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EVALUATING THE RISK FACTORS CAUSING HEMOLYSIS DURING CARDIOPULMONARY BYPASS: A HOSPITAL BASED OBSERVATIONAL STUDY

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ABSTRACT :

Introduction: A small number of research has been done in India regarding the risk factors causing hemolysis and complications associated with hemolysis in adult subject's undergoing open heart surgeries.

Aim and Objectives: Our goal was to analysis factors which cause hemolysis during cardiopulmonary bypass and note the effect of hemolysis on kidney function during post-operative period

Methods: In the following observational study , 96 patients underwent cardiopulmonary bypass surgeries wherein 46 number of patients had their valves replaced aortic valve replacement, mitral valve replacement , double valve replacement .Around 24 patients had their septal defects atrial septal defect , ventricular septal defects closed and about 26 patients underwent coronary artery bypass graft surgeries In order to note the factors that induce hemolysis parameters like pre operative hematocrit, creatinine, blood urea nitrogen , mean arterial pressures ,Urine output, intra operative Mean arterial pressures (MAP), Aortic cross clamp time(ACC) ,Cardiopulmonary bypass time (CPB) ,Urine output (U/O) were recorded. Following protamine assisted heparin reversal and termination of cardiopulmonary bypass(CPB) patients were shifted to post operative care unit. Patients parameters like Urine output, hematocrit, creatinine, blood urea nitrogen values were recorded following a period of 24 hours to rule out for any discernible variation during the pre operative and post operative period.

Results The following results indicated that patients that underwent mechanical valve surgeries an increased plasma free haemoglobin values were observed , post operatively after 24 hours of examination without a significant prolongation of aortic cross clamp (ACC) time and cardiopulmonary bypass (CPB)time. While higher plasma free levels were noted in CABG cases following prolongation of CPB time and ACC time. Low creatinine values reported during the post-operative period demonstrated that the mean arterial pressures were maintained and adequate perfusion was established. In the post-operative stage substantial hemolysis was indicated by decreased haematocrit levels and greater plasma free haemoglobin. The notably elevated urine output, during cardiopulmonary bypass indicated optimal kidney function

Conclusions Cardiopulmonary bypass associated hemolysis occurs when blood is encountered with sheer stress induced by the pumps.Low creatinine levels were reported in our study indicating adequate perfusion. In the post-operative stage hemolysis was indicated by decrease haematocrit levels and increased plasma free haemoglobin levels. In patients undergoing mechanical valve surgeries greater plasma free haemoglobin was recorded.

Key-words: Hemolysis**,** Hemoglobin, Haptoglobin, Plasma free hemoglobin, cardiopulmonary bypass

INTRODUCTION

The revolutionary enhancement of Cardiopulmonary bypass has allowed for breakthroughs through cardiac surgeries. A peculiar form of extracorporeal circulation is Cardiopulmonary bypass. This machine temporarily takes over the function of the primary role of the primeral heart and lungs, providing oxygenation and ventilation, and allowing surgeons to perform surgeries. It supports cardiac manoeuvres and allows a clear surgical field while maintaining organ perfusion and preserving hemodynamic stability. However, it is an essential technique for correcting cardiac defects that still have inherent features that cause damage to the body [12]. The constraints of the heart lung machine includes the possibility of haemocyte injury resulting in hemolysis. Cardiopulmonary bypass-induced hemolysis occurs due to blood exposure to mechanical shear stress generated by the pump and due to a nonendothealialized circuit which seems to have minimum impact on patients[11] This study focuses on the factors contributing to hemolysis and their implications. The study's goal is to comprehend the mechanisms and strategies for hemolysis during cardiopulmonary bypass.

Plasma normally contains a protein, haptoglobin which can bind to haemoglobin. In normal blood distribution, the rate of binding is roughly 1 mg haemoglobin per 1 ml of plasma. When the release of haemoglobin from the destructed erythrocytes does not surpass the capacity of haptoglobin to bind with it, the haptoglobin haemoglobin complex is discarded by the reticuloendothelial system and no free haemoglobin can be detected [10]. But if the haptoglobin-haemoglobin capacity is transcended, free haemoglobin circulates in the plasma where it breaks down into its haem and globin moieties.

These moieties incorporate with plasma albumin and result in methemoglobin and haemopexin formation respectively. Free haemoglobin can also be eliminated by the kidney, but not until the plasma concentration exceeds 150mg per 100ml plasma.

Hemolysis is the destruction of the RBC'S which results in increased plasma free haemoglobin (PFHb) and lactate dehydrogenase (LDH) and a decrease in the level of haptoglobin. These plasma-free haemoglobin bind to haptoglobin (hp) which is broken down in the liver. The haemoglobin-haptoglobin complex in normal circulation is cleared by surface scavenger receptors CD163. Haptoglobin is in charge of attaching to and transferring haemoglobin from the bloodstream to the bone marrow, spleen, and liver [8]. So under normal physiological conditions, haptoglobin prevents cumulation of plasma-free haemoglobin. So when the concentrations of plasma-free haemoglobin exceed that of haptoglobin in the plasma a detrimental effect occurs causing life-threatening complications like low blood oxygen levels, and kidney damage, it can also trigger an inflammatory response which can further lead to organ damage. Mild hemolysis is well tolerated in most of the patients however acute hemolysis can be fatal. Therefore we put forward that hemolysis is an essential yet generally obscure contributor of organ injury during a cardiovascular surgical procedure [7].

The severity of hemolysis depends on certain factors such as the duration of CPB, types of materials incorporated in the circuit, underlying medical condition of the patient, and the techniques used during the surgical procedure.

Many attempts have been made to minimize hemolysis caused by cardiopulmonary bypass components. However the way in which each component is contrived and controlled in the CPB circuit, might cause damage to the cell.

In addition to the management of the components number of procedures and drugs have been researched for their outcomes on reduction or extension of hemolysis. Pulsatility was one of the examples that shows high PFHb while pentoxifylline reduces the increase in PFHb.

The best advances in the prevention of hemolysis include minimizing blood loss by using cell salvaging, reducing blood contact by adjusting the flow rates and speed and maintaining the temperature at normothermia, ameliorating the circuit design by using heparin binding coating circuits and availing biomedical polymers and punctilious surgical techniques. A few treatment options include the administration of drugs that bind to free haemoglobin, dialysis or drugs supporting kidney function, and blood transfusions if hemolysis has led to anaemia.

AIMS AND OBJECTIVES

Aim: To evaluate the risk factors causing hemolysis during cardiopulmonary bypass.

- Primary objective: Analysis of factors which cause hemolysis during cardiopulmonary bypass.
- Secondary objective: Effect of hemolysis on kidney function during post-operative period.

MATERIALS AND METHODS

Source of Data:

Adult patients undergoing open-heart surgery requiring cardiopulmonary bypass (CPB) in the Department of Cardiovascular and Thoracic Surgery, KLE's Dr. Prabhakar Kore Hospital and Research Centre, Belgaum, Karnataka, India.

Study Design:

Observational Study

Study Period:

June 2024 – March 2025

Sample Size: 96

- **Sample size calculation:** According to the statistical analysis
- Sampling technique: n= Z1^2-α/2.SD^2
- (20%SD)2
- Where: Z = critical value
- SD = standard deviation
- 20% SD = tolerable error
- α= level of significance
- n = sample size
- 1.96 = standard normal variant
- value for 95% confidence interval
- 0.2 = 20% tolerable error
- n = 1.962
- (0.2)2
- n=96.04 ≈ 96
- n=96

- Total sample size = 96

Inclusion Criteria:

- Patients age limit of 25-75 years.
- Patients opted for cardiac surgery
- CABG Cardiopulmonary bypass with standard protocol

Exclusion Criteria:

- Emergency cardiac surgeries
- Pre-operative history of any renal issues
- Minimally invasive cardiac surgeries
- Re-do cardiac surgery

Data Collection Procedure:

Cardiopulmonary bypass surgery was performed for 96 patients to evaluate the risk of hemolysis The studies inclusion criteria were patient's aged25-75 years Informed consent forms and information regarding the study were handed out to each patient in the language they were proficient in The patients were enrolled in the study only after they confirmed their willingness to participate signed the consent form.

The patients as per scheduled for the surgery were intubated and had arterial, Central venous pressure (CVP) lines and Foley's catheter secured. The patient's body weight was taken into consideration while selecting and miniaturizing the circuit. Oxygenators such and Affinity NT ,Sorin Inspire were taken, adequate for achieving patients full flows .Dubois formula was used to achieve full flows based on patients body surface area (BSA).

The procedure was performed by skilled cardiac surgeons at KLES DR Prabhakar Kore hospital.

Using heparin, colloid and crystalloid solutions the cardiopulmonary bypass (CPB) circuit was primed corresponding with the patient's physiological needs. Prior to the initiation of cardiopulmonary bypass (CPB), patients having higher haematocrit levels autologous blood was withdrawn and those with lesser volumes packed cells were added. CPB was conducted subsequently after addition of unfractional heparin to attain ACT of 480 and above.

CPB being an integral part of cardiac surgeries, procedures which may indulge in hemolysis due to the construction of the extracorporeal circuit .Employment of roller pumps can further aggravate hemolysis and hence its necessary to adjust the occlusion settings in order to diminish the magnitude of hemolysis generated by the shear stress of compressing the tubing's against the roller pump blades.

The enormity of hemolysis depends of both the duration as well as the shear stress to which the blood is being exposed.

In order to note the factors that induce hemolysis parameters like pre-operative haematocrit, creatinine, BUN, MAP ,Urine output, intra operative Mean arterial pressures (MAP), Aortic cross clamp time(ACC) ,Cardiopulmonary bypass time (CPB) ,Urine output (U/O) were recorded. Following protamine assisted heparin reversal and termination of cardiopulmonary bypass (CPB) patients were shifted to post-operative care unit. Patient's parameters like Urine output, haematocrit ,creatinine, BUN values were recorded following a period of 24 hours to rule out for any discernible variation during the pre-operative and post-operative period.

Plasma free haemoglobin being a major indicator of hemolysis blood samples were collected via the CVP lines in the EDTA bulb to ascertain whether hemolysis has occurred or no and to measure the degree of plasma free haemoglobin.

The centrifugation of samples were done at 3,000 rpm for 10 minutes. Plasma was extracted from blood and gathered in tubes which were than preserved at – 80 degree Celsius. Following which these samples were analysed after a duration of 3 months

Ethical Consideration: Ethical approval was obtained from the JNMC Institutional Ethical Committee. **Ref No: MOC/JNMCIEC/310 dated: 29/05/2024**

Data Analysis /Statistical Analysis:

Data analysis was done using Microsoft excel and SPSS version 27. The frequency and percentage was computed for categorical variables. Descriptive statistics like Mean, Standard deviation, Median and Interquartile Range (IQR) were computed for normally and not normally continuous variables respectively. Wilcoxon sign rank test was used to compare medians of two groups. Spearman's rank correlation coefficient (R) was used to check the correlation between two variables. Statistical significance was considered at 5% level of significance ($p>0.005$).

RESULTS

A study was conducted for 96 patients undergoing cardiopulmonary bypass to evaluate the risk of hemolysis. The studies inclusion criteria were patient's aged 25-75 years. Informed consent forms and information regarding the study were handed out to each patient in the language they were proficient in. The patients were enrolled in the study only after they confirmed their willingness to participate and signed the consent form, as per the inclusion criteria. The Mean age of the study group was 48.23 ± 14.08 years. The Average height of the patients was 156.09 ± 11.87 cm. According to the data presented in table 1 the mean weight of the patients were 59.54 ± 14.76 kg .

The median BSA was 1.60 m^2 median max flow was 3.84l/min. The mean haematocrit was 39.48 % with average mean arterial pressure (MAP) of 78.39 mmHg. The mean creatinine of the following group was 1.33 mg/dl. The average of blood urea nitrogen (BUN) was 12.72, the pre-operative urine output was noted as 77.31 as summarized in table number 2.

The median MAP of the following patients was 74.00 and median ACC of the patients was 65.00 mins. The median of CPB time was 94.50 mins and average median of intra operative urine output 700.00 .

The median post-operative urine output was 2435.00 similarly average haematocrit for the following patients was 34.10 %. The median of plasma free haemoglobin for the following patients was 102.00 g/dl . As outlined in table 4 the mean serum creatinine level was 0.98 mg/dl .

A non-significant negative correlation was seen between pre-operative hematocrit and plasma free hemoglobin, analysis revealed as statistically significant positive correlation between post-operative hematocrit and plasma free haemoglobin .

There is a statistical significant difference noted between pre-operative hematocrit median of 39.48 with and post-operative hematocrit median of 34.10 as shown in table 6.There is a statistical significant difference noted between pre-operative creatinine median of 1.33 and post-operative creatinine median of 0.98 as outlined in table 7 . A negative correlation is observed with aortic cross clamp time and plasma free haemoglobin and a positive correlation is seen between cardiopulmonary bypass time and plasma free haemoglobin as shown in table 8.A clinically and statistically significant difference was observed between aortic cross clamp time and cardiopulmonary bypasss time. A negative correlation is observed between pre-operative mean arterial pressures and plasma free haemoglobin and intra operative mean arterial pressures and plasma free haemoglobin with a p value of 0.7686 and p=0.129 .There is a negative correlation observed between plasma free hemoglobin and pre-operative hematocrit levels in graph 1. A positive correlation between plasma free hemoglobin and post-operative haematocrit with a p value of 0.314 which is statistically insignificant .There is a negative correlation between plasma free hemoglobin and pre-operative creatinine with a p value of 0.356 .A statistically significant negative correlation between plasma free hemoglobin and post-operative creatinine(R= -0.072 and p value of 0.485). A negative correlation is observed with aortic cross clamp time and plasma free haemoglobin with R=0.032 which is statistically not significant with p values of 0.758.

As interpretated in graph 7 there is a statistical significant difference between aortic cross clamp time and cardiopulmonary bypass time with R= 0.907 and p value of 0.05 median levels .

A negative correlation is observed with p value of 0.7686 which is statistically not significant between pre-operative mean arterial pressures and plasma free haemoglobin , A negative correlation between intra operative mean arterial pressures and plasma free haemoglobin , R= -0.156 and which is statistically insignificant with p values of 0.129. The median of pre mean arterial pressure is 78 much higher than that of intra mean arterial pressure is 74. The pre-operative urine output is much lower than the intra and post-operative urine output. Post-operative urine output was highest at 2435 ml. The median of pre operative creatinine levels is 1.33 mg/dl , higher than that of post operative creatinine levels 0.98 mg/dl. The median of pre operative hematocrit levels is 39.48 % higher than that of post operative creatinine levels 34.1 mg/dl . The median age of the following study was 48.23 years . The median height was 156.09 cms , while the median weight of the study was 59.54 kg.

Discussion

DISCUSSION:

In our observational study, 96 patients underwent cardiopulmonary bypass (CPB) surgeries. Among them, 46 patients underwent valve replacement procedures, including aortic valve replacement (AVR), mitral valve replacement (MVR), and double valve replacement (DVR). Additionally, 24 patients had their septal defects—either atrial septal defects (ASDs) or ventricular septal defects (VSDs)—surgically corrected, while 26 patients underwent coronary artery bypass grafting (CABG).

The primary objective of the study was to assess the potential for hemolysis in patients undergoing CPB. Data were collected regarding the type of surgery performed, specifications of the CPB system used, and the necessity of blood transfusion within 24 hours postoperatively.

The results demonstrated that patients undergoing mechanical valve replacement surgeries exhibited elevated plasma-free hemoglobin levels postoperatively (at 24 hours), even in the absence of significantly prolonged aortic cross-clamp (ACC) and cardiopulmonary bypass (CPB) times. Conversely, in CABG patients, higher plasma-free hemoglobin levels were associated with prolonged ACC and CPB durations.

Priming, a critical step in cardiopulmonary bypass , typically involves the use of colloid or crystalloid solutions to dilute the patient's blood upon contact with the extracorporeal circuit. This hemodilution is inevitable and presents both advantages and challenges. Benefits include reduced hematocrit levels, decreased need for transfusion, and lowered blood viscosity. However, excessively high hematocrit levels during bypass may increase the risk of hemolysis due to elevated shear stress. Therefore, standard protocols recommend maintaining hematocrit levels between 22–25% during CPB to ensure adequate oxygen delivery and minimize hemolysis. Techniques such as circuit miniaturization or the use of albumin/colloid-based priming solutions can help reduce the degree of hemodilution and associated hemolysis.

Serum creatinine is a key indicator of renal function, and plasma-free hemoglobin is typically filtered by the kidneys. A statistically significant difference was observed between pre- and postoperative creatinine levels in our study. Postoperative reductions in creatinine suggested that mean arterial pressure was well-maintained, ensuring adequate renal perfusion. Moreover, substantial hemolysis was evident postoperatively, as reflected by decreased hematocrit levels and elevated plasma-free hemoglobin. Notably, high urine output during CPB indicated optimal kidney function.

Hemolysis-related organ damage—particularly renal injury—can occur due to increased circulating plasma-free hemoglobin [1]. Both acute and chronic kidney disease can result from the accumulation of heme-containing proteins within renal tissues [1]. In several patients, a visible change in urine color was observed following the termination of CPB. These patients also exhibited elevated plasma-free hemoglobin levels, but postoperative urine was clear, and creatinine levels had decreased within 24 hours, suggesting no acute kidney impairment and preserved renal function.

A comparison of pre- and postoperative hematocrit levels revealed a statistically significant difference:

- Preoperative median hematocrit: 39.48% (IQR: 8.95)

- Postoperative median hematocrit: 34.10% (IQR: 5.10)

p = 0.001

This finding supports the presence of significant hemolysis.

Similarly, a significant difference was observed in serum creatinine values:

- Preoperative median: 1.33 mg/dL (IQR: 0.33)
- Postoperative median: 0.98 mg/dL (IQR: 0.48)
- p = 0.001

These results highlight the impact of CPB on renal function and the occurrence of hemolysis.

Hemolysis associated with CPB is primarily due to mechanical shear stress from the pump systems [11]. • Hemolysis is essentially destruction of red cells which results in increase in plasma free haemoglobin levels and reduction in haptoglobin levels. In this study, lower postoperative creatinine levels reflected adequate perfusion. The decrease in hematocrit levels, coupled with increased plasma-free hemoglobin, served as reliable indicators of hemolysis. Notably, patients undergoing mechanical valve replacement surgeries had the highest plasma-free hemoglobin concentrations. Enhancing CPB techniques and adopting preventative strategies may help reduce the incidence and severity of CPB-associated hemolysis.

Table 1 Descriptive statistics of Demographic variables

Demographic Variable	Mean ± SD
Age	48.23 ± 14.08
Height	156.09 ± 11.87
Weight	59.54 ± 14.76

.Table 2 Descriptive statistics of Pre-operative parameters

Parameters	Median ± IQR
BSA	1.60 ± 0.29
Max flow	3.84 ± 0.68
Hct	39.48 ± 8.95
MAP	78.39 ± 22.50
Creatinine	1.33 ± 0.33
BUN	12.72 ± 6.09
pre U/O	52.50 ± 75.00

Table 3 Descriptive statistics of Intra operative parameters

Parameters	Median ± IQR
MAP	74.00 ± 10.50
ACC	65.00 ± 39.00
CPB time	94.50 ± 66.00
intra U/O	700.00 ± 700.00

Table 4 Descriptive statistics of Post-operative parameters

Parameters	Median ± IQR
post U/O	2435.00 ± 723.50
Hct	34.10 ± 5.10
plasma free Hb	102.00 ± 9.00
Creatinine	0.98 ± 0.48

Table 5 Correlation between Plasma Free Haemoglobin and Selected operative Parameters

Parameters	Plasma free HB	
	R	Sig.
Pre-operative HCT	-0.115	0.263

Post-operative HCT	0.104	0.314
Pre-operative creatinine	-0.095	0.356
Post-operative creatinine	-0.072	0.485

Table 6 Comparison of Pre-operative and Post-operative HCT Levels

HCT	Median ± IQR	Sig.
Pre-operative	39.48 ± 8.95	0.001
Post-operative	34.10 ± 5.10	

Table 7 Comparison of Pre-operative and Post-operative Creatinine Levels

Creatinine	Median ± IQR	Sig.
Pre-operative	1.33 ± 0.33	0.001*
Post-operative	0.98 ± 0.48	

Table 8 Correlation between Plasma Free Hemoglobin and Operative Parameters

Parameters	Plasma free HB	
	R	Sig
ACC	-0.009	0.928
CPB	0.032	0.758

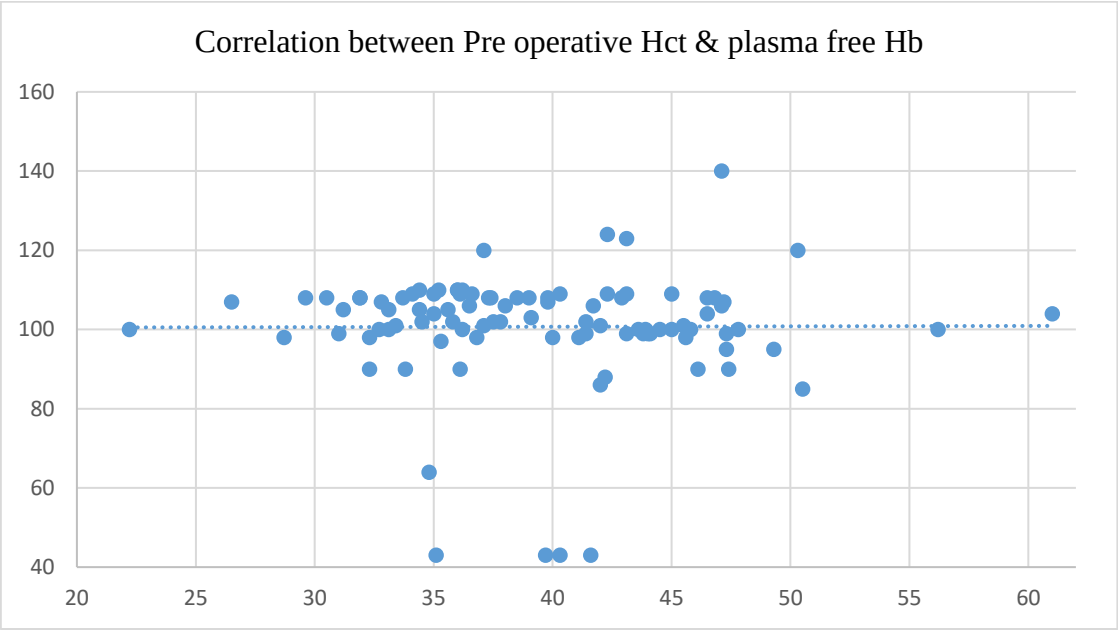
Table 9 Correlation between Cardiopulmonary Bypass (CPB) Time and Aortic Cross-Clamp (ACC) Time

Parameters	CPB	
	R	Sig
ACC	0.907	<0.05*

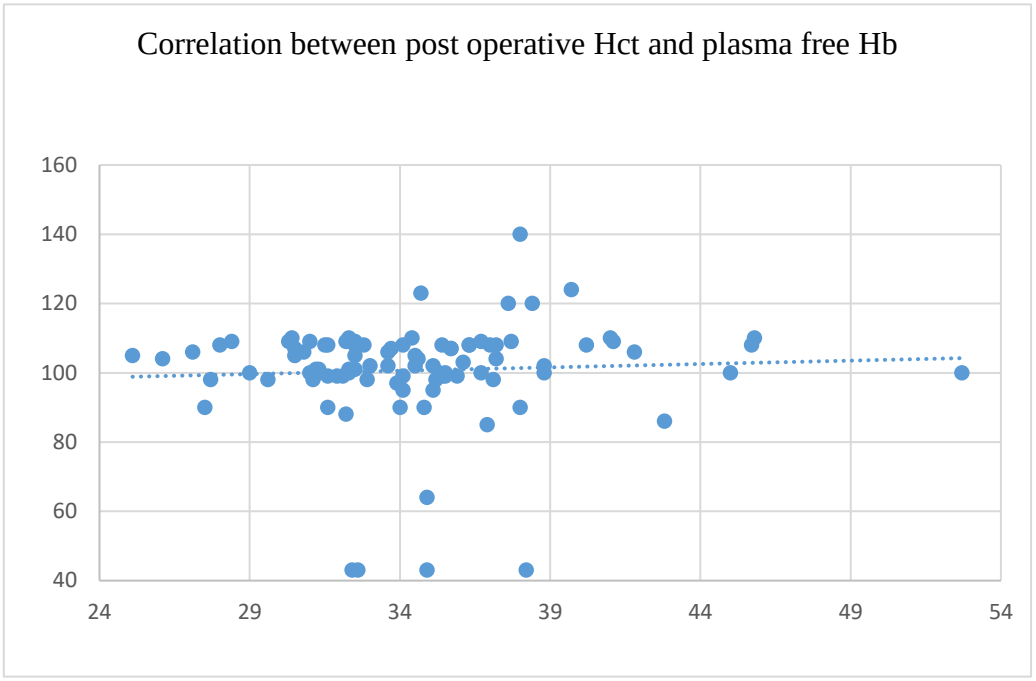
Table 10 Correlation between Mean arterial pressures (MAP) and Plasma free Hb

MAP		
	R	Sig
Pre-operative	-0.028	0.786
Intra-operative	-0.156	0.129

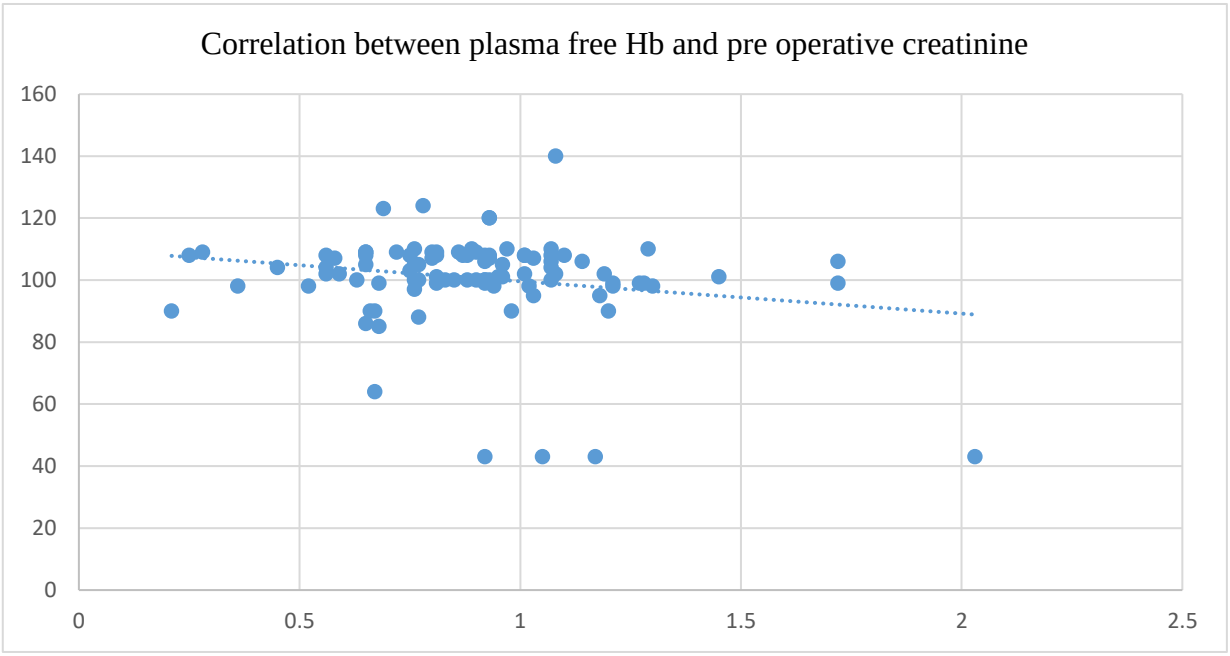
Graph 1 Correlation between Pre-op Hct & PFHb



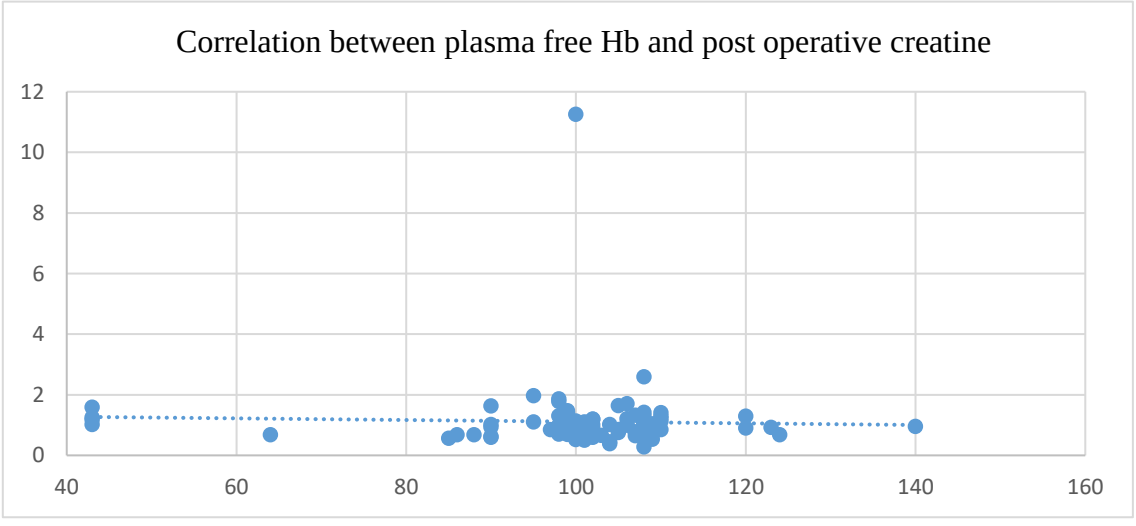
Graph 2 Correlation between post-operative Hct and plasma free Hb



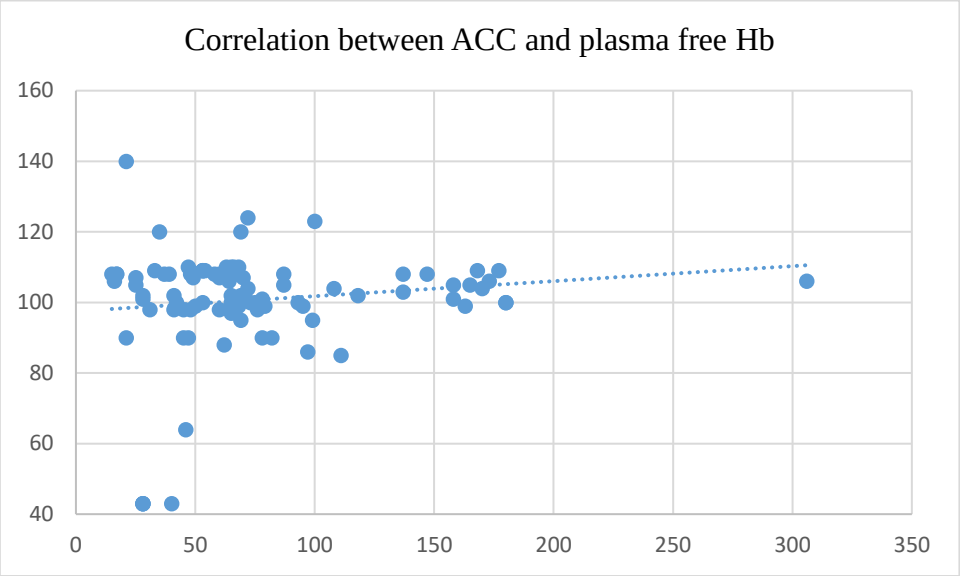
Graph 3 Correlation between plasma free Hb and pre-operative creatinine



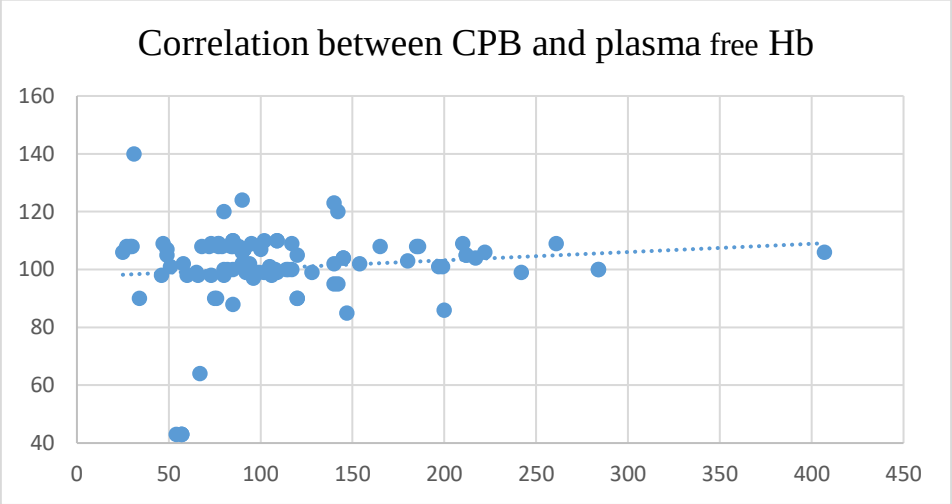
Graph 4 Correlation between plasma free Hb and post-operative creatinine



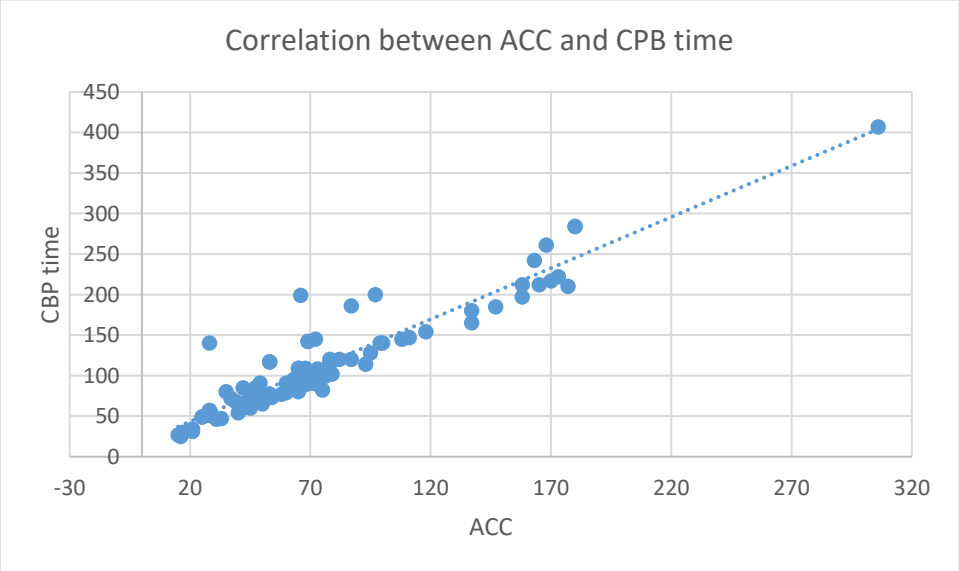
Graph 5 Correlation between ACC and plasma free Hb



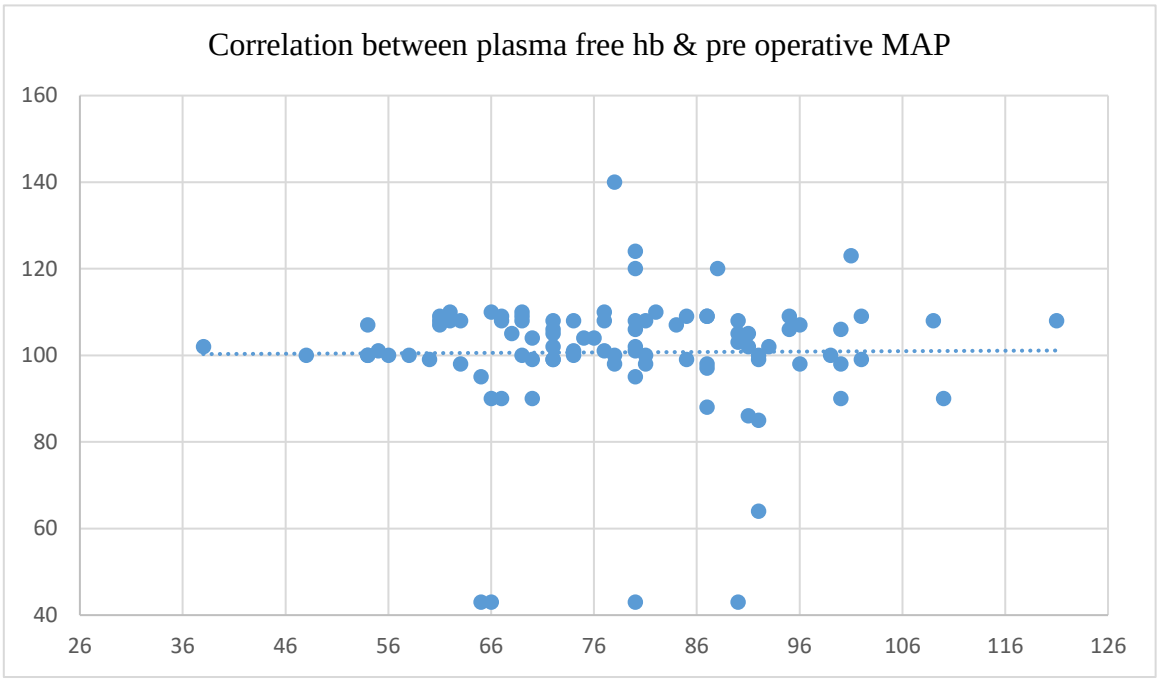
Graph 6 Correlation between CPB and plasma free Hb



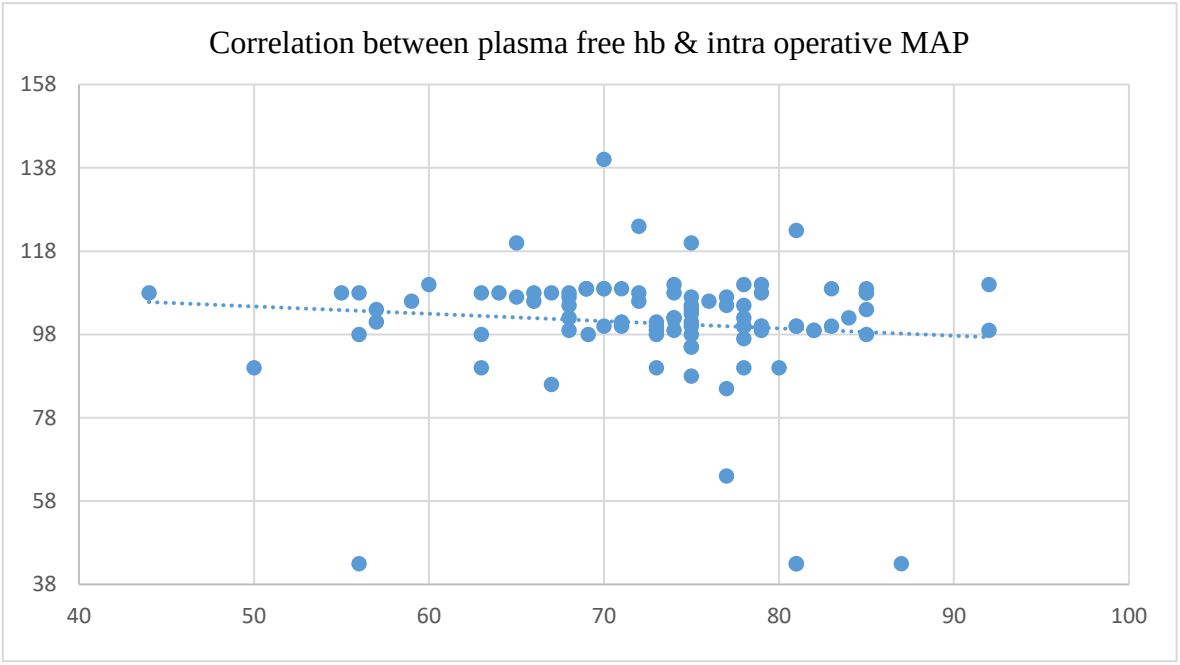
Graph 7 Correlation between ACC and CPB



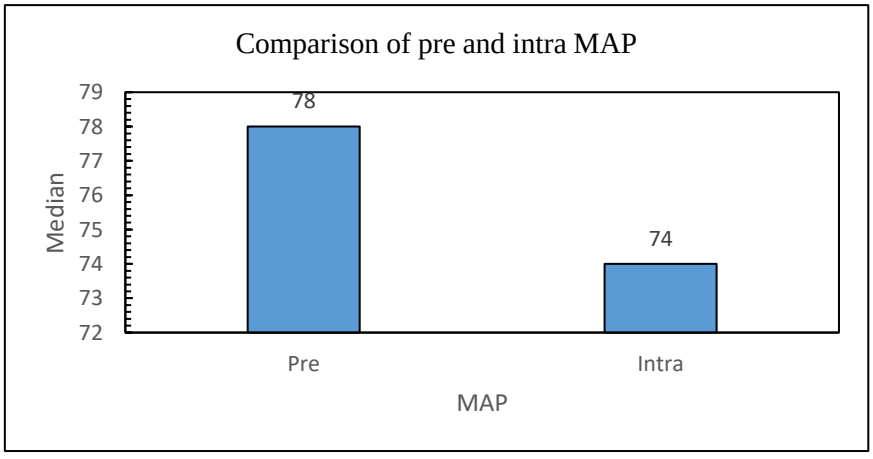
Graph 8 Correlation between Mean Arterial Pressure (MAP) and Plasma Free Hemoglobin Levels



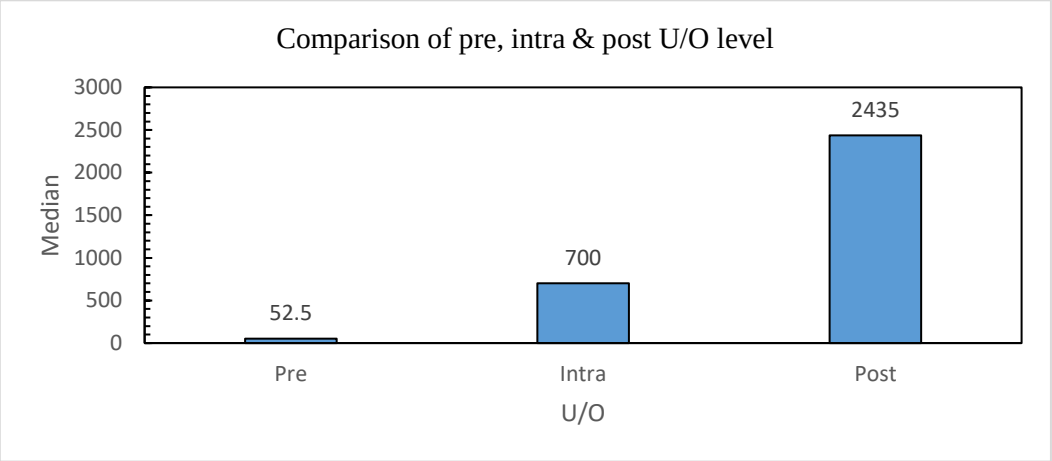
Graph 9 Correlation between plasma free Hb & intra operative MAP



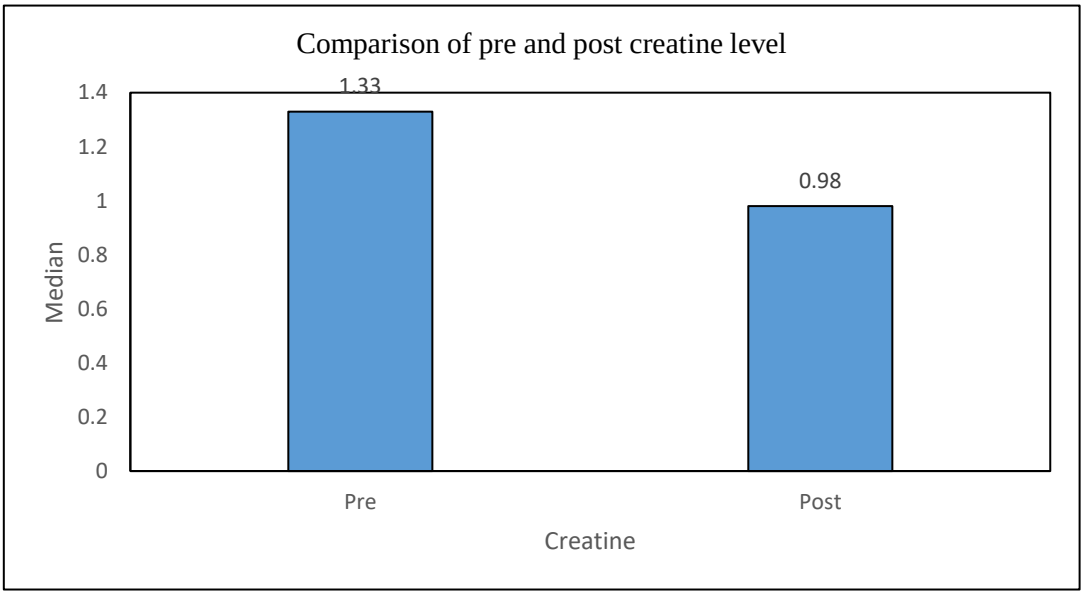
Graph 10 Comparison of pre and intra MAP



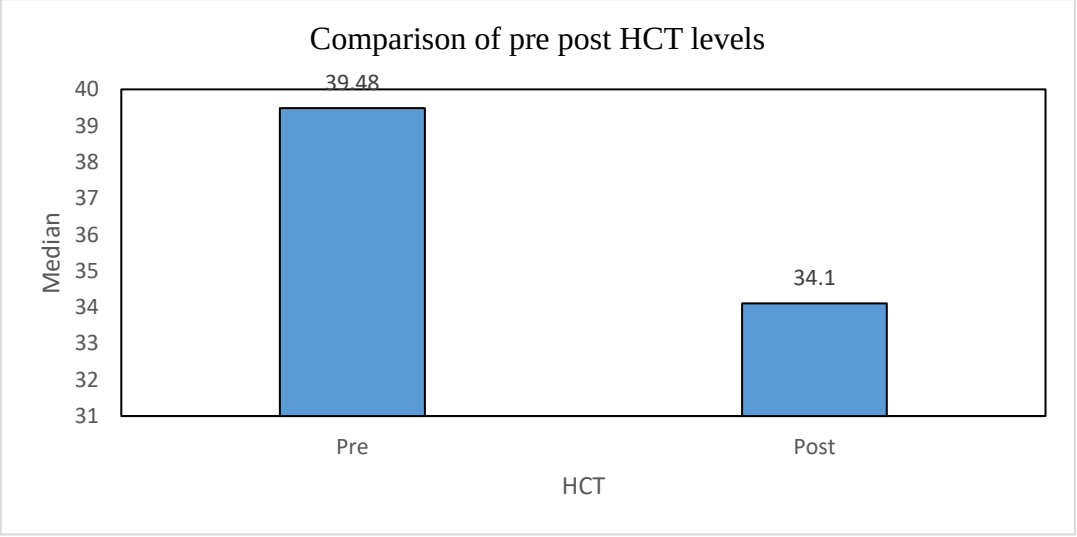
Graph 11 Comparison of pre, intra & post U/O level



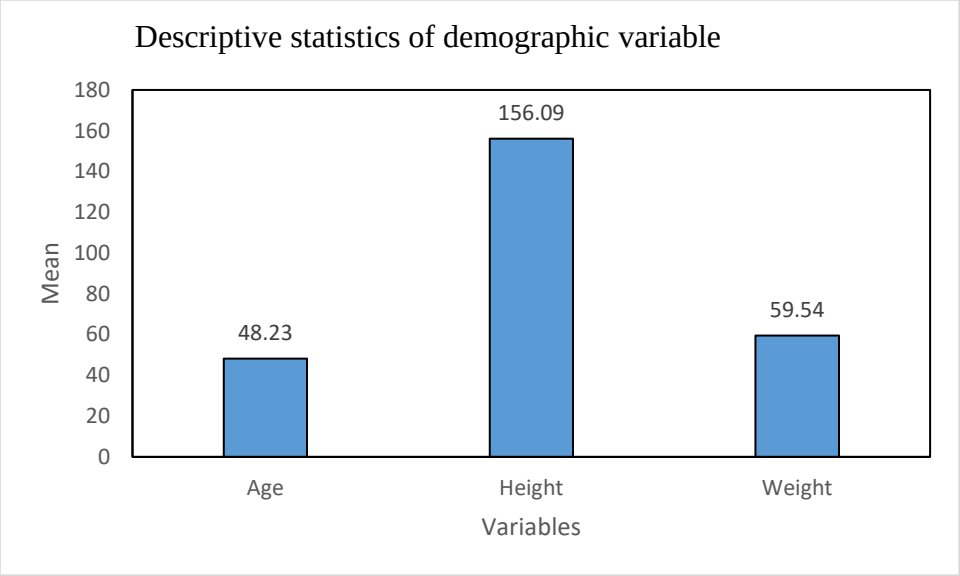
Graph 12 comparison of pre and postoperative creatinine level



Graph 13 Comparison of pre post HCT level



Graph14 Descriptive statistics of demographic variable



CONCLUSION:

Cardiopulmonary bypass associated hemolysis occurs when blood is encountered with sheer stress induced by the pumps. Hemolysis is essentially destruction of red cells which results in increase in plasma free haemoglobin levels and reduction in haptoglobin levels. Low creatinine levels were reported in our study indicating adequate perfusion. In the post-operative stage hemolysis was indicated by decrease haematocrit levels and increased plasma free haemoglobin levels. In patients undergoing mechanical valve surgeries greater plasma free haemoglobin was recorded. By enhancement of techniques cardiopulmonary bypass associated hemolysis can be minimized.

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