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Original Article

Pharmacology Section

Comparative Evaluation of Efficacy, Safety and Haemostatic Parameters of Enoxaparin and Fondaparinux in Unstable Coronary Artery Disease

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ABSTRACT

Aim: To compare the safety and efficacy of Enoxaparin (EX) and Fondaparinux (FD) in patients with Unstable Coronary Artery Disease (UCAD).

Materials and Methods: A prospective, open label, randomized comparative study was designed to study the comparative efficacy and safety of EX and FD in UCAD patients. Recovery, recurrence, major and minor bleeding and biochemical investigations were evaluated and compared among two arms.

Results: The baseline demographic characteristics were similar in both groups, with mean age of 56.05 and 56.05 years in EX and FD group respectively. Recovery was equal in two arms. Recurrent MI or angina was seen numerically more in EX group, but it did not statistically vary from that in the FD group. Incidence of haemorrhage was similar in both groups at 9 days, but at 30 days, EX showed a higher incidence ($p<0.05$). Deaths were prevented in both the treatment arms. Bleeding parameters such as BT, CT and platelet count were not altered in both groups.

Conclusion: FD appeared to be better than EX in efficacy, as was indicated by a numerically more decrease in recurrence of angina or MI. FD regimen group also had better safety profile, as there was no incidence of haemorrhage at 30 days Therefore, we conclude that FD is an attractive option than EX in UCAD patients.

Keywords: Anticoagulants, Low molecular weight heparin, Enoxaparin, Fondaparinux

INTRODUCTION

Cardiovascular diseases remain to be the most common cause of death in the world. This epidemic is receding in industrialized countries and in many low and middle income countries [1]. Among CVD, IHD is a leading cause of death and morbidity in all age-groups [2]. Unstable angina and non-ST-segment elevation myocardial infarction are collectively, known as Unstable Coronary Artery Disease.

Thrombosis is of prime significance, as was indicated by its presence at the event site [3], in unstable CAD and by improvement in clinical outcome, after antithrombotic therapy. Platelet activation and coronary vasoconstriction are other events that contribute to the initiation of unstable CAD. Over the last two decades, major improvements has been achieved in the management of unstable coronary artery disease by anti platelet agents, anticoagulants, thrombolytic therapy, combined with mechanical revascularization or reperfusion [4].

Before the introduction of aspirin as antithrombotic agent, the mortality was quite high in patients with unstable coronary heart disease [5,6]. Until recently, Aspirin was the only available, clinically effective antiplatelet drug [3]. But, Aspirin had its own limitations, with few absolute contraindications like allergy, active bleeding and resistance, which led to introduction of heparin.

Unfractionated heparin (UFH) is commonly used in patients with unstable CAD. However, UFH exhibits an unpredictable anticoagulant effect which requires frequent monitoring and it has low bioavailability due to high protein binding and induced thrombocytopaenia [7]. These limitations can be overcome with structural, molecular weight variations, with introduction of low molecular weight heparin (LMWH). Thus, LMWH preparations (Enoxaparin, Dalteparin, Nadoparin, and Reviparin) relate to better clinical outcome variability.

FD sodium, which is a synthetic, sulfated pentasaccharide, selective factor Xa inhibitor, is indicated for preventing thrombus formation in patients with acute coronary syndromes, including those with ST-segment Elevation Myocardial Infarction (STEMI), non-STEMI (NSTEMI), or unstable angina [8-11].

The comparative efficacy and safety of EX, a commonly used LMWH and fondaparinux in unstable coronary artery disease, has not been studied in detail, in Indian population. Therefore, the present study was undertaken to evaluate the safety and efficacy of EX and FD as antithrombotics in unstable CAD patients.

MATERIALS AND METHODS

This prospective open label, randomized comparative study was conducted in Post-graduate Department of Pharmacology, in collaboration with the Department of Cardiology, over a period of one year, starting from 1st January, 2010 to 31 December 2010. The study protocol was approved by the Institutional Ethics Committee vide no. Pharma/ IEC/ 2010/91, Dated: 15-03-2010. Written informed consents were obtained from all the subjects and all principles of bioethics were followed.

Total of 200 patients were screened in study. Twenty patients did not meet the inclusion criteria. One-hundred eighty patients were included in study and they were divided into two groups of 90 patients each, into i.e., EX group (n=90) and FD group (n=90). All the randomized patients completed the study and no drop-out was recorded for any reason.

Inclusion Criteria

Newly diagnosed patients reporting to the medical emergency (cardiac unit), suffering from unstable angina or non-ST-segment elevation MI, of either sex, who showed at least one the following inclusion criteria, were included in the study:

Patients with unstable coronary artery disease, with at least 1 mv (millivolt) new transient or persistent ST-depression or at least 1 mv new transient or persistent T-wave inversion on ECG, those patients with negative 10 hour troponin-T assay, who were classified to have unstable angina and those with a positive 10 hour troponin-T assay, who were considered as NSTEMI.

Exclusion Criteria

Patients were excluded from the study, if they had ST segment elevation, left bundle branch block at presentation, development of new Q-waves, permanent pacemakers, acute pericarditis, if they were on on-going treatment with either heparin or oral coagulants, if they had a history of any recent clinical infection and evidence of hospital acquired infections, malignancy, active peptic ulcer disease or gastrointestinal bleeding within the preceding three months, known hypersensitivity to either EX or FD, concurrent major renal and hepatic diseases.

Study Design and Drug Allocation

Patients were divided into two groups. Group 1 was given Enoxaparin (Clexane)® in the dose of 1 mg/kg body weight, subcutaneously, twice daily and Group 2 was given Fondaparinux (Arixtra by GSK)® in a dose of 2.5 mg/kg body weight, once daily, subcutaneously. Patients were followed for 9 days for primary endpoints and for 30 days for secondary endpoints. Randomization of the treatment was performed with the help of a table of random numbers. The baseline anti-anginal treatment as per the treatment protocol of hospital was given to both the treatment arms (nitrates, aspirin, clopidogrel, beta blockers)

Efficacy endpoints were denoted by recovery or recurrence. Recovery was defined if the patients remained uneventful throughout the study period. Recurrence was defined when there were repeat occurrences of MI, or angina. If these events happened within first 9 days on EX and FD treatment, these were classified as primary endpoints, while a recurrence or any fatal outcome at 30 days was taken as secondary endpoints.

Safety endpoints comprised of major and minor haemorrhagic episodes [12]. Major haemorrhage criteria included haemorrhage which was clinically overt, associated with death, requiring transfusion of more than 2 units of RBCs or whole blood, greater than 3mg/dl fall in haemoglobin, retroperitoneal, intracranial or intra-ocular haemorrhage and macroscopic haematuria. While minor haemorrhage included epistaxis lasting >5 minutes or requiring intervention, ecchymosis or haematoma larger than 5 cms, micro-scopic haematuria which was not associated with urinary catheter trauma or UTIs, subconjuctival haemorrhage requiring drug discontinuation and gastrointestinal haemorrhage not related to intubations or nasogastric tube placement.

Bleeding times (normal value 1-3 minutes), clotting times (normal value 3-9 minutes) and platelet counts (normal value 1.5-4.5 lakhs / cu. mm.) were also assessed.

STATISTICAL ANALYSIS

Data was analyzed using computer software, Microsoft Excel. Data was recorded either in n (%) or mean ± standard error of mean (SEM) and unpaired test was applied to assess the statistical significance. A p-value equal to or less than 0.05 was taken as significant.

RESULTS

The two groups matched in all the baseline characteristics. Males (76.11%) were more in number than females (23.89%) In EX group, maximum number of patients were in 48-57 years age group (33.33%) and this was similar to that in FD group [Table/Fig-1].

One-hundred seventy one patients in total, had risk factors (128 male and 43 females). Smoking was a major leading risk factor, followed by hypertension and diabetes in patients of UCAD in both groups [Table/Fig-2].

Baseline electrocardiogram characteristics revealed that 84.44% were non-ST elevation myocardial infarction cases and that 15.5% were unstable angina cases in EX group and that 93.33% were NSTEMI cases and 6.67% were unstable angina cases in FD group [Table/Fig-3].

At day 9, in EX group, 6.6% of the patients had recurrences, whereas 90% showed recovery. In FD group, at day 9, 4.4% of the patients had recurrences, while 94.4 % recovered. At day 30, in EX group, 4.4% of the patients had recurrences, while 84.4% showed recovery. At day 30, in FD group, 3.3 % had recurrences and 96.7% recovered [Table/Fig-4].

Comparison of EX versus FD at day 9 and 30 showed no significant variations in achieving recovery or recurrence, although FD appeared to be numerically better in FD group. Comparison of EX and FD at day 9 and day 30 remained non-significant.

Age group (Years)	Enoxaparin group		Fondaparinux group		Total	
	Male	Female	Male	Female	Male	Female
18-27	1	0	1	0	2	0
28-37	7	2	5	3	12	5
38-47	11	1	10	0	21	1
48-57	16	14	17	15	33	29
58-67	23	0	24	0	47	0
68 and Above	12	3	10	5	22	8
Total	70	20	67	23	137 76.1%	43 23.8%

[Table/Fig-1]: Age and Sex Profile of Patients of Unstable Coronary Disease

Risk Factors	Enoxaparin group		Fondaparinux group		Total	
	Male	Female	Male	Female	Male	Female
Smokers	50	3	48	2	98	5
Diabetic	30	7	30	5	60	12
Hypertension	42	8	40	10	82	18
Family History	5	3	7	2	12	5
Single factor	57	15	56	17	103	32
> than two factors	13	5	12	6	25	11

[Table/Fig-2]: Risk factors in patients of unstable coronary disease

Age in Yrs	NSTEMI Enoxaparin Fondaparinux	Unstable Angina Enoxaparin Fondaparinux	Total
18-27	1 1	0 0	2
28-37	8 7	1 1	17
38-47	10 8	2 2	22
48-57	28 30	2 2	62
58-67	20 24	3 0	47
68 and Above	9 12	6 3	30
	76 82	14 8	180

[Table/Fig-3]: ECG findings in patients of unstable coronary disease

Study Out come	Enoxaparin (n 90)		Fondaparinux(n90)	
	Day 9	Day 30	Day 9	Day 30
Recovery	81(90%)	76(84.4%)	85(94.4%)	87(96.7%)
Recurrent MI/Angina	6(6.6%)	4(4.4%)	4(4.4%)	3(3.3%)
Haemorrhage	3(3.3%)	10(11.1%)	1(1.1%)	0*
Death	0	0	0	0

[Table/Fig-4]: Efficacy and safety endpoints in enoxaparin and fondaparinux groups at day 9 and 30. *p>0.05

Parameter	Enoxaparin			Fondaparinux			p-value
	0 day	9 day	30 day	0 day	0 day	30 day	
Mean platelet count x10^9	239±59.2	240.2±55.7	253.1±60	285±80.9	263±73.1	277.8±50	>0.05
Mean clotting time(min)	5.5±0.5	5.45±0.3	5.48±0.4	5.6±0.7	5.6±.3	5.5±0.7	>0.05
Mean bleeding time	2.6±.5	2.67±0.6	2.7±0.6	2.8±.5	2.8±0.3	2.8±.3	>0.05

[Table/Fig-5]: Laboratory Parameters in Enoxaparin and Fondaparinux Groups

Major haemorrhage of 3.3% and 11.11% was observed in EX group, respectively, in comparison to 1.1% and 0% at day 9 and 30 respectively, in FD group, on comparing both groups on these lines No death was observed in any of the treatment arms. Laboratory parameters: platelet counts, clotting time and bleeding time were not significantly altered in both treatment group arms (p>0.05). On comparison, no significant difference was observed [Table/Fig-5].

DISCUSSION

UCAD is still associated with high mortality and morbidity despite considerable progress in therapy [13]. The combined use of anti-coagulants, e.g., UFH, LMWH, direct thrombin inhibitors, antiplatelet agents, glycoprotein IIb/IIIa inhibitors and undertaking an invasive strategy in patients with of UCAD, reduce ischaemic events, but at the same time, they may increase the risk of bleeding [14].

Unfractionated heparin has poor bioavailability and marked variability in anticoagulant response and it requires monitoring [15]. Because of these disadvantages, LMWHs (Enoxaparin, Dalteparin) which are obtained by chemical or enzymatic depolymerization of UFH have been introduced, they have better pharmacological properties, which are more predictable, have sustained anticoagulation with one or two dosage and they do not require laboratory monitoring. Fondaparinux is a selective factor Xa inhibitor [16].

In the current study, safety and efficacy of EX and FD in unstable coronary artery disease were studied. Recurrent myocardial infarction/angina episodes were recorded in 6.6% of the patients in EX group and in 4.4% patients in FD group at day 9 and in 4.4% cases in EX group and in 3.3% cases in FD group at 30 days. Similar results were observed in OASIS-6 trial, wherein FD showed a significant reduction in overall recurrences of MI and stroke. The reduction of death alone was 17% at 1 month (p=0.02) and it was 11% at 6 month (p=0.05).Moreover, the risk of stroke at 6 months was significantly (p=0.04) lower in the FD group (127/10,057, 1.3%) than in the EX group (161/10, 021, 1.7%) [17]. FD, in acute coronary artery disease, in doses of 2.5 mg/day, has been found to be non inferior to EX in reducing death and ischaemic events at day 9 [18].

The results of the present study on clinical recovery revealed 90% and 94.4% cases at day 9 and 84.4% and 96.7% cases at day 30 in EX and FD groups, respectively. These observations were in agreement with the findings of studies where FD was found to be comparable to EX in efficacy and ischaemic events, while studying patients with non-ST-elevation MI and unstable angina, as well as, those who were undergoing percutaneous coronary interventions [19,20].

Similarly, a recent trial suggested that a lower intensity of anti-coagulation (FD 2.5 mg/day as compared to EX 1 mg/kg bodyweight, twice daily) may be sufficient to prevent recurrent ischaemic events and death in patients with ACS, who were concurrently being treated with aspirin [21].

FD has been found to be better in reducing long-term mortality than EX [12,17]. However, in the current study, long-term mortality was not observed, as the study was only of 30 days duration.

Haemorrhage reduced in FD group in the current study, with significant reduction at 30th day (p<0.05) as compared to that in EX group. In OASIS-5 trial, major bleeding significantly reduced on day 9 with FD as compared to EX (2.4% vs 5.1%). Major bleeding was reduced with FD within hours after administration of first dose of study drug. While on day 30, FD was again found to be significantly superior to EX [12].

FD has been shown to be superior to EX in reducing the risk of major bleeding and in improving long-term mortality [12,17]. The variation from the present study, in form of early recording of markedly lower rate of major bleeding at nine days with FD, may have probably occurred because of small number of patients, different socio-demographic profile, duration of study and different inclusion criteria. FD has been shown to reduce major bleeding by 41% (3.4% versus 2.1%; HR, 0.59; P<0.00001) and it has a more favourable net clinical outcome than heparin (11.1% versus 9.3%; HR, 0.83; P<0.0001) [22].

FD's therapeutic superiority over EX in ACS relates to a reduced risk in all-cause mortality at 90 to 180 days and a better safety profile in terms of reduced incidences of major and minor bleeding [23].

The results of the current study suggest favourable effect with regards to bleeding complications and mortality in FD group and they could be explained on the basis of pharmacodynamic profile of the drug. FD has no direct activity against thrombin. Unlike conventional antithrombotics such as LMWHs, EX acts on multiple targets within a coagulation cascade, thereby increasing the propensity of causing more bleeding complications by conventional antithrombotics. Other potential explanations can be differences in intensity of anticoagulation and increased contact pathway activation of the coagulation system in patients who are treated with selective factor Xa inhibitor i.e. fondaparinux.

Though, the coagulation parameters were not significantly altered in the current study in both treatment groups, importance of the anticoagulant monitoring could not be underestimated and it remains to be of paramount importance in preventing complications. The results of the current study on the various coagulation parameters (BT, CT and Platelet Count) suggested no significant variations from the baseline in EX and FD arms respectively [Table/Fig-5]. Anticoagulant monitoring is extremely important, and inappropriate testing may lead to complications.

LIMITATIONS OF THE STUDY

However, the recommended biochemical investigation for the monitoring of the two drugs remains to be chromogenic anti-Xa heparin assay for EX and FD, which was not done due to the resource limited settings. The correlation of these biochemical parameters (platelet aggregation, bleeding time and prothrombin time and international normalized ratio) with the haemorrhagic events could not be studied, which remains the limitation of the current study. The study was of a short duration, with less number of patients, without evaluating the long-term effects on mortality outcome and inability to include patients with ST-elevation MI which may have altered the outcome of the study.

CONCLUSIONS

On comparative evaluation, FD appears to be better than EX in view of efficacy, as was indicated by numerical decrease in recurrence of angina or MI and safety, as was indicated by significant decrease in haemorrhage at day 30.

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