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A STUDY OF HEPARIN RESISTANCE IN CORONARY ARTERY BYPASS GRAFT PATIENTS IN A TERTIARY CARE CENTRE

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Abstract

Background: This study was conducted to determine preoperative characteristics that may predict heparin resistance (HR) in patients scheduled for CABG (Coronary Artery Bypass Graft) surgery, as well as to estimate the percentage of patients who have heparin resistance among those undergoing CABG.

Methods: This study involved 120 patients who underwent CABG at the Department of Cardiothoracic and Vascular Surgery, Government Medical College Hospital, Thiruvananthapuram. This retrospective study was conducted over a six-month period, from January to December 2018, with written informed consent from the study participants and approval from the institutional ethics committee.

Results: The pre-operative features of the HR and NHR groups did not significantly differ from one another. The mean peri-operative heparin dose required for the HR group to attain the target ACT was 35588.37 +/- 4962.20, which was clearly greater, and the p value was 0.02, which was statistically significant. For the NHR group, the required dose was 32328.71 +/- 4714.89. We conducted a univariate analysis of patient characteristics for heparin resistance to determine which pre-operative features were predictive of post-operative heparin resistance. Of the variables evaluated, only heparin resistance showed a statistically significant correlation with the length of time the patient received pre-operative heparinization (p = 0.04). Additional patients were divided into two groups: pre-op antiplatelets and pre-op heparin. The purpose of this was to evaluate which group performed better in terms of post-operative hemodynamics and blood needs. A thorough examination of several post-operative factors in both groups showed that the pre-operative heparin group had a mean post-operative drain of 314.09 ± 95.83, while the pre-operative anti-platelet group had a mean post-

operative drain of just 232.21 ± 88.80 (p = 0.009). The proportion of patients in both groups who needed post-operative transfusions also differed significantly. In the pre-operative heparin group, it was 23/47; in the pre-operative anti-platelet group, it was only 1/13, with a p-value of 0.009.

Conclusion: The only factor in our study that could predict heparin resistance was the length of pre-operative heparin use. Additionally, patients who got pre-operative heparin had a considerably higher blood loss and required more intraoperative blood transfusions than those who received pre-operative antiplatelet therapy.

Keywords: Heparin, Heparin Resistance, Non-Heparin Resistant, Antiplatelets, CABG (Coronary Artery Bypass Graft)

INTRODUCTION

CPB (Cardio-Pulmonary Bypass) related cardiac surgery strongly activates the hemostatic system. This results from blood coming into contact with the vast nonendothelial surfaces of CPB at the same time that tissue factors from surgical trauma are massively released and reinfused. Apart from this hemostasis-promoting factor, the contact system directly and indirectly activates the inflammatory system through thrombin and activated platelets.[1-3] Consequently, the inflammatory response is set off and platelets and plasma coagulation factors are gradually depleted. Strong anticoagulation is therefore necessary for CPB in order to reduce these processes. UFH (Unfractionated Heparin) is the usual anticoagulant during CPB, even with the advent of novel inhibitors of the plasma coagulation system, such as heparinoids and direct thrombin inhibitors. This is due to the fact that UFHs are the only anticoagulant that satisfies all three of the requirements for safe anticoagulation: prompt anticoagulant action, dependable monitoring through an operative room point of care system, and quick anticoagulant effect reversal through biological elimination or an antidote. On the other hand, a small percentage of patients exhibit UFH insensitivity, which is defined as an excessive need for UFH or an inability of UFH to provide the desired level of anticoagulation. At least one active clotting time less than 400 s after heparinization and/or the requirement for a purified antithrombin III (AT-III) injection were considered indicators of heparin resistance. Although the fundamental processes underlying this heparin resistance remain incompletely understood, factors such as age and high platelet counts are implicated in addition to increased binding of UFH by plasma proteins and a decrease in antithrombin (AT) III during prolonged UFH therapy.[4-6] Numerous patients undergoing heart surgery have been found to have heparin resistance (HR). This occurs in 4–22% of people having cardiopulmonary bypass surgery for heart problems.[4] This occurrence is becoming more common, which is concerning because it can lead to major consequences. These can include severe coagulopathy, subclinical disruptions in the coagulation cascade, or even catastrophic intraoperative coagulation of the CPB circuit.[7] A number of factors appear to contribute to the cause of HR, including thrombocytopenia, increased factor VIII activity, endocarditis, preoperative use of an IABP (Intra-Aortic Balloon Pump), and AT-III (Antithrombin III) deficiency brought on by heparin administration.[8] Currently, there is no definitive identification of the preoperative factors that lead to HR, and prior research has yielded inconsistent findings and likely exhibited bias due to the study population's non-uniformity and small sample size. This study aims to assess the percentage of patients undergoing CABG who are heparin-resistant. Finding preoperative variables that could predict HR (Heart Rate) in patients slated for CABG surgery is another goal of this research. Anticipating heparin resistance will enable us to adjust numerous treatment approaches, thereby mitigating intraoperative complications.

AIMS AND OBJECTIVES

- To estimate the proportion of patients who have heparin resistance among the patients who undergo CABG.
- To assess the factors associated with heparin resistance in our patient population.
- To study the heparin dose required to achieve the target ACT.

- To compare heparin requirement in patients who received pre-operative heparin and those who received a single anti platelet agent.
- To compare the heparin resistance and non-heparin resistance groups with regards to dose of protamine sulphate reversal, immediate post-operative chest drain and need for blood support.

MATERIAL & METHODS

This study involved 120 patients who underwent CABG at the Department of Cardiothoracic and Vascular Surgery, Government Medical College Hospital, Thiruvananthapuram. This retrospective study was conducted over a six-month period, from January to December 2018, with written informed consent from the study participants and approval from the institutional ethics committee.

Inclusion Criteria

- All patients who underwent CABG at our center from January 2018 to December 2019 were included.

Exclusion Criteria

- Patients on long-term anticoagulation.
- Patients with known coagulation disorders.

Statistical Methods

An Excel spreadsheet included the data. The statistical program SPSS version 25.0, were used for the analysis. An analysis of descriptive data was performed on the gathered clinical factors. The heparin pre-operative and anti-platelet pre-operative groups, as well as the HR and NHR groups, were compared and their significance determined using the student t-test and chi-square test. The study employed logistic regression analysis to determine the independent factors influencing HR.

RESULTS

Variables	**NHR Group (N = 86)**	**HR Group (N = 34)**	**P-Value**
Age	56.93+/-8.4	56.88+/-7.7	0.67
Gender			
Male	71	30	0.55
Female	15	4	
Diabetes	52	22	0.5
Hypertension	52	26	0.36
Myocardial Infarction	48	16	0.57
NYHA -1	24	4	0.22
2	40	24	
3	22	6	
Ejection Fraction	51.46+/-13.31	53.78+/-15.22	0.586
Pre-op Heparin	70	24	0.488
Ecosprin	16	10	0.29
Duration of Heparin	11.8+/-8.33	10.74+/-8.34	0.83
Heparin dose	32328.71+/-4714.89	35588.37+/- 4962.20	0.02
Comparison of Pre-Operative Characteristics			
Variable	**NHR Group (N = 86)**	**HR Group (N = 34)**	**P-Value**
Hemoglobin	12.70 +/- 1.31	12.60+/-1.60	0.80
Platelets	273376.74±83870.3	243911.76±88833.5	0.25
APTT	41.12±4.19	38.46±3.74	0.02
PT-INR	1.19±0.15	1.19±0.15	0.87
Comparison of Pre-Operative Blood Investigations			
Table 1			

Pre-operative features did not significantly differ between the HR and NHR groups, according to the assessment of the student t-test. The mean peri-operative heparin dose required to attain goal ACT varied significantly between the NHR and HR groups; it was 32328.71+/-4714.89 for the former and 35588.37+/- 4962.20 for the latter. The p-value of 0.02 demonstrated the statistical significance.

A student t-test comparison was used to evaluate the relationship between the pre-operative coagulation profiles of the NHR and HR groups. In both groups, hemoglobin, platelets, and PT-INR were comparable, and there was no discernible statistical difference.

There was only one statistically significant difference between the NHR and HR groups' APTT scores. The NHR group's mean APTT was 41.12±4.19, whereas the HR group's was 38.46±3.74, with a p-value of 0.02. The pre-operative APTT was lower in the HR group, which may indicate that individuals in this category are already predisposed to thrombosis. A deficit in AT-III is one of the many variables that could be causing this. We didn't perform the AT-III assay because it was outside the scope of our investigation, and it requires further evaluation.

Variable	**Odds Ratio**	**95% CI**	**P-Value**
Age	1.01	0.94 – 1.08	0.68
Sex Male Female	1.3	0.21 – 7.85	0.77
Diabetes	0.83	0.26 – 2.68	0.76
Hypertension	0.24	0.13 – 1.6	0.651
Myocardial Infarction	1.42	0.46 – 4.38	0.541
NYHA 1 2 3	3.6 1.6	0.68 – 18.9 0.2 – 11.6	0.13 0.62
EF	1.01	0.97 – 1.05	0.55
Duration of Pre-Op Heparin	0.99	0.92 – 1.06	0.04
Variable	**Odds Ratio**	**95% CI**	**P-Value**
Hemoglobin	0.944	0.61 – 1.44	0.79
Platelets	1.00	1.0 – 1.0	0.231
APTT	0.85	0.74– 2.09	0.03
PT INR	1.35	0.03 – 54.49	0.026
Creatinine	0.97	0.87– 1.08	0.66
ACT	0.97	0.92 – 1.01	0.215
Uni-Variate Analysis of Pre -Op Blood Investigations in HR			
Table 2			

A logistic regression analysis was used to determine the heparin resistance pre-operative predictors. The length of the patient's pre-operative heparin use was the only variable in the univariate analysis that showed a statistically significant association with heparin resistance ($p = 0.04$). The display of the several parameters evaluated in the univariate analysis.

In order to evaluate the pre-operative prediction characteristics among the pre-operative blood examinations, the HR group employed univariate analysis. A statistically significant correlation was discovered between the PT-INR and APTT readings. Pre-operative lower APTT/PT-INR values were predictive of peri-operative heparin resistance, in our opinion. The greater blood creatinine value and platelet count did not demonstrate any correlation, as shown.

Variables	Pre-Op Heparin (N = 94)	Pre-Op Antiplatelet (N = 26)	P-Value
Base Line ACT	117.15±10.722	104.15±12.89	0.004
Surgical Time	381.49±88.35	335.00±76.02	0.07
CPB Time	187.18±52.04	165.70±48.44	0.23
XC Time	105.87±30.57	101.00±39.63	0.72
Total HeparinDose	35242.30±5082.05	32576.92±4645.09	0.08
Protamine Dose	357.45±102.67	340.77±80.774	0.54
Comparing Pre-Op Heparin Group and Single Agent Antiplatelet Group			
Variables	**Pre-Op Heparingroup (N = 94)**	**Pre-Op Antiplatelet Group (N = 26)**	**P-Value**
Time from Termination of CPB to Skin Closure (MTS)	98.11±37.57	89.09±44.94	0.51
Post-Op Drain (ml)	314.09±95.83	232.21±88.80	0.009
LIMA	43/47	11/13	0.60
OPCAB	2/47	3/13	0.06
Post-Op HB	11.08±1.66	11.66±1.14	0.15
Number of Patients who Received Transfusions	23/47	1/13	0.009
Post-Op Blood Loss, Transfusion Requirements in Both the Groups			
Table 3			

The patients were further divided into two groups: pre-op antiplatelets and pre-op heparin. This was carried out to evaluate both groups' post-operative hemodynamics and blood requirements, as well as to assess each group's advantage in the early post-operative period. To compare the two groups, an independent t test analysis was conducted. The baseline ACT value was the only variable between the two groups that showed a statistically significant difference. The pre-operative heparin group's mean baseline ACT value was 117.15±10.722, while the pre-operative antiplatelet group's mean baseline ACT value was 104.15±12.89 with a p value of =0.04. Since the patient was heparinized before surgery, this disparity was anticipated. As demonstrated, there was no statistically significant difference between the pre-operative heparin and pre-operative platelet groups, and none of the other variables were determined to be confounding.

The independent t-test was utilized to compare several post-operative characteristics between the two groups. Among all the factors, two were determined to have a statistically significant connection. The pre-operative heparin group had a mean post-operative drain of 314.09±95.83, whereas the pre-operative antiplatelet group had a mean post-operative outflow of just 232.21±88.80. The proportion of patients in both groups who needed post-operative transfusions also differed significantly. In the pre-operative heparin group, it was 23/47; in the pre-operative anti-platelet group, it was just 1/13. It is obvious that a higher heparin dosage and higher protamine in the pre-operative heparin group could be the cause of the larger post-operative outflow. Higher heparin doses are a major contributing factor to increased post-operative outflow, as seen by the "rebound phenomenon" of heparin, which occurs even after the first protamine impact and is caused by the release of protein-bound heparin, additional anticoagulation, and bleeding.

The heparin group had a larger number of transfusion-related patients, which was associated with a higher post-operative drain and a higher heparin demand than the non-heparin group. In our study, the post-operative heparin group did not fare as well as the pre-operative antiplatelet group.

DISCUSSION

Numerous patients undergoing heart surgery have been found to have HR (Heparin Resistance).[1-4] This occurrence is becoming more common, which is concerning since it can lead to major consequences such as severe coagulopathy, subclinical disruptions in the coagulation cascade, or potentially catastrophic intraoperative coagulation of the CPB circuit.[1,7,8] AT-III insufficiency

brought on by preoperative heparin administration, thrombocytopenia,[10] increased factor VIII activity,[11] preoperative use of an IABP,[7] and endocarditis are among the factors that appear to contribute to HR.[5]
Currently, there is no definitive identification of the preoperative factors that lead to HR, and prior research has yielded inconsistent findings. These findings may be attributed to study population heterogeneity and sample size limitations. Finding preoperative variables that could predict heart rate in individuals slated for CABG surgery was the aim of this investigation.

Our population's incidence of heparin resistance was similar to that previously documented in the literature. An ACT of less than 400 s following a 300 IU/kg heparin loading dosage was classified as "inadequate heparinization" by Cloyd and coworkers,[9] who discovered that 30% of elective coronary patients had this syndrome. An ACT of less than 480 seconds following a 500 IU/kg heparin loading dose was defined as HR by Staples et al.[10] They discovered this condition in 22% of a sample of nonselected patients undergoing heart surgery. Marco Ranucci et al., identified five HR predictors[4] AT-III ≤ 60%; intravenous heparin therapy; preoperative subcutaneous heparin therapy; platelet count ≥ 300 000 cells/mm 3; age ≥ 65. The other characteristics in our investigation did not reach significance, and AT III was not conducted. Smoking and high fibrinogen levels before surgery are linked to HR, according to Satoshi Kawatsu et al.[12] However, our group was unable to investigate these factors.
People exposed to enoxaparin before surgery had higher heparin resistance, according to Hilde Pleym.[13] Numerous researchers have already noted the significance of heparin pretreatment in determining HR.[7,10,11] Although different mechanisms have been proposed, the majority of publications attribute this impact to the chronic ingestion of AT-III.[9,14] Regardless of AT-III levels, heparin pretreatment is an independent predictor of HR in our investigation. Additional pathways contributing to thrombocytopenia brought on by heparin therapy and an increase in factor VIII activity[15] are both involved in HR.[16] Numerous researchers have already noted the significance of heparin pretreatment in affecting HR.[1,6,7] Most writers attribute this impact to chronic ingestion of AT-III, but alternative mechanisms have also been proposed.[6-8] The length of heparin pretreatment was found to be an independent predictor of coagulation parameters, platelet count, and HR in our investigation. Two further processes that may contribute to HR during heparin medication are heparin-induced thrombocytopenia and an increase in factor VIII activity.[10]
In line with earlier research, we were unable to find a statistically significant drop in platelet count in individuals receiving heparin prior to treatment.[1,6-8] The theory behind heparin-induced thrombocytopenia and HR is that PF4 (Platelet Factor 4), which exhibits an extremely strong affinity for heparin and counteracts its anticoagulant action, is released by chronically activated platelets. Our study did not find a significant association between high amounts of circulating platelets and HR risk, which runs counter to this idea. Even though Staples et al.[10] state in their explanation of their findings that platelets were more plentiful in HR patients than in controls-unfortunately, they do not disclose the values and their significance; this information is new.
Regardless of heparin pre-treatment, thrombocytosis is not an independent risk factor for HR, according to our research. Since CPB is a potent platelet activator, it is possible to hypothesize that the higher the value of circulating platelets prior to CPB, the greater the amount of PF4 released. The amount of activated platelets is related to the release of PF4 during CPB. Moreover, aprotinin restricts the amount of heparin that platelets can bind, whether it is activated or not.[16,17] Therefore, there is a clear correlation between circulating platelets and heparin sequestration, which may be used to explain why patients with high circulating platelet counts have a higher risk of heart attack.
We were unable to show that the older the person, the greater the risk of heart failure in our analysis of age as a factor in heparin resistance. Since it was not taken into account as a grouping variable in any of the HR-related studies, there is no information on this topic available in the literature. In any case, elderly patients are recognized to have a thrombogenic risk. The coagulant activity of von Willebrand factor and factor VIII increases with age, as shown by Conlan et al.[18] Given that one of the mechanisms behind HR is a more pronounced factor VIII activity,[19] this may be the justification

for looking at age as a risk factor for HR. Despite the fact that factor VIII and von Willebrand factor coagulant activity are both more prominent in diabetics, diabetes is not linked to a greater risk of HR in our dataset.
Additionally, our study contrasted preoperative heparin and single antiplatelet agent users. Research revealed that patients in the antiplatelet group required fewer post-operative transfusions and had lower post-operative drains. However, there needs to be more evaluation because the antiplatelet group's sample size was limited.

The relatively high incidence of HR in heart operations, the potentially disastrous intraoperative and postoperative outcomes of a severe or undetected HR, and the availability of a variety of therapeutic approaches to counteract an HR pattern once it is identified or suspected all serve to justify the need for a preoperative predictive model for HR. Among these, we would consider:
1) Reduced duration of pre-operative heparinisation.
2) A single pre-operative antiplatelet regimen is a safer alternative.
3) Reduced need for systemic heparinization by means of heparin-bonded circuits.
4) AT-III or fresh frozen plasma supplementation during and after CPB.
5) Direct, non-AT-III-mediated thrombin inhibitors (Gabexate mesylate).

This study did have several drawbacks, though, mainly due to the small size of the heparin resistance group, which reduced the number of variables available for logistic regression. Another explanation is that the antiplatelet group was smaller than the heparin group; therefore, a larger sample size needs to be used in future research. Among our other shortcomings, this study did not standardize ACT, and it did not test AT III. To get over these restrictions, more extensive, multicenter, prospective observational research has to be conducted.

CONCLUSION

Thirty percent of our population had heparin resistance. The duration of pre-operative heparin was found to be a predictor of HR ($p = 0.04$) by univariate analysis; however, our investigation did not find significant differences with other established predictors. Our research also revealed a considerably higher blood loss ($p = 0.009$) and increased need for intraoperative blood transfusions ($p = 0.009$) among individuals who received preoperative heparin as opposed to preoperative antiplatelet. To get around these restrictions, a larger, multicenter, prospective observational study is required.

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