (LBBB), hepatic disease, platelet count of $<100,000/cm^3$, pregnancy or lactation, angina secondary to acute pulmonary oedema, tachyarrhythmia, valvular heart disease, thyrotoxicosis and anaemia (Hb <10gm/dl), presence of a terminal illness, oral anti-coagulant within the previous 5 days or

treatment with IV therapeutic doses of heparin within the last 24 hours and patients who have contraindications to anti-coagulation (eg. active peptic ulcer or any other active bleeding), infective endocarditis, uncontrolled hypertension (systolic BP > 200mmHg, diastolic BP >120mmHg), stroke within 6 months, proliferative diabetic retinopathy, acute or chronic renal failure with serum creatinine >1.8 mg/dl.

The patients included were randomly assigned to three treatment arms, each comprising of 30 patients. The study drugs were to be administered for a period of 5 days to all the patients.

Group A was assigned to Enoxaparin in a dose of 1mg/kg-body weight, subcutaneous twice daily.

Group B received Dalteparin in a dose of 100u/kg-body weight, subcutaneous twice daily.

Group C received UFH in a weight adjusted protocol of 80 u/kg-body weight followed by 18u/kg/hour i.v infusion that was adjusted to an activated Partial Thromboplastin Time (aPTT) of 1-half to 2.3 the control value using the Rasckhe Protocol (1993) [17]. The aPTT was measured at baseline and then every 6 hours until two consecutive aPTT values were in the therapeutic range. Thereafter it was monitored on a daily basis as well as 6 hours after any dosage change.

Primary end points:

1. **Death** (All-cause mortality).
2. **Q-wave myocardial infarction**
3. **Refractory USA:** defined as ongoing ischaemia with ongoing signs (dynamic ST segment deviation) or symptoms (chest pain) despite maximal anti-ischaemic and anti-coagulant therapy (including IV Glyceral Trinitrate) for a period of more than 24 hrs.
4. **Recurrent USA**: defined as necessitating either of the following:
   - An extended stay beyond the pre-specified period of 5 days, or requiring readmission during the followed up period
   - Made an emergent/urgent cardiac catheterisation mandatory
5. **Major bleeding:** defined as a bleed, resulting in
   - Death of the patient
   - A fall in Hb of 3 gm/dl or more
   - A retroperitoneal, intra-cranial or intra-ocular haemorrhage

Secondary end points:

Minor bleeding: defined as spontaneous haematomas or bleeding at puncture sites.

Patients were evaluated for primary and secondary end points, on day 6 (time of discharge), and at one month after discharge from the unit.

Analysis of data was performed using SPSS-13 statistical package. Outcomes were compared using the paired *t*-test.

RESULTS

The initial qualifying event was unstable angina in 96.67%, 100%, and 96.67% of patients and non-STEMI in 3.33%, 0% and 3.33% of patients in the UFH group, enoxaparin group and dalteparin groups respectively.

The composite of all the primary end points were compared between the three treatment arms, at the end of hospitalization and over all study period. At day 6, there were 4, 5, and 2 events and at the end of the study period, there were 11, 7, and 5 events in the standard heparin (Group A), enoxaparin (Group B), and dalteparin (Group C) group respectively (Table 1). When the paired t-test was applied, it was found that the major events were non-significantly less frequent in Group C than in Group A (p=0.2952) or Group B (p=0.1257) as shown in Table 2 and 3. Turning to the double composite end point of death and myocardial infarction there were 4, 0, and 2 events in Group A, B and C respectively during the overall study period.

In group A, there were 2 patients who died and yet another 2 patients who sustained MI. While both the deaths occurred during the first 24 hours of hospitalization, the 2 patients that had an infarct had these events during the follow-up period of the study. In Group B, although there were no MIs and death in this group, there were nonetheless 2 patients who had refractory USA. In Group C, there were 2 deaths and interestingly these too occurred early during the hospitalization period, both within the first 48 hours.

Recurrent USA was 2, 3, and 0 at the end of hospitalization period and 7, 5, and 3 at the end of the study period in Groups A, B and C respectively.

There was no incidence of any major haemorrhage. There were 8, 22 and 20 incidences of minor bleeding in Groups A, B and C respectively.

DISCUSSION

An antithrombotic agent is an important element in the therapy of ACS, regardless of whether ST elevation is present. However, there are important limitations associated with UFH, which prompted a search for alternative compounds.[18] One promising class of agents was the LMWHs, which offered potential advantages in terms of clinical efficacy, safety, and ease of use in the setting of ACS.[19]

The LMWHs enoxaparin and dalteparin have shown superior and equivalent efficacy, respectively, over UFH in USA or NSTEMI.[20] In a number of large clinical trials, the superiority of enoxaparin over UFH has been demonstrated.[21,22] Our study has also revealed similar results.

Table-1: Comparison of the composite and individual primary end points in the three treatment groups (n=90)

Time point	End point	Standard Heparin (Group A) n=30	Enoxaparin (Group B) n=30	Dalteparin (Group C) n=30
Events recorded at the time of discharge from the unit (day6)	Death	2	-	2
	Myocardial infarction	-	-	-
	Refractory USA	-	2	-
	Recurrent USA	2	3	-
	Major bleeding	-	-	-
	Composite end-point	4 (13%)	5 (17%)	2 (7%)
One month follow-up period (after hospital discharge)	Death	-	-	-
	Myocardial infarction	2	-	-
	Refractory USA	-	-	-
	Recurrent USA	5	2	3
	Major bleeding	-	-	-
	Composite end-point	7 (23%)	2 (7%)	3 (10%)
Over-all study period	Death	2	-	2
	Myocardial infarction	2	-	-
	Refractory USA	-	2	-
	Recurrent USA	7	5	3
	Major bleeding	-	-	-
	Composite end-point	11 (37%)	7 (23%)	5 (17%)

USA-unstable angina (Data are expressed as number or (approximate) percent of patients)

Table-2: Comparison of Standard unfractionated Heparin with Enoxaparin

Type of heparin	Composite of all primary end points (end of hospitalization)	Composite of all primary end points (over all study period)	Mean±SD	*p*
Standard unfractionated heparin	4	11	7.5±4.9	0.656
Enoxaparin	5	7	6.0±1.4	0

Table-3: Comparison of Standard unfractionated Heparin with Dalteparin

Type of heparin	Composite of all primary end points (end of hospitalisation)	Composite of all primary end points (over all study period)	Mean±SD	*p*
Standard unfractionated heparin	4	11	7.5±4.9	0.295
Dalteparin	2	5	3.5±2.1	2

Efficacy of LMWH against UFH has been tested in different trials. The FRIC (FRagmin In unstable Coronary artery disease) trial randomized 1,482 patients with NSTE ACS to dalteparin or UFH and there was no significant difference in the composite endpoint of death, MI or recurrent angina in the two groups (7.6% UFH vs 9.3% dalteparin, p=0.33).[23]

Another large LMWH and UFH comparison study, the ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave Coronary Events) trial, randomized 3,171 patients and demonstrated a significant reduction in death, MI or recurrent angina at 14 days in the enoxaparin group compared to UFH group (16.6% vs 19.8% p= 0.019). This significant benefit was sustained at 30 days (p=0.016) and at one year (32.0% vs 35.7% p=0.022).[24,25]

Based on the available evidence, the 2007 ACC and AHA guidelines list the use of either LMWH or unfractionated heparin as a class I recommendation for the treatment of UA/NSTEMI (level of evidence, A).[26]

CONCLUSION

Both the LMWHs fared well in our study. They were safe, effective and easy to administer. With regards to UFH, the reservations so often expressed about it, have strengthened with this study. In my view, the LMWHs have been a blessing for the developing world, not just for the reason that their use does not involve any technical or practical hurdles, but also because they are more effective and safe as compared to the UFH.

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