

# Impact of Activated Clotting Time on Post Cardiopulmonary Bypass Blood Loss

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## ABSTRACT

**Aim:** To find the relationship of activated clotting time (ACT) value with clinical and laboratory profile of patient and the impact of activated clotting time (ACT) values on post operative blood loss.

**Methods:** This was a prospective study, performed at Cardiac Surgery Department, King Edward Medical University/ Mayo Hospital Lahore. There were 42 patients who underwent cardiopulmonary bypass (CPB) over a period of three months (01-10-2014 to 31-12-2014). To obtain desired anticoagulation for Cardiopulmonary Bypass, the patients were given heparin in a dose of 400 IU/Kg. Patients were divided into two equal groups elevated ACT value (> 550 seconds to 999 seconds) (n = 21) and normal ACT value for CPB( $\leq$  550 seconds) (n = 21) group. The patients were excluded from this study if they underwent off pump CABG, redo operations, had pre-existing coagulopathy, dysfunction of liver, were receiving warfarin, having a preoperative hematocrit < 25%; or were transfused with leukocyte rich blood products including Fresh Frozen Plasma, thirty days before the surgery. Hemoglobin, platelet, white blood counts, prothrombin time (INR) and partial thromboplastin time were measured by hematology laboratory according to institutional protocols.

**Results:** There was notable association in blood loss and serum ACT values. Group one of low ACT value has higher blood loss as compared to other group of high ACT values. .Group one of low ACT value has decreased platelet count as compared to other group of high ACT values having increased platelet count. Other variables like, RBC's, APTT, PT, BSA, Hematocrit, Bypass time, Cross clamp Time and blood urea were not significantly influenced by ACT.

**Conclusion:** Higher ACT values result in decreased postoperative blood loss and should be practiced.

**Keywords:** Activated Clotting Time, Cardiopulmonary bypass, cardiac surgery, Blood Conservation

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## INTRODUCTION

Postoperative bleeding in cardiac surgery results from coagulation abnormalities and is one of the most important difficulty which a cardiac surgeon has to address. There are many reasons for this increased postoperative bleeding namely utilization of coagulation factors during CPB, residual heparin effect, hemodilution and activation of mechanism to dissolve clots.

To prevent blood from clotting during cardiopulmonary bypass, fixed doses of heparin sulphate are used as loading and maintenance to obtain desired anticoagulation. The level of circulating heparin is usually tested in laboratory by antifactor Xa assay. This test is not easy and plasma is used and precious time is lost in separating the plasma from blood. We can save this time by estimating the level of circulating heparin by making use of an automated protamine titration instrument. Complete blood heparin concentration could be estimated using an automated protamine titration instrument. There is clear positive association

between these two methods namely plasma antifactor Xa and hapcon calculated values of plasma concentration of heparin<sup>1</sup>.

In a few patients the activated clotting time over estimates the concentration of heparin in circulation. Therefore it is obligatory to evaluate the influence of elevated ACT values with the clinical and laboratory report of the patient<sup>2</sup>. Another complexity of higher value of ACT is also related with more blood loss into the drains postoperatively and consequently more blood transfusion with its potential risks<sup>3</sup>.

The reasons for increased postoperative bleeding after open heart surgery include consumption and dilution of clotting factors during cardiopulmonary bypass (CPB)<sup>4</sup>. The important constituent in clotting cascade is thrombin and its reduced production is related to more bleeding after surgery. A noticeable decrease in thrombin production was seen in initial postoperative period after open heart surgery. This fall in thrombin production has been associated with heparin effects and was not related to decrease in individual clotting factors. The continued heparin effect is responsible for the postoperative reduction in thrombin generation capacity<sup>5</sup>.

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The principal objective of observing hemostasis is to improve the safety of the patients undergoing cardiac surgical procedures<sup>6</sup>. The heparin is used to prevent coagulation of blood during cardiopulmonary bypass and ACT is used to measure anticoagulation during cardiopulmonary bypass. The two important machines for this purpose are used as Hemotech (R) and Hemochron (R) having different contact activation systems celite and kolin respectively<sup>7</sup>. It is therefore vital to outline the crucial association of ACT value with clinical and laboratory report of the patient and the influence of ACT values on post operative blood loss. This association can help us to reduce postoperative blood loss and need of donor blood transfusions.

Therefore, the current study is intended to explore the role of ACT value in averting the blood loss postoperatively after CPB.

## MATERIALS AND METHODS

This study was performed by taking an informed consent of participating patients at the Department of Cardiovascular Surgery, King Edward Medical University/ Mayo Hospital Lahore. The study was conducted on 42 consecutive adult patients, (20 years or older) meeting the inclusion and exclusion criteria, planned for CPB over a period of three months (01-10-2014 to 31-12-2014). All the patients were given 400 units/Kg of IV Heparin for anticoagulation. The patients (n=21) were assigned to a group 1 and (n=21) to Group 2. The group 2 includes patients with elevated ACT (> 550 seconds to 999 seconds). The patient (n=21) with normal ACT value (≤550 seconds) were included in Group 1.

**Base line Assessment and Data Collection:** The patients excluded from this study were patients undergoing redo surgeries, off pump CABG, having a preoperative hematocrit < 25% or they were transfused with leukocyte rich blood products including FFP thirty days before the start of surgery. Patients with pre-existing coagulopathy addressed as (baseline international normalized ratio INR of prothrombin time greater than 1.5 seconds, activated partial thromboplastin time greater than 40 seconds and platelet count below 100 to 109 per litre), dysfunction of liver (standardized liver function laboratory tests were 2-fold of above normal values) were also excluded. Detailed and complete demographic data, preoperative laboratory values, operative data, heparin bolus dose and anti blood coagulation data having ACT values was collected. Length of stay in hospital was recorded in days, with the surgical day and last admitted day in hospital as whole days. Hemoglobin, platelet, and white blood counts, prothrombin time and international

normalized ratio and activated partial thromboplastin time were determined by hematology laboratory according to the institutional protocols.

**Procedure:** A standard procedure for dosage of heparin (B-BRAUN Melsungen, Germany) and protamine sulphate (HOWARDS) were determined in all the patients: systemic-anticoagulation was completed with porcine heparin. Pre-cardiopulmonary bypass heparin dose first time consisted of 400 IU per kilogram of the body weight. After re-warming treatment of patient at 37°C (calculated from the venous line of the CPB circuit), CPB was turned off. Heparin was neutralized by protamine (1.0 milligram protamine per milligram of full heparin).

Height of the patient was determined using a Stadiometer. Data of height and weight were used to calculate body surface area (BSA) using Mosteller formula. Height was measured in centimeters and weight in kilograms. The test for anticoagulation were done on patient's blood sample at baseline before heparinization, after heparinization; after one hour of CPB initiation and after reversal of heparin with protamine after CPB. Kaolin (activator) activated ACT had been utilized by Hemochron (International, Technidyne Corporation; Edison, NJ) Hepcon. The quantity of post-Cardiopulmonary bypass blood loss was considered through chest tubes drainage in initial 24 postoperative hours.

All the patients were anesthetized using fentanyl 30-100 pg/ kg; loaded with isoflurane 0.25-0.5 expired minimum alveolar anesthetic quantity, muscle relaxants (vecuronium 10-20 mg, pancuronium 10 to 15 milligram, or metocurine 15 to 20 milligram), and lorazepam 2-4 mg. Surgery was always performed by the same surgeon. Chest was opened by median sternotomy in all the patient and cardiopulmonary bypass was established in all patients. The perfusion protocols were kept the same in both the groups.

The CPB was performed using a roller pump (cobe) and a membrane oxygenator of hollow fiber (Dideco; Compactflo EVO; Sorin Group USA). The CPB system was usually primed using 1.5 liters of Ringer Lactate Solution 25 g mannitol; 5000 IU porcine heparin. At the time of cardioplegia administration, systemic temperature remained at 32°C. Perfusion flow rates were considered as 2.4 l/ min/ m<sup>2</sup> of body surface area. Additional amounts of heparin were delivered before and during CPB to attain and sustain the ACT higher than 480 s, respectively.

Instantly after applying aortic cross clamp cardioplegia was delivered antegradely into the aortic root to arrest the heart. Crystalloid Cardioplegia (15 ml /kg; including 30 mEq/ L KCl) was initially delivered. After cardiac arrest the crystalloid

cardioplegia was delivered retrogradely through coronary sinus. Then Blood Cardioplegia (10 ml/kg; comprising 15 mEq/L KCl) was delivered retrogradely every twenty minutes. Cardioplegia was delivered through aortic route (antegrade) at 75-85 mmHg pressure and through coronary sinus route (Retrograde) at 30-35 mmHg in two groups. Coronary sinus was cannulated through a purse string in right atrium blindly, according to the method proposed by Gundry and colleagues. The precise positioning of the retrograde cannula into the coronary sinus by measuring the coronary sinus pressure, dark coloured blood in cannula and palpating the balloon of cannula on inferior surface of the heart in the posterior interventricular vein.

The cardiopulmonary bypass was terminated after the nasopharyngeal temperature was 37°C and heparin was then neutralized using protamine (1 mg protamine/ 1 milligram of the total heparin delivered prior to and during CPB). All the patients were evaluated for increased non-surgical blood loss after protamine neutralization of heparin and need for donor blood transfusion. The following parameters were recorded to access the effect of higher and lower ACT values:

**Blood Loss:** The blood loss was measured by chest tubes drainage every hour for 24 hours after completion of surgery. The Thorametrix 2300mls system was used as a post-operative drainage system which drains air and blood from the chest cavity. It had clear chambers to identify the level of fluid drained. This system provide the adequate amount of vacuum in patients and a controlled level of suction. Water seal chamber was filled with 60cc sterile water and water seal port with 20 cc of water. The patient tube was connected to the collection chamber and adjusted the regulated suction source to minimum level suction source. Then it was gradually increased until bubbling appeared in the suction control chamber. Calibration was in 5cc increments up to 280 cc and 10cc increments up to 1150cc.

**Blood transfusion:** The requirement for donor blood transfusion was determined by taking into account the blood loss through chest tubes, patient's hemoglobin concentration and hemodynamic monitoring the patient. For the improvement of hematocrit and fluid replacement in response of blood loss properly cross matched whole blood was transfused to the patient. Two people verified: Patient Name ID number ABO and RH type Expiration date. Transfusion form was also completed

**Haemogram or Complete Blood Count:** A preoperative assessment that could identify and correct the post-operative and intra-operative bleeding was platelet count and function. Therefore,

a better picture of this variable could reduce the risks and complications of postoperative bleeding.

**Statistical Design:** Data were presented as mean  $\pm$  SD being normally distributed; the Student independent *t* test were employed to evaluate means of normally distributed variables like blood loss, blood transfusion, platelet count and hemoglobin values. Dependent *t* test used to find the means of Hb during the CPB. The P value < 0.05 was considered as statistical significance. Statistical analysis had been done by applying SPSS version 13.

## RESULTS

A total of consecutive 42 patients were enrolled in this study from 01 October 2014 to 31 December 2014. Two patients were excluded from the data due to calculations and clinical profile error. Two groups were made, each containing data of 20 patients. Group 1 containing those patients having normal ACT values and Group 2 included patients having ACT values higher than that of normal values. As expected, the results supported the hypothesis made for this study. Table 1 summarizes the values of baseline characteristics of the individuals. According to study, there was no statistical difference ( $p > 0.05$ ) between both groups related to majority of the variables like weight, height and body surface area. The age of the patients having higher values of ACT (Group-2) were older ( $p < 0.05$ ) than in group-1 ( $53.27 \pm 1.66$ ) that had normal ACT values. The random blood sugar during the surgery tended ( $p = 0.09$ ) was higher in the Group-2 compared with the Group-1 (Table 1).

According to Table 2, there was no statistical difference with regard to total leukocyte count ( $p > 0.05$ ) in both the groups. Total RBC's count of the patients in both groups ( $p > 0.05$ ) was also not significant. Similarly, PT and aPTT also showed no statistical difference between two groups (Table 2). The platelet count was higher ( $p < 0.05$ ) in the Group-2 ( $233.00 \pm 43.56$ ) than in the Group-1 ( $194.28 \pm 69.20$ ).

Table 3 describes that there was no statistical difference ( $p > 0.05$ ) between both the groups related to observed variables such as blood urea and serum creatinine. The mean values of bypass time ( $91.22 \pm 22.13$  sec vs.  $106.11 \pm 37.52$  sec) and cross clamp time ( $57.05 \pm 19.41$  sec vs.  $67.56 \pm 37.76$ ), baseline ACT ( $113.35 \pm 21.46$  sec to  $103.32 \pm 20.46$ ) and body surface areas ( $52.84 \pm 0.15$  vs.  $52.74 \pm 0.13$ ) were comparable with ( $p > 0.05$ ) between both the groups (Table 3).

Table 4 reveals that there was no statistical difference ( $p > 0.05$ ) found between both the groups related to variables like pre bypass Hb, balanced

output of the patients and the concentration of Hb. On the other hand, the Hb level was significantly different ( $p < 0.05$ ) in group-1 when values were compared before and during the bypass. Similar results ( $p < 0.05$ ) were obtained in the Group 2 (Table 4). There was a statistical difference ( $p < 0.05$ ) in blood loss of 24 hours from chest drains between

both the group. The Group-1, having low ACT value had more ( $p < 0.05$ ) blood loss ( $1090.0 \pm 528.40$  mL) compared to Group-2 of high ACT values ( $744.74 \pm 319.2$ ). As expected, more volume of blood was infused in patients in Group-1 ( $1103.1 \pm 693.17$ ) compared to the Group-2 ( $663.16 \pm 476.63$ ) after the bypass operation.

Table 1: Basic characteristics of patients

Variables	Group-1	Group-2	p. Value
	Mean $\pm$ SE	Mean $\pm$ SE	
Age (Years)	51.21 $\pm$ 3.01	53.27 $\pm$ 1.66	0.001
Weight (Kg)	71.57 $\pm$ 2.54	69.05 $\pm$ 2.25	0.591
Height (cm)	1.66 $\pm$ 1.62	1.69 $\pm$ 2.07	0.333
Blood Sugar level (During CPB)	1.33 $\pm$ 6.06	1.55 $\pm$ 9.84	0.091

Group-1(Normal ACT values), Group-2(High ACT values)

Table 2: Baseline characteristics of study patients

Variables	Group-1	Group-2	p. Value
	Mean $\pm$ SE	Mean $\pm$ SE	
Total Leukocyte count ( $10^3$ / uL)	9.05 $\pm$ 2.64	8.64 $\pm$ 2.28	0.630
Total RBC count ( $10^6$ / uL)	3.81 $\pm$ 0.44	3.75 $\pm$ 0.765	0.793
Prothrombin time (seconds)	13.07 $\pm$ 1.89	12.81 $\pm$ 1.97	0.718
aPTT time (seconds)	28.07 $\pm$ 5.51	29.93 $\pm$ 4.15	0.309
Platelet count ( $10^3$ / uL)	194.28 $\pm$ 69.20	233.00 $\pm$ 43.56	0.045

Group1 (Normal ACT values), Group2(High Act values). RBC's= Red Blood Cells, aPTT= activated partial thromboplastin time PT= Prothrombin time.

Table 3: Biochemical &amp; intra-operative characteristics of study patients

Variables	Group-1	Group-2	p Value
	Mean $\pm$ SE	Mean $\pm$ SE	
Blood Urea (mg/dl)	36.77 $\pm$ 11.35	37.38 $\pm$ 12.35	0.876
Serum Creatinine (mg/dl)	1.12 $\pm$ 0.31	1.12 $\pm$ 0.27	0.332
Bypass Time (minutes)	91.22 $\pm$ 22.13	106.11 $\pm$ 37.52	0.156
Cross Clamp Time(minutes)	57.05 $\pm$ 19.41	67.56 $\pm$ 37.76	0.307
Baseline ACT (seconds)	113.35 $\pm$ 21.46	103.32 $\pm$ 20.46	0.160
Body Surface Area(m <sup>2</sup> )	52.84 $\pm$ 0.15	52.74 $\pm$ 0.13	0.222

Group-1= Normal ACT values, Group-2= Higher ACT values, ACT activated clotting time.

Table 4: Hemodilution related parameters in study patients

Variables	Group-1	Group-2	p. Value
	Mean $\pm$ SE	Mean $\pm$ SE	
Pre-Bypass Hb (mg/dl)	11.43 $\pm$ 2.32	12.16 $\pm$ 2.39	0.341
Hb on Bypass (mg/dl)	6.18 $\pm$ 1.35 <sup>a</sup>	6.70 $\pm$ 2.17 <sup>a</sup>	0.384
Hb after Bypass (mg/dl)	10.96 $\pm$ 1.73 <sup>b</sup>	11.54 $\pm$ 1.50 <sup>b</sup>	0.432
Balance output (mls)	-238.5 $\pm$ 670.66	-497.89 $\pm$ 802.88	0.309
Blood Loss (mls)	1090.0 $\pm$ 528.40	744.74 $\pm$ 319.12*	0.023
Blood Infused (mls)	1103.1 $\pm$ 693.17	663.16 $\pm$ 476.63	0.034

Group1 (Normal ACT values), Group 2 (High Act values). Hb = Hemoglobin, Balance output= Volume infused – urine out-input.

a, b Means with different subscript differ significantly in column before and after bypass ( $P < 0.00$ )

## DISCUSSION

During cardiopulmonary bypass the level of anticoagulation achieved by heparin is assessed by ACT as it is an easy, accurate, reliable and quick method<sup>8</sup>. The blood coagulation cascade is subdued more effectively by higher concentrations of heparin by decreasing the excessive activation of clotting factors as compared to usual heparin doses selected

on the basis of ACT. These findings elucidates the substantial decline in blood loss and subsequent need for donor blood transfusions when higher heparin concentrations are maintained<sup>9</sup>. Increased ACT values during CPB are related with reduced fibrin values<sup>10</sup> and had been explained to stop clot-bound, thrombin more efficiently<sup>11</sup>. The postoperative bleeding in patients who undergo CPB necessitates

use of donor blood with its attended risks including transfusion reactions, decreased immunity, and disease transmission<sup>12</sup>. According to the findings of our study, Group-2 (High ACT value) had less donor blood transfusions as compared group 1 of low ACT. It showed that the low ACT values are related to more use of donor blood after bypass confirming the hypothesis.

In the current study, there was no difference of ACT based variable of gender. On the other hand, it has been found that younger women represented a high-risk group for in-hospital complications and mortality after CABG surgery compared with men. In view of our findings, additional investigation is needed to determine why in-hospital mortality is higher in women after CABG, with particular attention focused on younger women<sup>13</sup>.

The finding of the current study revealed that more blood transfusions was carried out in patients who had low normal ACT values (Table 4). It is also important to mention that more blood loss was occurred in the same group as compared to the Group-2. It seems that there was preservation of clotting factors in the patients having higher ACT values. These preserved clotting factors were used to minimize the blood loss after the surgical intervention. The patients are sorted out on the basis of blood loss through chest tubes for the need for blood transfusion. There is a relation of in hospital mortality in cardiac surgical patients and massive blood transfusions<sup>14</sup>. The higher the pre cardiopulmonary bypass heparin concentration, the lower is the amount of blood loss and need for donor blood transfusions<sup>15</sup>. The current results showed that Group-2 of high ACT value had lower blood loss compared to the group-1 of low ACT.

As depicted in the Table-1, the Group-2 patients were older than the patients of Group-1. According to a study (Hager et al. 1989), there was an age-dependent increase of thromboembolic events. Plasma coagulation parameters in healthy elderly blood donors are better in comparison with young and elderly diseased blood donors. Moreover, it was also known that partial thromboplastin and thrombin clotting times were slightly shortened without any alteration in the prothrombin times. It was also demonstrated that activation of coagulation and fibrinolysis happened more often in elderly healthy people<sup>16</sup>. As for as our results are concerned, the patients having higher act values were the elderly patients which supported the concept of coagulation changes with the enhancing age.

It has been confirmed that normally coagulation tests drawn preoperatively can indicate blood drain after CPB<sup>17</sup>. But results did not favor this statement as we could not found significant effect of ACT values

on RBC's count PT, aPTT, leukocyte count and Hb values (Table 2).

Platelets perform an important part in stabilizing usual hemostatic function; their loss of function is a basic reason of higher bleeding in the initial postoperative time after CPB<sup>18</sup>. Platelet function loss may also be concerned to activation of coagulation<sup>19</sup>. Pre-operative thrombocytopenia could be related to higher bleeding risk. Excessive bleeding after CPB might give to higher mortality; morbidity; transfusion demands and re-intervention<sup>20</sup>. There have also been some reports where splenectomy was performed in an attempt to improve platelet counts pre-cardiac surgery and also the use of off-pump cardiac surgery to reduce post-operative bleeding<sup>21</sup>. Present findings revealed that Group-1 of low ACT value had lower platelet count compared with the other group-2 of high ACT values having increased platelet count. Therefore, the higher ACT values were related to platelet count.

In conclusion, higher ACT values prevent the blood loss after bypass and can lead to a decrease risk of cardiovascular shock. Therefore, ACT values may be maintained at higher level than the recommended normal level to avoid any complication after the bypass.

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