



## COMPARATIVE STUDY ABOUT THE EFFICACY OF LOW MOLECULAR WEIGHT HEPARIN WITH UNFRACTIONATED HEPARIN (ENOXAPARIN) IN CORONARY HEART DISEASE PATIENTS.

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### ABSTRACT

**BACKGROUND:** Coronary heart disease is a medical emergency most often caused by occlusive coronary thrombus. Approximately 30% of patients with coronary heart disease die, one half of them within the first hour of symptom onset. Mortality can be significantly reduced by rapid management. Heparin is injectable rapidly acting anticoagulant. Aim of present study was to evaluate the effect of low molecular weight heparin (LMWH) and unfractionated heparin specifically in patients with coronary heart disease and to compare the effects of low molecular weight heparin with unfractionated heparin and identify the best of either type of heparin.

**TYPES OF STUDY:** This study was designed on 60 patients arranged in two groups i.e., group A and group B. Each group containing equal number of patients. Patients were collected from National Institute of Cardiovascular Diseases (NICVD) and respected study was followed in the Department of Pharmacology and Therapeutics, BMSI, JPMC, Karachi, for the period of three months. Either patient received 1 mg of Enoxaparin (LMWH) per kg body weight administered subcutaneously twice daily or continues I/V unfractionated heparin. Therapy was continued for minimum 48 hours to a maximum for 8 to 10 days and follow-up data was collected on important coronary endpoints such as hemorrhage, myocardial infarction, recurrent angina and death, over a period of 90 days.

**RESULTS:** Incidence of recurrence in group A - myocardial infarction with low molecular weight heparin, hemorrhage observed in 6 (20%) patients and in group B - myocardial infarction with unfractionated heparin, hemorrhage observed in 15 (50%) patients. Similarly, incidence of re-infarction in group A, found in 8 (26%) patients and in group B, it was found in 17 (56%) patients. Similarly, incidence of recurrent angina in group A, observed in 8 (26%) patients and in group B, it was observed in 17 (56%) patients. Similarly, incidence of death occurred in 5 (16.6%) patients and in group B, incidence of death occurred in 14 (46.6%) patients. When compared between group A and B, more incidence of complications are observed in group B than group A.

**CONCLUSION:** Results of this study showed that low molecular weight heparin is more effective in comparison with unfractionated heparin, as it is easy to administer, does not require any monitoring as required in unfractionated heparin. Low molecular weight heparin has fewer side effects. The safety and efficacy of low molecular weight heparin is better than that of unfractionated heparin in coronary heart disease patients.

### KEY WORDS:

LMWH = Low molecular weight heparin  
UFH = Unfractionated heparin

### INTRODUCTION

The Coronary heart disease is a medical emergency that is most often caused by occlusive coronary thrombus. Approximately, 30% of patients with coronary heart disease die, one-half of them within the first hour of symptom onset. Mortality can be significantly reduced by rapid transport to hospital.

Coronary heart disease is the commonest cause of cardiovascular disability and death. Men are more often effected than women, by an overall ratio of 4:1, but before age 40 years the ratio is 8:1 and beyond age 70 years, it is 1:1. In men the peak incidence of clinical manifestation is at age 50 to 60 years, in women at age 60 to 70 years<sup>1</sup>.

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The site of discomfort is usually retrosternal, but radiation is common usually occurs down the ulnar surface of the left arm, commonly the right arm and outer surfaces of both arms are also involved<sup>2</sup>.

The risk factors of myocardial infarction are atherosclerosis, hypertension, hypercholestraemia, cigarette smoking, diabetes mellitus, family history, physical inactivity and use of oral contraceptive.

Diagnosis depends upon history, presenting symptoms and clinical examination, but the electrocardiogram investigations are required to reach an ultimate diagnosis<sup>3</sup>.

Heparin is a heterogeneous mixture of sulfated mucopolysaccharide. It binds to endothelial cell surfaces; its biological activity is dependent upon the plasma protease inhibitor anti-thrombin-III.

Heparin prolongs clotting time of blood by preventing fibrin formation. Heparin increases the activity of anti-thrombin-III, anti-thrombin-III inhibit the conversion of prothrombin to thrombin by thromboplastin<sup>4</sup>.

There are two types of heparin, (1) the high molecular weight heparin and (2) the low molecular weight heparin. The high molecular weight fraction of heparin is 5000 to 30000 daltons and the low molecular weight fraction of heparin is 2000 to 6000 daltons.

### Objective of study:

AIMS OF PRESENT STUDY WERE:

1. To evaluate the effects of low molecular weight heparin and unfractionated heparin specifically in patients with coronary heart disease.
2. To compare the effects of low molecular weight heparin with unfractionated heparin in patients of coronary heart disease.
3. To identify the best of either heparin in coronary heart disease.

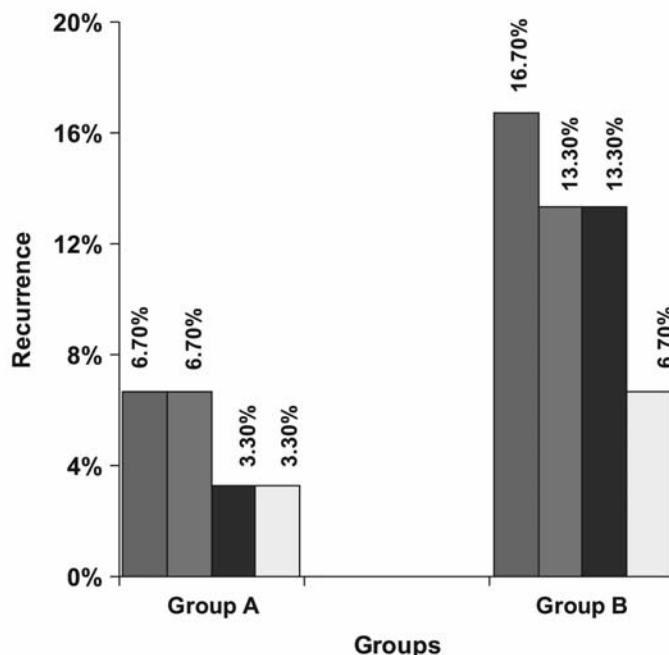
### MATERIAL METHODS

This study was carried out in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute (BMSI), JPMC, Karachi.

The patients selected were the admitted cases of coronary heart disease patients at the National Institute of Cardiovascular Diseases (NICVD), Karachi, for the period of three months.

This study was carried on 60 registered patients arranged in two groups, each group contain equal number of patients i.e. 30. The following inclusion and exclusion criteria were used to include or exclude the patients in this study.

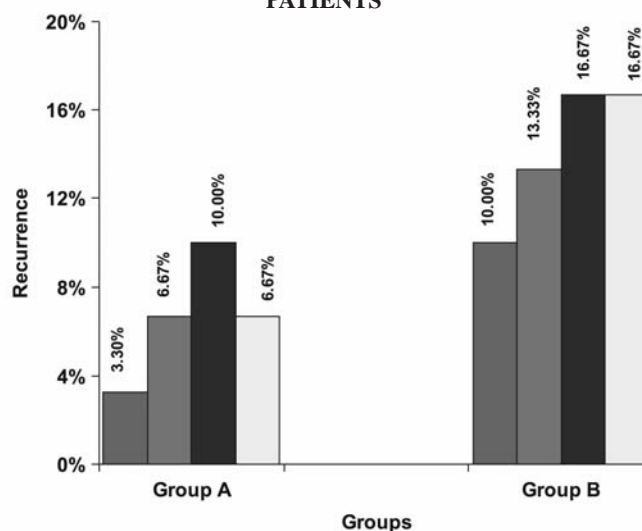
**FIGURE – 1**  
**INCIDENCE OF HAEMORRHAGE IN CORONARY HEART DISEASE.**



KEY:

- Day 0-5
  - Day 15
  - Day 45
  - Day 90
- Group A = Coronary heart disease patients with LMWH  
 Group B = Coronary heart disease patients with UFH  
 LMWH = Low molecular weight heparin  
 UFH = Unfractionated heparin

**FIGURE – 2**  
**INCIDENCE OF RECURRENT ANGINA IN CORONARY HEART DOISEASE PATIENTS**



KEY:

- Day 0-5
  - Day 15
  - Day 45
  - Day 90
- Group A = Coronary heart disease patients with LMWH  
 Group B = Coronary heart disease patients with UFH  
 LMWH = Low molecular weight heparin  
 UFH = Unfractionated heparin

**Inclusion Criteria**

1. The patients were of either sex between the age 20 to 70 years.
2. Patients with established diagnosis of myocardial infarction.

**Exclusion Criteria**

1. Patients suffering from renal disease.
2. Patients suffering from liver disease
3. Pregnant women
4. Patients with any underlying pathology or debilitating disease.
5. History of alcoholism/or any other addiction.
6. Patients having contra-indication to the use of these drugs.

After examination the patients of coronary heart disease were selected according to the inclusion criteria. Each patient was followed up for three months.

The information like serial number, registration number, bed number, date of case entry, patient's name, age, sex, history of hypertension, family history, history of diabetes mellitus, occupation, address, presenting complaints, present medication, blood pressure, pulse rate, respiratory system, gastrointestinal tract, central nervous system, electrocardiogram, and laboratory investigations of each patient was recorded on a proforma especially designed for this study.

The selected patients were divided in two groups. Each group contained equal number of patients, i.e. 30.

**GROUP-A**

Patients with established diagnosis of coronary heart disease with low molecular weight heparin Enoxaparin (Clexane) (dose 1 mg/kg body weight) 12 hourly subcutaneous.

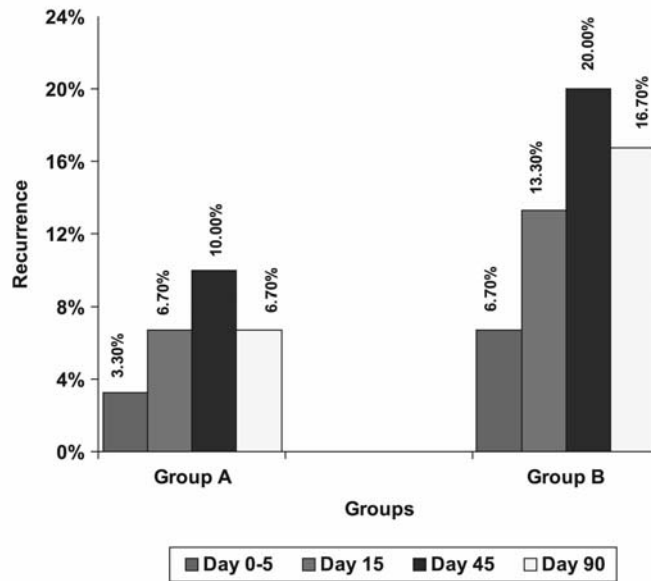
**GROUP-B**

Patients with established diagnosis of coronary heart disease with unfractionated heparin; initial dose 60-80 u/kg stat (bolus) maximum 5000 u bolus, initial 1000 u/hour initial infusion (14-18 units/kg/hour I/V infusion).

Therapy was continued for a minimum of 48 hours to a maximum of 8-10 days. All the patients were dispensed medication according to their group affiliation as given above. Follow up data was collected on important coronary endpoints such as hemorrhage, recurrent myocardial infarction and deaths.

The patients were observed daily for blood pressure, pulse rate, ECG, prothrombin time, and APTT during their admission period. Patients were attended the Department of

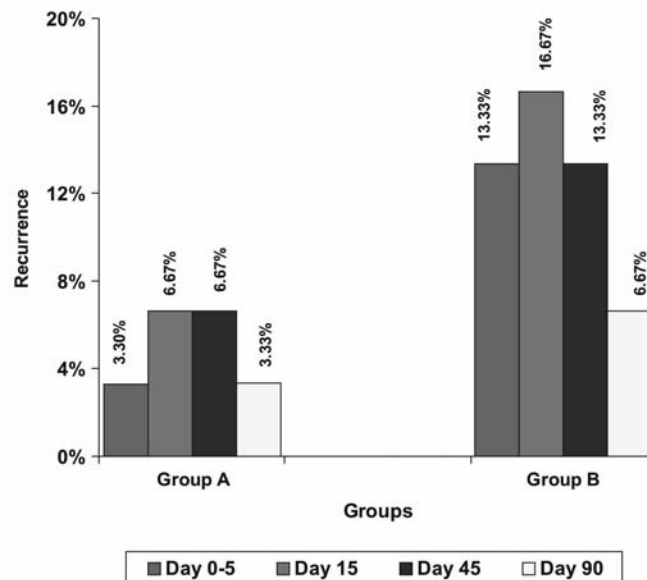
**FIGURE – 3**  
**INCIDENCE OF RE-INFARCTION IN CORONARY HEART DISEASE PATIENTS**



KEY:

- Group A = Coronary heart disease patients with LMWH
- Group B = Coronary heart disease patients with UFH
- LMWH = Low molecular weight heparin
- UFH = Unfractionated heparin

**FIGURE – 4**  
**INCIDENCE OF DEATH IN CORONARY HEART DISEASE PATIENTS**



KEY:

- Group A = Coronary heart disease patients with LMWH
- Group B = Coronary heart disease patients with UFH
- LMWH = Low molecular weight heparin
- UFH = Unfractionated heparin

Pharmacology and Therapeutics, BMSI, JPMC, regularly fortnightly basis for three months follow up.

## RESULTS

**Incidence of Haemorrhage in Coronary heart disease Patients.**

Group A, coronary heart disease patients with low molecular weight heparin, from day 0-5 occurred 2 (6.67%) patients, Day 15 occurred 2 (6.67%) patients while on Day 45 occurred 1 (3.33%) and Day 90 occurred 1 (3.33%) patient; total 6 (20.00%) patients were observed.

Similarly, in group B, coronary heart disease patients with unfractionated heparin from Day 0-5 occurred 5 (16.67%), on Day 15 occurred 4 (13.33%) and Day 45 occurred 4 (13.33%) patients, and on Day 90 occurred 2 (6.67%) patients. Over all 42 patients were observed with a P value <0.05 that showed significant group-wise comparison. Results showed that low molecular weight heparin is safer than unfractionated heparin because of less complication of haemorrhage occurs as compared with unfractionated heparin (As depicted in Figure-1).

**Incidence of Recurrent Angina in coronary heart disease Patients.**

Group A, coronary heart disease patients with low molecular weight heparin, from day 0-5 found 1 (3.33%) case, on Day 15 found 2 (6.67%) cases, Day 45 found 3 (10.00%) cases, and on Day 90 found 2 (6.67%) cases. Total 8 (26.67%) cases were observed.

Similarly, coronary heart disease patients with unfractionated heparin in group B, from Day 0-5 occurred 3 (10.00%) cases, on Day 15 occurred 4 (13.33%) cases, Day 45 occurred 5 (16.67%) cases, Day 90 occurred 5 (16.67%) cases. Total 17 (56.7%) cases observed; P<0.05 which was significant. As comparison between two groups less recurrence occurs in low molecular weight heparin as compared to unfractionated heparin. It means that low molecular weight heparin is better than unfractionated heparin (As depicted in Figure-2).

**Incidence of Re-Infarction in Coronary heart disease Patients**

Group A, Coronary heart disease patients with low molecular weight heparin, from Day 0-5 occurred in 1 (3.33%) patient, on Day 15 occurred in 2 (6.67%) patients, Day 45 occurred in 3 (10.00%) patients, and on Day 90 occurred in 2 (6.67%) patients. Total 8 (26.67%) cases were reported.

Similarly, incidence of re-infarction in coronary heart disease patients with unfractionated heparin therapy in group B; from Day 0-5 found 2 (6.67%) cases, on

Day 15 found in 4 (13.33%) patients, Day 45 found 6 (20.00%) patients, and on Day 90 found 5 (16.67%) patients. Total 17 (56.67%) cases were reported; P<0.05 which was significant.

The comparison between A and B groups showed that in group B more incidences of re-infarction occurred and in group A, low molecular weight heparin showed less incidences of re-infarction occurrence. This mean that low molecular weight heparin is better because of safety and efficacy-wise than that of unfractionated heparin (As depicted in Figure-3).

**Incidence of Death in coronary heart disease Patients**

Group A, coronary heart disease patients with low molecular weight heparin, from Day 0-5 occurred in 1 (3.33%) patient, on Day 15 occurred in 1 (3.33%) patient, Day 45 occurred in 2 (6.67%) patients, and on Day 90 occurred in 1 (3.33%) patient. Total 5 (16.67%) cases were reported.

Similarly, incidence of death in coronary heart disease patients during unfractionated heparin in group B from Day 0-5 occurred in 2 (6.67%) patient, on Day 15 occurred in 4 (13.33%) patients, on Day 45 occurred in 5 (16.67%) patients, on Day 90 occurred in 3 (10.00%) patients. Total 14 (46.67%) cases reported; P<0.05 which was significant. In comparison between groups A and B, group A of low molecular weight heparin has less incidence of death reported, because of better efficacy of drug as compared to unfractionated heparin in group B (As depicted in Figure-4).

## DISCUSSION

There is sufficient evidence to indicate that thrombolytic therapy in the form of unfractionated heparin and low molecular weight heparin has been shown to reduce early and long-term mortality by about 20% when administered to patients with coronary heart disease.

Antman et al (1999)<sup>5</sup> also shown, when compared the unfractionated heparin with the low molecular weight heparin, that there was a 20% reduction in clinical events in patients with coronary heart disease.

Cohen et al (1997)<sup>6</sup> reported that low molecular weight heparin was at least as good as, if not better than UF heparin in preventing coronary heart disease. They stated that the efficacy and safety of low molecular weight heparin administered at home could be compared with hospital intravenous unfractionated heparin. Recently clinical studies have been published indicating that low molecular weight heparin may be beneficial in treating arterial disease. Our study shows same results that low

molecular weight heparin when compared with unfractionated heparin in treating coronary heart disease patients. The low molecular weight heparin gives better results than unfractionated heparin.

Eikelboon et al (2000)<sup>7</sup> showed that unfractionated heparin and low molecular weight heparin, when administered with aspirin, reduce the incidence of non-fatal myocardial infarction or death by about 50%. This analysis treated patients with acute coronary syndrome without ST elevation. A reduction in recurrent angina and revascularization was seen with low molecular weight heparin. Our study matches with the above study in which unfractionated heparin reduces the incidence of non-fatal myocardial infarction and death about 40%<sup>7</sup>. Cohen (1999)<sup>8</sup> showed the randomized study compared unfractionated heparin treatment with low molecular weight heparin in the acute management of patients with coronary heart disease. Low molecular weight heparin demonstrates superiority to unfractionated heparin in the treatment of myocardial infarction regards to composite endpoint without increasing the risk of major haemorrhagic events. Our observations matches with their findings that low molecular weight heparin has superiority to unfractionated heparin in the treatment of coronary heart disease patients without increasing the risk of major haemorrhagic events.

Simoons et al (2002)<sup>9</sup> showed that low molecular weight heparin has been given in acute coronary syndromes, particularly in patients admitted with unstable angina or myocardial infarction without persistent ST-segment elevation. The results show superiority over and clinical efficacy at least equal to unfractionated heparin. In the efficacy and safety of subcutaneous enoxaparin in non-Q-wave coronary events (ESSENCE) and TIMI-IIIB studies low molecular weight heparin in comparison with unfractionated heparin resulted in a reduce rate of thrombotic complications: death, re-infarction and recurrent angina.

Our comparative study of low molecular weight heparin with unfractionated heparin indicates the efficacy and safety of subcutaneous enoxaparin, reduces the rate of thrombotic complications such as death, re-infarction, recurrent angina, and haemorrhage.

Werf et al (2001)<sup>10</sup> compared UF heparin, adjunctive therapy with enoxaparin reduces ischaemic complication of acute myocardial infarction. These reductions were found to be present early after the start of treatment. Enoxaparin (low molecular weight heparin) is a desirable anti-coagulant in conjunction

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with less fibrin specific agent. Our comparison of unfractionated heparin with low molecular weight heparin, as adjunctive therapy reduces complications of coronary heart disease patients, and these reductions were found to be present early after the start of treatment.

Paul W. Arm Strong et al (2006) shown that new thrombolytic agent trial, they showed that the combination of enoxaparin (LMWH) and tenecteplase was more effective than unfractionated heparin plus telencteplase in reducing ischemic complications in patients treated with six hours of onset of symptoms of STEMI. Our study matches with the above study that combination of enoxaparin (LMWH) was more effective than unfractionated heparin in reducing ischemic complications in patients treated with STEMI.

Elliott M ANTman, et al (2006) in patients receiving fibrinolysis for ST – elevation myocardial infraction, treatment with enoxaparin (LMWH) throughout the index hospitalization is superior to treatment with unfractionated heparin in 48 hours, with associated an increase in major bleeding episodes.

Our observations matches with above findings that treatment with enoxaparin (LMWH) throughout the index hospitalization is superior in efficacy as compared with unfractionated heparin

(UFH).

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