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The Influence of Tranexamic Acid on Platelet Function in Patients Undergoing Open Heart Surgery Using Cardiopulmonary Bypass (CPB)

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Abstract

Introduction: Platelet dysfunction is consideredto be a major cause of bleeding after cardiac surgery following Cardiopulmonary Bypass (CPB), resulting in an increased need for transfusions. Lysine analogues such as tranexamic acid, inhibit fibrinolysis by attachment to the lysine binding sites on plasminogen and plasmin and prevent fibrinolysis by blocking engagement of these fibrinolytic proteins with fibrinogen and fibrin. *Aim:* In this study, we sought to determine whether Regimen 1 (continuous infusion of tranexamic acid) preserves platelet function when compared to Regimen-2 (bolus dose of tranexamic acid). *Material and Methods:* Regimen-1 Tranexamic acid 10mg/kg IV after induction before skin incision followed by 1mg/kg/hr infusion. Regimen-2 Tranexamic acid 10mg/kg IV after induction before skin incision followed by 5mg/kg bolus in pump prime and 5mg/kg IV after protamine administration. *Results:* There was no statistically significant difference between the two groups or within the same group at different time periods with regard to platelet aggregation. *Conclusion:* Either continuous or intermittent methods of tranexamic acid in patients undergoing open heart surgery may be used for pharmacological prophylaxis for bleeding.

Keywords: CPB; Tranexamic Acid; Platelet Aggregation.

Introduction

Excessive bleeding after cardiac surgery contributes to postoperative morbidity and mortality [1]. Platelet dysfunction is considered to be a major cause of bleeding after cardiac surgery following cardiopulmonary Bypass (CPB), resulting in an increased need for transfusions [2]. CPB results in a systemic inflammatory response produced by the kinin-kallikrein, the fibrinolytic coagulation and complement system that generate proinflammatory mediators through a series of consecutive proteolytic cleavages [3,4]. Increased plasma concentration of plasmin and thrombin leads to platelet dysfunction after CPB. Anti- fibrinolytic drugs reduce bleeding and postoperative transfusion requirements Two different classes have been developed, the lysine analogues, including ε aminocaproic acid and tranexamic acid (TA), and serine protease inhibitors namely aprotinin. Lysine analogues inhibit fibrinolysis by attachment to the lysine binding sites on plasminogen and plasmin and prevent fibrinolysis by blocking engagement of these fibrinolytic proteins with fibrinogen and fibrin [4,5]. A recent study evaluating the influence of tranexamic acid on platelet function has found a reduction in platelet aggregation during CBP [6].

At our Institution (Nizam's Institute of Medical Sciences) two standard protocols exist for administration of tranexamic acid- Regimen-1 Tranexamic acid 10mg/kg IV after induction before skin incision followed by 1mg/kg/hr infusion and Regimen-2 Tranexamic acid 10mg/kg IV after induction before skin incision followed by 5mg/kg

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bolus in pump prime and 5mg/kg IV after protamine administration.

In this study, we sought to determine whether Regimen-1, continuous infusion preserves platelet function when compared to Regimen-2.We determined the effect of tranexamic acid in patients undergoing cardiac surgery with CPB on haemostatic outcome, with two different regimens using a new point of care (POC) optical aggregation in PRP (aggregometers (CHRONOLOG)). We hypothesized that continuous infusion of tranexamic acid preserves the platelet function better than intermittent administration of tranexamic acid.

We designed a randomized study comparing the effect of bolus and infusion of Tranexamic acid on platelet function in patients undergoing open heart surgery using CPB.

Material and Methods

After approval by the Institutional Ethical Committee and written informed consent, 30 patients of either sex in the age range of 40-70 years undergoing open heart surgery using CPB were studied.

Exclusion criteria included history of bleeding diathesis, abnormal coagulation tests (Activated Partial Thromboplastin Time>40 sec, International Normalized Ratio > 1.25), thrombocytopenia (Platelet Count <1,50000/mL), previous cardiac surgery or oral therapy with antiplatelet drugs within the last seven days preoperatively.

Patients were randomized in to two groups one group(n15) (Group 1) received (regimen-1) Tranexamic acid 10mg/kg intravenous bolus after induction followed by 1mg/kg/hr till the end of surgery and the other group (n-15) (Group 2) received (Regimen-2) 10mg/kg IV after induction before skin incision, 5mg/kg in pump prime and 5mg/kg IV after protamine administration. Patients were given tramadol 1 mg/kg and promethazine 0.5mg/kg IM 1hr before surgery. Anaesthesia was induced by midazolam (0.1mg/kg) fentanyl (2μg/kg), sevoflurane. Rocuronium 1mg/kg was given to facilitate endotracheal intubation. After endotracheal intubation, anaesthesia was maintained with sevoflurane and intermittent administration of fentanyl, midazolam and vecuronium with 50% oxygen in air. The ventilation rate was adjusted to end-expiratory carbon dioxide concentration (32-42 mmHg).

Prior to induction of anaesthesia (T0), after the administration of bolus (T1), and after the administration of protamine (T3) blood samples were obtained for platelet aggregation studies. Platelet function was assessed by "Optical aggregation in PRP"using whole blood aggregometry.

Platelet Aggregation Method Used in the Study

Blood sample collection: 0.6ml of 3.8% sodium citrate was placed in a polypropylene tube. 5.4 ml of blood was added in to it (in a ratio of 1:9). The test tube was capped and gently inverted 8-10 times for proper mixing of blood.

Procedure

The centrifuge was adjusted to 20°C temperature and centrifugation speed to 600-800 rpm and the test tube was centrifuged for 15min. After centrifugation was complete, the upper platelet rich plasma layer (PRP about 2ml) was transferred into the labeled storage vial with the help of micro pipette without disturbing the blood cell layer that is in the bottom. The remaining blood sample was centrifuged again at 3000 rpm for 5 minutes to get platelet poor plasma (PPP). 0.5ml of platelet poor plasma (PPP), and platelet rich plasma (PRP) were pipetted out into 2 cuvettes having no disposable stir bars. 0.5ml of platelet rich plasma (PRP) was pipetted out into 2 cuvettes having disposable stir bars. (Mix the plasma samplebefore pipetting) [39]. Adjustment of baseline to zero using Calibrate knob of the instrument was done. Once the baseline was stabilized (i.e., when the cursor was in a straight line which usually took 2-3minutes.5μl of ADP (10μM/ml) was added with the help of Hamilton syringe in to the cuvettes containing PRP in channel-1 & channel-2 at 0.15 min. After 6 minutes, the test was stopped. Slope and amplitude were computed. The results were reported as % aggregation. If the results of both the channels showed a variation of morethan 15%, then the test was repeated again in one of single channel.

Normal range in healthy subject in fasting condition is 60–90%.

Statistical Methods

Descriptive statistics were presented as median and interquartile range (IQR). Where applicable, data were summarized graphically as box-plots. Box and whisker diagrams, or Box Plots, use the concept of breaking a data set into fourths, or quartiles, to create a display. The box part of the diagram is based on the middle (the second and third quartiles) of the data

set. The whiskers are lines that extend from either side of the box. Whiskers represent 1.5 times interquartile range. Box-plots depict a lot of information about distribution, location and spread of the represented data. They are particularly valuable because several box plots can be placed next to each other in a single diagram for easy comparison of multiple data sets. Categorical data were analyzed by chi-squared analysis and continuous data were analyzed by non-parametric Mann-Whitney U test. Intra group comparison of platelet aggregation data at different time periods was done with Friedman test. A p value <0.05 was considered significant. Minitab version 14 for windows was used to facilitate data analysis.

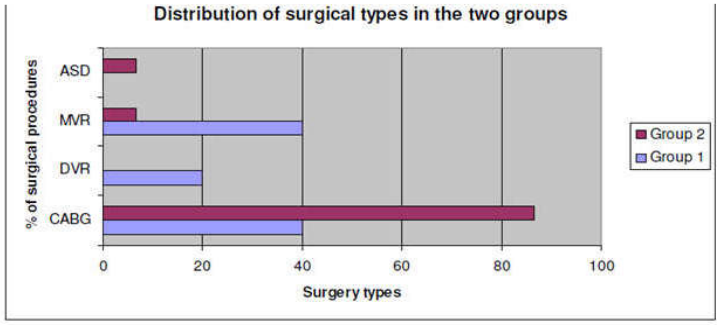
Data Analysis and Results

Among demographic variables,the age ranged from 25 to 70 years in the continuousgroup and 21 to 65 years in intermittent group. The weight ranged from 40 to 101Kg in the continuous group and from 45 to 93 Kg in the intermittent group. Among theoperative variables, duration of surgery ranged from 210 to 480 minutes inthe continuous group and 195 to 420 minutes in the intermittent group. Cardiopulmonary bypass time ranged from 80 to 248 minutes in the continuous group and 50 to 191minutes in the intermittent group (Table 1).Boxplots of distribution of surgery type between groups, (Figure 1) platelet aggregation (Figure 2), blood unit transfused (Figure 3), fresh frozen plasma (Figure 4), and plate rich plasma (Figure 5) are constructed.

Group 1: continuous; Group 2: intermittent; Period 1: Pre-induction baseline, Period 2: After tranexamic acid administration; Period 3: After protamine administration Statistical comparison of platelet aggregation data: Between the two groups, atall the time periods there was no statistically significant difference (Mann-WhitneyU test). There was a clear trend towards decrease in platelet aggregation afterbolus (2nd time period) and after protamine administration (3rd time period). However, in each group, there was no stastistically significant difference inplatelet aggregation data at different time periods.

Table 1: Distribution of demographic variables between groups

Variable	Group 1 (Continuous) (N=15)	Group 2 (Intermittent) (N=15)	P value
Age (years)	49 (45 to 56)	53 (42 to 55)	Not significant
Weight (kg)	60 (46 to 70)	67 (50 to 72)	Not significant
Duration of Surgery (min)	300 (270 to 420)	300 (270 to 365)	Not significant
Cardiopulmonary bypass time(min)	114 (88 to 150)	118 (93 to 164)	Not significant



	CABG	DVR	MVR	ASD
Group 1	40	20	40	0
Group 2	86.67	0	6.67	6.67

CABG: Coronary artery bypass graft;
DVR: Double valve replacement
MVR: Mitral valve replacement
There was no statistically significant difference between the two groups with regard to surgical procedure types.

Fig. 1: Boxplots of distribution of surgery type between groups.

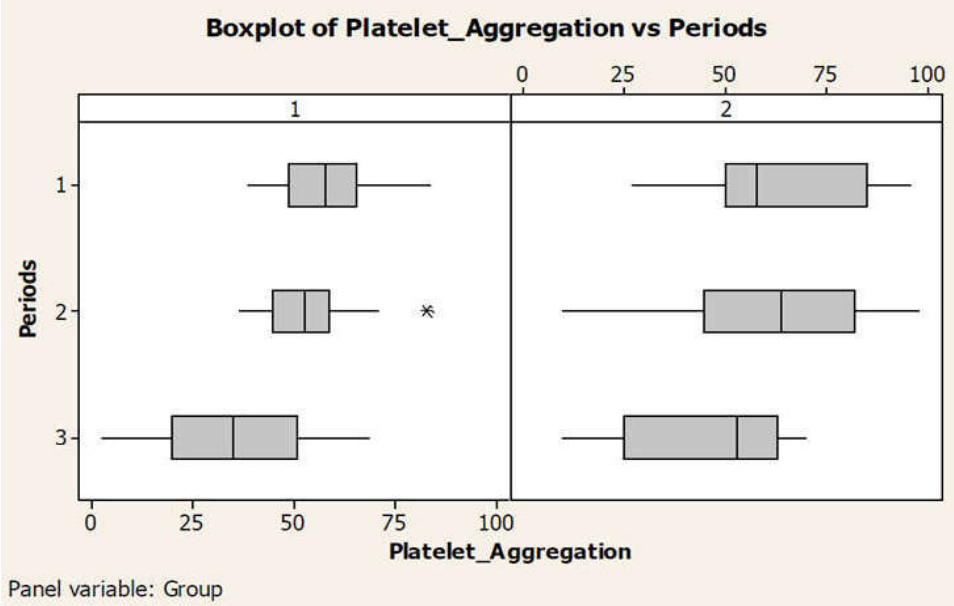
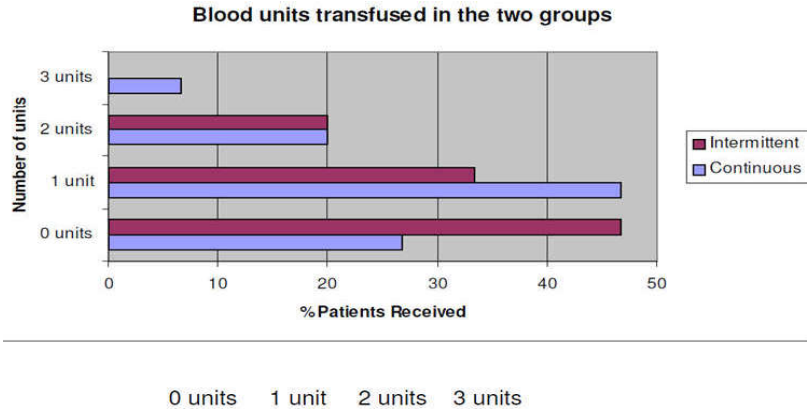
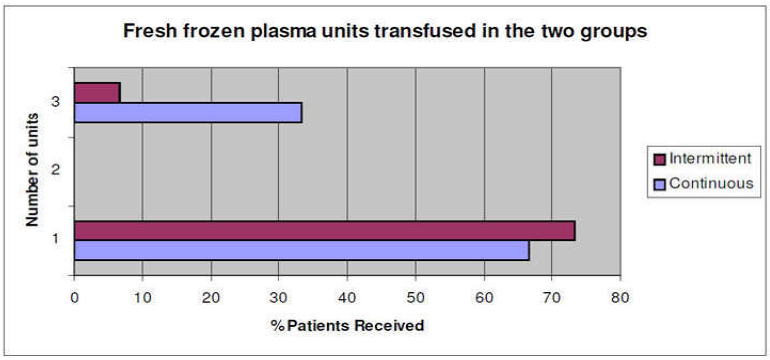


Fig. 2: Boxplot of platelet aggregation at various time periods



0 units	1 unit	2 units	3 units

Fig. 3: Boxplot of blood units transfused in the two groups
P value Not significant (chi-squared test)



	0 units	1 unit	2 units
Continuous	66.67	0	33.33
Intermittent	73.33	0.2	6.67

Fig. 4: Comparison of fresh frozen plasma transfused between groups.
P value Not significant (chi-squared test)

	0 units	1 unit	2 units	3 units	4 units
Continuous	26.67	0	66.67	0	6.67
Intermittent	20	0	80	0	0

Fig. 5: Comparison of platelet rich plasma transfused between the two groups
P value Not significant (chi-squared test)

Power Analysis

Considering the sample 3 data in two the groups, the power ofthe study was to be 0.33 at alpha level of 0.05

Discussion

Post-cardiopulmonary bypass bleeding has complicated cardiac surgery. Normalblood circulation maintains pro and anti- thrombotic factors that are carefullybalanced in number and function to preserve blood fluidity, and yet this balancecan transform instantly to seal off a site of bleeding. Cardiopulmonary bypass (CPB) challenges this hemostatic system simultaneously activating coagulantand inflammatory processes, creating a hemostatic impairment that can lead toexcessive bleeding and transfusion requirements. Therefore, pharmacological prophylaxis for post-CPB bleeding hasbecome necessary. Traditionally, aprotinin, a nonspecific serine proteaseinhibitor that has been used primarily as a hemostatic drug in cardiac surgery with CPB. The major known targets of aprotinin within the hemostatic system are plasma kallikrein, plasmin, activated protein C (aPC), thrombin, proteaseactivated receptor-1 (PAR-1) on platelets, and tissue factor.

Mangano et al conducted an observational study involving 4374 patientsunder going revascularization, and prospectively assessed three agents (aprotinin[1295 patients], aminocaproic acid [883], and tranexamic acid [822]) ascompared with no agent (1374 patients) with regard to serious outcomes bypropensity and multivariable methods [7]. Use of aprotinin was associated with adoubling in the risk of renal failure requiring dialysis among patients undergoingcomplex coronary-artery surgery. Similarly, use of aprotinin in the latter group wasassociated with a 55 percent increase in the risk of myocardial infarction or heart failure and a 181 percent increase in the risk of stroke or encephalopathy. They also found that neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac, or cerebral events. All the agents reduced blood loss. They concluded that association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives.

Martin et al investigated postoperative complications and mortality after administration of aprotinin (n=596) compared to tranexamic acid (n=592) in an unselected, consecutive cohort undergoing cardiac surgery [8]. They found that among primary coronary artery bypass surgery

patients, there were more acute myocardial infarctions and renal dysfunction in aprotinin group. The 1-yr mortality was significantly higher after aprotinin treatment in the high risk surgery group. They concluded that administration of aprotinin should be avoided in coronary artery bypass graft and highrisk patients.

Therefore, alternatives to aprotinin for pharmacological prophylaxis for bleeding in patients undergoing cardiac surgery under CPB became necessary. Among antihemorrhagic drugs used to prevent hemostatic derangement in cardiac surgery performed concomitant with CPB, ε-aminocaproic acid and tranexamic acid (two synthetic, low-cost, antifibrinolytic drugs) recently were studied as alternatives to the more expensive drug aprotinin. Epsilonaminocaproic acid and tranexamic acid both act by forming a reversible complex with plasminogen and plasmin through the lysine-binding sites, thus blocking interaction with the specific lysine residues of fibrin. Tranexamic acid is approximately 10 times more potent than e-aminocaproic acid.

Therefore tranexamic acid became more popular in cardiac surgery [9]. A recent study by Mengistu et al, evaluated platelet function after CPB and cardiac surgery to determine the effect of either aprotinin (n=25) or tranexamic acid (n=25) [6]. Coagulation and platelet function were assessed preoperatively, after CPB, 3 and 24 h after surgery using modified thromboelastography and whole blood aggregometry. They found that platelet function measured by whole blood aggregometry is better preserved by aprotinin than tranexamic acid.

In the present study, we sought to determine whether continuous methodof tranexamic acid, although decreased, preserves platelet function better thanintermittent method. We hypothesized that continuous method by exposure ofthe drug less intensively compared to bolus method preserves the platelet function better.

The key findings in the present study may be noted. Patient variables (age, weight, CPB time, duration of surgery, types of surgical procedures) were allcomparable in both the groups. However, gender was maldistributed despiterandomization by use of computer generated random numbers. Distribution of male gender in group 1 was 60% and 93.3% in group 2 (P = 0.002) (chi-squared test). However, gender not known to have a differential pharmacokinetic orpharmacodyamic effects of tranexamic acid in patients undergoing open heart surgery [10].

There was also no significant difference in requirement of blood, fresh frozen plasma, or platelet rich plasma.There was no statistically significant difference between the two groups orwithin the same group at different time periods i.e. sample 2 and 3 with regard to platelet aggregation. However, it is important to know the trends in platelet aggregation. Since the timing of sample 1 and 2 are common in both the groups, comparision of sample 1 and 3 would verify the results of by Mengistu et al [6]. In continuous group, the baseline platelet aggregation value was 58 and sample 3value was 35 whereas in intermittent group the values were 58 and 53 respectively. In other words, the results were contrary to our stated hypothesis. At the same time, it may be premature to conclude intermittent administration, albeit decreased platelet aggregation, preserves the platelet function compared to continuous group because of lack of statistical significance. Further studies evaluating the effects of tranexamic acid on platelet function including only one type of surgical procedure (for e.g. only CABG) coupled with pharmacokinetic profile of the drug during CPB would likely to elucidate the properties in a betterway.

Considering the sample 3 data in two the groups, the power of the study was to be 0.33 (beta error 0.67) at alpha level of 0.05. Therefore, future studies with increase in sample size of more than15 in each group and eliminating the possible confounding factors that can influence platelet aggregation under CPB e.g. confining to patients undergoing only CABG may be planned. Such studies may be useful to elucidate the effects of tranexamic acid on platelet aggregation in a better way.

We conclude that notwithstanding the low power of the study, eithercontinuous or intermittent methods of tranexamic acid in patientsundergoing open heart surgery may be used for pharmacologicalprophylaxis for bleeding. This study could not find any beneficial effects ofcontinuous method over intermittent usage of tranexamic acid. In fact,intermittent administration of tranexamic acid may be preferred frompractical standpoint (ease of administration).

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