ECONOMIC EVALUATION OF LOW MOLECULAR WEIGHT HEPARIN (LMWH) AND UNFRACTIONATED HEPARIN (UFH) FOR ACUTE MYOCARDIAL INFARCTION: SINGLE CENTER STUDY, PUNE

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ABSTRACT

Background: Healthcare cost, including the cost of therapy for treatment of cardiac diseases are a growing burden on public domain, the standard care on which public money is spent during hospitalization is a matter of concern. Benefits of UFH in Acute Coronary Syndrome (ACS) have been well-established. However, now extensive variety of newer anticoagulants like low molecular weight heparin, direct thrombin inhibitor and selective factor Xa Inhibitor are available for clinical use. The objective of the study was to evaluate the cost of enoxaparin versus unfractionated heparin in Myocardial infarction. Methods and material: This prospective observational study included patients admitted in ICU and HDU which were divided into three groups. Group 1 received treatment with low molecular weight heparin (LMWH) (n=30), group 2 received treatment with unfractionated heparin (UFH) (n=24) and group 3 received treatment with both LMWH and UFH (n=30). Demographic data & direct cost of pharmacological treatment was collected for each patient. Finally, the total cost for all drugs received by the patients during six months period was calculated. Results: 84 out of 196 patients were included with the primary diagnosis of acute myocardial infarction over the interval of six months. A total of 319 drugs was prescribed in 84 patients and mean number of drugs prescribed per patient were 10±1.9 (range 8-12) in Group-I, 10±1.5 (range 8-12) in Group-II and 13±2.6 (range 10-19) in Group-III. The average cost of anticoagulants was more in Group III (Rs. 7461 ± 2604.19) as compared group I (Rs.3936 ± 1655.46) and group II (Rs. 409 ± 347.37). Conclusion: For treating acute myocardial infarction in hospitalized patients unfractionated heparin can be initiated and then switching to enoxaparin appears to be cost saving and more beneficial, although cost implications depends on local revascularization practice. For treating acute myocardial infarction in hospitalized patients, enoxaparin is an economical attractive option. The higher acquisition cost of enoxaparin is compensated by reduction in catheterization, revascularization procedures, decreased hospital stay resulting in overall cost-saving.

KEYWORDS: ACS, ICU and HDU.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality worldwide and by the year 2020 it will be first in the leading cause of disability and will be responsible for total of 11.1 million deaths globally. 1,2,3,4,5,6 In developed countries, ischemic heart disease is predicted to rise by 30-60% between 1990-2020.4,7,8 It has been reported that more than 80% of the deaths occurred in low and middle income countries.9,10 Regional studies have also showed that CVD is the leading cause of deaths in urban as well as rural populations.11,12,13 Also it has been observed that poor patients were less likely to get evidence-based treatments and had greater 30-day mortality than wealthy patients (8% vs. 6%).14,15,16,17,18 India is going through an epidemiological transition whereby the burden of communicable diseases have decline slowly, but that of non-communicable diseases have risen rapidly, thus leading to a dual burden.19,20 There has been a fourfold rise of CHD prevalence in India during past 40 years. Current estimates from epidemiologic studies from various parts of the country indicate a prevalence of CHD to be between 7 – 13% in urban and 2 – 7% in rural populations.21,22,23,24,25 Epidemiologic studies have shown that there are at present over 30 million cases of CHD in this country among which 1.27 million have acute coronary syndrome.5,8,9,11 Incidence of myocardial infarction (MI) is 37.1% in above 50 years of age and is more in laborers and farmers and risk of myocardial infarction is similar in men and women.12 In OECD (Organization for
Economic Co-operation and Development) countries, treatment of cardiovascular disease generally consumes about 10-15% of total healthcare budgets. As health cost are increasing within the public domain of public responsibility, the standard care on which public money is spent during hospitalization is a matter of concern. In patients with ST-segment elevation myocardial infarction (STEMI) or acute coronary syndrome without ST elevation (non-STEMI or unstable angina), early mechanical or pharmacological reperfusion, anti-thrombotic therapy with aspirin, thienopyridine, glycoprotein IIb/IIIa inhibitors, and unfractionated heparin (UFH) have been widely used for decreasing mortality and myocardial infarction. UFH has many disadvantages like unpredictable pharmacokinetic and pharmacodynamics parameters, need of intravenous administration, regular anticoagulation monitoring and adverse effects such as heparin induced thrombocytopenia. While LMWH has greater benefits like longer half-life, predictable anticoagulation, lesser need of laboratory monitoring and lower incidence of adverse effects.

Various combination of reperfusion therapy is practiced for management of AMI. There are many literatures on cost effective comparisons done between various anticoagulant agents performed in developed countries. There is hardly any outcome analysis done to assess the cost burden of anticoagulant therapy for management of AMI in developing countries.

The focus of our study is based on cost implications due to different anticoagulant therapies and identifying the area for reducing the cost burden on patients. This will help us to imply intervention strategies to decrease the cost burden on patients.

MATERIAL AND METHODS
A prospective observational study was carried out in intensive care unit (ICU) and high dependency unit (HDU) of a tertiary teaching hospital after obtaining approval from the institutional ethics committee. The study was carried out over a period of six months from September 2015 to February 2016.

Inclusion criteria
i. Age > 40 years of either gender.
ii. Patients with primary diagnosis of AMI.
iii. Patients receiving UFH or enoxaparin or both.

Exclusion criteria
i. Patients with age < 40 years.
ii. Patients with secondary hospitalization.
iii. Patients discharged against medical advice.
iv. Patients receiving anticoagulants other than enoxaparin or UFH.
v. Pregnant or nursing women.

Patients admitted to ICU and HDU who fulfilled study criteria were enrolled in the study. They were divided into three groups. Group 1 received treatment with low molecular weight heparin (LMWH) (n=30), group 2 received treatment with unfractionated heparin (UFH) (n=24) and group 3 received treatment with both LMWH and UFH (n=30). Demographic data including patients’ clinical data such as diagnosis, detailed history of illness, past history, family history were noted in case record form. Information on drugs prescribed and administered was obtained from the patient’s medication chart. Cost analysis was performed from patient’s perspective and the cost of the drug was defined as the acquisition cost to the patient. Aspirin and other medications were administered to respective groups immediately, in accordance with the standard practice after admission to hospital and were continued depending upon the medical condition of the patient. The direct cost of pharmacological treatment was calculated by using patient’s pharmacy bills. In each case, the price was calculated finally on a per unit basis for the strength, a dosage form used and then multiplied by the number of units administered to determine the cost of each drug received by a patient. Cost figures were assembled for each drug received by a patient and for all drugs prescribed during hospitalization. Finally, the total cost for all drugs received by the patients during six months period was calculated.

STATISTICAL ANALYSIS
Data was analyzed with Microsoft Excel spreadsheet. T-test and p-value were applied to compare the cost outcome of respective groups. A 5 per cent level of significance was accepted for all statistical tests.

RESULTS
84 out of 196 patients were included with the primary diagnosis of acute myocardial infarction over the interval of six months. Mean age of patients in LMWH group was 59± 12.48, in UFH was 61 ± 13.12 and in LMWH+UFH was 56 ± 13.72 and the majority of the patients were male i.e. 70%, 62.5%, and 70% respectively. In the LMWH group majority of patients were from the age group 56-70 (n= 15), while in UFH age group was 40-55 (n= 12) and LMWH+UFH age group was 40-55 (n=15) with the mean length of stay 5 ±1.22, 5 ± 1.13 and 8 ± 3.42 respectively (Table no. 1). The co-morbid conditions found in the patients in LMWH group were hypertension 12 (40%) followed by diabetes mellitus 9 (30%), UFH group were hypertension 12 (50%) followed by diabetes mellitus 6 (20%) and LMWH+UFH group were hypertension 15 (50%) followed by diabetes mellitus 9 (30%) (Figure no.1). A total of 319 drugs was prescribed in 84 patients and mean number of drugs prescribed per patient were 10±1.9 (range 8-15) in Group-I, 10±1.5 (range 8-12) in Group-II and 13±2.6 (range 10-19) in Group-III.

Antiplatelet drugs were most frequently prescribed drugs in 52 (92.8%) of the patients. Aspirin 26 (92.8%) and clopidogrel 26 (92.8%) were most frequently prescribed drug in respective groups. Streptokinase was used as
initial fibrinolytic agent only limited to 11 (39.2%) of patients.

The other class of drugs prescribed were antihyperlipidemia (Atorvastatin) 24 (85.7%) and antiemetic (Ondansetron) prescribed in 25 (89.3%). Proton pump inhibitor (Pantoprazole and Rabeprazole) were prescribed in 71.4% patients. Total 12 (42.8%) antimicrobial drugs were administered among which commonly prescribed was ceftriaxone 8 (28.5%). Table no.2 shows frequently prescribed drugs (n=28).

The average duration of anticoagulants prescribed was 3±1.2 days in LMWH group, 2±1.7 days in UFH group and 7±4.9 days in LMWH+UFH group. The average cost of pharmacological reperfusion therapy for LMWH group was Rs. 4418.6, for UFH group was Rs. 4019.23 and LMWH+ UFH group was Rs. 10650.08 (Figure No.2).

The average cost of anticoagulants was more in Group III (Rs. 7461 ± 2604.19) as compared group I (Rs.3936 ± 1655.46) and group II (Rs. 409 ± 347.37) (Figure No.3). The average cost of anticoagulants per day during hospitalization was found to be highest in LMWH+UFH group (Rs.1034) followed by LMWH group (Rs. 844) and UFH group (Rs. 334). Percent carrying cost of PRT from total cost for LMWH+UFH group was found to be highest with 79% while LMWH group had 59% and UFH group had 46% (Figure no. 4).

Duration of stay for LMWH group is positively correlated with number of drugs (Pearson’s correlation R=0.7857, P value = 0.00706, significant at p < 0.05). Cost of therapy is positively correlated with duration of stay (Pearson’s correlation R= 0.9419, P value = 0.0004646, significant at p < 0.05) and with number of drugs (Pearson’s correlation R=0.7946, with P= 0.006027, significant at p < 0.05). In UFH group duration of stay is moderately correlated with number of drugs (Pearson’s correlation R=0.615, P value = 0.104644, not significant at p < 0.05). Cost of therapy is weakly correlated with duration of stay (Pearson’s correlation 0.619044, p value = 0.619044, not significant at p < 0.05) and positively correlated with number of drugs (Pearson’s correlation 0.2626, P value= 0.529792, not significant at p < 0.05). In LMWH+UFH group duration of stay is positively correlated with number of drugs (Pearson’s correlation R=0.8887, P value = 0.000586, significant at p < 0.05). Cost of therapy is positively correlated with duration of stay (Pearson’s correlation R=0.7711., P value = 0.009016, significant at p <0.05) and with number of drugs (Pearson’s correlation R=0.7758, with P= 0.008349, significant at p < 0.05).

Table No. 1: Demographic Details.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LMWH n=30 (%)</th>
<th>UFH n=24 (%)</th>
<th>LMWH+UFH n=30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (70)</td>
<td>15 (62.5)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (30)</td>
<td>9 (37.5)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Age distribution (in years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40- 55</td>
<td>9 (30)</td>
<td>12 (50)</td>
<td>15 (50)</td>
</tr>
<tr>
<td>56- 70</td>
<td>15 (50)</td>
<td>9 (37.5)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>6 (20)</td>
<td>3 (12.5)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Mean age ± S.D.</td>
<td>59 ± 12.48</td>
<td>61 ± 13.12</td>
<td>56 ± 13.72</td>
</tr>
<tr>
<td>Length of stay (in days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>21 (70)</td>
<td>3 (12.5)</td>
<td>0</td>
</tr>
<tr>
<td>5-8</td>
<td>6 (20)</td>
<td>21 (87.5)</td>
<td>21 (70)</td>
</tr>
<tr>
<td>9-12</td>
<td>0</td>
<td>0</td>
<td>6 (20)</td>
</tr>
<tr>
<td>13-16</td>
<td>3 (10)</td>
<td>0</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Mean length of stay ± S.D.</td>
<td>5 ±1.22</td>
<td>5 ± 1.13</td>
<td>8 ± 3.42</td>
</tr>
</tbody>
</table>

Table 2: Drugs Prescribed.

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>ATC Code</th>
<th>LMWH n (%)</th>
<th>UFH n (%)</th>
<th>LMWH+UFH n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
<td>B01AC06</td>
<td>9 (90)</td>
<td>7 (87.5)</td>
<td>10 (100)</td>
<td>26 (92.85)</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>B01AC04</td>
<td>9 (90)</td>
<td>7 (87.5)</td>
<td>10 (100)</td>
<td>26 (92.85)</td>
</tr>
<tr>
<td>PPI</td>
<td>Pantoprazole</td>
<td>A02BC02</td>
<td>6 (60)</td>
<td>4 (50)</td>
<td>5 (50)</td>
<td>15 (53.57)</td>
</tr>
<tr>
<td></td>
<td>Rabeprazole</td>
<td>A02BC04</td>
<td>1 (10)</td>
<td>1 (12.5)</td>
<td>3 (30)</td>
<td>5 (17.85)</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>Ondansetron</td>
<td>A04AA01</td>
<td>7 (70)</td>
<td>8 (100)</td>
<td>10 (100)</td>
<td>25 (89.28)</td>
</tr>
<tr>
<td>HMCoR reductase inhibitor</td>
<td>Atorvastatin</td>
<td>C10AA05</td>
<td>9 (90)</td>
<td>7 (87.5)</td>
<td>8 (80)</td>
<td>24 (85.71)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>IsosorbideMononitrate</td>
<td>C01DA14</td>
<td>2 (20)</td>
<td>-</td>
<td>2 (20)</td>
<td>4 (14.28)</td>
</tr>
<tr>
<td>Loop Diuretics</td>
<td>Furosemide</td>
<td>C05CA01</td>
<td>1 (10)</td>
<td>2 (25)</td>
<td>2 (20)</td>
<td>5 (17.85)</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Metoprolol</td>
<td>C07AB02</td>
<td>5 (50)</td>
<td>1 (12.5)</td>
<td>4 (40)</td>
<td>10 (35.71)</td>
</tr>
<tr>
<td>CCB</td>
<td>Amlodipine</td>
<td>C08CA01</td>
<td>-</td>
<td>1 (12.5)</td>
<td>-</td>
<td>1 (3.57)</td>
</tr>
</tbody>
</table>
ACE inhibitors | Ramipril | C09AA05 | - | - | 2 (20) | 2 (7.14)
Insulin | A10AC01 | 1 (10) | - | 2 (20) | 3 (10.71)
Antidiabetic | Metformin | A10BA02 | - | 1 (12.5) | - | 1 (3.57)
Gliclazide | A10BB09 | - | 1 (12.5) | - | 1 (3.57)
Antibiotics | Ceftriaxone | J01DD04 | 2 (20) | 2 (25) | 4 (40) | 8 (28.57)
Cefixime | J01DD08 | 1 (10) | - | 1 (10) | 2 (7.14)
Cefuroxime | J01DC02 | 1 (10) | - | - | 1 (3.57)
Cefazolin | J01DB04 | 1 (10) | - | - | 1 (3.57)

Figure no. 1: Patients with co-morbidities.

Average cost of pharmacological reperfusion therapy per admission

Fig. 2: Average cost of pharmacological reperfusion therapy per admission.
DISCUSSION
In the present study mean age of patients was found to be 58 years which was comparable to the studies which reported that the average age for men is 65 year while the average age for women is 72 years and increases with age.[12,13,14,30,31,32] The incidence of myocardial infarction in the present study was higher in males as compared females showing similar results reported in the number of studies.[15,16,33,34] In LMWH and UFH group the length of stay was 5 days while in LMWH+UFH group length of stay was 8 days which is comparable to the result which showed that the average duration of hospitalization was 8.05 days.[17,18,35] The reason for the variation in length of stay could be because of older age, history of heart failure, angina or hypertension as well as other co-morbid conditions and also may be due to the difference in practicing policies in different hospital.[19,20,36] Patients admitted with acute myocardial infarction also presented with co-morbidities like hypertension and diabetes mellitus which is showed in various studies.[17,21,35,37] The average cost of pharmacological reperfusion therapy for LMWH was Rs. 4418.6, for UFH group was Rs. 4019.23 and LMWH+UFH Rs. 1065.08 which is comparable to the study which suggested that the average cost of pharmacotherapy is Rs. 3738.84.[38] In the present study, the average duration of anticoagulants prescribed was 3 days in LMWH group, 2 days in UFH group and 7 days in LMWH+UFH group which was comparable to the study in which the average duration for which patient was receiving LMWH was between 4-8 days and UFH was 2-4 days.[39] The average cost of anticoagulants per day during hospitalization was found to be highest in LMWH+UFH group (Rs.1034) followed by LMWH group (Rs. 844) and UFH group (Rs. 334). This result is similar to the comparative study of enoxaparin with UFH in patients with CHD conducted in South Indian Teaching Hospital reported that average cost of LMWH
per day was Rs. 457.32 and for UFH was 268.72 and concluded that UFH is less expensive than LMWH.\[24]\n
**CONCLUSION**

Anticoagulant therapy comprises the largest portion of the costs associated with the treatment of AMI, it is therefore important to find the most cost effective treatment that is both safe and effective. For treating acute myocardial infarction in hospitalized patients, enoxaparin is an economical attractive option. The higher acquisition cost of enoxaparin is compensated by reduction in catheterization, revascularization procedures, decreased hospital stay resulting in overall cost-saving. More studies are required to evaluate the cost-effectiveness of anti-coagulants in AMI. Enoxaparin reduces average cost in AMI treated conservatively, however it is not an cost-effective option in patients who are treated with early invasive strategy. The suggested treatment of myocardial infarction should comprise of enoxaparin and unfractionated heparin with antiplatelet. By observing clinical outcomes and cost comparison analysis we conclude that although UFH is less expensive than enoxaparin, however enoxaparin has better overall clinical outcomes such as higher prothrombin time, less recurrence of angina and less occurrence of ADRs compared to UFH.\[24]\n
Use of anticoagulant in management of AMI should be based on further clinical considerations and not only limited to lower acquisition cost.

Moving from unfractionated heparin to enoxaparin appears cost saving and more beneficial in hospitalized patients with acute myocardial infarction, although cost implications depend on local revascularization practice.

**RECOMMENDATIONS**

1. In India, branded drugs are used which are having higher cost than the generic drugs with same chemical entity, hence to improve cost effective treatment use of generic drugs can be promoted.
2. Streptokinase followed by UFH (least cost) for the inpatients associated with least risk factors and no observed contraindications as they are under continuous monitoring in the ICU.

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**Declarations**

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**Conflict of interest:** None declared.

**Ethical approval:** Not required.

**REFERENCES**


27. 1999 Organisation for Economic Co-operation and Development Health Database. Comparative analysis of 29 countries.


