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A Prospective Observational Study on Intravenous Heparin Dosing and Therapeutic Activated Partial Thromboplastin Time (aPTT) in Patients with Cardiovascular Diseases

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Abstract:*A prospective observational study was carried out for a period of six months in the Cardiology department of a 700 bedded multispecialty tertiary care teaching hospital. Patients admitted to Cardiovascular Intensive Care Unit (CVICU) and Coronary Care Unit (CCU) of the cardiology department with cardiovascular disease and receiving unfractionated heparin were included in the study. The primary outcome was to understand the practice of heparin dosing in CVD patients in the selected study site and also to monitor the number of patients achieving therapeutic aPTT on Unfractionated Heparin (UFH) during first 6, 24 and 48 hours of admission. The anticoagulant effect of heparin was evaluated by aPTT values obtained. The results obtained were compared with standard dosing guidelines of heparin. The daily doses of heparin administered to the patients were also recorded. The aPTT values of the patients at 6, 24 and 48 hours were evaluated in terms of intensity of anticoagulation and dose adjustment of heparin. Of the 54 patients, aPTT measurements at 6th hour was done for all patients, at least two aPTT measurements were carried out for 31 patients and continuous aPTT measurements were done at 6, 24 and 48 hours only for 19 patients. At 6th hour, thirty-one patients were found to have subtherapeutic aPTT, 15 therapeutic aPTT and 7 supratherapeutic aPTT. At 24th hour, aPTT measurements were done for 31 patients of whom, five showed overanticoagulation. Among the 19 patients who had continuous aPTT monitoring at 6, 24 and 48 hours, five achieved therapeutic range at 48th hour, twelve were in subtherapeutic and 2 in supratherapeutic range. Nineteen adverse drug reactions were reported during the study period.*

Keywords:*Unfractionated Heparin (UFH), aPTT, Anticoagulation, cardiovascular diseases, Heparin Induced Thrombocytopenia (HIT), Coagulation profile.*

I. Introduction

Cardiovascular disease is a heart and blood vessel disease which includes numerous problems, many of which are related to a process called atherosclerosis. Atherosclerosis is a condition that develops when a substance called plaque builds up in the wall of arteries[1, 2]. This build up narrows the arteries and it can stop the blood flow. Among the various CVDs the major types include angina, arrhythmia, congenital heart disease, Coronary Artery Disease (CAD), heart attack,myocardial infarction, heart failure, mitral regurgitation, peripheral venous disease, stroke, peripheral artery disease, aneurysm and atherosclerosis.Cardiovascular diseases are the leading cause of death worldwide compared to any other diseases. In the year of 2012 as per WHO, approximately 17.4 million died from CVD. The two most common complications of CVD are stroke and CAD which account for about 6.7 and 7.4 million deaths respectively.As per the statistical data given by Aggarwal, the President of Heart Care Foundation of India, about 2.4 million Indians die due to heart diseases. The number of deaths due to CVDs will keep increasing because of various risk factors such as hypertension, smoking, hyperlipidemia, diabetes mellitus, lack of physical activity and stress [4].

Drugs used for treating cardiovascular diseases include ACE inhibitors, ARBs, calcium channel blockers, diuretics, vasodilators, beta blockers, anticoagulants and antihyperlipidaemic drugs.Unfractionated Heparin (UFH) is an antithrombotic agent used as first line therapy in the prophylaxis nd management of thrombotic disorders and acute coronary syndrome[10].Heparin is an indirect thrombin inhibitor, which complexes with antithrombin (AT), a naturally occurring anticoagulant protein found in blood and converts this circulating co-factor from a slow-to-rapid inactivator of thrombin, factor Xa, and to a lesser extent, factors XIIa, X1a and IXa. Major limitations of heparin include narrow therapeutic window of adequate anticoagulation and a highly variable dose response relationship that necessitates monitoring heparin therapy by laboratory testing.Heparin is conventionally given as IV in bolus doses of 5,000-10,000 U (children 50-100U/kg) every 4-6 hours; the initial bolus dose is followed by continuous infusion of 750-1000U/hr which may reduce the total dose needed and the incidence of bleeding. The two primary complications due to heparin therapy are hemorrhage due to overanticoagulation and Heparin-Induced Thrombocytopenia (HIT). Heparin dosing is to be considered

important because too less heparin cannot sufficiently inhibit clotting and overdose can cause life threatening bleeding. The anticoagulant effect of Unfractionated Heparin (UFH) is usually monitored by the clot based test, activated Partial Thromboplastin Time (aPTT). Other clot-based tests such as Prothrombin Time (PT) and International Normalized Ratio (INR) are less frequently used. The aPTT should be obtained at baseline before commencing therapy and then monitored 6 hours after commencing heparin therapy. Subsequent dosing adjustments are based on these results. aPTT measures one part of clotting pathway known as the "intrinsic pathway", this is mainly for the patient's plasma to clot after the addition of an intrinsic pathway activator, phospholipid, and calcium. The aPTT ratio is used to determine the therapeutic effect which is measured by dividing the observed aPTT by the mean of the normal laboratory control of the aPTT. A therapeutic aPTT ratio of 1.5- 2.5 times the mean (30 seconds) has gained wide acceptance in the routine clinical practice[10]. Close monitoring of the activated Partial Thromboplastin Time (aPTT) and heparin dose adjustment is necessary to reduce the risk of thrombotic events and bleeding.The importance of frequent monitoring of aPTT in heparinized patients and dose adjustment of heparin has also been highlighted by Alsayegh*et al.,* in a prospective observational study conducted in CCU patients[10]. The current study aimed to understand the practice of anticoagulation using UFH, monitoring of aPTT and dose adjustment of heparin in the cardiology department.

II. Objective

- To study the current practice of dose adjustment of heparin.
- To monitor the activated Partial Thromboplastin Time (aPTT) in heparinized patients.
- To assess the number of patients who attained therapeutic aPTT with heparin therapy within the first 6, 24 and 48 hours of their admission.

III. Methodology

Study site: Cardiology department of a 700 bedded multi-specialty tertiary care private corporate hospital.
Study duration: 6 months (December 2014 - May 2015).
Study design: Prospective observational study

Major outcome measures:

The primary outcome was to understand the practice of heparin dosing in CVD patients in the selected study site and also to monitor the number of patients achieving therapeutic aPTT on Unfractionated Heparin (UFH) during first 6, 24 and 48 hours of admission.

Inclusion criteria:

Patients admitted to Cardiovascular Intensive Care Unit (CVICU) and Coronary Care Unit (CCU) of the cardiology department with cardiovascular disease and receiving UFH were included in the study.

Exclusion criteria:

Patients who did not receive UFH during their stay in CVICU and CCU and patients with insufficient data in their records were excluded from the study.

IV. Method

The protocol of the study was approved by the hospital ethical committee (Annexure I). Patient characteristics, details of prescribed drugs (generic and brand name of drugs, dosage form, frequency and route of administration) coagulation profile and diagnosis are recorded in the structured proforma (Annexure II) for a period of 6 months. The anticoagulant effect of heparin was evaluated by aPTT. A therapeutic aPTT ratio is 1.5–2.5 times the mean while aPTT ratio is considered to be subtherapeutic when it is less than 1.5. A ratio higher than 2.5 is considered over anticoagulated state. The aPTT ratio is noted at the time of admission, after 6, 24 and 48 hours of starting heparin therapy for the selected patients. The data obtained were then compared with the baseline aPTT data. The daily doses of heparin administered to the patients were also recorded. The results obtained were compared with standard dosing guidelines of heparin which is given below. The dose adjustment of heparin in order to keep aPTT in the therapeutic range was evaluated.

Adjustment of IV heparin dose

S. No	aPTT ratio	INFUSION RATE CHANGE
1.	>7	Stop for 30 min – 1 hr and reduce by 500 U/hr (1ml/hr)
2.	5.1 – 7.0	Reduce by 500 units/hr (1 ml / hr)
3.	4.1 – 5.0	Reduce by 300 units/hr (0.6 ml / hr)
4.	3.1 – 4.0	Reduce by 100 units/hr (0.2 ml / hr)
5.	2.6 – 3.0	Reduce by 50 units/hr (0.1 ml / hr)

6.	1.5 – 2.5	NO CHANGE
7.	1.2 – 1.4	Increase by 200 units/hr (0.4 ml / hr)
8.	< 1.2	Increase by 400 units/hr (0.8 ml / hr)

V. Results and discussion

The study included 54 patients with a mean age of 56.87±12.61 (range 14 – 79years). In the total population, 69% were male shown in fig 1. A total of 620 drugs were prescribed in the study population with a mean of 11.11 ± 2.84 (7-17) and number of drugs prescribed per patient is shown in fig 2. The demographic data of the study subjects are presented in TABLE 1. The major diagnoses include Ischemic Heart Disease (25.92%), followed by Left Ventricular Failure (20.37%), Valve Abnormalities (18.51%) and Deep Vein Thrombosis (14.81%). The details of major diagnoses are shown in TABLE 2.TABLE 3 shows the co-morbidities of the patients included in the study. Type 2 diabetes mellitus (36.36%) and SHT (22.72%) were the most frequent concomitant diseases.Eleven different categories of drugs were prescribed in the selected subjects. These include cardiovascular drugs (46.12%), gastro intestinal drugs (10%), vitamins (9.67%) and antibacterial and antifungal drugs (8.2%). TABLE 4 summarizes the various therapeutic categories of drugs prescribed in the present study.Of the two hundred and eighty six cardiovascular drugs prescribed (TABLE 5), anticoagulants (28.2%), antiplatelets (26.6%), drugs for congestive heart failure(25%) and antihyperlipidemic drugs(12.09%) constituted the maximum.The dose of various drugs prescribed and the pharmaceutical formulation are summarized from TABLE 6 to13.Indication for anticoagulation and heparin dosing in the study subjects are shown in TABLE 14 along with the duration of treatment with heparin. One patient received long term treatment of heparin uptofourteendays. Six patientsreceived short course for three days. The mean duration of heparin therapy was 5.98 ± 2.56 (range 3 - 14) days.

TABLE 15 describes coagulation profile which includes aPTT, International Normalized Ratio(INR), rothrombin Ratio, International Standardized Index(ISI), Prothrombin Time, bleeding time and clotting time.The aPTT values at 6, 24 and 48 hours for patients with various indications are shown in table 16. Of the 54 patients, aPTT measurements were done at 6, 24 and 48 hours for 19 patients and at least two aPTT measurements were carried out for 31 patients and aPTT measurements at 6^{th} hour were done for all patients.The intensity of anticoagulation at 6, 24 and 48 hours has been shown in TABLE 17. Of the 54patients, 31 were found to have subtherapeutic aPTT, 15 therapeutic aPTT and 7 supratherapeutic aPTT at 6^{th} hour. At 24^{th} hour, aPTT measurements were done for 31 patients of which five showed overanticoagulation. Among the 54 patients, 19 patients had continuous monitoring of aPTT at 6, 24 and 48 hours of which 5 achieved therapeutic range at 48^{th} hour. Twelve were in subtherapeutic and 2 were in supratherapeutic range.

Nineteen adverse drug reactions were reported during the study period. These include heparin inducedthrombocytopenia (27.77%), bleeding (5.55%) and 1 case of death (1.85%). The bleeding episodes were haematuria (1.85%), intracranial bleeding (1.85%) and epistaxis (1.85%).It was found that 14.19% of prescribed drugs had drug–drug interactions. The most commonly seen interacting drug combinations were heparin with clopidogrel(15.78%), heparin with aspirin(7.45%), atorvastatin with clopidogrel(7.45%) and clopidogrel with aspirin(7.01%).A contraindicated combination of amiodarone with fluconazole was also observed during the study.

Table 1: Demographic details (n=54)

S. No.	Age group (years)	No. of patients (%)	Mean age (years) ±s	Gender	Duration of hospitalization (days)	No. of drugs prescribed
1.	Adolescent (13-18)	1 (1.8%)	56.87± 12.61	MALE 37 (69 %) FEMALE 17 (31%)	5	13
2.	Early adulthood (19-35)	1 (1.8%)			5	10
3.	Adulthood (36-50)	14 (25.9%)			7.64±3.17	11.35±3.62

4.	Late adulthood (51-65)	22 (40.7%)			6.81±2.78	11.27±3.02
5.	Young adulthood (66-74)	14 (24.9%)			7.64±2.59	10.71±2.16
6.	Old adulthood (75-84)	2 (3.7%)			7.50±3.53	9.50±0.70

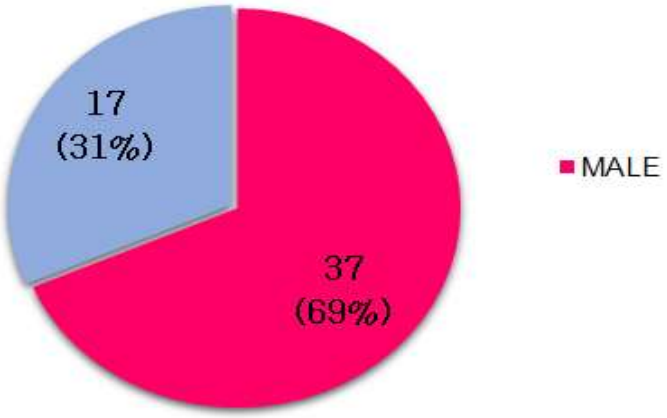

Figure 1: Gender distribution

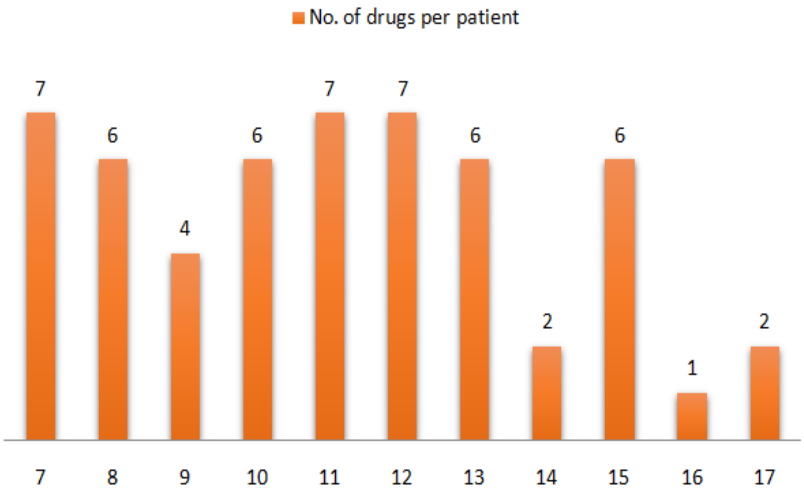

Figure 2: No. of drugs per patient

Table 2: Major diagnosis (n = 84)

S.No.	Diagnosis	No. of patients	Percentage (%)
1.	Ischemic Heart Disease (IHD)	14	14.89
2.	Left Ventricular Failure(LVF)	11	11.70
3.	Valve Abnormalities	10	10.63
4.	Deep Vein Thrombosis (DVT)	8	8.51

5.	Coronary Artery Disease (CAD)	7	7.44
6.	Left Ventricular Dysfunction (LVD)	6	6.38
7.	Myocardial Infarction (MI)	6	6.38
8.	Acute Coronary Syndrome (ACS)	5	5.31
9.	Rheumatic Heart Disease (RHD)	5	5.31
10.	Congestive Cardiac Failure (CCF)	4	4.25
11.	Atrial Fibrillation (AF)	3	3.19
12.	Angina	3	3.19
13.	Left Ventricular Aneurysm	1	1.06
14.	Complete Heart Block	1	1.06

Table 3: Co-morbidities (n= 44)

S.no.	Co-Morbidities	No. of patients	Percentage (%)
1	Type 2 Diabetes Mellitus (T_2DM)	16	36.36
2	Systemic Hypertension (SHT)	10	22.72
3	Acute Renal Failure (ARF)	3	6.81
4	Iron Deficiency Anaemia (IDA)	2	4.54
5	Gangrene	2	4.54
6	Mitral Stenosis	2	4.54
7	Cytomegalo Virus Infection	1	2.27
8	Chronic Obstructive Pulmonary Disease (COPD)	1	2.27
9	Hypothyroidism	1	2.27
10	Chronic Ulcer	1	2.27
11	Hypokalemia	1	2.27
12	Pulmonary Edema	1	2.27
13	Respiratory Infection	1	2.27
14	Chronic Renal Failure (CRF)	1	2.27
15	Pulmonary Hypertension	1	2.27

Table 4: Therapeutic Categories of Prescribed Drugs (n=620)

S.no.	Therapeutic categories	No. of drugs	Percentage (%)	No. of patients	Percentage (%)
1.	Cardiovascular drugs	286	46.12	54	100
2.	Gastrointestinal drugs	62	10	40	74.07
3.	Vitamins	60	9.67	32	59.25
4.	Antibacterial and antifungal drugs	51	8.22	36	66.66
5.	Autacoids and related drugs	43	6.93	30	55.55
6.	Drugs acting on kidneys	41	6.61	28	51.85
7.	Drugs acting on central nervous system	30	4.83	22	40.7
8.	Hormones and related drugs	23	3.70	17	31.48
9.	Drugs acting on respiratory system	19	3.06	16	29
10.	Drugs acting on peripheral nervous system	3	0.48	3	5.55
11.	Alkylating agents	2	0.32	2	3.70

Table 5: Cardiovascular Drugs (n=286)

S.no.	Cardiovascular drugs	No. Of drugs	Percentage (%)
1.	Anticoagulants	70	28.22
2.	Antiplatelet drugs	66	26.61
3.	Drugs for congestive heart failure	62	25
4.	Antihyperlipidemic drugs	30	12.09
5.	Antianginals	26	10.48
6.	Antihypertensives	21	8.46
7.	Antiarrhythmic drugs	10	4.03
8.	Fibrinolytics	1	0.40

Table 6:antihypertensives (n=21

S.no.	Antihypertensives	Dose	Frequency	No. of drugs	Percentage (%)
1.	**ANGIOTENSIN RECEPTOR BLOCKERS(ARB)**				**9.52**
	i. T.Losartan	50 mg	OD	1	4.76
	ii. T.Telmisartan	40 mg	OD	1	4.76
2.	**CALCIUM CHANNEL BLOCKERS(CCB)**				**28.57**
	i. T.Cilnidipine	10mg	OD	2	9.52
	ii. T.Amlodipine	5mg	OD	3	14.28
	iii. T.Nifedipine	10 mg	OD	1	4.76
3.	**BETA ADRENERGIC BLOCKERS**				**38.08**
	i. T.Nebivolol	5mg	OD	2	9.52
	ii. T.Metoprolol	25mg	OD	4	19.04
	iii. T.Propranolol	25mg	OD	2	9.52
4.	**ALPHA AND BETA BLOCKERS**				
	i. T.Carvedilol	3.125mg	OD	5	23.80

Table 7:antianginals (n=26)

S.no.	Antianginals	Dose	Frequency	No. of drugs	Percentage (%)

1.	**NITRATES**				**23.07**
	i. T.Sorbitrate	5 mg	SOS	1	3.84
	ii. T.Isosorbidemono-nitrate	5 mg	SOS	4	15.38
	iii. T.Nitroglycerine	2.6 mg	OD	1	3.84
2.	**POTASSIUM CHANNEL OPENER**				**7.69**
	i. T.Nicorandil	5 mg	BD	2	7.69
3.	**OTHERS**				**85.71**
	i. T.Trimetazidine	35 mg	BD	15	57.69
	ii. T.Ivabradine	5 mg	BD	2	7.69
	iii. T.Ranolazine	500mg	BD	1	3.84

Table 8: Drugs for Congestive Heart Failure (CHF) (n=62)

S.No.	Drugs for CHF	Dose	Frequency	No. Of drugs	Percentage (%)
1.	**IONOTROPIC DRUGS**				**30.6**
	i. T.Digoxin	0.25mg	OD	6	9.67
	ii. Inj.Dopamine	200mg	OD	3	4.83
	iii. Inj.Dobutamine	250 mg	BD	6	9.67
	iv. T.Cilostazol	50 mg, 100mg	BD	4	6.45
2.	**DIURETICS**				**38.7**
	i. T.Furosemide	40 mg	OD	19	30.64
	ii. T.Torsemide	10 mg	OD	4	6.45
	iii. Inj.Mannitol	10g	OD	1	1.61
3.	**INHIBITORS OF RENIN ANGIOTENSIN SYSTEM**				**6.45**
	i. T.Ramipril	5mg	BD	4	6.45
4.	**ALDOSTERONE ANTAGONISTS**				**22.58**
	i. T.Spironolactone	50 mg	OD	14	22.58
5.	**OTHERS**				**1.61**
	i. T.Pentoxifylline	400 mg	OD	1	1.61

Table 9: Anticoagulants (n=70)

S.No.	Anticoagulants	Dose	Frequency	No. Of drugs	Percentage (%)
1.	**PARENTRAL**				**77.14**
	i. Inj.Heparin	3000 – 10,000U	Q6H	53	
	ii Inj.Fondaparinux	7.5 mg		1	
2.	**ORAL**				**22.85**
	i. T.Acenocoumarol	1 mg	OD	3	
	ii. T.Warfarin	5mg	OD	13	

Table 10: Fibrinolytics (N=1)

S.no.	Fibrinolytics	Dose	Frequency	No. Of drugs	Percentage (%)
1.	Inj.Streptokinase	15,00,000 IU	OD	1	100

Table 11: Antiplatelet Drugs (n=66)

S.no.	Antiplatelet drugs	Dose	Frequency	No. Of drugs	Percentage (%)
1.	**IRREVERSIBLE COX INHIBITORS**				**33.3**
	i. T.Aspirin	75 mg	OD	22	33.3
2.	**ADENOSINE DIPHOSPHATE RECEPTOR INHIBITOR**				**66.6**
	i. T.Clopidogrel	150mg	OD	42	63.63
	ii. T.Ticagrelor	90 mg	OD	2	3.03

Table 12: Antiarrhythmic Drugs (N=10)

S.no.	Antiarrhythmic drugs	Dose	Frequency	No. Of drugs	Percentage (%)
1.	**CLASS III**				**50**
	i. T.Amiodarone	100 mg	OD	5	50
2.	**INOTROPES**				**50**
	i. Inj.Adrenaline	1 mg	OD	4	40
	ii. Inj.Nor adrenaline	2 mg	OD	1	10

Table 13: Antihyperlipidemic **Drugs (n=30)**

S. No.	Antihyperlipidemic Drugs	Dose	Frequency	No. Of Drugs	Percentage (%)
1.	**HMG-CoA Reductase Inhibitor** i. T.Atorvastatin	40 Mg	Od	30	100

Table 14: Indication for Anticoagulation and Heparin Dosing (N=53)

S.no.	Indication	Heparin dosing	No. Of patients	Percentage (%)	Mean duration of heparin therapy (days) (range)
1.	Ischemic Heart Disease	5000	8	15.09	5.5±2.13 (2-8)
2.	Valve Abnormalities	5000 10000	7 1	13.21 1.88	7.5±3.81 (1-13)
3.	Left Ventricular Failure	3000 5000	3 3	5.66 5.66	4.83±1.83 (5-8)
4.	Rheumatic Heart Disease	5000 10000	4 1	7.54 1.88	7.2± 1.92 (5-10)
5.	Deep Vein Thrombosis	5000 10000	3 2	5.66 3.77	5.8±3.03 (3-11)
6.	Myocardial Infarction	5000	4	7.54	3.75± 0.95(3-5)
7.	Coronary Artery Disease	5000 10000	2 2	3.77 3.77	6.75±0.95 (6-8)
8.	Acute Coronary Syndrome	3000 5000	1 3	1.88 5.66	4.75± 1.50(4-7)
9.	Angina	5000	3	5.66	5.66± 1.15(5-7)
10.	Complete Heart Block	5000	1	1.88	3
11.	Atrial Fibrillation	5000	1	1.88	7
12.	Left Ventricular Dysfunction	3000 5000	1 1	1.88 1.88	9.5±6.36 (5-14)
13.	Left Ventricular Aneurysm	5000	1	1.88	5
14.	Congestive Cardiac Failure	5000	1	1.88	6

Table 15: coagulation profile (n=54)

S. no.	APTT	No. Of patients	APTT at 6^{th} hour	APTT at time of discharge	International normalized Ratio (INR)	Prothrombin ratio (PR)	International standardised index (ISI)	Prothrombin time(PT) (Sec)	Bleeding time (min)	Clotting time (min)
1.	<30	13	25.30± 2.52	42.84 ±16.09	1.13±0.15	1.11±0.16	1.05±1.17	16±2.13	2.4±0.51	6.22±0.44

2.	30-51	23	38.28±5.68	35.87±9.37	1.19±0.26	1.14±0.20	1.01±0.02	15.83±2.61	2.5±1.41	6.12±1.72
3.	52-67	8	57.85±3.18	38±15.55	1.3	1.25±0.071	1.04±0.01	17.16±1.72	4.33±2.31	6
4.	68-95	5	78.4±11.6	43.33±13.31	-	-	-	19±4.24	-	-
5.	>95	5	108.66±3.20	39.66±14.22	1.6±0.45	1.63±0.40	1.05	18.4±5.595	2	6

Table 16: aPTT values at 6, 24 and 48 hrs (n=54)

S.no	Indications	aPTT		
		6hr	24 hr	48 hr
1.	Valve Abnormalities	107	53	-
		48	-	-
		25	70	58
		60	-	-
		32	-	-
		34	30	180
		40	-	-
		28	-	-
2.	Ischemic Heart Disease	92	-	-
		24	180	33
		35	45	45
		43	-	-
		44	44	-
		72	-	-
		32	-	-
		68	-	-
3.	Left Ventricular Failure	110	37	-
		45	32	-
		70	58	-
		38	-	-
		38	-	-

S.no	Indications	aPTT		
		6hr	**24 hr**	**48 hr**
		32	-	-
4.	Deep Vein Thrombosis	24	37	41
		25	23	38
		20	130	36
		31	143	45
		39	-	-
5.	Coronary Artery Disease	29	36	28
		112	64	27
		37	30	-
		45	30	-
		56	-	-
6.	Rheumatic Heart Disease	133	30	30
		41	47	23
		32	41	25
		29	35	-
		30	-	-
7.	Myocardial Infarction	60	-	-
		54	-	-
		62	-	-
		48	-	-
8.	Acute Coronary Syndrome	180	110	37
		90	110	60
		25	42	-
		36	-	-
9.	Angina	59	45	47
		27	18	36
		46	-	-
10.	Left Ventricular Dysfunction	28	52	-

S.no	Indications		aPTT		
			6hr	24 hr	48 hr
			35	-	-
11.	Complete Heart Block	24	46	-	
12.	Atrial Fibrillation	54	49	-	
13.	Left Ventricular Aneurysm	26	35	90	
14.	Congestive Cardiac Failure	29	28	31	

Table 17: Intensity of Anticoagulation at 6, 24 And 48 hrs(N=54)

S.NO.	aPTT (RATIO)	6h	24h	48h
1.	Subtherapeutic	32(59.25%)	16 (51.61%)	12 (63.15%)
2.	Therapeutic	15(27.77%)	10 (32.25%)	5 (26.31%)
3.	Supratherapeutic	7(12.96%)	5 (16.12%)	2 (10.52%)
	Total number	**54**	**31**	**19**

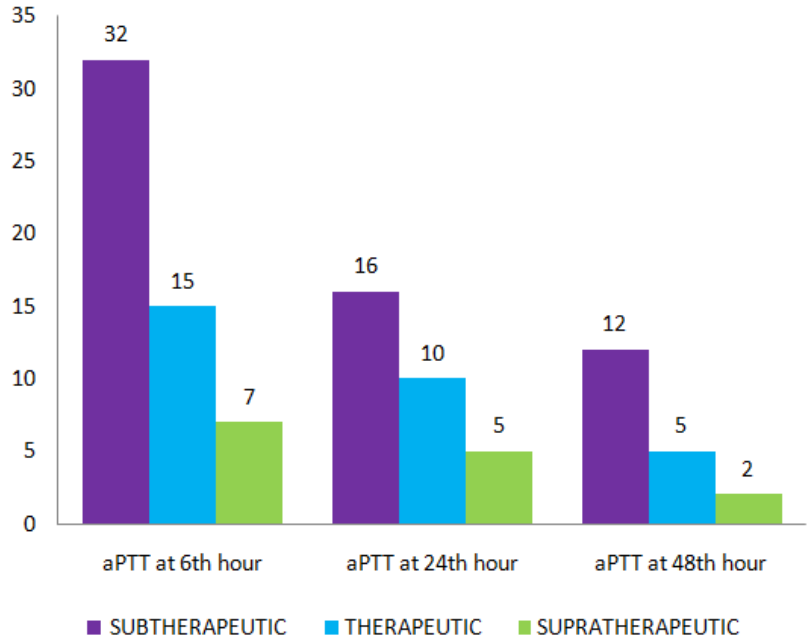

Figure 3: Intensity of Anticoagulation at 6, 24 and 48 hrs (n=54)

Table 18: Adverse Drug Reactions (N=19)

S.no.	Adverse drug reactions	No. Of patients	Percentage (%)
1.	Heparin Induced Thrombocytopenia	15	27.77
2.	Bleeding	3	5.55
3.	Death	1	1.85

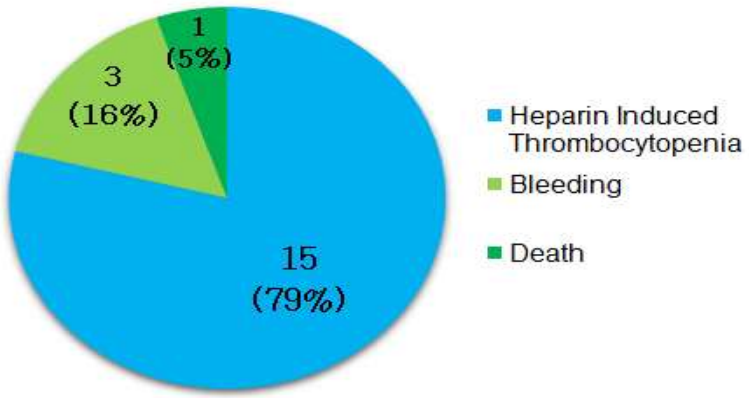

Figure 4: Adverse Drug Reactions (n=19)

Table 19: Drug Interactions (N=88)

S. No	Interacting drugs	Effect	Severity	No of patients
1	**Heparin + Clopidogrel**	**Increased risk of bleeding**	**Major**	**36**
2.	**Heparin + Aspirin**	**Increased risk of bleeding**	**Major**	**17**
3.	Atorvastatin + Clopidogrel	Decreased formation of clopidogrel active metabolite	Moderate	17
4.	**Clopidogrel + Aspirin**	**Increased risk of bleeding**	**Major**	**16**
5.	**Clopidogrel + Warfarin**	**Increased risk of bleeding**	**Major**	**11**
6.	Heparin + Warfarin	Increased risk of bleeding	Moderate	7
7.	**Diazepam + Morphine**	**Additive respiratory depression**	**Major**	**4**
8.	Aspirin + Spironolactone	Nephrotoxicity and hyperkalemia	Moderate	4
9.	Aspirin + Furosemide	Decreased diuretic and antihypertensive efficacy	Moderate	4
10.	Amiodarone + Atorvastatin	Increased risk of myopathy	Moderate	3
11.	**Morphine + Promethazine**	**Increased risk of paralytic ileus and CNS depression**	**Major**	**3**
12.	**Cilostazol + Pantoprazole**	**Increased cilostazol exposure**	**Major**	**3**
13.	Atorvastatin + Pantoprazole	Increased blood levels and effects of atorvastatin	Moderate	3
14.	Clopidogrel + Pantoprazole	Reduce effectiveness of clopidogrel in preventing heart attack	Moderate	3
15.	Aspirin + Insulin	Hypoglycemia	Moderate	3
16.	**Heparin + Nitroglycerin**	**Decrease the partial thromboplastin time**	**Major**	**2**
17.	**Furosemide + Insulin**	**Increased hyperglycemic risk**	**Major**	**2**
18.	Aspirin + Torsemide	Decreased diuretic effect	Moderate	2
19.	Diazepam + Digoxin	Digoxin toxicity	Moderate	2
20.	**Cilostazol + Clopidogrel**	**Increased risk of bleeding**	**Major**	**2**
21.	Warfarin + Ceftriaxone	Increased risk of bleeding	Moderate	2
22.	Pantoprazole + Warfarin	Increased INR and PT	Moderate	2
23.	Ticagrelor + Heparin	Either of the drug increases the effect of anticoagulant	Moderate	2
24.	Aspirin + Calcium	Decrease the effects of calcium	Moderate	2
25.	**Piperacillin/Tazobactam + Warfarin**	**Increased risk of bleeding**	**Major**	**1**
26.	**Clopidogrel + Nifedipine**	**Increased risk of thrombotic events**	**Major**	**1**

27.	**Amiodarone + Ondansetron**	**Increased QT interval**	**Major**	**1**
28.	**Carvidelol + Morphine**	**Increased morphine exposure**	**Major**	**1**
29.	Acetaminophen + Warfarin	Increased risk of bleeding	Moderate	1
30.	Carvedilol + Digoxin	Increased risk of bradycardia	Moderate	1
31.	Alprazolam + Nifedipine	Increased bronchial asthma and pharmacodynamic effects of alprazolam	Moderate	1
32.	Aspirin + Ramipril	Decreased ramipril effectiveness	Moderate	1
33.	Insulin + Ramipril	Increased risk of hypoglycemia	Moderate	1
34.	Furosemide + Digoxin	Hyperkalemia	Moderate	1
35.	Digoxin + Atorvastatin	Leads to nausea, anorexia and visual changes	Moderate	1
36.	**Amlodipine + Clopidogrel**	**Decreased antiplatelet effect**	**Major**	**1**
37.	Amlodipine + Aspirin	Increased risk of GI hemorrhage	Moderate	1
38.	Amiodarone + Clopidogrel	Ineffective inhibition of platelet aggregation	Moderate	1
39.	**Moxifloxacin + Ondansetron**	**QT interval prolongation**	**Major**	**1**
40.	**Moxifloxacin + Warfarin**	**Increased risk of bleeding**	**Major**	**1**
41.	**Heparin + Streptokinase**	**Increased risk of bleeding**	**Major**	**1**
42.	Streptokinase + Clopidogrel	Increased risk of bleeding	Moderate	1
43.	Aspirin + Hydrocortisone	Combination makes aspirin less effective	Moderate	1
44.	**Potassium Chloride + Spironolactone**	**Hyperkalemia**	**Major**	**1**
45.	Aspirin + Prednisolone	Increased risk of GI ulceration	Moderate	1
46.	**Amiodarone + Ticagrelor**	**Increased exposure of both drugs**	**Major**	**1**
47.	**Aspirin + Ticagrelor**	**Increased risk of bleeding**	**Major**	**1**
48.	**Phenytoin + Ticagrelor**	**Decreased ticagrelor concentration**	**Major**	**1**
49.	Alprazolam + Amiodarone	Increased bronchial asthma	Moderate	1
50	Amiodarone + Phenytoin	Increased risk of phenytoin toxicity	Moderate	1
51.	Clopidogrel + Torsemide	Increased risk of torsemide toxicity	Moderate	1
52.	Furosemide + Ramipril	Postural hypotension	Moderate	1
53.	**Morphine + Acetaminophen**	**Increased risk of CNS depression**	**Major**	**1**
54.	**Promethazine + Acetaminophen**	**Increased risk of seizure**	**Major**	**1**
55.	Levothyroxine +Warfarin	Increased risk of bleeding	Moderate	1
56.	Promethazine + Torsemide	Both have additive effects of lowering BP	Moderate	1
57.	Midazolam + Torsemide	Reduces BP	Moderate	1
58.	Diazepam + Torsemide	Reduces BP	Moderate	1
59.	**Ciprofloxacin + Ondansetron**	**Increased risk of QT interval prolongation**	**Major**	**1**
60.	Amlodipine + Ciprofloxacin	Increased amlodipine exposure	Moderate	1
61.	Amikacin + Piperacillin/Tazobactam	May result in loss of aminoglycoside efficacy	Minor	1
62.	Glimepiride + Furosemide	Increased hyperglycemia risk	Moderate	1
63.	Glimepiride + Warfarin	Excessive hypoglycemia	Moderate	1
64.	Furosemide + Metformin	Results in worsening of glycemic control	Moderate	1
65.	Glimepiride + Spironolactone	Increased insulin requirement	Moderate	1

66.	**Atorvastatin + Ranolazine**	**Increases blood levels of atorvastatin**	**Major**	**1**
67.	Carvedilol + Ranolazine	Ranolazine may increase the blood levels and effects of carvedilol	Moderate	1
68.	Tramadol + Ranolazine	Increase blood levels and effects of tramadol	Moderate	1
69.	Calcium Supplement/Vitamin D + Carvedilol	Calcium decreases the effects of carvedilol	Moderate	1
70.	Furosemide + Pantoprazole	Hypomagnesemia	Moderate	1
71.	Warfarin + Tramadol	Increaded INR	Moderate	1
72.	**Clopidogrel + Paracetamol**	**Reduces the effectiveness of clopidogrel in preventing heart attack or stroke**	**Major**	**1**
73.	**Alprazolam + Digoxin**	**Digoxin toxicity**	**Major**	**1**
74.	Dobutamine + Insulin	Impaired glucose regulation	Moderate	1
75.	Aspirin + Nebivolol	Decreased antihypertensive effect	Moderate	1
76.	Insulin + Nebivolol	Hypoglycemiaor hyperglycemia	Moderate	1
77.	Insulin +Spironolactone	Hypoglycaemia or hyperglycemia	Moderate	1
78.	**Budesonide/Formoterol+ Linezolid**	**Increased risk of cardiovascular adverse effects**	**Major**	**1**
79.	**Budesonide/Formoterol+ Ondansetron**	**Increased risk of ventricular arrhythmias**	**major**	**1**
80.	**Clopidogrel + Rabeprazole**	**Increased risk of thrombosis**	**Major**	**1**
81.	Aspirin + Carvedilol	Decreased antihypertensive effect	Moderate	1
82.	Bromelain + Heparin	Increased risk of bleeding	Moderate	1
83.	Warfarin +Ceftriaxone	Increased risk of bleeding	Moderate	1
84.	**Cilostazol +Amiodarone**	**Increased amiodarone and cilostazol exposure**	**Major**	**1**
85.	**Cilostazol +Fluconazole**	**Increased cilostazol exposure**	**Major**	**1**
86.	**Amiodarone + Fluconazole**	**Increased amiodarone exposure and risk of cardio-toxicity**	**Contraindicated**	**1**
87.	Propanolol + Pantoprazole	Increased propanolol exposure	Moderate	1
88.	Aspirin + Ranitidine	Decreased salicylated plasma levels and decreased antiplatelet effect of aspirin	Minor	1

VI. Conclusion

Diabetes mellitus and hypertension were the two common co-morbid conditions observed in the study population[13]. High glucose levels in the blood stream damages the arteries causing them stiff and hard. Fatty material builds up in the blood vessel block the blood flow to the heart leading to heart failure. Several studies[14,15] indicate that the co-existence of DM and SHT will lead to cardiovascular diseases such as ischemic heart disease, acute coronary syndrome, deep vein thrombosis and myocardial infarction. Unfractionated heparin (UFH) has been commonly used in Cardiovascular Intensive Care Unit (CVICU) and Coronary Care Unit (CCU) of the cardiology department for the treatment of cardiac diseases such as ischemic heart disease, left ventricular dysfunction, acute coronary syndrome and valve abnormalities.Various UFH dosing nomograms have been used in different types ofcardiovascular disease treatment settings. These include weight based nomograms[9,16], disease based nomograms[11], aPTT based nomograms[12,17,18] and intensity based nomograms[19]. In the current study, standard UFH dosing guidelines have been followed. The various initial dosing of UFH observed in the current study ranged from 3000-10,000 units based on the cardiovascular disease condition and severity. Ten thousand units of heparin was used only in 3 subjects; a case of valve abnormality with severe aortic sclerosis, rheumatic heart disease and deep vein thrombosis. In these patients UFH was administered as infusion at a rate of 100 units/kg/hr. Eight patients with valve abnormalities and 5 patients with deep vein thrombosis received 5000 units of heparin as bolus dose except one case who received as infusion at the rate of 100 units/kg/hr. The anticoagulant effect of UFH was monitored in the current study by means of measuring

activated Partial Thromboplastin Time (aPTT). The therapeutic aPTT ratio of 1.5- 2.5 times the mean (30 seconds) is widely used in routine clinical practice. aPTT range below 45 seconds is considered as subtherapeutic and above 75 seconds as supratherapeutic.

The aPTT values were monitored at 6, 24 and 48th hour. At 6th hour, the aPTT measurements were carried out for all the patients and found that 15 of them achieved therapeutic range (45-75 seconds) and therefore the same initial dose of UFH was continued in these patients. Thirty-two of them were in subtherapeutic range but dose was increased only in 12 cases. Similarly, 7 were over-anticoagulated however, the dose of heparin was reduced only in 2 cases. The results of aPTT measurements showed that at 6th hour 39 patients were either in subtherapeutic or supratherapeutic aPTT, indicating the need for continuous aPTT measurements in these patients. However, it was observed that the measurements of aPTT were carried out only in 31 patients at 24th hour. Of the 31 subjects who had their aPTT values at 24th hour, ten were found to achieve therapeutic range whereas 16 were in subtherapeutic range but dose was increased in 4 patients. Of the five patients in supratherapeutic range, heparin was stopped in two patients and tablet clopidogrel 75 mg OD or warfarin 5 mg OD was initiated. In one patient heparin infusion rate was reduced by 0.2 units/kg/hr. In two patients, it was observed that the dose of heparin was not reduced. According to NHS foundation trust clinical guidelines, infusion can be stopped for 30 minutes or the rate of infusion can be decreased by 0.1 ml/hr[18].

Among the 54 study subjects, only 19 patients had aPTT measurements at 6, 24 and 48 hrs. Of these, 5 patients achieved therapeutic aPTT values at 48th hour, whereas 12 were in subtherapeutic and 2 in supratherapeutic range, indicating possibilities of thrombotic events and overanticoagulation respectively. For these patients the dose of UFH was modified based on the aPTT values. According to adult full-dose heparin protocol, the dose of UFH can be either increased or decreased at a rate of 2 units/kg/hr in those patients with aPTT values less than 45 and more than 75 respectively[20].

Based on the study conducted by Alsayegh et al.[10](2009) in the CCU at Kuwait hospital, a high rate of inadequate heparinization was seen in 41.1%, 42.3% and 46.7% patients at 6, 24 and 48 hrs respectively, thereby exposing the patients to the risk of thrombotic events. The main reason for inadequate heparinization can be due to the altered heparin pharmacokinetics, pharmacodynamics, weight variability and age; hence resulting in inappropriate initial dosing and dosage adjustments. In current study inadequate heparinization was observed in 59.52%, 51.61% and 63.15% at 6, 24 and 48 hrs respectively. aPTT monitoring was done at 6thhr for 54 patients, at 24thhr and 48thhr for 31 and 19 patients respectively.

In the present study, Heparin Induced Thrombocytopenia (HIT) was seen in 15 patients, bleeding in 3 patients and also a case of death. The platelet count was found to decrease from the range of 5,09,000 cells/mm^3 to 68,000 cells/mm. One patient was admitted with heparin induced bleeding where heparin was indicated for PTCA (Percutaneous TransmembraneCoronary Angioplasty) for triple vessel disease. The patient developedaltered sensorium, aphasia, right sided weakness after administration of heparin. Left fronto-parietal hematoma was observed in CT brain scan. For this case, aPTT was found to be 112 seconds and hence heparin was stopped and injection Protamine sulphate was initiated at the rate of 0.5mg/kg. Due to the inevitable condition for anticoagulation low molecular weight heparin was given to keep the patient away from thrombotic events. Later, it was noticed that aPTT reached the therapeutic range in this patient.During the study, eighty-eight drug- drug interactions (14.19%) were noted, out of which major drug interaction accounted for 37.5%. The most common major drug interactions were between heparin with clopidogrel and aspirin.

Clopidogrel causes an increased risk of bleeding due to synergistic effect when administered along with aspirin/heparin/warfarin. It should be used concurrently only if potential benefit outweighs the significant risk of bleeding. If used, aPTT should be monitored closely. Such additive effects are also possible with the combination of heparin and streptokinase or bromelain.Another potentially dangerous interacting combination observed during the study between cilostazol – a phospho-diesterase inhibitor and pantoprazole. Pantoprazole increases the toxicity of Cilostazol by affecting hepatic enzyme CYP_2C_{19} metabolism. Therefore, the dose of cilostazol should be reduced and patient should be monitored closely for adverse effects of cilostazol such as bleeding. Recommended dose of cilostazol is 50mg BD in the presence of pantoprazole.

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