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A Study of Prescribing Habits of Low Molecular Weight Heparin in Cardiovascular Disease in Tertiary Care Hospital

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Abstract

Background and Objective: Cardiovascular Diseases (CVDs) are the leading non-communicable diseases and also leading cause of morbidity and mortality worldwide. Low Molecular Weight Heparin (LMWHs) is frequently prescribed medication in CVDs. Prescribing pattern of LMWHs in CVDs is necessary to recommends modifications to achieve rational and cost-effective medical care.

Methodology: An inpatients hospital based observational prospective study for a period of six months was carried out. Data was collected from patient medication sheet and analyzed by suitable methods and standard references.

Results and Discussion: In our study, a total of 120 patients were enrolled out of 120 patients 84 were male and 36 were female. Antiplatelet drug is maximum prescribing drug in 98 (81.34%) patients out of 120, then after hypolipidaemic drugs in 94 (78.02%), Anticoagulant in 92 (76.36%), Antibiotics in 90 (74.70%), Antianginal in 69 (57.27), Antihypertensive in 64 (53.12%), Diuretics in 59 (48.97%). LMWHs are prescribed in 78 (65%) in which Enoxaparin is prescribed in 67(55%) and Dalteparin in 11(10%) patients out of 120 patients. Total 259 Drug-Drug Interactions (DDI) were found in which 67 were Major, 140 were Moderate, and 52 were Minor.

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Conclusion: The study show LMWHs are highly prescribed category of anticoagulant. Enoxaparin is prescribed morethan Dalteparin. Antiplatelet drugs are prescribed to every patient who is prescribed with LMWHs to prevent embolic event. Chance of DDI is increases with these combinations. LMWHs and Fibrinolytic drugs are very costly and impart maximum economic burden to middle class family.

Keywords: Cardiovascular diseases, Drug- Drug Interactions, Heparin, Low Molecular Weight Heparin.

1. INTRODUCTION

Cardiovascular diseases (CVDs) are related with heart and blood vessels& specially included coronary artery diseases (CAD), pulmonary embolism (PE) and deep vein thrombosis (DVT), congenital heart diseases & rheumatic heart diseases. People died from CVDs in 2008 were 17.3 million (30% of all global deaths). Out of 17.3 million CVDs global mortality, 7.3 million were by coronary heart diseases and 6.2 million by stroke (WHO Fact sheet, 2011). Similarly in Indian scenario cardiovascular mortality was one-fourth of all mortality in 2008. With 9.2 % annual growth CVDs were fastest-growing chronic illness between 2005 and 2015(Chauhan et al., 2001; Cardiovascular Diseases in India 2010). Cardiovascular diseases include Coronary artery disease, deep vein thrombosis, and pulmonary embolism. Coronary artery disease (CAD) can classify into Ischemic Heart Disease (IHD) and Acute Coronary Syndrome (ACS). IHD is chiefly caused by the formation of coronary atherosclerotic plaque that creates an imbalance between oxygen supply and demand resulting ischemia in the myocardium. While ACS is a clinical condition when an atherosclerotic plaque get ruptured with following platelet adherence, activation, aggregation, and clotting cascade that eventually leads a clot formed by fibrin and platelets (Enas et al., 2007). Blockage of the main artery or one of its branches of lungs by an embolus that has traveled from elsewhere in the body through the blood stream is called pulmonary embolism (Balady et al., 2007). Formation of thrombus within a deep vein chiefly in the legs is called Deep vein thrombosis (DVT) (Dipiro, 2008). Drugs categories such as antiplatelet, anticoagulants, beta blockers, angiotensin-converting enzyme inhibitor (ACEI) / Angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), diuretics, and statins are involved in the treatment of CAD, DVT, and PE. In high- income countries drug utilization strategies for CAD is well established but in India, these strategies have not been fully implemented (Goldhaber et al., 2005). The study of prescribing habits is a part of the medical assessment that involves monitoring and assessment of the prescribers as well

as suggests necessary alterations in drug therapy achieve rational, cogent, and cost-beneficial care. Studies of prescribing habits in CVD patients are useful to identify the harms and provide feedback to prescribers for awareness about rational drug use (Srishyla et al., 1994). Therefore, this study was able to analyze the current prescription pattern of LMWHs with cardiovascular drugs that prescribed during the study and Drug-Drug Interactions between these drugs. The study also analyzes cost of CVDs and explore economic burden on patients.

2. METHODOLOGY

A prospective observational study was carried out in a tertiary care hospital over the duration of 6 months from December 2013 to June 2014. The study was approved by the ethical committee vide approval letter number IECBLDECOP/2014/06.

2.1 Study Criteria

The patients admitted to intensive care unit of the department by considering following criterion.

2.2 Inclusion criteria

All patients diagnosed with CVDs (Ischemic Heart disease, acute coronary syndrome (ACS), Deep vein thrombosis (DVT), and Pulmonary embolism (PE), of either sex and are more than 18 years admitted to the intensive care unit were included.

2.3 Exclusion criteria

In patients diagnosed other than CVDs and all Inpatients admitted other than ICU, ICCU, and New Emergency Wards.

3. DATA COLLECTION

Data was collected on data collection format from the patients who came under inclusion criteria. Patient demographic detail (age, sex), diagnosis, laboratory investigations, and advised medications were noted down on data collection format from the medical records.

To study the drug prescribing habits in cardiovascular disease, all patients diagnosed with coronary artery disease, Deep vein thrombosis, and pulmonary embolism were included in the study for analysis. The trade names of drugs were interpreted and classified into their pharmacological groups like aspirin,

clopidogrel used as antiplatelet agents; beta-blockers (BB), Angiotensin-Converting Enzyme Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARBs), and calcium channel blockers (CCBs) used as antihypertensive agents; HMG-CoA reductase (Statins), and fenofibrate used as lipid-lowering medicines; Nitrates, potassium channel openers (e.g. Nicorandil) used as antianginal drugs for chest pain; Unfractionated heparin (UFH) and Low Molecular Weight Heparin (LMWHs) were used as anticoagulants; streptokinase used as fibrinolytic. Other classes of drugs such as diuretics, bronchodilators, antibiotics, multivitamins, anti-diabetic medications were also included. Analysis of utilization of different classes of drugs as well as individual drugs was evaluated and depicted as the percentage.

4. RESULTS

During the entire study period, 120 patients were enrolled. Out of 120 patients, 84 were male and 36 were female. The male to female ratio among the patients was 7:3. The average age for all enrolled patient was 68.16 ± 4.49.

Aging increases chance of cardiovascular morbidity. In present study maximum, 72 (60%) enrollment occurred in the age group between 60 to 80 years. Various age wise distribution of CVD patients are shown in Table **1**.

During whole study diagnosed patients were categorized into ischemic heart disease (IHD), acute coronary syndrome (ACS), pulmonary embolism (PE), and deep vein thrombosis (DVT). During study period maximum 76 (63.80 %) had ischemic heart disease (IHD), then 38 (31.54%) ACS was diagnosed.

The risk of cardiovascular diseases in patients who have whether prehypertension or hypertension is very high. Hence in present study depicted that highest comorbid condition is Hypertension and then on the second position were diabetes Various Co-morbid conditions are described in Table **2**.

Table 1: Age distribution of patients.

S. No.	Age group (years)	No of patients (n=120)	Percent (%)
1.	20–39	08	6.7
2.	40–59	34	28.3
3.	60–80	72	60
4.	>80	06	5

Table 2: Co-morbid conditions with cardiovascular disease.

S. No.	Co-morbid conditions	No. of patients (n=120)	Percent (%)
1.	IHD	18	15
2.	ACS+IHD	10	8.3
3.	ACS	14	11.7
4.	IHD+HTN	8	6.7
5.	IHD+Type2 DM	15	12.5
6.	IHD+LVF	5	4.2
7.	IHD+CHF	6	5
8.	IHD+HTN+Type2 DM	18	15
9.	ACS+LVF+IHD	1	0.8
10.	ACS+HTN	2	1.7
11.	IHD+CHF+ Type2 DM	2	1.7
12.	IHD+MR	4	3.3
13.	ACS+DM Type2	9	7.5
14.	ACS+LVF	2	1.7
15.	PE+HTN	3	2.5
16.	DVT	3	2.5
17.	**Total**	**120**	100

Acute Coronary Syndrome (ACS), Deep Vein Thrombosis (DVT), Diabetes Mellitus (DM), Hypertension (HTN), Ischemic Heart Disease (IHD), Left Ventricular Failure (LVF), Mitral Regurgitation (MR)

The treatment of cardiovascular diseases involves different categories of drugs such as antiplatelet drug, anticoagulant, fibrinolytics, anti-anginal drugs, antihypertensive, antihypertensive, antihyperlipidemic agent, bronchodilators, and antibiotics. Details of different categories of prescribed drugs are given in table 3.

Table 3: Different Categories of Drugs Prescribed to the 120 Patients.

S.N.	Drug Categories	No. of Patients out of 120	% of patients
1.	Antiplatelet	98	81.34
2.	Hypolipidaemic Drug	94	78.02
3.	Antibiotics	90	74.70
4.	Antianginal	69	57.27
5.	Anti HTN	64	53.12
6.	Anti coagulant	92	76.36
7.	Diuretics	59	48.97
8.	Bronchodilators	45	37.35
9.	Antacids	98	81.34
10.	OHA	46	38.18
11.	NSAIDs	48	39.84

Out of 120 patients, 15 patients were thrombolized with streptokinase for dissolving fibrin clots and for preventing re-occlusion anticoagulants are prescribed in which LMWHs are prescribed in 78 patients and 9 patients with Unfractionated heparin. Details of prescribed anticoagulants are shown in Table 4.

Table 4: Description of LMWHs prescribed to the Patients.

S. No.	Drug	No. of Patients out of 120	% out of 120 patient
1.	Enoxaparin Sod.	67	56
2.	Dalteparin sod.	11	9
3.	Heparin	9	7
4.	Patient without anticoagulation therapy	36	30

Table 5: Detail of antiplatelet drug andLMWHs with various categories.

S. No.	Drug prescribed with LMWHs	No. of Patients out of 120	Percentage out of 120 patient
1.	LMWH + Antiplatelet	78	65
2.	LMWH + Antiplatelet + Antihypertensive	73	61
3.	LMWH + Antiplatelet + Anti-acid drugs	98	81
4.	LMWH + Antiplatelet + Hypolipidaemic	78	65
5.	LMWH + Antiplatelet + Antibiotics	60	50

Table 6: Details of different DDIs occur in Patients.

Type of DDIs	No. of DDIs (N* = 259)	Percent (%)
Major	67	25.9
Moderate	140	54.1
Minor	52	20.0

*Total no DDIs occur in study.

During the whole study period total of 259 DDIs were reported out of which 140 is moderate type of DDIs were predominant. The moderate drug-drug interactions were mainly occurred in between antiplatelet and low molecular weight heparin (LMWHs) in 78 (76%) patients. The major DDIs between antiplatelet and heparin was found in 9 (7.5%) and moderate DDIs between aspirin and Streptokinase was found in 15 patients. DDIs between antiplatelet, low molecular weight heparins, unfractionated heparin and streptokinase can cause potential bleeding.

5. DISCUSSION

The present study showed the utilization pattern of LMWHs. Clinical importance of LMWHs was showed in the meta-analysis of more than 7500 patients that states LMWHs reduce mortality and chance of reinfarction compared to placebo (Eikelboom, 2005). On comparing with unfractionated

heparin, chances of reinfarction are more if UFH is not given in combination with fibrin-selective agents like alteplase, reteplase, and tenecteplase (Gruppo, 1990). These fibrin selective agents are very costly approximately 19800 INR in India (Alteplase, 2017) while non-fibrin selective agent streptokinase (STK) is 1900 INR (Streptokinase, 2017). Due to the affordable cost of streptokinase, it is used frequently in India. Use of UFH with STK has no benefit (Gruppo, 1990). In such situation, LMWHs are the drug of choice after thrombolysis with STK. By this study importance of LMWHs is shown, it is prescribed in 68% of patients and also suggest for the reduction of prices in fibrin selective agents. Cardiovascular illness causes nearly 2400 deaths in Americans every day, or an average of 1 mortality in every 33 seconds. Morality by coronary artery disease impacts 52% of deaths out of total cardiovascular mortality. Mortality in men become earlier from coronary artery diseases than women, and aging leads higher mortality in both sexes (Dipiro, 2008). In a retrospective study conducted on the 140 patients, out of them 96 patients were male and 44 of them were female with an average age of 62 years (Range 36-83 years) and 61 years (Range 30-80 years) respectively (Sandozi & Nausheen, 2010). In the present study Out of 120 patients, 84 were male and 36 were female. The male to female ratio among the patients was 7:3. The present study also showed consistency results with previous studies that male were more prone to coronary artery disease compared to female and the risk is increased with increasing age. Treatment Goals for cardiovascular diseases includes early re-establishment of blood flow to the infarct-related artery to prevent infarct development (in the case of MI) or prevent complete occlusion and MI (in unstable angina), relief of ischemic chest discomfort, prevention of coronary artery re-occlusion, and prevention of mortality and other complications (Dipiro, 2008).

Antiplatelet and anticoagulant are indicated for the prevention of further re-occlusion. Aspirin has become preferred antiplatelet agent for ACS (Antman, 2004) and administration of aspirin within first 24 hours of hospitalization is an indicator of good quality care (Krumholz, 2006). Aspirin inhibits platelet cyclooxygease-1 (Cox-1) irreversibly by which synthesis of thromboxane A2 is inhibited. Administration of its non-enteric-coated formulation rapidly (<10 minutes) inhibits thromboxane A2 production in the platelets. Aspirin also reduces C-reactive protein that showed its effectiveness in ACS (Krumholz, 2006).The study conducted by Muntwyler, et al., showed high prescription rate for antithrombotic agents (90%), then beta blockers, ACEI/ARBs, and lipid-lowering agents were 58%, 50% and 63% respectively (Muntwyler et al., 2003).In our study antithrombotic agents, antihypertensive agents and lipid-lowering agents were 81.34, 53.12 and 78.02 respectively. In our study, we

found every patient were prescribed with aspirin that was quality care indicator for all coronary heart diseases.

Administration of anticoagulant, unfractionated heparin (UFH) involves two steps first as an IV bolus and second is a continuous infusion that is a first-line anticoagulant treatment for the patients of ST-elevated ACS, and for patients undergoing percutaneous interventions (PCI) (Levine, 2006). Mechanism of action of UFH is to bind with antithrombin and then inhibits the function of clotting factors Xa and IIa (thrombin) while LMWHs also bind to antithrombin but due to their short saccharide chain lengths, they preferentially inhibit factor Xa over IIa, which is required larger chain lengths for binding and inhibition. On comparing adverse effects (ADRs) of these two UFH and LMWHs, the UFH has most frequent ADR that is thrombocytopenia and bleeding, which frequency is up to 5% of patients treated with UFH while thrombocytopenia is less common in patients on LMWHs (Antman, 2004; Levine, 2006).

Relative benefits between LMWHs and UFH is recently compared in a trial Thrombolysis in Myocardial Infarction (TIMI) that stated enoxaparin significantly reduced the risk of mortality or nonfatal MI compared to UFH administered patients (Dipiro, 2008). In present study showed that utilization of UFH was only in 7.47 percent patients while LMWHs was 78% that support result of large TIMI trial by more utilization of LMWHs while study conducted by Sandozi et al. showed prescription rates for Unfractionated heparin is more (55.71%) in compare to Low molecular weight heparin (20.00%) (Sandozi, 2010).

6. CONCLUSION

The study shows that LMWHs are the highly prescribed category of anticoagulants for cardiovascular diseases. Hypertension and diabetes were the highly diagnosed co-morbid conditions associated with coronary artery disease. Enoxaparin is administered in more patients than Dalteparin. Antiplatelet drugs are prescribed to every patient who is prescribed LMWHs to prevent an embolic event. Polypharmacy was noticed in almost every prescription. The rational drug prescription can be improved simultaneously chance of DDI can be reduced by minimizing polypharmacy. LMWHs and fibrinolytic drugs are very costly and impart maximum economic burden to the middle class family.

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