



DRUG UTILIZATION EVALUATION AND ASSESSMENT OF ECONOMIC BURDEN OF ANTICOAGULANTS IN A TERTIARY CARE HOSPITAL IN SOUTH INDIA

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ABSTRACT

Anticoagulants used for many indications, both prophylaxis and therapeutic treatment, are associated with high risk, hence drug utilization evaluation is essential. Objective: The objectives of the study were to evaluate the drug utilization of anticoagulants, assessment of anticoagulant cost in the prescription, identify and assess drug interactions with the use of anticoagulants. Method: This is a 6 months, prospective cross sectional study, evaluating 263 patients for their prescriptions containing anticoagulants in a tertiary care hospital in south India. Results: During the study period, among anticoagulants prescribed, Heparin is found most commonly prescribed for treatment as well as prophylaxis mainly in the cardiology and neurology wards. Acenocoumarol was the second most prescribed anticoagulant followed by Dalteparin Warfarin and Rivaroxaban. Intravenous heparin was prescribed in majority of inpatients of all the departments followed by Acenocoumarol and Enoxaparin. Only few Patients from departments other than cardiology and neurology are prescribed with Enoxaparin, Dalteparin Warfarin and Rivaroxaban. In the discharge prescriptions, Acenocoumarol and Enoxaparin were mainly observed. Among all the prescriptions, 7 cases are found to be prescribed with anticoagulants without any indication, which may increase treatment cost burden on patients. Dose adjustment for lower molecular weight heparin for patients with renal impairment was observed in the present hospital. But the monitoring parameters PT, PTT & INR are performed only in few patients. Moderate drug interactions are found in the prescriptions with mainly heparin and Acenocoumarol.

Key words: Anticoagulants, Drug utilization, Drug interactions.

INTRODUCTION

Anticoagulants are the drugs which are usually referred as blood thinners¹ and these are prescribed in clinical settings to treat hospitalized patients like acute and deep venous thromboembolism (VTE), unstable angina, atrial fibrillation² and to prevent coronary arteries from blockage and in cardiac invasive procedures¹.

Anticoagulants are highly prescribed in cardiology and neurology departments. For more than 40years the only anticoagulants available to clinicians are Coumarins and unfractionated Heparin (UFH)³. With the simplicity of subcutaneous administration treatment and prevention of thromboembolism by Unfractionated Heparins and Coumarins are potentially now replaced during past decade by Enoxaparin and Dalteparin which are low molecular weight heparins ¹. In atrial fibrillation (non-valvular) to prevent systemic embolism and stroke Dabigatran etexilate a direct thrombin inhibitor was approved by Food Drug Administration (FDA) in the year 2015 under brand name Pradaxa⁴. In 2011 Rivaroxaban under brand name Xarelta was approved as first factor Xa inhibitor given orally indicated for prophylaxis of venous thromboembolism (VTE) in patients undergoing knee and hip replacement surgery⁵. FDA has approved new anticoagulant named Rivaroxaban indicated for pulmonary embolism (PE) and deep vein thrombosis (DVT) in the year 2012⁶.

Anticoagulants are used for the indications of both prophylaxis and therapeutic treatment of venous and arterial

thromboembolism. An estimated 7 million worldwide are taking oral anticoagulant therapy for chronic diseases^{7, 8}. Joint Commission Sentinel Event Database Of all adverse medication events reported anticoagulants contribute to 7.2%⁹. With the intention of reducing the patient harm associated with the usage of anticoagulant therapy a National Patient Safety Goal (formerly 3E) was introduced by the Joint Commission in 2008¹⁰.

Among available drugs in the market anticoagulants are associated with significant rate of medication errors with 7%^{11, 12} and are the leading cause for hospitalization among older adults and 20% increased risk of death. Warfarin, Heparin, Enoxaparin are listed in top 10 drugs associated with medical errors with ranks 5, 9 and 10 respectively¹³. Among identified medical errors omission of anticoagulant prophylaxis is widely recognised error. During anticoagulant therapy bleeding is considered as primary complication and occurs even when administered within therapeutic doses are risk of all anticoagulants^{14, 15}. While using direct oral anticoagulants drug interactions may arise from pharmacokinetic or pharmacodynamics mechanisms. Pharmacokinetics drug interactions are dependent on varying degrees of activities of hepatic and gastrointestinal P-glycoprotein and P450 3A enzymes of cytochrome. Pharmacodynamics alterations can be seen while using drugs like antiplatelets, nonsteroidal anti-inflammatory drugs (NSAIDs) and selective serotonin and selective noradrenaline reuptake inhibitors¹⁶.

Besides these, lack of feasible laboratory test for monitoring drug levels and to optimize clinical benefit further complicated the use of novel anticoagulants. Unexpected drug accumulation that resulting in life threatening haemorrhage can occur when proper monitoring was not done. Monitoring of unfractionated, low molecular weight heparins and Warfarin can be done by indirect or specific quantitative assays. Most of the newer anticoagulants are not monitored or monitored by indirect methods which include activated partial thromboplastin time and clotting time¹⁷.

In India the factors influencing in achieving optimal health care are low income groups, illiteracy, utilizing of multiple health care systems, dispensing prescription drugs as over the counter drugs, competition in pharmaceutical and medical market place and availability of limited drug information¹⁸. For achieving optimal benefit from drug therapy one of the important factors to be assessed is rational drug use in patient care¹⁹. Attaining rational drug use and formulary management can be done by using drug utilization analysis. Drug utilization helps health care providers to recognise various prescribing patterns and to attain better clinical outcomes. Further drug utilization assists in preventing medication errors, adverse drug reactions, drug-drug interactions, toxicity, therapeutic duplications²⁰. Improving medication use and identifying areas in which there is a need for education and further information for healthcare professionals can be done by drug utilization studies²¹.

MATERIALS AND METHODS

Site of the study: The present study was conducted in Andhra Hospital's, a tertiary care hospital located at Vijayawada city with in Andhra Pradesh, India.

Study design: This is a prospective cross sectional study presenting the data on drug utilization and cost assessment of anticoagulants in different wards of Andhra hospitals. Prior Ethical clearance was obtained from the institutional ethical committee before initiation of the study. Informed concern form was taken from subjects and study was in accordance with ICH GCP Guidelines.

Total 263 case sheets containing anticoagulants were evaluated during the study period between November 2017 to April 2018 from different wards of the hospitals mainly from cardiology and neurology. Inpatients of age above 30 years of both sex and all indications were included in the study. Outpatients, patients on hemodialysis and critical care, receiving anticoagulants are excluded from the study. Pre designed data collections forms were used to record the data of a patient such as age, gender, habitat, occupation, education, income, underlying disease, indication of anticoagulant use and various diagnostic data regarding diagnosis and anticoagulant therapy monitoring (PT, INR, aPTT) before and till the time of discharge.

Dose adjustment of lower molecular weight heparin for the patients with renal impairment is suggested by American College of Chest Physicians (ACCP), is another monitoring

parameter assessed during the study²². During the study period the medication charts were also monitored for drug- drug interactions, and economic assessment of total drug cost was carried out based on dose frequency and days of hospital stay. Average Prescribed Daily Dose was calculated by ATC code assigned to each anticoagulant agent and Defined Daily Dose given by WHO Collaborating centre for Drug Statistics Methodology. The data was analyzed using Microsoft excel^{23,24}.

RESULTS

During the study period 263 patients prescribed with anticoagulants were observed. The study population include 65.3% male and 34.6% female with a mean age of 60 years. Majority of patients receiving anticoagulant therapy are middle class (33.8%) and lower middle (37.2%) class people shown in table-1 and figures 1(a), 1(b). From table-2 and figure 2(a), 2(b) during our observational study period, majority of anticoagulant prescribing was found in cardiology (128) and neurology (96), among them Heparin (165) was found in majority of prescriptions followed by, Acenocoumarol (43), Enoxaparin (26), Dalteparin (26) mostly prescribed in other departments gastroenterology, gynecology, orthopaedic), Warfarin (2), Rivaroxaban (1) prescription with stroke and femur fracture respectively. As shown in table-3, majority of patients received anticoagulant for two indications, Coronary artery disease-81 and Cerebrovascular accident-64 followed by Congestive heart failure-20. As shown in table 4, Average Prescribed Daily Dose of each anticoagulant was calculated as PDD/DDD ratio and found that Heparin and Enoxaparin are prescribed above the optimal dose range (1.3 and 1.1 respectively) while Acenocoumarol and Warfarin are prescribed below the optimal dose range (0.77 and 0.53 respectively) and Dalteparin and rivaroxaban are prescribed within the WHO range. As shown in table-5 and figure-3, the prescriptions containing anticoagulants are checked for any possible drug- drug interactions and found moderate interactions of all anticoagulants with antiplatelet drugs (Aspirin, Clopidogrel). As shown in table-6 and figure-4, it was observed that, monitoring parameter (PT with INR) for anticoagulant was performed in only 79 patients (30%) out of 263. Patients administered with Anticoagulants along with Angiotensin converting enzyme inhibitors (Enalapril) should be monitored for hyperkalemia which was not observed during the study. In the study for monitoring parameters, renal function test was performed in all the patients receiving low molecular weight heparin. PT (Prothrombin Time), PTT (Partial Thromboplastin Time), and INR (International Normalized Ratio) were monitored for only 30 % patients. Out of 263 prescription 226 prescriptions (86%) are appropriate for indication and 102 prescriptions (39%) are appropriate in dose. As shown in table- 7, in the assessment of cost of anticoagulants, lower molecular weight heparins, Enoxaparin (single unit=387 INR) and Dalteparin (single unit=387 INR), are found to be highly expensive followed by Rivaroxaban (single unit=140 INR), Heparin (single unit=78 INR). Were as Acenocoumarol (single unit=9.5 INR) and Warfarin (single unit= 2 INR) are less cost drugs.

Table: 1: Demographic profile among study subjects (n= 263)

Patient's profile	Patients (n=263)		Percentage (%)
Gender			
Male	172		65.3
Female	91		34.6
Age:	Male	Female	
31-40	12	10	8.3
41-50	25	12	14
51-60	46	26	27.3
61-70	64	23	33.0
71-80	21	16	14.0
81-90	4	4	3
Socioeconomic Status:			
Upper class	16		0.6
Middle class	89		33.8
Lower middle class	98		37.2
Lower class	60		22.8

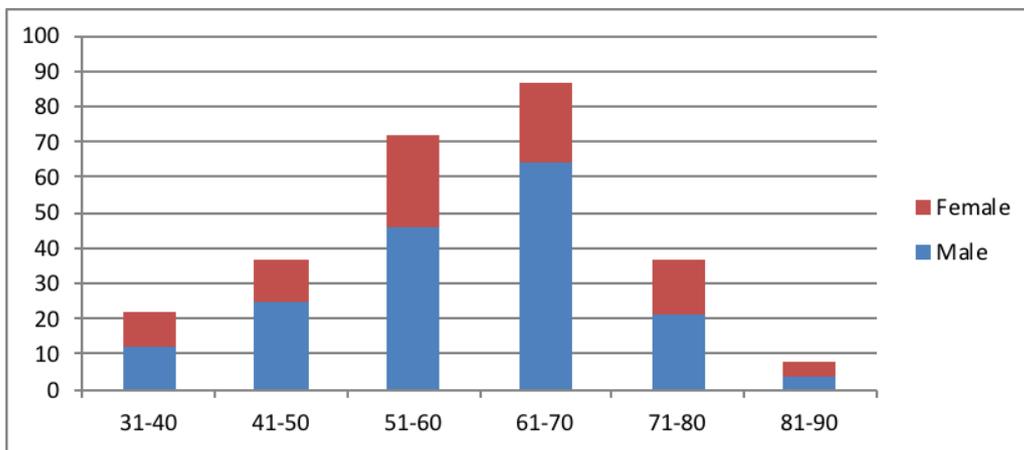


Figure: 1(a): Demographic profile among study subjects (n= 263)

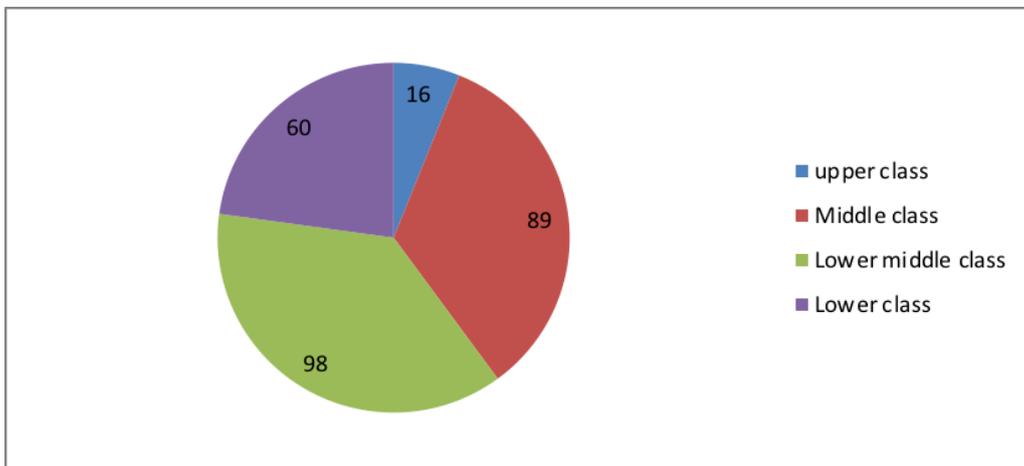


Figure: 1(b): Sales

Table-2: Frequency of drug utilization (n= 263)

Drug	Cardiology	Neurology	Others	Total
Heparin	86	64	15	165
Acenocoumarol	17	19	7	43
Enoxaparin	13	8	5	26
Dalteparin	12	03	11	26
Warfarin	0	02	0	2
Rivaroxaban	0	0	01	1
TOTAL	128	96	39	263

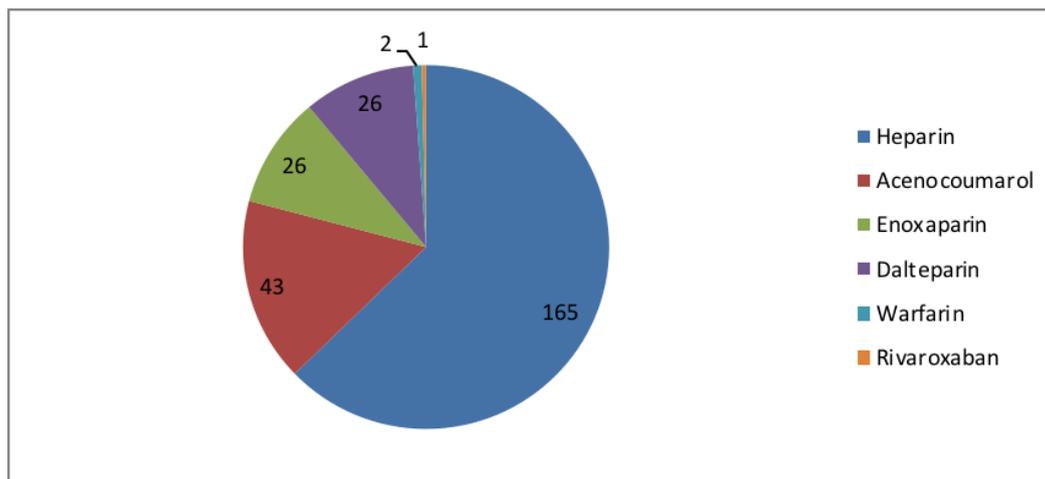


Figure-2: Frequency of drug utilization (n= 263)

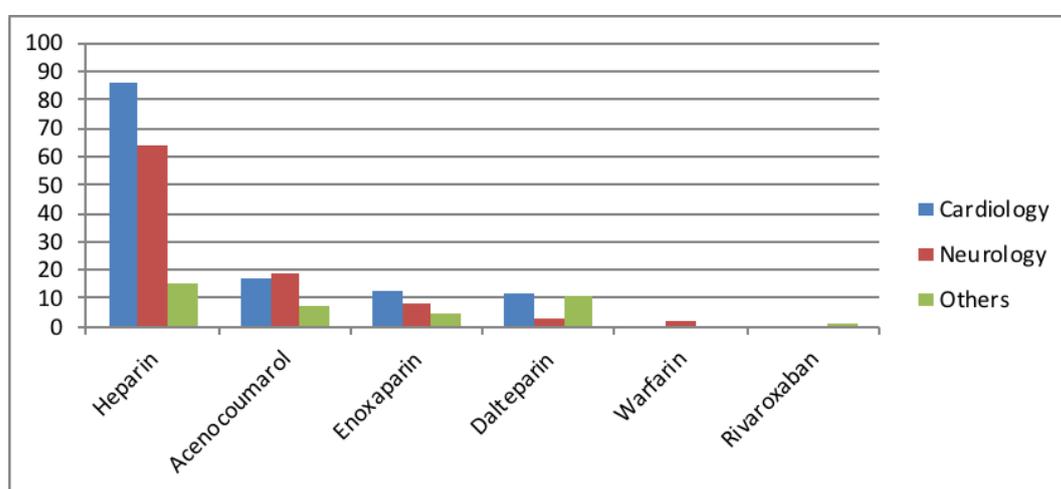


Figure-2(b): Frequency of drug utilization (n=263)

Table-3: Reasons for Hospital Admission (n= 263)

Cardiovascular Conditions	Neurological	Others
Coronary artery disease-81	Cerebrovascular accident-64	Sub-acute Intestinal obstruction-5
Unstable angina-8	Cerebral venous sinus thrombosis (CVST)-10	Cholecystitis-2
Dilated cardiomyopathy (DCM)-15	transient ischemic attack (TIA)-6	Appendicitis-3
Rheumatic heart disease-3	Seizures-4	Cirrhosis-liver-2
Congestive heart failure-20	Meningioma-1	Myalgic Encephalopathy-2
Paroxysmal supraventricular tachycardia-1	Embolitic stroke-1	Myalgic liver disease-5
	TB-meningitis-2	Metabolic acidosis-3
	Ataxia -3	benz poisoning-1
	Vertigo-5	Gangrene-6
		Venous ulcer-1
		Septicemia- 2
		Deep vein thrombosis (DVT)-2
		Renal tubular acidosis (RTA)
		Adenomyosis-2
		Fibroid polyp -3
Total= 128	Total=96	Total=39

Table-4: PDD/DDD ratio of anticoagulants

Drug	ATC code	DDD	PDD	PDD/DDD
Heparin	B01AB01	10,000U(P)	13,092U	1.3
Acenocoumarol	B01AB05	5mg(O)	3.89mg	0.77
Enoxaparin	B01AB04	2000U(P)	2,272U	1.1
Dalteparin	B01AB03	2500U(P)	2500U	1
Warfarin	B01AF01	7.5mg(O/P)	4mg	0.53
Rivaroxaban	B01AA07	20mg(O)	20mg	1

P-parenteral, O-oral

Table -5: Drug-Drug interactions found (n= 263)

Drug interaction found	Number of cases	Effect
Heparin, Acenocoumarol + Aspirin	90	May potentiate the risk of bleeding
Heparin, Acenocoumarol + Telmisartan	9	May increase the risk of hyperkalemia
Enoxaparin, Dalteparin + Aspirin	3	In patients with spinal puncture, the risk of development of hematoma
Enoxaparin, Dalteparin + Clopidogrel	5	May potentiate the risk of bleeding
Enoxaparin, Dalteparin + Telmisartan	1	May increase the risk of hyperkalemia-monitor

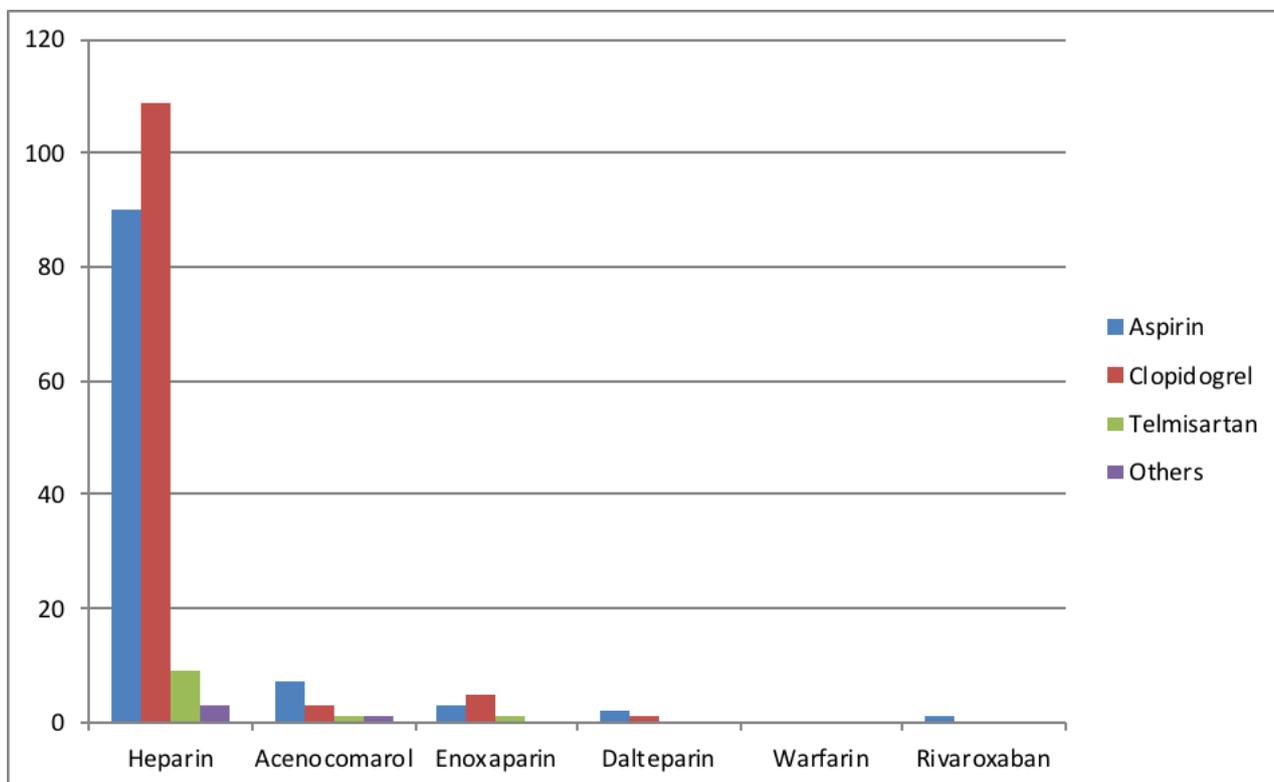


Figure -3: Drug-Drug interactions found (n= 263).

Table-6: Monitoring by PT with INR measurement

Monitoring parameter	No. Of prescriptions	Percentage%
Performed	79	30
Not performed	184	70

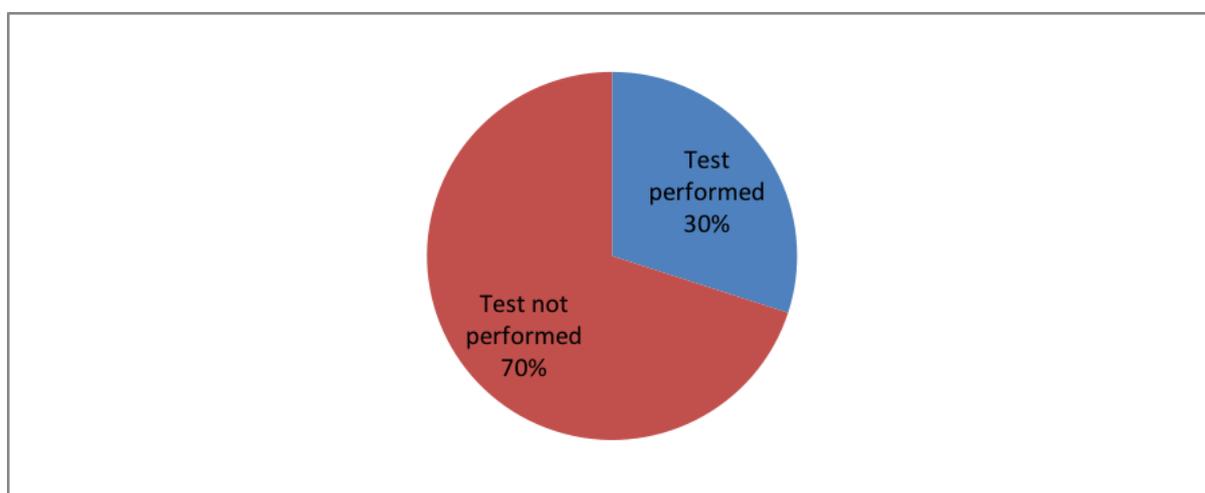


Figure-4: Monitoring by PT with INR measurement

Table 7: Cost estimation of anticoagulants (n= 263)

Variables	Heparin INR	Acenocoumarol INR	Enoxaparin INR	Dalteparin INR	Warfarin INR	Rivaroxaban INR
Cost of single unit	78	9.5	387	302	2	140
Drug cost /day	234	19/-	387/-	302/-	2/-	140/-
7 days drug cost	1,638	133	2,709	2,114	14	980

INR- Indian rupee

DISCUSSION

In the six month study period, anticoagulants are found most commonly prescribed for treatment as well as prophylaxis mainly in the cardiology and neurology wards. Drug use indicators are tools for drug evaluation studies. These indicators include prescribing, facility, patient care, process and outcome indicators. During this period, 263 patients were administered with different anticoagulants for many indications with diagnosis varied from Ischemic heart disease (IHD), deep vein thrombosis (DVT), pulmonary embolism (PE), cardiovascular accident and others. Intravenous heparin was prescribed as a prophylaxis therapy in majority of inpatients of all the departments followed by Acenocoumarol and Enoxaparin. Few other patients from departments other than cardiology and neurology are prescribed with Dalteparin Warfarin and Rivaroxaban. Acenocoumarol and Enoxaparin intended to prevent clots and treat deep vein thrombosis were seen mainly in discharge medication. Among all the prescriptions, 14% cases are found to be prescribed with anticoagulants without any indication, which may increase the burden of drug cost on the patient. As suggested by ACCP, dose adjustment for lower molecular weight heparin for patients with renal impairment was observed in the present hospital. But the monitoring parameters PT, PTT & INR are performed only in few patients and it is advised to perform the monitoring diagnostic test for better therapeutic outcomes. During the search for drug-drug interactions, moderate interactions with Heparin, Acenocoumarol are found in majority of cases. This interaction is due to pharmacokinetic mechanism commonly found was inhibition of vitamin K activity; synergistic effect was the mechanism of pharmacodynamic interaction. In the assessment of cost of anticoagulants, lower molecular weight heparin, Enoxaparin and Dalteparin are found to be highly expensive. However, prescribed according to ACCP guidelines for the treatment of many cardiac and neurological coagulation disorders like, deep vein thrombosis, myocardial infarction and others²³.

CONCLUSION

Anticoagulant, being most commonly prescribed in the treatment of many indications should follow ACCP guidelines for appropriate prescribing for a right indication in a right dose for a right duration. Anticoagulant drug utilization pattern need continuous and repeated monitoring not only to observe therapeutic efficacy, but also to check any possible drug- drug interactions and ADR's. Drug cost of anticoagulants along with diagnosis and monitoring cost may increase the total economic burden on the patients. Hence measures should be taken for making the treatment cost effective and affordable for all socioeconomic communities.

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