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ORIGINAL ARTICLE

Incidence of Heparin Resistance after Preoperative Heparin Therapy in patients undergoing Open Heart Surgery

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ABSTRACT

Aim: Incidence of Heparin Resistance after preoperative heparin therapy in patients undergoing open heart surgery.
Methods: The Prospective Observational study included 124 patients of different heart diseases undergoing open heart surgery, at cardiac surgery department of Punjab Institute of Cardiology; Lahore Pakistan was performed between 5th October 2013 to 16 March 2014. Both genders age 18-75 were included. All those patients who present with diseases other than heart diseases, age <18 and > 75 were excluded in the study. Data was analyzed using Statistical Package for Social Sciences (SPSS) version 16.0. P-value ≤ 0.05 were considered significant.
Results: Our results showed that out of 124 patients, 87(70.16%) were male while 37(29.84%) were females. Clinical characteristics i.e. (hypertension, diabetes mellitus, emergency bypass, smoking, alcohol intake, hyperlipidemias, obesity and family history) were insignificantly associated with heparin resistance. The clinical characteristics i.e. (baseline activated clotting time, albumin and cross clamp time) were significantly associated with the development of heparin resistance as (p-value <0.05 .015, .041 and .025 respectively).
Conclusion: The results indicate that the incidence of heparin resistance after preoperative heparin therapy was 8.06%.

INTRODUCTION

Heparin administration is the most prevalent means of modulating the human coagulation system during cardiopulmonary bypass[1]. Heparin, a found naturally mucopolysaccharide, accelerates the coagulation of antithrombin III (AT III) and other coagulation proteases to variable degrees[2]. Heparin's distribution is confined to the plasma volume, and it is removed through the reticuloendothelial system. Heparin has a half-life of about 90 minutes. Because the half-life of this medicine increases as plasma concentration increased, this can be classified as a concentration-dependent drug.[3] Heparin therapy is becoming more used in a variety of therapeutic situations. Given the seriousness of the diseases treated with heparin, it is critical to reach the treatment aim in a short period of time in order to reap the greatest benefit. Anticoagulation also is required for operations like cardiopulmonary bypass and hemodialysis[4].

TThe majority of universities utilise an ACT level of 400 to 480 seconds as an acceptable ACT level for CPB. Hypothermia, hemo dilution, poor platelet function, and low fibrinogen are some of the conditions that can prolong ACT, even when heparinisation is inadequate[5]. Clinical illnesses involving congenital or acquired AT-III deficiency are connected to heparin resistance. Although hemodilution during CPB can lower AT-III levels, it is also connected to dilution of procoagulant chemicals, therefore heparin resistance is rarely seen. The most prevalent cause of heparin resistance in cardiac surgery patients is AT-III depletion or dysfunction, which is caused by prior heparin administration[6]. AT III activity reduction (sometimes accompanied by heparin resistance) is more common in certain patient groups. Lower preoperative AT III activity, advanced age, and diabetes, as well as following a combination operation or prolonged cardiopulmonary bypass, have all been linked to reduced postoperative AT III activity. In other circumstances, however, reduced AT III activity is helpful[7].

Heparin-induced thrombocytopenia is a potentially fatal condition caused by unfractionated or (less typically) low-molecular-weight heparin exposure. Patients typically have a low platelet count (less than 150,000 per cubic millimetre) or a relative loss of 50% or more from baseline,1,2, though in certain cases the drop may be less (e.g., 30 to 40%). Approximately 20 to 50% of patients experience thrombotic problems [8].

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When fresh frozen plasma is given to patients who have developed heparin resistance, their heparin/ACT dose response curve is normalised. During cardiopulmonary bypass, there is also a reduction in total heparin needs. These findings suggest that one or more plasma-clotting factors are deficient[9].

Cardiopulmonary bypass was started after the confirmation of adequate ACT in normothermia or moderate hypothermia (34°C) with topical cooling. At 400 seconds, heparinization with 300 IU kg–1 unfractionated heparin was utilised to achieve the goal value of ACT. A Hemochron 401 coagulation monitoring instrument was used to quantify ACT (Technidyne Corp., Edison, NJ, USA). After cardiopulmonary bypass was stopped, protamine sulphate was given in a 1:1 ratio to reverse the original heparin dose[10].

Aims and objectives

1. To determine the Incidence of Heparin Resistance after preoperative heparin therapy in patients undergoing open heart surgery
2. To study the association of Heparin Resistance after preoperative heparin therapy in open heart surgery
3. To study the association of Heparin Resistance after preoperative heparin therapy with demographical and clinical characteristics among patients undergoing open he

MATERIALS AND METHODS

It was hospital based study, so the population to be dealt was the patients undergoing open heart surgery. After permission from Ethical Committee, a Prospective Observational study conducted at Punjab Institute of Cardiology, Punjab from 5th, October 2013 to 16 March 2014. Minimum sample size is calculated by the following formula, Non-probability purposive sampling technique was used.

$$\frac{(Z_{1-\alpha/2}\,\lambda_o + Z_{1-\beta}\,\lambda_a)^2}{(\lambda_o - \lambda_a)^2}$$

Where:
$Z^2_{1-\alpha/2}$ = for 95% confidence level = 1.96 (standard value)
λo= population incidence = 42%
λa= Anticipated population incidence = 58%
(Reference – Dilek K. et al; 2013)
d = Margin of error = 5%
Sample size = 124

Inclusion Criteria

1) Both gender age 18-75 years

2) All patients undergoing cardiac surgery with cardiopulmonary bypass
3) Patients undergone coronary angiography five or more days prior to surgery

Exclusion Criteria

1) Patients less than 18 years or more than 75 years of age
2) Patients with severe liver disease, renal failure or known cancer
3) Patients with known coagulation disorders

Table 1: Demographical characteristics of the patients according to Heparin resistance.

Variables	ACT < 400	ACT > 400	P-value
Age	42.6000±15.98750	44.7368±14.72885	.747
Male	7(70.0%)	80(70.2%)	1.000
Female	3(30.0%)	34(29.8%)	1.000
Weight	59.4000±13.59902	66.0877±15.23187	.801
Height	157.1000±9.19481	160.7544±11.19542	.500
Body surface area	1.6040±.18662	1.7033±.22180	.792
Flow Rate	3.8780±.48646	4.0927±.54113	.893
Hypertension	3(30.0%)	46(40.4%)	.739
Diabetes Mellitus	2(20.0%)	44(38.6%)	.320
Emergency bypass	0(0%)	2(1.8%)	1.000
Smoking	0(0%)	25(21.9%)	.210
Alcohol Intake	0(0%)	1(9%)	1.000
Hyperlipidemias	1(10.0%)	17(14.9%)	1.000
Obesity	2(20.0%)	17(14.9%)	.605
Family History	0(0%)	21(18.4%)	.210
Operation type			
CABG	5(50.0%)	72(63.2)	.412
Valve	4(40.0%)	32(28.1%)	.412
Congenital	1(10.0%)	3(2.6%)	.412
Other	0(.0%)	7(6.1%)	.412

Table 2: Clinical characteristics of the patients according to heparin resistance.

Variables	ACT < 400	ACT > 400	P-value
White Blood Cell Count (×109/L)	7.53000±2.48017	8.0316±1.78377	.181
Platelet Count (×109/L)	218.9000±52.84453	234.8509±80.38697	.300
Neutrophil (%)	56.5200±17.96644	63.0088±8.10604	.733
Prothrombin Time(s)	12.2000±1.61933	12.4035±2.37509	.401
Activated Partial Thromboplastin Time (s)	34.4000±7.45654	36.5614±14.16467	.223
Hematocrit (%)	41.5000±5.89256	42.1316±6.77517	.866
Baseline Activated Clotting Time (s)	108.4000±9.59398	118.2807±8.41670	.015
Blood Sugar Random (mg/dl)	153.4000±108.01358	155.2807±78.32330	.748
Creatinine Phosphokinase (U/L)	311.1000±418.74003	303.8532±409.55931	.279
Creatinine Kinase-MB (U/L)	40.0000±41.10150	43.0275±77.86176	.480
Blood Urea (mg/dl)	38.3000±18.48152	31.6404±12.10509	.681
Serum Creatinine (mg/dl)	1.0400±.40056	.8456±.28320	.113
Albumin (g/dl)	6.2000	3.3741±.67970	.041
Globulin (g/dl)	4.0000	3.3259±.83094	.405
Albumin/Globulin Ratio	2.2000	1.0704±.35172	.050
C-Reactive Protein (mg/dl)		48.0000	.225
Cardiopulmonary Bypass Time (minutes)	107.1000±47.90140	102.0877±35.08613	.225
Cross Clamp Time (minutes)	67.5000±36.08709	56.9561±25.64440	.025
Total Drain Volume (ml)	541.0000±201.13290	565.7727±408.07513	.464

Data Collection Procedure: The patients presenting in the preoperative intensive care unit of operation theater for open heart surgery (CABG or Valvular) are evaluated. The patients were evaluated for heparin resistance after preoperative heparin therapy. A questionnaire is developed to delineate heparin resistance after preoperative heparin therapy. The questionnaire consists of possible expected factors, it includes demographic factors, pre, intraoperative and post operative variables.

Intraoperative: Initial dose of heparin, ACT at start of CPB and during CPB, Protamine dose and post protamine ACT.

Postoperative: Cardiopulmonary bypass time, Cross clamp time, occurrence of complications.

Statistical Analysis: SPSS version 20.0 was used to enter and analyse the data. For quantitative variables, the mean and standard deviation were reported. For qualitative factors, frequencies, percentages, and graphs were provided. The Pearson Chi square test was used to examine the relationship between qualitative and quantitative variables, while the independent t test was utilized to examine the relationship between quantitative and qualitative variables. A P-value is ≤ 0.05(level of significance) considered as significant.

Ethical Consideration: As the study involves heparin dose and effect, which is already used in standard cardiopulmonary bypass, there were no such questions which were ethically questionable. The informed consent was taken. The data collected from Hospital has been confidential and used only for statistical analysis. Ethical clearance for the study was taken from the ethical research committee.

Table-3: In-hospital outcome of the patients according to the Heparin resistance.

Variables	ACT < 400	ACT > 400	P-value
Neurological Complications	1(10.0%)	9(7.9%)	.583
Arrhythmias	0(.0%)	15(13.2%)	.608
Respiratory Complications	0(.0%)	8(7.0%)	1.000
Wound Infections	1(10.0%)	5(4.4%)	.403
Acute Myocardial Infarction	0(.0%)	6(5.3%)	1.000
Low Cardiac Output Syndrome	0(.0%)	5(4.4%)	1.000
Renal Failure	5(50.0%)	46(40.4%)	.739
Gastrointestinal Complications	0(.0%)	5(4.4%)	1.000

RESULTS

Our results showed that out of 124 patients, 87(70.16%) were male while 37(29.84%) were females. The mean age of the patients was 44.56 ±14.77, although the mean age of the patients with heparin resistance after pre operative heparin therapy was 42.60±15.99. The incidence of the heparin resistance after pre operative heparin therapy was 8.06%. Out of 124 patients (91.94%) received heparin once (n=114) and (8.06%) received heparin twice (n=10). Out of 10 (8.06%) heparin resistance patients, 7(70%) were male and 3(30%) were females.

The mean weight of the patients with heparin resistance after pre operative heparin therapy was 59.40±13.60. The mean height of the patients with heparin resistance after pre operative heparin therapy was 157.10±9.19. The mean body surface area of the patients with heparin resistance after pre operative heparin therapy was 1.604±.1866. The mean flow rate of the patients with heparin resistance after pre operative heparin therapy was 3.8780±.48646. Clinical characteristics i.e. (hypertension, diabetes mellitus, emergency bypass, smoking, alcohol intake, hyperlipidemias, obesity and family history) were insignificantly associated with heparin resistance. Out of 10(8.06%) heparin resistance patients, 5(50%) were CABG, 4(40%) valve and 1(10%) congenital.

The clinical characteristics (baseline activated clotting time, albumin and cross clamp time) were significantly associated with the development of heparin resistance with mean 108.40±9.594, 6.20 and 67.50±36.08 with significant p-value < 0.05 .015, .041 and .025 respectively. The clinical characteristics i.e. (hematocrit, Prothrombin time, white blood cells, platelets, creatinine kinase-MB, blood urea, neutrophils, activated partial Thromboplastin time, creatinine phosphokinase, serum creatinine, globulin, albumin/globulin ratio, c-reactive protein, cardiopulmonary bypass and time total drain volume) were insignificantly associated with heparin resistance. In-hospital outcome of the patients according to the Heparin resistance were insignificantly associated.

DISCUSSIONS

Despite the correct heparin dose and plasma concentration, heparin resistance is characterised as the inability to raise blood ACT to predicted levels. 11 Because assessing heparin plasma concentration is not a standard process, heparin response is usually assessed using ACT. Most doctors believe that a safe minimum ACT value of 400 seconds is required for CPB; however, this belief is not supported by research[12]. Metz et al. demonstrated that during cardiopulmonary bypass, there were no thrombotic problems in 51 individuals with an ACT of less than 400 seconds[13].

Nonetheless, most cardiothoracic hospitals would accept our local ACT-based definition of heparin resistance (ACT less than 400 seconds after 300 U/kg heparin). As a result, if defined heparin resistance is not associated with an increased risk of death (as was the case in our study), it is unlikely to be harmful to patients. However, such an approach is based on a fallacious premise and is therefore intrinsically incorrect. Resistance to heparin isn't a conventional binary variable (even if we consider it as such). With increasing heparin dosages, we can typically attain adequate ACT; thus, the phrase "altered heparin responsiveness" seems to be more suitable[14].

Heparin is an anticoagulant medication that has been on the market for more than 50 years. Despite its effectiveness, it has pharmacokinetic, biophysical, and biological limitations. Because the anticoagulant response to traditional heparin varies significantly between patients, the activated partial thromboplastin time (aPTT) and/or clotting time should be measured before starting treatment. Furthermore, treatment should be directed dynamically by titration based on clinical course observation and monitoring of the linked parameters. Before entering CPB, heparin is administered to provide anticoagulation in open heart surgery. With ACT, an acceptable anticoagulation level is maintained after the administration. Additional heparin is used if enough ACT is not collected[15].

However, Kanbak et al. discovered that nitroglycerin raised HR in a prior study in which they looked at the effects of nitroglycerin on coagulation and heparin sensitivity in patients who received it during CPB[16] found that nitroglycerin had no effect on the heparin response in both in vitro and in vivo experiments[17].

In their investigation on the association between HR and postoperative problems in open heart surgery[18], discovered that 4.3% of their patients had an ACT of less than 400 seconds after receiving 400 IU/kg heparin. FFP and AT-III are frequently utilised in the treatment of patients who develop HR. While the majority of patients react to FFP, more resistant instances require AT-III. Different medications have been utilised in the past few years to treat patients who develop HR[19].

Kikura et al. employed nafamostat mesylate (Naf) and found that the patients were able to achieve a sufficient ACT. Furthermore, no significant differences were detected between individuals who got Naf and those who did not when it came to perioperative ischemic stroke, the most serious hazard related with its usage[20].

CONCLUSION

The results indicate that the incidence of heparin resistance after preoperative heparin therapy was 8.06%. The clinical characteristics i.e. (baseline activated clotting time, albumin and cross clamp time) were significantly associated with the development of heparin resistance as (p-value <0.05 .015, .041 and .025 respectively).

Conflict of interest: Nil

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