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A prospective randomized controlled study to assess the efficacy of aprotinin in paediatric cardiac surgery

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Abstract: *Children undergoing cardiopulmonary bypass (CBP) for repair of congenital heart defects are at substantial risk for excessive bleeding due to hemodilution, hypothermia, systemic inflammatory response causing platelet dysfunction and increased fibrinolysis, contributing greatly to morbidity and mortality. The antiplasmin and antikallikrein action of aprotinin provides a significant anti-fibrinolytic and anti-inflammatory effect. Hence, it was used to decrease bleeding and the need for transfusion.*

Methods: *Forty patients of either sex scheduled for surgical closure of either Ventricular Septal Defects (VSD) or Atrial Septal Defects (ASD) were randomly allocated into two groups. Group (A) patients received 20000 KIU/kg (Kallikrien Inhibitor Units) of aprotinin bolus after induction, 20000 KIU/kg in prime and maintenance infusion dose of 10000 KIU/kg/min till skin closure. Group (P) patients received equal volume of Ringer Lactate solution. The time interval from protamine administration to skin closure, the volume of blood loss in chest drain for initial 24 hours and the volume of blood transfused postoperatively were studied.*

Conclusion: *For the parameters studied, reduction in the frequency and amount of blood transfusion, and reduced operative closure times remains as important benefits of aprotinin.*

Key words: *Aprotinin, antifibrinolytics, blood conservation*

I. Introduction

Cardiac surgery requiring cardiopulmonary bypass has detrimental effects on the haemostatic system, namely activation of coagulation, inflammation, and fibrinolysis especially in children .[1,2] Bleeding is a major source of morbidity and mortality after cardiac surgical procedures. A 4-fold increase in mortality and increase in the rate of sternal infection were seen in patients who return to operating room following bleeding[3]. In order to decrease perioperative blood loss and transfusion, antifibrinolytic drugs have been widely used in cardiac surgery for decades**,** with aprotinin being the most effective agent in that respect. [4] The antiplasmin action of aprotinin coupled with inhibition of kallikrein provides a significant anti-fibrinolytic and anti-inflammatory effect.[5,6,7,8] Our study sought to investigate the use of aprotinin and the risk of adverse events in acyanotic paediatric cardiac surgeries.

II. Subjects and methods

The protocol of the study was approved by the ethical committee of the institution and written informed consent was obtained. Forty patients of either sex scheduled for surgical closure of either VSD or ASD satisfying the selection criteria were included in the study. Children less than 12 years undergoing surgical closure of either VSD or ASD using CPB are considered eligible for entry into the study. Patients with a known metabolic disorder, sepsis or renal dysfunction, patients previously exposed to aprotinin or with a known allergy to aprotinin are not included in the study. All patients who fulfilled the criteria were enrolled and randomized using computer generated chart into either of the two groups. Group (A) patients received 20000 KIU/kg of aprotinin bolus after induction, 20000 KIU/kg in prime and maintenance infusion dose of 10000 KIU/kg/min till skin closure, group (P) patients received equal volume of Ringer Lactate solution as per randomisation by anaesthesiologist (not a part of the study) who prepared either of the drugs[1]. The anaesthesiologist conducting the case as well as recording the data was unaware of the drug being administered.

Patients received no premedication, and upon arrival of patients into the operating room, preinduction monitors such as ECG, pulse oximetry and non invasive blood pressure were attached and baseline values recorded. The patient was preoxygenated with 100% oxygen for 3 minutes. Anaesthesia was induced with combination of midazolam 0.15mg/kg, fentanyl 2 mcg/kg, thiopentone 5 mg/kg, vecuronium 0.1mg/kg followed by intubation after 3 minutes of ventilation with 100% oxygen and isoflurane. Anaesthesia was maintained using isoflurane in air/oxygen (50:50) and fentanyl together with intermittent doses of vecuronium. Under strict aseptic precautions, a right sided internal jugular line and a left radial arterial line were cannulated and transduced for Central Venous Pressure (CVP) and Invasive Blood Pressure (IBP) monitoring respectively.

The patient was given a test dose of aprotinin 10000 KIU intravenously after intubation and observed for 10 minutes for anaphylactic reactions and hemodynamic changes. After confirmation of no adverse reactions, loading dose of aprotinin 20000 KIU/kg was given as an intravenous bolus over 20 minutes, with a

pump priming dose of 20000 KIU/kg and a continuous infusion of 10000 KIU/kg/hour from the beginning of surgery to the skin closure. Group P patients were given an equivalent volume of Ringer Lactate infusion.

Perfusion techniques were standardized. The bypass machine was primed with a mixture of fresh whole blood mixed with crystalloid to achieve a predicted haematocrit of 25% to 30% in patients undergoing bypass. Flow rates were maintained at optimum levels not exceeding 2.4 litres per meter square per minute, using a non-pulsatile roller occlusive pump. [(9)] The activated clotting time (ACT) was serially measured every 30 minutes using kaolin based ACT monitoring.[(9)] Baseline ACT value was recorded before administration of heparin. Heparin was reversed with protamine in the ratio of 1:1 under ACT monitoring, as per the institutional protocol.[(10)] Time from protamine administration to skin closure (minutes) was noted. Postoperative ACT value was noted after 2 hours of skin closure. After surgery, the patient was electively ventilated and extubated after adequate recovery and stable haemodynamics. To standardize the blood transfusion regimen postoperatively, fresh blood was transfused to maintain the patient's haematocrit at or more than 35%.[(9)]

Over the first 24 hours, total chest drain blood loss (ml/kg), and total amount of fluid, blood given were measured. Blood samples were taken preoperatively on the morning of the surgery and 24 hours postoperatively to compare renal (blood urea, creatinine) and haematologic functions (haemoglobin, haematocrit, platelet count, bleeding time, clotting time, ACT).

Adverse events like renal dysfunction and anaphylaxis were observed and documented as 'Present' or 'Absent'. Renal dysfunction was defined as postoperative creatinine of atleast 2mg/dl or an increase over preoperative baseline levels of atleast 0.7mg/dl.[(10)] The anaphylactic reaction was defined as major changes from baseline value of systolic blood pressure 20 percent or greater, heart rate 20 percent or greater, inspiratory pressure greater than 5cm of H_2O or a skin reaction within 10 minutes of 10,000 KIU of test dose aprotinin.[(11)]

Power analysis was based on the difference between the means +/- standard deviations of 24 hour postoperative chest drain blood loss of both the groups using EPI Info software. With $\alpha = 0.05$ and power of 90%, sample size was calculated to be 20 patients per group. Descriptive statistics are provided as means and standard deviations for normally distributed data. The statistical analyses were performed with SPSS - statistical software package. The comparison of the mean levels of all variables between two groups was made by the unpaired t‑test. P value was calculated, and $P < 0.05$ was considered to be statistically significant

III. Results

The two groups were similar with respect to age, sex & weight (Table 1). There was statistically significant reduction (p-0.0001) in the mean time interval from protamine administration to skin closure in Group A (31.45 +/- 6.08 min) compared to Group P (52.05 +/- 8.71 min) (Table 2). The mean volume of blood loss in chest drain for initial 24 hours postoperatively in Group A was 7.01 +/- 3.13 ml/kg and in Group P was 8.72 +/- 3.09 ml/kg, which was statistically insignificant (p-0.09). The mean volume of blood transfused postoperatively in Group A was 8.36 +/- 5.49 ml/kg compared to Group P was 11.76 +/- 4.62 ml/kg, which was statistically significant (p-0.041).

Table 1. Demographic variables

Parameters	Group	N	Mean	Standard Deviation
Age (years)	A	20	7.15	2.97
	P	20	7.60	2.21
Sex	A	20	1.30	0.47
	P	20	1.45	0.51
Weight (kg)	A	20	16.85	4.30
	P	20	16.95	4.11

Table 2. Study parameters

Parameters	Group	Mean +/- SD	p value
Time interval from protamine administration to skin closure (min)	A	31.45 +/- 6.08	p - 0.0001
	P	52.05+/- 8.71	
24 hour drain blood loss (ml/Kg)	A	7.01+/- 3.13	p - 0.090
	P	8.72+/-3.09	
Volume of blood given postoperatively (ml/Kg)	A	8.36+/-5.49	p - 0.041
	P	11.76+/-4.62	

Data was analysed using unpaired t -test. Statistically significant at $p < 0.05$. SD – Standard deviation.

There was no statistical significance in the preoperative and postoperative ACT done two hours after the surgery, haemoglobin, haematocrit, platelet count, bleeding time values between the two groups (Table 3). Preoperative mean clotting time values of Group A was 296.5 seconds and Group P was 269.85 seconds, which was statistically significant (p-0.011). Observations showed none of the patients in both the groups had anaphylaxis, elevated serum creatinine levels and renal dysfunction postoperatively as per the defined criteria.

IV. Discussion

Patients undergoing cardiac surgery with CPB are at risk for increased perioperative blood loss. Excessive perioperative bleeding can be associated with a variety of negative outcomes such as increased mortality, renal dysfunction, atrial arrhythmias, prolonged ventilator support, longer intensive care and hospital stay.

Blood conservation has become a major area of concern for the anaesthesiologist and the surgeon. The increased postoperative bleeding can be a result of preexisting coagulation disorders, hypothermia and the effects of CPB such as haemodilution, platelet dysfunction, increased fibrinolysis, complement activation, platelet and neutrophil activation. [12, 13] The prophylactic use of antifibrinolytics drugs to reduce perioperative blood loss from CPB-induced fibrinolysis has been studied and demonstrated to be effective. [14]

Brown et al reported the results of a meta-analysis of randomized trials comparing the effectiveness and adverse outcomes of the three antifibrinolytic agents such as aprotinin, tranaxemic acid (TA) and epsilon amino caproic acid (EACA) in cardiac surgery.[4] The study results showed that all three antifibrinolytic agents significantly reduce blood loss after cardiac surgery. However, aprotinin was significantly more effective in reducing bleeding than EACA or TA. The incidence of return of the patients to operating room to control bleeding was less with aprotinin. None of the agents was associated with an increased risk of dialysis dependent renal failure, mortality, or stroke. Aprotinin was associated with an increased risk of presumably transient renal dysfunction because it did not include an increased risk of progression to dialysis or death.

In 2006, Mangano and Karkauti reported an increased number of post-operative renal dysfunctions in the aprotinin group in their studies. The Blood conservation trial using Antifibrinolytics: a Randomised Trial in a cardiac surgery population study (BART) found similar result.[15] Subsequently, the FDA required the manufacturer to withdraw aprotinin from the market. Recently, the data of the BART trial have been called into question. Health Canada, published a safety review of aprotinin in September 2011,[16] which concluded that the benefit of using aprotinin in non-complex cardiac surgery might outweigh the risk. The European Medicines Agency also recommended lifting the suspension of aprotinin in February 2012 after a review of the risks and benefits of antifibrionlytic drugs. [17] Those decisions are based on several perceived shortcomings of the BART trial.

Table 3. Other perioperative parameters

Parameters	Group	Mean +/- SD	p value
ACT after two hours of skin closure (sec)	A	132.40 +/- 15.50	p - 0.254
	P	137.50 +/-12.15	
Bleeding time (Preop) sec	A	141.50 +/- 24.60	p - 0.359
	P	150.25 +/- 34.16	
Bleeding time (Postop) sec	A	147.25 +/- 30.88	p - 0.35
	P	174.00 +/- 45.09	
Clotting time (Preop) sec	A	296.50 +/- 32.40	p - 0.011
	P	269.85 +/- 30.82	
Clotting time (Postop) sec	A	326.00 +/- 30.37	p - 0.545
	P	320.25 +/- 29.17	
Platelet counts (Preop) sec	A	3.14 +/- 0.67	p - 0.369
	P	2.94 +/- 0.72	
Platelet counts (Postop)sec	A	2.08 +/- 0.32	p - 0.115
	P	2.27 +/- 0.40	
Haemoglobin (Preop) g%	A	11.88 +/- 1.29	p - 0.518
	P	12.14 +/- 1.22	
Haemoglobin (Postop) g%	A	13.24 +/- 1.29	p - 0.204
	P	12.74 +/- 1.14	
PCV % (Preop)	A	37.39 +/- 3.04	p - 0.732
	P	37.74 +/- 3.26	
PCV % (Postop)	A	40.18 +/- 3.27	p - 0.526
	P	39.36 +/- 3.81	

Data was analysed using unpaired t -test. Statistically significant at $p < 0.05$. SD – Standard deviation, ACT – Activated Clotting Time, PCV – Packed Cell Volume

In children, the definition of renal dysfunction is not very specific. Moreover, the complexity of the operations, the severity of low output syndromes, systemic inflammatory response to CBP and the amount of bleeding and hypotension are superimposed on the existing terminological problems. The other challenging problem is the independent relationship between the amount of transfusion and acute kidney dysfunction. One can argue that antifibrinolytics reduce bleeding and, thus the amount of transfusion and risk of acute kidney dysfunction. [15]

According to the large multicentre retrospective study using the Pediatric Health Information Systems Database to evaluate aprotinin in children (0–18y) undergoing congenital heart surgery at 35 US children's

hospitals from 2003– 2007, it was concluded that aprotinin was not associated with increased mortality or renal failure requiring dialysis in children undergoing congenital heart surgery. [18]

A retrospective analysis - The Impact of Aprotinin on Postoperative Renal Dysfunction in Neonates Undergoing Cardiopulmonary Bypass concluded that the occurrence of postoperative renal dysfunction in neonates was more significantly predicted by the duration of CPB than by the intraoperative administration of aprotinin. CPB time of more than 100 minutes appeared to be a critical marker for the development of postoperative renal dysfunction. [19]

Furthermore, Montes and colleagues have reported that incidence of seizures in 28 of 903 (3.5%) patients undergoing cardiac surgery on CPB with tranaxemic acid. [20] It was also reported that the seizure rate is doubled after intraoperative treatment with TA (7.6%) compared with EACA (3.3%) in adult patients undergoing open heart surgery, and renal dysfunction occurred more frequently with EACA (30.1% vs. 20.0%).[21]

Seizures and renal failure have been shown to be the major problems with TA and EACA. On the contrary, bleeding and blood transfusion have increased since the withdrawal of aprotinin, and there is no evidence for improved mortality. Bearing in mind the potential advantages and side effects of aprotinin and as the current evidence does not suggest that TA and EACA are effective and safe alternatives to aprotinin,[22] we decided to evaluate the efficacy of aprotinin in paediatric cardiac surgery.

Aprotinin is a natural serine protease inhibitor which inhibits plasma kallikrein, plasmin, aPC, thrombin on platelets and tissue factor. Apart from antifibrinolytic action, it decreases neutrophil and macrophage activation and chemotaxis, attenuates release and activation of proinflammatory cytokines, and reduces oxidative stress. [23]

Fibrin degradation increases during CPB, and fibrin degradation products have been implicated in impaired fibrin formation, platelet dysfunction, and endothelial disruption resulting in capillary injury. [24,25] Moreover, plasmin, a potent platelet inhibitor, reportedly degrades platelet adhesion receptors Gp Ib and Gp IIb in vitro, and by 50% in vivo during CPB, most notably at hypothermic temperatures[1] When added to washed platelets, plasmin reduces platelet membrane Gp Ib content by approximately 75%.[25] Taken together, these observations suggest that stimulation of the fibrinolytic system in CPB may result in decreased platelet function. Thus by its antifibrinolytic activity, aprotinin preserves platelet function and reduces bleeding.

In this study, a total of 40 patients were recruited. Twenty patients were entered into group A and 20 patients into group P. The demographic details were summarized in Table 1. There were no statistically significant differences in age, weight, or sex within the groups. The patients in this study underwent surgical closure of either VSD or ASD with average CPB time of less than 100 minutes. None of the patients had any untoward complications during study and all were included in the study.

Our study found out that aprotinin was associated with reduced sternal closure times when compared to control group. The mean time interval from protamine administration to skin closure (Table 2) in Group A was 31.45 +/- 6.08 minutes and control Group P was 52.05 +/- 8.71 (Fig.1) minutes compared to Miller et al 1998 study where the mean time interval from protamine administration to skin closure in control group was 88 +/- 41minutes, low dose aprotinin group was 64 +/- 22 minutes.[7] Results were found to be significant in aprotinin groups. The reason for reduced sternal closure time was attributed to significantly dry operative field due to anti-fibrinolysis and preservation of platelet function by aprotinin. However, when volume of 24 hour drain blood loss was assessed, a clinically significant reduction was seen in those patients receiving aprotinin (Fig.2). But it failed to reach statistical significance (p-0.09). Aprotinin group children had reduced blood transfusion requirements and transfusion (Fig.3) postoperatively which was statistically significant and comparable to high dosage regimen study by Mossinger et al, who concluded that aprotinin effectively attenuated haemostatic activation, reduced blood loss and transfusion requirements in paediatric cardiac surgery. [26] This avoids unwanted exposures of donor banked blood products and untoward transfusion related complications.

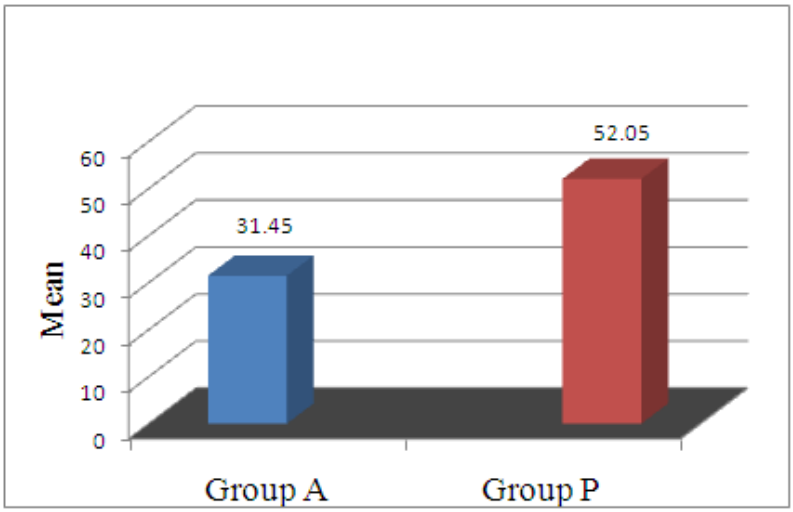

Fig 1. Time interval from protamine administration to skin closure (min)

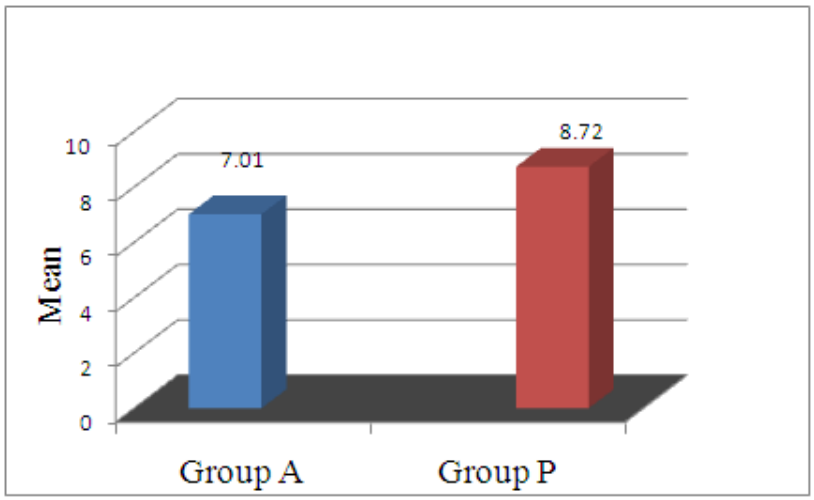

Fig 2. Twenty four hour post operative drain blood loss (ml/kg)

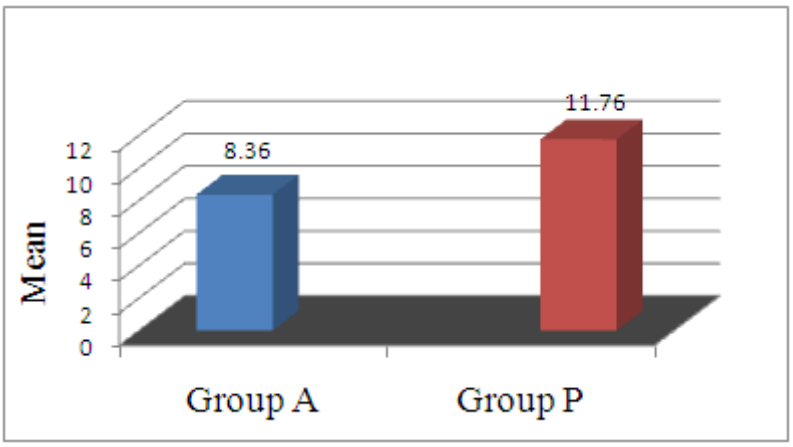

Fig 3. Volume of blood transfused postoperatively (ml/kg)

The values of preoperative and postoperative parameters like ACT done two hours after surgery, bleeding time, clotting time, haemoglobin, PCV and platelet counts supports that aprotinin was effective in relation to blood conservation, platelet loss and haemostasis (Table.3).

Our study demonstrates that aprotinin was safe in the paediatric population in terms of renal dysfunction. We investigated pre and post operative serum creatinine levels in all children and analyzed the risk of renal dysfunction. Since we found that none of them had raised creatinine levels postoperatively and our main

objective was to assess the advantages of aprotinin as a blood conservative and anti-inflammatory agent, we documented it as renal dysfunction 'present' or 'absent'. None of the children had adverse reactions or anaphylaxis to aprotinin.

In our study, only acyanotic heart disease cases were included, which required CBP time of less 100 minutes with no incidence of postoperative renal dysfunction. Since the high risk and complex acyanotic heart diseases and redo surgeries are not included in our study, safety profile of aprotinin in pediatric surgeries is still uncertain and it remains as a major limitation of our study. The other limitations were the smaller size of the groups and the non availability of certain laboratory investigations such as thromboelastography, functional platelet assay in our hospital to evaluate further. But given the potential benefits and perhaps more favourable safety profile in acyanotic cardiac patients, there is interest in further study and usage of aprotinin in paediatric cardiac surgeries, especially in low risk acyanotic heart disease children.

V. Conclusion

In our study, patients receiving aprotinin as part of a blood conservation strategy represent a low risk acyanotic cardiac patients with decreased duration of CBP time. For the parameters studied, we conclude that reduction in the frequency and amount of blood transfusion, and reduced operative closure times remains as an important benefits of intraoperative aprotinin usage and it is not an independent risk factor for renal dysfunction,

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