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HEPARIN;

DOES HEPARIN RESISTANCE LEAD TO POOR EARLY OUTCOME IN PATIENTS UNDERGOING ON PUMP CORONARY ARTERY BYPASS GRAFTING?

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ABSTRACT… Background: Heparin resistance (HR) is a well-known phenomenon in patients undergoing cardiac surgery. Its effect on outcome has not been studied well. **Study Design:** Prospective observational study. **Setting:** Department of Cardiac Surgery, Punjab Institute of Cardiology Lahore. **Period:** April 2013 to March 2015. **Materials and Methods:** The study included 300 consecutive patients undergoing on pump coronary artery bypass grafting (CABG). Those with severe left ventricular dysfunction, multiple cardiac procedures and emergency CABG were excluded from the study. Data was collected on proformas with perioperative variables. The data was analyzed using Statistical Package for Social Sciences version 10. **Results:** A total of 300 patients were included in the study. This included 60(20%) female patients. The mean age of the patients was 50.76 ±4.67 years. Out of the studied cohort, 30(10%) patients showed heparin resistance. Clinical characteristics i.e. hypertension, diabetes mellitus, smoking, hyperlipidaemias and obesity did not show any significance when patients with and without heparin resistance were compared. Total drain was significantly more in group 1 (700±150.13 ml) compared to group 2 (500±120.33 ml) with p=0.023. Similarly, renal failure in group 1 vs group 2 (30.0% vs 15.4%. p=.017), use of blood products more than two units in group 1 vs group 2 (83.30% vs 10.7%, p= .003), re-exploration for bleeding in group 1 vs group 2 (30.0% vs 5.5%, p=.003) was significantly more in group 1 vs group 2 respectively. Mortality was insignificant in both groups. **Conclusion:** Heparin resistance occurred in 10% of the patients. Patients with heparin resistance lead to poor postoperative outcomes like increased renal failure, bleeding, rate of re-exploration and increased use of blood products but does not lead to increased mortality in patient with comparatively lower risk profile.

Key words: Heparin resistance, Coronary artery bypass grafting, outcomes

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INTRODUCTION

Even with the popularity of off pump coronary artery bypass grafting (CABG), cardiopulmonary bypass (CPB) is still used in most of the CABG surgeries throughout the world.[1] CPB is not possible without anti-coagulation and the most common method of anti-coagulation for CPB is the use of heparin.[1] Heparin is a naturally occurring mucopolysaccharide. It combines with antithrombin III (AT III) and potentiates its effect.[2] The half-life of heparin is approximately 90 minutes and it increases with an increase in plasma concentration; therefore, it can be considered a concentration dependent drug.[3]

The Activated anticoagulation test (ACT) is a functional assay of heparin anticoagulant and is the most widely employed test. The safe level for conducting CPB is usually 400-480 seconds. ACT level can be abnormally increased because of patient factors like Hypothermia, haemodilution, platelet function abnormalities and a decreased fibrinogen level. This can occur even if there is incomplete heparinization.[4]

The most common initial dose of heparin for CPB is 300-400 IU/kg. Supplemental heparin doses can be given by monitoring of ACT. When the intended ACT cannot be obtained even with standard heparin dose, the condition is called heparin resistance.

Antithrombin III (AT-III) deficiency, whether congenital or acquired, is associated with heparin resistance (HR). Other factors leading to heparin resistance include hemodilution during CPB, prior treatment with heparin and large quantities of heparin binding protein in the circulation, which binds to and inactive heparin.[4]

For patients undergoing heart surgery, many studies have reported the incidence of HR to be between 4 and 22%, with the most frequent causes being AT deficiency, increases in the clearance of heparin the protein that joins with heparin, and high levels of factor VIII, fibrinogen, and platelet factor (PF) IV. In addition, HR has also been reported as a result of using medications such as aprotinin and nitroglycerin.[5] Heparin resistance can lead to administration of additional doses of Heparin that can later on cause coagulopathy in the intensive care unit (ICU) and increase the rate of re-exploration for bleeding as well as lead to other adverse effects such as acute kidney injury. Heparin resistance has not been studied very well. We studied some of the more important adverse effects in patients because of heparin resistance.

MATERIALS AND METHODS

A prospective observational study was conducted including patients who underwent CABG on elective basis from April 2013 to March 2015 at a tertiary care hospital. All those patients who underwent on pump CABG were included in the study. Patients who had emergency CABG, hemoglobinopathies, coagulation disorders, or cardiac procedures in addition to CABG were excluded from the study. Patients were divided into two groups. Group 1 included all those patients who had heparin resistance while Group included all those patients without heparin resistance. Heparin resistance was defined as a failure in the increase in ACT above 480 seconds after administering a 400 IU/Kg dose of heparin. Heparin from the same manufacturing company was used for all the patients. Perioperative data was collected on pre-formed proforma.

Surgical procedure

Surgical procedure was identical for all the patients and the same anaesthetic and perfusion protocols were used for all the patients. Diseased coronary arteries were grafted with an internal mammary artery and vein grafts as required. Cardiopulmonary bypass was performed under normothermia or moderate hypothermia (34°C) with topical cooling and was initiated after the confirmation of satisfactory ACT. Heparinization with 400 U/kg of unfractionated heparin was used to reach the target value of ACT at 480 seconds. ACT was measured with the use of a Hemochron 401 coagulation monitoring instrument (Technidyne Corp., Edison, NJ, USA). During cardiopulmonary bypass, ACT measurements were repeated every 30 minutes and 50–100 IU of heparin were administered if ACT dropped below 460 seconds. After the termination of cardiopulmonary bypass, protamine sulfate was given to reverse the initial heparin dose at a 1:1 ratio.

DATA ANALYSIS

The collected data was stored and analysed in SPSS version 10 for windows. Mean + SD was calculated for numerical variables like age. Frequencies and percentages were calculated for categorical variables like gender etc. a two-tailed p-valve less than 0.05 was considered significant.

RESULTS

Total number of patients included in the study was 300. Out of which 240 (80%) were males and 60(20%) were females. Preoperative and some of the intraoperative variables are shown in table I.

The mean age of the patients was 50.76 ±4.67 years. The mean age of the patients with heparin resistance was 48.66±9.95 years. A total of 30 (10%) patients showed heparin resistance. The mean body surface area of the patients with heparin resistance was 1.50±0.23 m^2 while that of patients without heparin resistance was 1.50±0.22 m^2. Clinical characteristics i.e. hypertension, diabetes mellitus, smoking, hyperlipidaemias and obesity were insignificantly associated with heparin resistance. Postoperative variables and their comparison in both the groups are shown in table 2. The clinical baseline activated clotting time, was significantly associated with the development of heparin resistance with mean

108.40±9.594 s in patients with heparin resistance against 67.50±36.08 s with no heparin resistance (p= 0.05). Total drain was significantly more in group1 (700±150.13 ml) compared to group 2 (500±120.33 ml) with p=0.023. Similarly, renal failure in group 1 vs group 2 (30.0% vs 15.4%. p=.017), use of blood products more than two units in group 1 vs group 2 (83.30% vs 10.7%, p=.003), re-exploration for bleeding in group 1 vs group 2 (30.0% vs 5.5%, p=.003) was significantly more in group 1 vs group 2 respectively. Mortality was insignificant in both groups.

VARIABLES		GROUP 1 N=30	GROUP 2 N=270	P-VALUE
Age (years)		48.66±9.950	51.7368±4.764	.677
Gender	Male	22(73.33%)	218(80.02%)	.500
	Female	8(26.67%)	52(86.67%)	.900
Weight (Kg)		75.67±4.6	55.08±5.67	.980
Height (cm)		160.77±8.98	166.78±7.76	.567
Body Surface Area (m^2)		1.50±0.23	1.50±0.22	.343
Baseline Activated Clotting Time (s)		108.40±9.59	118.28±8.41	.015
Hypertension		9(31.70%)	100(40.4%)	.675
Diabetes Mellitus		6(21.50%)	102(39.76%)	.342
Smoking		10(33.30%)	67(25.9%)	.210
Hyperlipidemias		5(16.50%)	42(15.9%)	.800
Obesity		10(33.33%)	40(15.09%)	.605
Preoperative unfractionated heparin use		4(13.33%)	41(15.7%)	.230
Cardiopulmonary Bypass Time (minutes)		112.67±40.34	119.08±20.98	.322
Cross Clamp Time (minutes)		80.12±25.89	75.32±12.33	.263

Table-I. Preoperative demographics and important intraoperative variables.

	GROUP 1	GROUP 2	P-VALUE
Total Drain Volume (ml)	700±150.13	500±120.33	.023
Neurological Complications	3(10.0%)	10(3.9%)	.583
Arrhythmias	2(5.0%)	12(10.2%)	.220
Respiratory Complications	1(3.0%)	8(7.0%)	.764
Wound Infections	1(3.0%)	9(3.4%)	.324
Acute Myocardial Infarction	0(.0%)	6(2.3%)	.098
Low Cardiac Output Syndrome	1(3.0%)	6(2.3%)	.080
Acute kidney injury	5(30.0%)	41(15.4%)	.017
More than two units blood products received	25(83.30%)	28(10.7%)	.003
Re-exploration for bleeding	5(30.0%)	14(5.5%)	.003
Mortality	1(3.0%)	4(2.4%)	.086

Table-II. Comparison of postoperative variables in group 1 versus group 2.

DISCUSSIONS

The phrase 'heparin resistance' has been somewhat contested in literature. Shore-Lessorson and colleagues argue that since an optimum level of ACT is achieved, with a higher dose of heparin though, the term 'altered heparin resistance responsiveness' is more appropriate.[4] But Knapik and colleagues still define heparin resistance as the inability to achieve an ACT above 480s after using a 400 U/Kg dose of heparin.[1]

The incidence of heparin resistance has varied in literature. Maurin described a 20 % incidence in open heart surgery. Spiess noted a 22% incidence of heparin resistance in his study including patients undergoing cardiac surgery with cardiopulmonary bypass.[6,7]

Some perioperative drugs have been linked to an increased incidence of HR. Ranucci et al reported the use of nitrates as one of the associated factors[5]. Similar findings were reported by Kanbak and

colleagues.[8] But it appears that only long-term use of nitroglycerine can lead to HR as Lepor and colleagues did not show any increased incidence of HR with short term use of nitrates.[9]

Heparin resistance prompts the use of additional heparin. The resultant overdose of heparin can cause its accumulation in the peripheral tissues especially fat and its slow release in the immediate postoperative period. This phenomenon is called heparin rebound.[10] The late re-appearance of heparin not only causes increased bleeding but also leads to increased use of blood products increase the rate of re-exploration.[11] This observation was confirmed in our study with a significantly high incidence of re-exploration and drain output in patients with HR.

The incidence of acute kidney injury was more in patients with HR in our study. This can be explained by the fact that these patients need more blood products and thus more prone to transfusion related acute kidney injury[1]. Multiple transfusions were an independent predictor of acute kidney injury in a study by Karkouti.[12]

Heparin resistance did increase mortality in some reports published previously.[1,13] This trend was not noted in our study. This may be because of the fact that we did not include patients with severe left ventricular dysfunction and those undergoing emergency CABG.

The lack of a control group and exclusion of patients with high risk profile are some of the limitations of our study. Similarly, the preoperative antithrombin III levels were not taken into consideration. Another important limitation is the fact that ACT, though used widely, is less sensitive and specific compared to heparin sensitive index for assessing heparin anti-coagulation.
It can be concluded that heparin resistance is an important entity with an incidence of about 10% in the contemporary practice. It can lead to adverse early outcomes in patients undergoing coronary artery bypass grafting. A thorough understanding of the problem and further research may lead to preventive strategies in future.

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The art of being wise is knowing what to overlook.

– William James –

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3	Ajwad Farogh	Intellectual content	
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