# ROLE OF APROTININ IN PAEDIATRIC CARDIAC SURGERY

*Dissertation submitted to*

***THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY***

in partial fulfillment for the award of the degree of

**DOCTOR OF MEDICINE**

IN

*ANAESTHESIOLOGY*

**BRANCH X**

**BRANCH – X**

**DEPARTMENT OF ANAESTHESIOLOGY**

**MADRAS MEDICAL COLLEGE**

**CHENNAI – 600 003.**

**MARCH 2009**

# CERTIFICATE

This is to certify that the dissertation entitled, **"ROLE OF APROTININ IN PAEDIATRIC CARDIAC SURGERY"** submitted by **Dr. Ramkumar .D**, in partial fulfillment for the award of the degree of Doctor of Medicine in Anaesthesiology by the Tamilnadu Dr. M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Department of Anesthesiology, Madras Medical College, during the year 2006 – 2009.

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## *ACKNOWLEDGEMENT*

I am extremely thankful to **Dr.T.P.Kaliniti, M.D.,** Dean, Madras Medical College, for his kind permission to carry out this study.

I am immensely grateful to **Prof.Dr.Kamilini Sridharan, M.D., D.A.,** Professor and Head of the Department, Department of Anaesthesiology, for her concern and support in conducting this study.

I am very grateful to **Prof. Dr.T.Venkatachalam, M.D.,D.A., Prof. Dr.C.R.Kanyakumari, M.D.,D.A., Prof.Esther Sudharshini Rajkumar, M.D.,D.A., Prof.Dr.Gandhimathi M.D.,D.A., Prof. Dr.Shantha Parthiban, M.D.,D.A.,** Madras Medical college, for their constant motivation and valuable suggestions.

I am greatly indebted to my guide **Prof.Dr.T.Murugan, M.D.,D.A.,** Professor of Paediatric Cardiothoracic Anaesthesia, Institute of Child Health, Madras Medical College, Chennai for his inspiration, guidance and comments at all stages of this study.

I am very thankful to **HOD & Prof.P.Moorthy M.S., Mch.,** Department of Paediatric Cardiothoracic Vascular Surgery, Institute of Child Health, Madras Medical College, Chennai for providing immense support in completing this study.

I am greatly indebted to Assistant Professors **Dr.A.Ganesh,M.D., Dr.M.Vijayashankar,M.D., Dr. S.Vinodh Kumar,**

**M.D., Dr.V.Kailash,D.A.,** for their inspiration, guidance and comments at all stages of this study.

I am thankful to all other Assistant Professors for their guidance and help. I am thankful to all my colleagues for their help rendered in carrying out this dissertation.

I am thankful to Dr.F.Catherine Sunitha for her help in analysis of data and completion of this study.

Last, but not the least, I thank all the parents for willingly submitting their children for this study.

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PROFORMA

MASTER CHART

## *INTRODUCTION*

The children undergoing open-heart surgery are likely to have major blood loss due to surgical interventions performing on major vascular structures as well as the coagulation abnormalities that accompany extracorporeal techniques. Certain characteristics are unique to paediatric patients with congenital heart disease undergoing heart surgery, that makes them prone to excessive bleeding and transfusion of blood and blood products[(1)]. They are:

- Decreased levels of coagulation factors compared with normal children of the same age group.
- Hemodilution resulting from high priming volume relative to small blood volume.
- Delayed hepatic maturation secondary to poor organ perfusion.
- Complex operative procedures requiring long duration of cardiopulmonary bypass.
- Multiple extra cardiac suture lines.

- Deep hypothermic circulatory arrest.

The use of aprotinin in children undergoing cardiopulmonary bypass attenuates the activation of the coagulation and fibrinolytic systems, preserves platelets function and reduces systemic inflammatory responses. Improved clinical outcomes have been consistently demonstrated in children undergoing primary and repeat sternotomies in aprotinin recipients. Many studies have demonstrated benefits in terms of[2,3,4] -

- Significant reduction in chest tube drainage
- Time to skin closure
- Postoperative transfusion requirements
- Decreased requirements of banked blood and donor exposures[4,5]
- Substantial savings in cost[4,5]

These clinical outcomes create a strong argument for the routine administration of aprotinin in paediatric cardiac operations undergoing cardiopulmonary bypass. Aprotinin is a potent part of an anesthesiologist arsenal when dealing with children undergoing cardiopulmonary bypass and its cost effective improvement of clinical outcomes justifies its consideration when planning the management strategy of these children.

## *AIM OF THE STUDY*

The purpose of the study was to assess the efficacy and use of aprotinin in paediatric open heart surgeries by comparing the time interval from protamine administration to skin closure, the volume of blood loss (ml/kg) in chest drain after 24 hours, and the volume of blood and blood products (ml/kg) transfused postoperatively with that of control group[4,8].

# APROTININ

## Introduction

Cardiopulmonary bypass is associated with a systemic inflammatory response, a spectrum of pathophysiologic changes ranging from mild organ dysfunction to multisystem organ failure. Complications include coagulation disorders (bleeding diathesis, hyperfibrinolysis) from platelet defects and plasmin activation, as well as pulmonary dysfunction from neutrophil sequestration and degranulation. Diverse injuries are a consequence of multiple inflammatory mediators (complement, kinins, kallikrein, cytokines). Both plasmin and kallikrein amplify the inflammatory response by activating components of the contact activation system. High dose of aprotinin, a serine protease inhibitor approved for reducing blood loss and transfusion requirements in cardiopulmonary bypass, inhibits kallikrein and plasmin, resulting in suppression of multiple systems involved in the inflammatory response. Overall, evidence indicates that aprotinin attenuates the systemic inflammatory response associated with cardiopulmonary bypass.

## Historical perspective

1960 - Aprotinin was first used in man

1987 - First clinical study of high dose regime in cardiac surgery

1993 - Approved by FDA for use during cardiac surgery

1999 - Meta-analysis suggests little clinical efficacy difference between aprotinin and aminocaproic acid

2004 - Two small studies report reduced bleeding in CABG patients on anti-platelet therapy

2005 - Meta-analysis suggests aprotinin is safe in paediatric surgery

## Mechanism of action

Aprotinin is a basic polypeptide, 58 amino acid residues long and of bovine origin[9], inhibits a wide variety of serum proteases. The main mechanism of action of aprotinin is inhibition of plasmin. The high-dose aprotinin regimen also inhibits kallikrein, produced from prekallikrein during activation of factor XII by the artificial surfaces of the bypass equipment and the exposed surfaces of surgically cut vessels.

The antiplasmin action of aprotinin coupled with inhibition of kallikrein[10] provides a significant antifibrinolytic and anti-inflammatory effect. By inhibiting kallikrein, aprotinin reduces the activation of complement[10], the angiotensin system and bradykinin.

### Antifibrinolytic action

Fibrin clots are formed at the sites of surgical incision and function to maintain hemostasis during surgery. Activation of the fibrinolytic pathway converts the zymogen plasminogen to the protease plasmin. Plasmin degrades fibrin plugs by proteolytically digesting fibrin. In addition to generating proinflammatory fibrin split products, plasmin amplifies the inflammatory response by directly activating FXII. Members of the kinin-kallikrein pathway augment activation of the fibrinolytic pathway by ultimately upregulating plasmin levels.

During and after CPB, D-dimer levels, a measurement of the amount of fibrin degraded by plasmin, were lower in patients receiving aprotinin therapy compared with controls, indicating that plasmin activity was attenuated in aprotinin patients [11]. Reduced plasmin activity can be attributed to decreased plasmin production, direct inhibition of plasmin, or a combination of these two events. Observations suggest that reduced fibrinolytic activity resulting from aprotinin administration most likely results from direct binding and inhibition of plasmin, rather than inhibition of t-PA-mediated plasmin generation.

**Effect on platelets**

Fibrin degradation increases during CPB [12], and fibrin degradation products have been implicated in impaired fibrin formation, platelet dysfunction, and endothelial disruption resulting in capillary injury [13]. Moreover, plasmin, a potent platelet inhibitor, reportedly degrades platelet adhesion receptors Gp Ib and Gp IIb in vitro[14,38], and by 50% in vivo during CPB [15], most notably at hypothermic temperatures[16]. When added to washed platelets, plasmin reduces platelet membrane Gp Ib content by approximately 75%[15]. 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.

## Anti-inflammatory effect of aprotinin

Aprotinin inhibits kallikrein and plasmin, resulting in suppression of multiple systems involved in the inflammatory response. Specifically, inhibition of factor XII, bradykinin, C5a, neutrophil integrin expression, elastase activity, and airway nitric oxide production are observed[39,40]. Clinical correlates include reduced capillary leak, preserved systemic vascular resistance and blood pressure, and improved myocardial recovery following ischemia.

## Kinin-kallikrein pathway

During CPB, autoactivation of the inert factor XII (FXII), when bound to anionic surfaces, yields factor XIIa (FXIIa) and factor XIIf (FXIIf). In the presence of high molecular weight kininogen (HMWK), FXIIa converts prekallikrein to kallikrein, and in a positive feedback loop, kallikrein and FXIIa enzymatically activate additional FXII[17]. Kallikrein also cleaves surface-bound HMWK to liberate bradykinin (BK), a potent vasodilator that promotes smooth muscle contraction and capillary permeability[17]. Products of the kinin pathway also participate in the cellular inflammatory response by directly stimulating neutrophils. Neutrophil superoxide and hydrogen peroxide formation are reportedly upregulated in the presence of kallikrein [18].

Overall, evidence indicates that aprotinin attenuates the systemic inflammatory response associated with cardiopulmonary bypass.

**Pharmacokinetics**

Plasma aprotinin concentration decrease rapidly after intravenous administration because of redistribution to peripheral tissues[34]. During elimination phase, which is primarily renal, accumulation of aprotinin takes place in proximal tubular epithelial cells of the kidneys, where the drug may be gradually broken down over several days[37]. Approximately 80% of an injected dose of aprotinin can be localized in kidneys, 4 hours after injection.

Clearance of aprotinin is 35.5 ml/min and the volume of distribution at steady state is 26.5 litres [34]. The elimination half time of aprotinin after administration of a single intravenous dose is 7 hours.

**Dosage**

The enzymatic activity of aprotinin is generally expressed in kallikrein inactivator units (KIU). One KIU is defined as the amount of aprotinin that decreases the activity of 2 biologic kallikrein units by 50%.

One mg of aprotinin is equivalent to 7143 KIU. Effective inhibition of plasmin requires a plasma concentration of 50 KU/ml and 200 KIU/ml of aprotinin to inhibit plasma kallikrein[21,22].

**Dosage regimens**

A wide range of dosing regimen has been used in adults and children. The classical adult dosage regimen consists of $2x10^6$ KIU loading dose administrated over a 20 min after a test dose, after induction of anaesthesia, followed by a continuous infusion of 6,00,000 KIU/hour until the patient is transferred to the ICU. In addition, $2x\ 10^6$ KIU is added to pump to overcome the dilution effect[19,20].

In paediatric population, varying dosing regimens have been used based on body weight and body surface area (BSA). With weight-based regimens loading doses have ranged from 15000 to 50,000 KIU/kg and infusion have ranged from 0 to 30,000 KIU/kg/hour. Pump priming doses usually have been the same as the child's loading dose[4,7,15,23].

Based on the body surface area, loading and pump prime doses have ranged from 120 to 240 $mg/m^2$ in smaller children with 250 to 280 $mg/m^2$ being used in children whose BSA exceeds $1.16m^2$ [8,24,25].

Infusion range varies from 28 to 56 mg/$m^2$/hour with 70 mg/$m^2$/hour being given to the larger children.

**Interaction with heparin**

Adequate heparinisation is usually maintained by monitoring activated clotting time (ACT) values of > 400 seconds. Aprotinin inhibits contact activation of the intrinsic clotting system and therefore prolong the results of coagulation assays such as celite ACT. Aprotinin does not have an inhibitory effect on extrinsic clotting cascade, so that heparin level must always be sufficient to prevent the clot formation. Maintaining the celite ACT above 400 to 450 seconds may not be a reliable indicator of adequate heparinisation. The current recommendation regarding monitoring of anticoagulation in the presence of aprotinin is to maintain celite ACT values at > 750 seconds during CPB or to use kaolin ACT, heparin – protamine titration test[(29)]. The kaolin ACT adsorbs about 98% of aprotinin and any intrinsic antithrombin effect that aprotinin has is therefore mitigated. It is recommended to use kaolin ACT and keep the length of ACT times the same as if aprotinin was not being used[(26,27,28)].

### Indications

1. Reduction of blood loss, particularly hyperfibrinolytic hemorrhage
2. Traumatic, hemorrhagic, pancreatogenic and endotoxic shock.
3. Fat-embolism syndrome
4. Acute pancreatitis

### Contraindication

Aprotinin is contraindicated in patients who have demonstrated hypersensitivity.

## THERAPEUTIC USE OF APROTININ

### Reoperations

Patients having repeat surgery through prior median stermotomy are known to be at a greater risk for perioperative bleeding and therefore require more homologous blood transfusion. Aprotinin has significantly reduced the duration of procedure, perioperative blood loss and

postoperative transfusion. Benefits were shown in pediatric patients undergoing reoperations[4,5,6] and complex surgical intervention[7].

**Primary myocardial revascularisation**

Aprotinin is effective in terms of reduction in number of patients receiving donor blood and the total donor blood transfusions. Aprotinin recipients have a significantly drier operative field. The efficacy of aprotinin in counter balancing the increased risk of perioperative hemorrhage in CABG patients pretreated with aspirin, without increasing risk of myocardial infarction has been demonstrated.

**Paediatric cardiac surgeries**

The studies have demonstrated benefits in terms of significant reduction in chest tube drainage, time to skin closure and transfusion requirements[21]. There is a decreased requirement of banked blood and donor exposures. The anti inflammatory effects of aprotinin can be particularly important in paediatric population in attenuating the whole body inflammatory reaction.

**Other uses**

Aprotinin has also been found to be useful in major vascular surgery, acute pancreatitis ,patient with sepsis and endocarditis undergoing open-heart surgery, carcinoid syndrome, heart lung transplantation, and total hip replacement[35]. There is significant decrease in total blood loss and the amount of blood transfused.

**Adverse effects**

**a) Anaphylactic reactions**

An animal protein, aprotinin can cause anaphylaxis[30]. The incidence is 1 in 1000[31,32] patients and more in-patients reexposed to aprotinin. The anaphylactic reaction was defined as major changes from baseline within 10 minute of aprotinin administration, of systolic blood pressure 20 percent or greater, heart rate 20 percent or greater, inspiratory pressure greater than 5cm of water or a skin reaction[33]. Anaphylactic reactions were classified as mild (no intervention required), moderate (circulation restored within 15 min of reaction onset via use of vasopressors), or severe (longer-lasting circulatory depression and instability despite administration of vasopressors).This can be prevented by giving test dose of 10000 KIU intravenously and observed for hemodynamic changes.

**Preventive measures for repeated use and/or allergic predisposition**

1. IV dose of $H_1$ and $H_2$ antogonists, 15 min prior to the first aprotinin dose.

2. Subsequently 1ml (10000KIU) aprotinin IV with a 10 min observation period.

3. After that a slow infusion of the loading dose can be started.

In individual cases an anaphylactic response still can occur, in which case aprotinin should be stopped immediately.

b) **Renal dysfunction**

Renal dysfunction was defined as postoperative creatinine of atleast 2mg/dl or an increase over preoperative baseline levels of atleast 0.7mg/dl . The use of high doses of aprotinin and hypothermia during cardiopulmonary bypass can produce dose-related transient and reversible increases in plasma creatinine concentrations. Aprotinin may cause afferent renovasoconstriction [(36)].

***REVIEW OF LITERATURE***

**Miller et al 1998[(4)]**

They evaluated the haemostatic and economic effects of aprotinin in children undergoing reoperative cardiac procedures with cardiopulmonary bypass. Control, low-dose aprotinin, and high-dose aprotinin groups were established with 15 children per group.

The control group received no aprotinin. The low-dose group received an aprotinin loading dose of 20,000 kallikrein inhibiting units (KIU) (2.8 mg) per kilogram before skin incision, 20,000 KIU/kg in the pump prime, and an infusion of 10,000 KIU/kg/h beginning with completion of the loading dose and terminating with skin closure. The high-dose group received a loading dose of 40,000 KIU/kg, 40,000 KIU/kg in the pump prime, and an infusion of 20,000 KIU/kg/h after the loading dose to the end of skin closure.

Platelet counts, fibrinogen levels, and thromboelastographic values at baseline and after protamine sulfate administration, number of blood product transfusions, and 6-hour and 24-hour chest tube drainage were used to evaluate the effects of aprotinin on postbypass coagulopathies. They concluded that in children undergoing reoperative cardiac surgical procedures, aprotinin is effective in attenuating postbypass coagulopathies, decreasing blood product exposure, improving clinical outcome, and reducing patient charges.

**Dietrich et al 1993[23]**

They studied the effect of high-dose aprotinin treatment on hemostatic activation during cardiopulmonary bypass in paediatric patients having cardiac operations. Sixty patients weighing less than 10 kg undergoing cardiac operations for different types of congenital heart diseases were studied. 20 patients were treated with aprotinin 2 x 15,000 KIU/kg, 20 patients with 2 x 30,000 KIU/kg, and 20 patients without aprotinin treatment served as the control group. Different split products of fibrinogen and/or fibrin and the fibrinolytic activity on fibrin plates were measured to assess fibrinolytic.

They observed there is an attenuation of hemostatic activation during cardiopulmonary bypass with less plasmin formation and, because of inhibition of contact activation, less thrombin generation with aprotinin treatment. Thus the thrombotic-thrombolytic equilibrium is kept more balanced after cardiopulmonary bypass. This recommends high-dose aprotinin treatment for paediatric patients undergoing cardiac operations.

**D'Errico et al 1996[5]**

They performed a prospective, randomized, placebo controlled, double-blind trial to assess the efficacy of and cost of aprotinin in 61 children (median age 3.7 yr) undergoing reoperative open heart surgery (OHS). Three demographically similar groups were studied: large-dose aprotinin (ALD), small- dose aprotinin (ASD), and placebo (I'). Over the first 24 postoperative hours fewer patients in the aprotinin groups received packed red cells (ALD, 53%; ASD, 89%; and I', 95%; P = 0.00l), platelets (ALD, 32%; ASD, 50%; and P, 65%; P = 0.04), 60%; P = 0.003) than placebo patients.

They showed that aprotinin patients had fewer exposures to banked blood components (ALD, median 1 U; and ASD, median 2 U) than P (median 6 U; P = 0.00l), with no difference in overall complication rate. In conclusion, aprotinin decreased the number of units of banked blood components used during the first 24 postoperative hours in reoperative pediatric OHS. Aprotinin thus decreases the risks associated with exposure to banked blood components and reduces hospital charges.

**Mossinger et al 2003[(21)]**

They conducted a double-blind, randomized, and placebo controlled study, to assess the efficacy of aprotinin in attenuating the hemostatic and inflammatory activation during cardiopulmonary bypass in 60 patients weighing less than10 kg. Secondary endpoints were the

influence of aprotinin on the reduction of blood loss and allogeneic blood requirement, as well as postoperative oxygenation and length of mechanical ventilation. They concluded that high-dose aprotinin effectively attenuated hemostatic activation and reduced blood loss and transfusion requirement in paediatric cardiac surgery.Postoperative ventilation was also shortened in the aprotinin group.

**Royston et al 1987[42]**

They studied the effect of aprotinin on need for blood transfusion after repeat open heart surgery . Of 22 patients undergoing repeat open-heart surgery through a previous median sternotomy wound, 11 were randomised to receive aprotinin in high dosage (about 700 mg intravenously from the start of anaesthesia to the end of operation, depending on the length of the surgical procedure). Their mean blood loss was 286 ml compared with 1509 ml in the 11 control patients ($p < 0.001$), and mean haemoglobin losses were 8.3 g and 78 g, respectively ($p < 0.001$). Blood transfusion requirements were eightfold higher in the control group than in the aprotinin group, 7 of whom received only the single unit of their own blood taken before cardiopulmonary bypass.

**Mossinger et al 1998[43]**

They studied the characteristics of the hemostatic system in children undergoing cardiac operations and addressed the effect of aprotinin on hemostasis. Hemostatic parameters were measured in 96 pediatric patients using three different doses of aprotinin. The high-dose group (group 1) received 30,000 KIU/kg (4.2 mg/kg) of aprotinin after induction of anaesthesia and an additional bolus of 30,000 KIU/kg (4.2 mg/kg) into the pump prime. In the low-dose group (group 2), both the initial bolus and the pump-prime dose of aprotinin were halved to 15,000 KIU/kg (2.1 mg/kg). Group 3 received the high dose with an additional bolus of aprotinin to the pump prime.

They observed that plasma levels of aprotinin in both groups 1 and 2 were lower than the 200 KIU/ml (0.03 mg/ml) value usually reached in adults with high-dose aprotinin treatment. Group 3 patients had levels greater than 200 KIU/ml (0.03 mg/ml) throughout the procedure. Biochemical indices of fibrinolysis (fibrin degradation products, D-dimers) revealed significant and dose dependent inhibition at all three aprotinin concentrations. They concluded that the inverse relationship between a small patient's blood volume and the large pump-prime volume requires additional aprotinin to be added to the prime to achieve plasma levels sufficient to inhibit activation of the coagulation cascade.

**Dietrich et al 2001[33]**

This investigation examined the incidence of anaphylactic reactions in patients reexposed to aprotinin and the relation to preformed antiaprotinin immunoglobulin IgG and IgE antibodies. This prospective observational study evaluated patients undergoing repeat cardiac surgery reexposed to aprotinin .

Antiaprotinin IgG and IgE antibody measurements, using an enzyme-linked immunosorbent assay and an immunofluorescence assay, respectively, were performed preoperatively and postoperatively. This study found the incidence of anaphylactic reactions after aprotinin reexposure during cardiac surgery to be 2.5%. The propensity of a patient to react adversely to aprotinin treatment was highly dependent on the length of the aprotinin exposure–reexposure interval.

**Davies et al 1997[8]**

They conducted a prospective, randomized, double-blind study of high-dose aprotinin in pediatric cardiac operations . Forty-two patients were randomly assigned to receive either high-dose aprotinin or placebo. Aprotinin efficacy was assessed using time from protamine administration to skin closure, postoperative blood loss and hemoglobin loss, and postoperative transfusion requirements. Measures of

fibrinolysis (fibrin degradation product titers) and platelet preservation (b-thromboglobulin levels) were also assessed. Results show that there were no statistically significant differences between groups in any of the blood loss or transfusion parameters.

They concluded that aprotinin appears to provide no clinical benefit in routine pediatric cardiac operations. There were no differences in the drainage loss between controls and the aprotinin-treated groups. However, there was statistically significant difference between surgical groups in drainage volume loss. The redo operation group, had a significantly lower drainage volume in the first 24 hours postoperatively. Reduction in fibrinolysis, with perhaps an early preservation of platelet structure, is seen in the aprotinin group.

**Van Oeveren et al 1987[(12)]**

They studied the effects of aprotinin on hemostatic mechanisms during cardiopulmonary bypass. In this study , the protease inhibitor aprotinin was given in high doses to 11 patients to achieve plasma concentrations of more than 150 kallikrein inactivator units per milliliter during CPB. At such concentrations, kallikrein and plasmin are effectively inhibited. This treatment resulted in platelet preservation

during CPB. Platelet numbers were virtually unaffected, and thromboxane release was prevented in the aprotinin-treated group in contrast to the control group. Postoperatively, hemostasis was significantly better preserved after aprotinin treatment (blood loss of 357 ml in the treated group versus 674 ml in the untreated group; p less than 0.01). Since tissue-plasminogen activator activity was similar in both groups, the improved hemostasis most likely should be attributed to platelet preservation. Furthermore, aprotinin lessened neutrophilic elastase release, which might contribute to decreased pulmonary dysfunction in patients at risk.

**Wong et al 2000[(44)]**

They compared the efficacy of aprotinin with tranexemic acid in reducing post operative blood loss for high risk cardiac surgery. 80 patients undergoing elective high transfusion risk cardiac procedures (repeat sternotomy, multiple valve, combined procedures, or aortic arch operation) were randomized in a double-blind fashion, to receive either high dose aprotinin or tranexamic acid. Patient and operative characteristics, chest tube drainage and transfusion requirements were recorded.

They found that there was no significant difference between the 2 treatment groups with respect to age, cardiopulmonary bypass time, complications (myocardial infarction, stroke, death), chest tube drainage (6, 12, or 24 hours), blood transfusions up to 24 hours postoperatively, total allogeneic blood transfusions for entire hospital stay, or induction/postoperative hemoglobin levels. However, multiple regression analysis revealed a positive relationship between cardiopulmonary bypass time and 24 hour blood loss in the tranexamic acid group ($p = 0.001$), unlike the aprotinin group where 24 hour blood loss is independent of cardiopulmonary bypass time ($p = 0.423$). Overall, there was no significant difference in blood loss, or transfusion requirements, when patients received either aprotinin or tranexamic acid for high transfusion risk cardiac operation. Aprotinin, when given as an infusion in a high-dose regimen, was able to negate the usual positive effect of cardiopulmonary bypass time on chest tube blood loss.

**Blauhut et al 1991[32]**

They studied the effects of high-dose aprotinin on blood loss, platelet function, fibrinolysis, complement, and renal function after cardiopulmonary bypass. They administered a mean aprotinin dose of $4.2 \times 10^6$ kallikrein-inhibiting units to 13 patients with coronary disease undergoing cardiopulmonary bypass for 74 +/- 5 minutes (mean +/- standard error of the

mean); 13 comparable patients having cardiopulmonary bypass served as control subjects, and all were studied postoperatively for 24 hours.

Aprotinin reduced postoperative blood loss by 50% ($p = 0.0082$). Two of the 13 patients who received aprotinin needed one red cell unit each versus a total of 18 units in eight of 13 control patients ($p = 0.0096$). In control patients fibrinogen degradation products (D dimer) doubled, and alpha 2-antiplasmin activity was halved during and after cardiopulmonary bypass (p less than 0.01 to p less than 0.001), whereas aprotinin patients showed no changes. Serum electrolytes, osmolality, and creatinine remained normal in both groups of patients. Creatinine clearance was normal or above normal and virtually identical in both groups.No adverse clinical effects attributable to aprotinin were seen. They concluded that aprotinin offers advantages for cardiopulmonary bypass.

**Harder et al 1991[(41)]**

To determine whether aprotinin can provide a significant improvement of hemostasis in cardiopulmonary bypass using a membrane oxygenator, they tested this drug in a prospective, randomized, double-blind, placebo- controlled clinical trial. The subjects were 80 male patients undergoing cardiopulmonary bypass for coronary

artery bypass grafting. Forty patients received aprotinin and 40 patients served as placebo controls. Aprotinin ($4 \times 10^6$ KIU) was given as a continuous infusion, starting before operation and continuing until after cardiopulmonary bypass; additionally, $2 \times 10^6$ KIU aprotinin was added to the pump prime. They concluded that aprotinin reduces intraoperative and postoperative blood loss in membrane oxygenator cardiopulmonary bypass.

## MATERIALS AND METHODS

### Study design

This study was conducted in Paediatric Cardiothoracic Department at Institute of Child Health, an attached institution of Madras Medical College, Chennai between June 2008 and August 2008 on forty patients, posted for elective major cardiac surgery. This study was done after institutional approval and written informed consent was obtained from the parents of each child included in the study.

This study was done in a prospective randomized manner. Forty patients of either sex posted for major elective cardiac surgeries

satisfying the selection criteria were randomly allocated into the two groups (Group A and Group P)

Group(A)- Patients in this group received aprotinin 20000 KIU/kg bolus after induction, 20000 KIU/kg in prime and maintenance infusion dose of 10000 KIU/kg/min till skin closure.[14]

Group(P)- Patients in this group received equal volume protocol of Ringer Lactate solution.

**SELECTION OF CASES**

**Inclusion criteria**

Child under any age of less than 12 years undergoing open heart surgery using cardiopulmonary bypass (CPB) is considered eligible for entry into the study.

Exclusion criteria

- Patient refusal
- Patients with known bleeding disorder; those taking aspirin, dipyridamole,or anticoagulants 7 days before surgery

- Patients with a known metabolic disorder, sepsis, or renal failure
- Patients previously exposed to aprotinin or with a known allergy to aprotinin
- Patients with a hemoglobin level of more than 19 g/dl.

### Preanaesthetic evaluation

Patients included in this study underwent thorough preoperative evaluation which included history, detailed physical examination and investigation.

Patients who satisfied the selection criteria were explained about nature of the study and the anaesthetic procedure. Written informed consent was obtained from parents of each child.

Two persons were required during the study. One was the operator (myself) who gave the drug. Second was the observer who recorded the parameters. All the parameters and events were observed and recorded in the proforma by the observer throughout the procedure.

### **Pilot study**

The operator (myself) did a pilot study on 10 patients, who were selected based on above mentioned criteria, under expert guidance and supervision of senior anesthesiologists. Aprotinin was given to 5 patients and Ringer Lactate solution was given to 5 patients. After pilot study, the observations and results were analyzed in detail and based on safety profile, the institutional ethical committee approval was obtained for conducting the study.

**Anaesthetic procedure**

Each child's weight and height was noted. Standard monitoring for paediatric cardiac patients was done. Intravenous access with a cannula on right hand was achieved. Premedication, anesthetics, and perfusion techniques were similar for all patients. The patient was given IV fentanyl 2-5µg/kg, IV glycopyrrolate 10µg/kg, IV methyl prednisolone 30mg/kg, IV midazolam 0.15mg/kg was given. The patient was preoxygenated with 100% oxygen for 5 minutes. Induction of anesthesia used IV thiopentone sodium (2.5%) 5-7mg/kg, IV vecuronium bromide (0.1mg/kg) followed by intubation after 3 minutes of IPPV with 100% oxygen. Under strict aseptic precautions, a central venous line and an arterial line were cannulated. Anaesthesia was maintained with nitrous oxide and oxygen (50:50) together with intermittent doses of

vecuronium bromide 0.02 mg/kg, inhalational agent isoflurane at 1 MAC and incremental doses of IV fentanyl to a maximum of 20µg/kg or IV morphine to a maximum dose of 0.1 mg/kg, IV midazolam 0.2mg/kg/hour.

The patient was given 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 until skin closure at the end of surgery. Group P patients were given an equivalent volume protocol of Ringer Lactate solution.

The bypass machine was primed with a mixture of fresh (less than 5 days old), whole citrate-phosphate-dextrose blood, mixed with crystalloid to achieve a predicted hematocrit of 25% to 30% in patients undergoing bypass. The crystalloid component of the prime was Ringer Lactate solution with added heparin (2,500 IU per unit of blood, and 1,500IU per 500 ml of crystalloid), sodium bicarbonate (7.5% at 60 ml/l of prime), and 20%  mannitol (2 ml/kg). Perfusion techniques were

standardized and the patient core temperature was lowered to the appropriate level using arteriovenous cooling on bypass. Flow rates were maintained at optimum levels not exceeding 2.4 litres per meter square per minute, using a nonpulsatile roller occlusive pump. The activated clotting time was serially measured every 30 minutes using Kaolin based ACT machine and values were maintained above 400 seconds for optimal heparinisation. Baseline ACT value was recorded before administration of heparin. Ultrafiltration was not used. Before Aortic decannulation, heparin was reversed with protamine in the ratio of 1:1.3 respectively under ACT monitoring, as per the Institutional protocol. Time from protamine administration to skin closure (minutes) was noted. Postoperative ACT value was calculated after 2 hours of skin closure. Perioperatively patients received prophylactic antibiotics(Cefotaxime) and cardiosupportive drugs (dopamine and nitroglycerin). After surgery, the patient was electively ventilated and extubated after adequate recovery. To standardize the blood transfusion regimen postoperatively, fresh blood was transfused to maintain the patient's hematocrit at or more than 35%.

Over the first 24 hours postoperatively, total chest drain blood loss (ml/kg), and total amount of fluid, blood and blood products given (ml)

were measured. Blood samples were taken preoperatively and at the times given below to compare renal function (blood urea, serum levels of creatinine, sodium, bicarbonate and potassium) and hematologic functions (hemoglobin, hematocrit, white cell total count, differential count, platelet count, bleeding time, clotting time). Sequential blood samples were taken at the following times: 30 minutes before surgery, 6 hours postoperatively and 24 hours postoperatively.

Adverse events like anaphylaxis and renal dysfunction were recorded during this study. The anaphylactic reaction was defined as major changes from baseline within 10 minute of 10,000 KIU of test dose aprotinin administration, of systolic blood pressure 20 percent or greater, heart rate 20 percent or greater, inspiratory pressure greater than 5cm of water or a skin reaction[33]. Renal dysfunction was defined as postoperative creatinine of atleast 2mg/dl or an increase over preoperative baseline levels of atleast 0.7mg/dl.

**Parameters observed**

1. The time interval (min) from protamine administration to skin closure.
2. The volume of blood loss (ml/kg) in chest drain after 24 hours.

3. The volume of blood and blood products (ml/kg) transfused postoperatively.
4. The postoperative Activated Clotting Time (sec) after 2 hours of skin closure.
5. The preoperative and postoperative bleeding time (sec).
6. The preoperative and postoperative clotting time (sec).
7. The preoperative, pump and postoperative platelet count (lakh/$mm^3$).
8. The preoperative, pump and postoperative haemoglobin (g/dl)
9. The preoperative, pump and postoperative Packed Cell Volume (PCV%)
10. Anaphylactic reactions
11. Renal Dysfunction

**1. The time interval from protamine administration to skin closure:-**

The duration (minutes) between administration of total dose protamine and start of skin closure was noted. This includes mainly the duration of adequate hemostasis and sternotomy closure.

**2. The volume of blood loss (ml/kg) in chest drain after 24 hours:-**

The volume of blood (ml/kg) after 24 hours in the chest drain was calculated by measuring the difference between the level (ml) of saline measured immediately after connecting the ICD tube to the drain and level (ml) at the end of 24 hours postoperatively. This measured volume is divided by patient's body weight (kg) to get volume of blood loss in ml/kg.

**3. The volume of blood and blood products (ml/kg) transfused postoperatively:-**

The volume of blood and blood products(ml/kg) transfused postoperatively was calculated by measuring volume of blood and blood products (Fresh frozen plasma and platelets) transfused to the patient to maintain the Packed Cell Volume (PCV%) above 35% investigated at serial intervals. This measured volume is divided by patient's body weight (kg) to get the volume of blood and blood products given in ml/kg.

**4. The postoperative Activated Clotting Time (sec) after 2 hours of skin closure:-**

The Activated Clotting Time (ACT) was measured after 2 hours of skin closure in postoperative ward using Kaolin based ACT catridge and Medtronic ACT II machine.

5. **The preoperative and postoperative bleeding time (sec)**;-

The bleeding time (sec) of the patient was measured preoperatively 30 minutes before surgery and postoperatively 24 hours after surgery.

**6. The preoperative and postoperative clotting time(sec):-**

The clotting time (sec) of the patient was measured preoperatively 30 minutes before surgery and postoperatively 24 hours after surgery.

**7. The preoperative, pump and postoperative platelet count (lakh/$mm^3$):-**

The platelet count values (lakh/$mm^3$ ) were investigated preoperatively 30 minutes before surgery, during cardiopulmonary bypass after 20 minutes start of the pump and postoperatively 24 hours after surgery.

**8. The preoperative, pump and postoperative haemoglobin (g/dl):-**

The haemoglobin values (g/dl) were investigated preoperatively 30 minutes before surgery, during cardiopulmonary bypass after 20 minutes start of the pump and postoperatively 24 hours after surgery.

**9. The preoperative, pump and postoperative Packed Cell Volume (PCV%):-**

The Packed Cell Volume (PCV%) was investigated preoperatively 30 minutes before surgery, during cardiopulmonary bypass after 20 minutes start of the pump and postoperatively 24 hours after surgery.

**10. Anaphylactic reactions:-**

Patients were monitored for hemodynamic changes due to anaphylaxis to aprotinin given after induction. The anaphylactic reaction was defined as major changes from baseline within 10 minute of 10,000 KIU of test dose aprotinin administration, of systolic blood pressure 20 percent or greater, heart rate 20 percent or greater, inspiratory pressure greater than 5cm of water or a skin reaction[33]. If anaphylactic reaction was present, it was recorded as (P) PRESENT, otherwise (A) ABSENT.

11. **Renal Dysfunction**:-

The preoperative and postoperative serum creatinine levels were investigated 30 min before surgery and 24 hour after surgery respectively. Renal dysfunction was defined as postoperative creatinine of atleast 2mg/dl or an increase over preoperative baseline levels of atleast 0.7mg/dl. If creatinine levels were elevated as per the above criteria, renal dysfunction was recorded as (P) PRESENT, otherwise (A) ABSENT.

## OBSERVATIONS AND RESULTS

Forty children of either sex posted for major elective cardiac surgeries satisfying the selection criteria were randomly allocated into two groups. (Group A, Group P – 20 patients each)

**Group A:** Patients in this group received aprotinin 20000 KIU/kg bolus after induction, 20000 KIU/kg in prime and

maintenance infusion dose of 10000KIU/kg/min till skin closure.

**Group P:** Patients in this group received equal volume protocol of Ringer Lactate solution.

**1. Demographic profile**

| Parameter | Group | N | Mean | S.D. | 't' test |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Age (years) | A | 20 | 7.15 | 2.97 | p = 0.591 |
| | P | 20 | 7.60 | 2.21 | |
| Sex | A | 20 | 1.30 | 0.47 | p = 0.340 |
| | P | 20 | 1.45 | 0.51 | |
| Weight (kgs) | A | 20 | 16.85 | 4.30 | p = 0.941 |
| | P | 20 | 16.95 | 4.11 | |

The two groups were similar with respect to age, sex & weight

**2. The time interval (min) from protamine administration to skin closure**

| Parameter | Group | N | Mean | S.D. | 't' test |
|---|---|---|---|---|---|
| Time interval (min) | A | 20 | 31.45 | 6.08 | p=0.000 |

| | | | | | |
|---|---|---|---|---|---|
| from protamine administration to skin closure | P | 20 | 52.05 | 8.71 | |

The mean time interval (min) from protamine administration to skin closure in

Group A - 31.45 +/- 6.08 min

**Group P - 52.05 +/- 8.71 min**

There is significant reduction in duration of time from protamine administration to skin closure in group A.

**3. The volume of blood loss(ml/kg) in chest drain after 24 hours**

| Parameter | Group | N | Mean | S.D. | 't' test |
|---|---|---|---|---|---|
| 24 hour drain blood loss | A | 20 | 7.01 | 3.13 | p=0.090 |
| | P | 20 | 8.72 | 3.09 | |

The mean volume of blood loss (ml/kg) in chest drain after 24 hours in

Group A- 7.01 +/- 3.13 ml/kg

Group P – 8.72 +/- 3.09 ml/kg

There is no significant reduction in volume of blood loss in chest drain in Group A.

**4. The volume of blood and blood products (ml/kg) transfused postoperatively**

| Parameter | Group | N | *Mean* | S.D. | 't' test |
|---|---|---|---|---|---|
| Blood and blood products given | A | 20 | 8.36 | 5.49 | p=0.041 |
| | P | 20 | 11.76 | 4.62 | |

The mean volume of blood and blood products (ml/kg) transfused postoperatively in

Group A - 8.36 +/- 5.49 ml/kg

Group P - 11.76 +/- 4.62 ml/kg

There is significant reduction in volume of blood and blood products transfused postoperatively in Group A.

**5. The postoperative Activated Clotting time (ACT) after 2 hours of skin closure**

| **Parameter** | **Group** | **N** | **Mean** | **S.D.** | **'t' test** |
|---|---|---|---|---|---|
| ACT after 2 hours of skin closure (sec) | A | 20 | 132.40 | 15.50 | p = 0.254 |
| | P | 20 | 137.50 | 12.15 | |

The postoperative Activated Clotting Time after 2 hours of skin closure in Group A (132.4 +/- 15.50) when compared to Group P (137.5 0 +/- 12.15) was found to be statistically insignificant.

## 6. The preoperative and postoperative bleeding time

| Parame | Gro | n | Mea | S.D | 't' |
|---|---|---|---|---|---|

| ter | up | | n | . | test |
|---|---|---|---|---|---|
| Bleeding time preop | A | 20 | 141.50 | 24.60 | p= 0.359 |
| | P | 20 | 150.25 | 34.16 | |
| Bleeding time postop | A | 20 | 147.25 | 30.88 | p=0.35 |
| | P | 20 | 174.00 | 45.09 | |

There is no statistical significance in preoperative and postoperative bleeding time between the two groups.

**7. The preoperative and postoperative clotting time (sec)**

| Parameter | Group | n | Mean | S.D. | 't' test |
|---|---|---|---|---|---|
| *Clotting time* | A | 20 | 296.50 | 32.40 | p =0.011 |
| Preop | P | 20 | 269.85 | 30.82 | |

| | | | | | |
|---|---|---|---|---|---|
| Clotting time | A | 20 | 326.00 | 30.37 | p =0.545 |
| Postop | P | 20 | 320.25 | 29.17 | |

There is no statistical significance in preoperative and postoperative clotting time between the two groups

**8. The preoperative, pump and postoperative platelet count (lakh/mm$^3$)**

| Parameter | Group | N | Mean | S.D. | 't' test |
|---|---|---|---|---|---|
| Platelet count preop | A | 20 | 3.14 | 0.67 | p=0.369 |
| | P | 20 | 2.94 | 0.72 | |
| Platelet count Pump | A | 20 | 1.33 | 0.17 | p=0.003 |
| | P | 20 | 1.12 | 0.23 | |
| Platelet count | A | 20 | 2.08 | 0.32 | p=0.115 |

| | | | | | |
|---|---|---|---|---|---|
| Postop | *P* | 20 | 2.27 | 0.40 | |

There is statistical significance in platelet count during pump time between the two groups. The preoperative and postoperative platelet count values were found to be insignificant between the two groups.

**9. The preoperative, pump and postoperative haemoglobin (g/dl)**

| **Parameter** | **Group** | **N** | **Mean** | **S.D.** | **'t' test** |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| Hb preop | A | 20 | 11.88 | 1.29 | p=0.518 |
| | P | 20 | 12.14 | 1.22 | |
| Hb pump | A | 20 | 8.90 | 0.77 | p=0.462 |
| | P | 20 | 8.74 | 0.62 | |
| Hb postop | A | 20 | 13.24 | 1.29 | p=0.204 |
| | P | 20 | 12.74 | 1.14 | |

There is no statistical significance in preoperative, pump and postoperative hemoglobin values between the two groups

**10. The preoperative, pump and postoperative packed cell volume (PCV)**

| Parameter | Group | N | Mean | S.D. | 't' test |
|---|---|---|---|---|---|
| PCV preop | A | 20 | 37.39 | 3.04 | p=0.732 |
| | P | 20 | 37.74 | 3.26 | |

| | | | | | |
|---|---|---|---|---|---|
| PCV pump | A | 20 | 27.55 | 2.48 | p=0.350 |
| | P | 20 | 28.20 | 1.80 | |
| PCV postop | A | 20 | 40.18 | 3.27 | p=0.526 |
| | P | 20 | 39.46 | 3.81 | |

There is no statistical significance in preoperative, pump and postoperative packed cell volume (PCV%) values between the two groups.

**11. Anaphylactic reactions**

Observations showed none of the patients in both the groups had anaphylactic reactions. The results were statistically insignificant between the groups.

**12. Renal Dysfunction**

Observations showed none of the patients in both the groups had elevated serum creatinine levels and renal dysfunction postoperatively. The results were statistically insignificant between the groups.

## *DISCUSSION*

The observations and results showed a clear benefit in reducing the duration of surgical procedure and transfusion of blood and blood products in routine paediatric open heart surgeries using cardiopulmonary bypass. These findings were similar to the results of previously published studies and meta-analysis of randomized controlled studies done on evaluation of efficacy of aprotinin in paediatric cardiac surgery .

### Demographic profile

Many prospective randomized controlled studies were conducted to evaluate the hemostatic benefits of aprotinin in paediatric open heart surgeries: Mossinger et al 2003[21] ,Miller et al 1998[4] , Davies et al 1997[8], Harder et al 1991[41].

The present study included the paediatric patients posted for major open heart surgeries like atrial septal defect closure, ventricular septal defects closure . This clinical setting was chosen based on periods of hands on training under expert guidance. Furthermore, this controlled environment of paediatric cardiothoracic vascular theatre and postoperative Intensive Care Unit(ICU) provided excellent facilities and

safety features for conduct of the study. In the present study, both the groups were similar with respect to age, sex and weight.

**The time interval (min) from protamine administration to skin closure**

In Miller et al 1998[4] study, the mean time interval from protamine administration to skin closure in control group is 88 +/- 41minutes, in low dose group is 64 +/- 22 minutes and high-dose group is 56 +/-16 minutes. Results were found to be significant in aprotinin groups.

In the present study, the mean time interval from protamine administration to skin closure in Group A is 31.45 +/- 6.08 minutes and Group P is 52.05 +/- 8.71 minutes. There is significant reduction in duration of time from protamine administration to skin closure in group A.

**The volume of blood loss (ml/kg) in chest drain after 24 hours**

In Miller et al 1998[4] study, there was no significant difference in chest tube drainage between groups at 6 hours (control, 13.0 +/- 8.6 ml/kg; low-dose, 14.1 +/- 6.8 ml/kg; and high-dose, 16.3 +/- 14.5 ml/kg) or 24 hours (control, 28.9 +/- 17.2 ml/kg; low-dose, 31.6 +/- 23.1 ml/kg; and high-dose, 36.0 +/- 26.4 ml/kg) postoperatively.

In the present study, the mean volume of blood loss (ml/kg) in chest drain after 24 hours in Group A is 7.01 +/- 3.13 ml/kg and Group P is 8.72 +/- 3.09 ml/kg. In this study also there is no significant difference in chest tube drainage between groups at 24 hours.

**The volume of blood and blood products(ml/kg) transfused postoperatively**

In Royston et al 1987[42] study, out of 22 patients undergoing repeat open-heart surgery ,11 were randomised to receive aprotinin. Their mean blood loss was 286 ml compared with 1509 ml in the 11 control patients ($p < 0.001$). Blood transfusion requirements were eightfold higher in the control group than in the aprotinin group, 7 of whom received only the single unit of their own blood taken before cardiopulmonary bypass.

In the present study, the mean volume of whole blood (ml/kg) transfused postoperatively in Group A is 8.36 +/- 5.49 ml/kg and Group P is 11.76 +/- 4.62 ml/kg. There is significant reduction in volume of blood and blood products transfused postoperatively in Group A.

**The postoperative Activated Clotting time (ACT) after 2 hours of skin closure**

There is no statistical difference in ACT values calculated after 2 hours of skin closure between the two groups.

**The preoperative and postoperative bleeding time (sec)**

There is no statistical significance in preoperative and postoperative bleeding time between the two groups.

**The preoperative and postoperative bleeding and clotting time (sec)**

There is no statistical significance in preoperative and postoperative clotting time between the two groups.

**The preoperative, pump and postoperative platelet count (lakh/$mm^3$ )**

There is statistical significance in the platelet count during pump time between the two groups . The preoperative and postoperative platelet count values were found to be insignificant between the two groups.

**Anaphylactic reactions**

In Davies et al 1997[8] study, there were no episodes of anaphylaxis in any of the patients who received aprotinin.

In the present study, observations showed none of the patients in both the groups had anaphylactic reactions. The results were statistically insignificant between the two groups.

**Renal Dysfunction**

In Davies et al 1997[8] study, there were no episodes of renal dysfunction observed in any of the patients who received aprotinin.

In the present study, observations showed none of the patients in both the groups had elevated serum creatinine levels and renal dysfunction postoperatively. The results were statistically insignificant between the two groups.

# SUMMARY

In this study the efficacy and use of aprotinin in paediatric cardiac surgery was assessed based on following parameters:

1. The time interval (min) from protamine administration to skin closure.
2. The volume of blood loss (ml/kg) in chest drain after 24 hours.
3. The volume of blood and blood products (ml/kg) transfused postoperatively.

1. The mean time interval (min) from protamine administration to skin closure in

   Group A - 31.45 +/- 6.08 min

   Group P - 52.05 +/- 8.71 min

   There is significant reduction in duration of time from protamine administration to skin closure in group A.

2. The mean volume of blood loss (ml/kg) in chest drain after 24 hours in

Group A- 7.01 +/- 3.13 ml/kg

Group P – 8.72 +/- 3.09 ml/kg

There is no significant reduction in volume of blood loss in chest drain in Group A.

3. The mean volume of blood and blood products (ml/kg) transfused postoperatively in

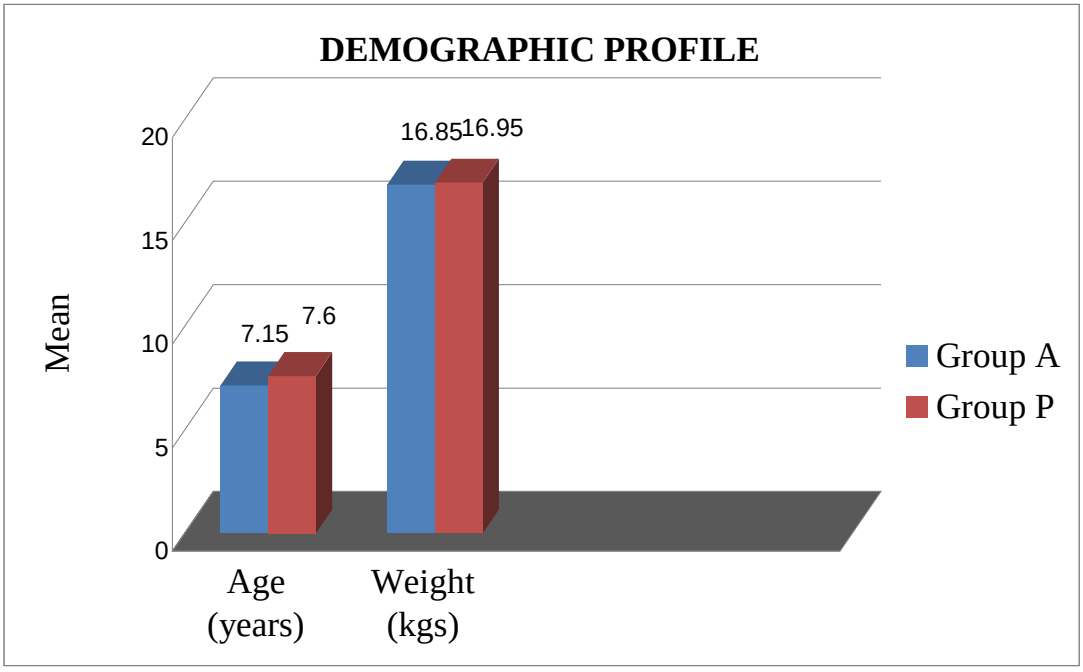
Group A - 8.36 +/- 5.49 ml/kg

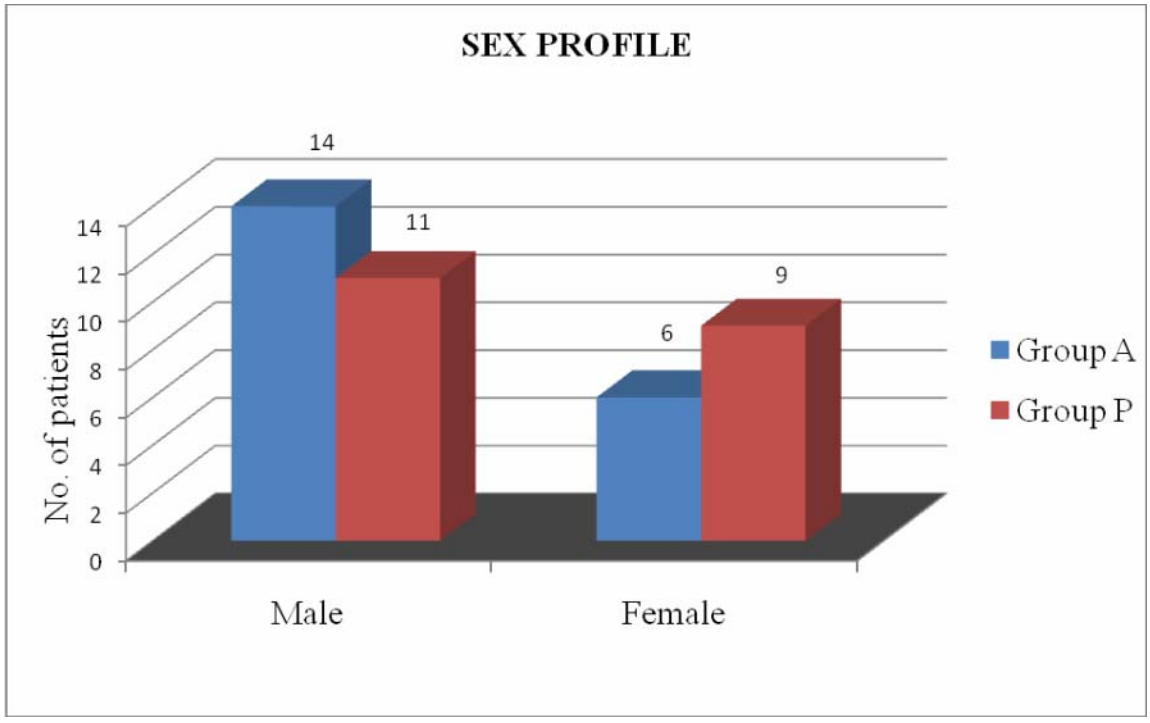
Group P - 11.76 +/- 4.62 ml/kg

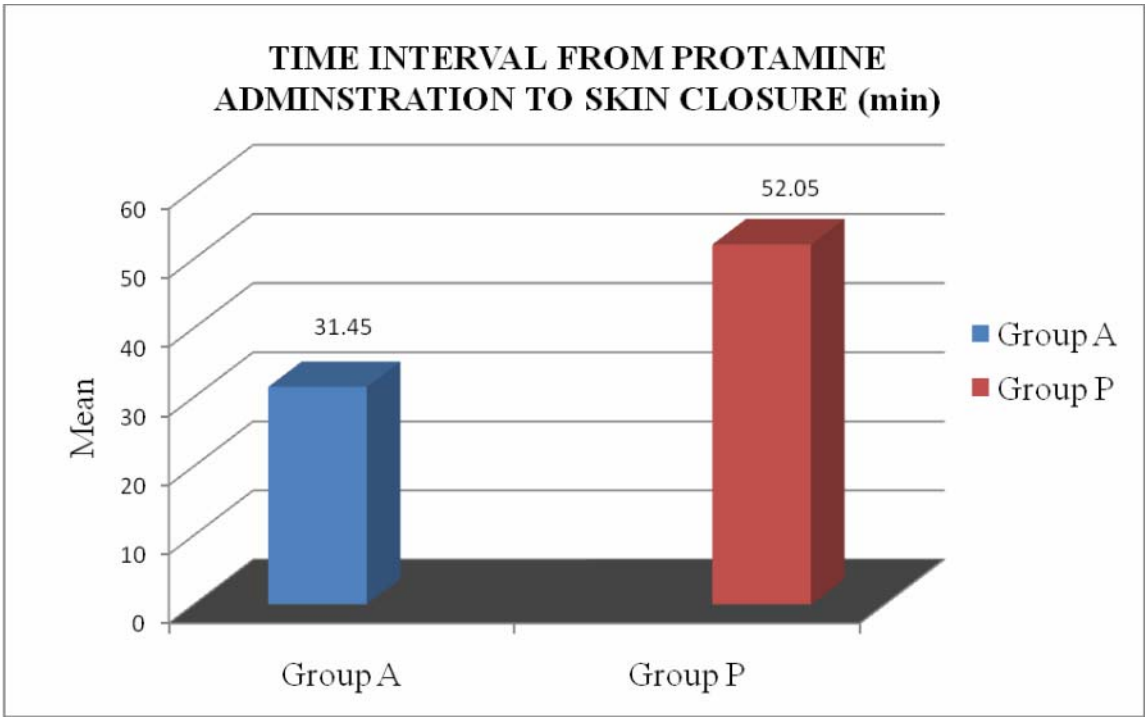
There is significant reduction in volume of blood and blood products transfused postoperatively in Group A.

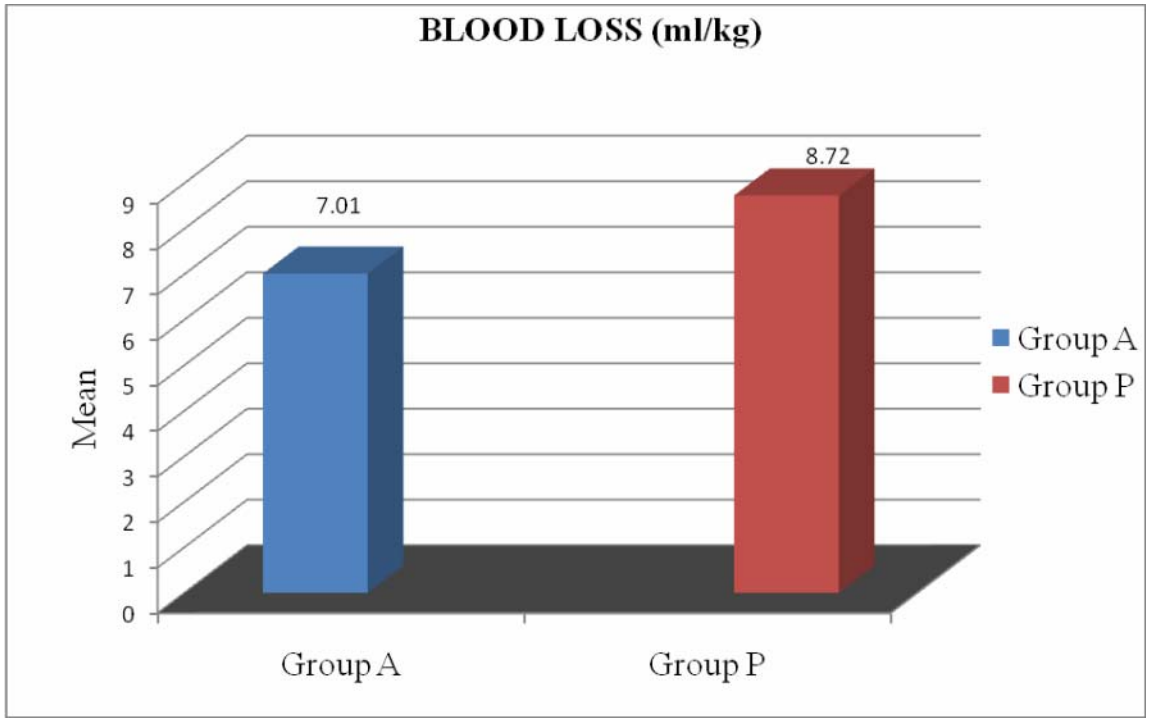
## CONCLUSION

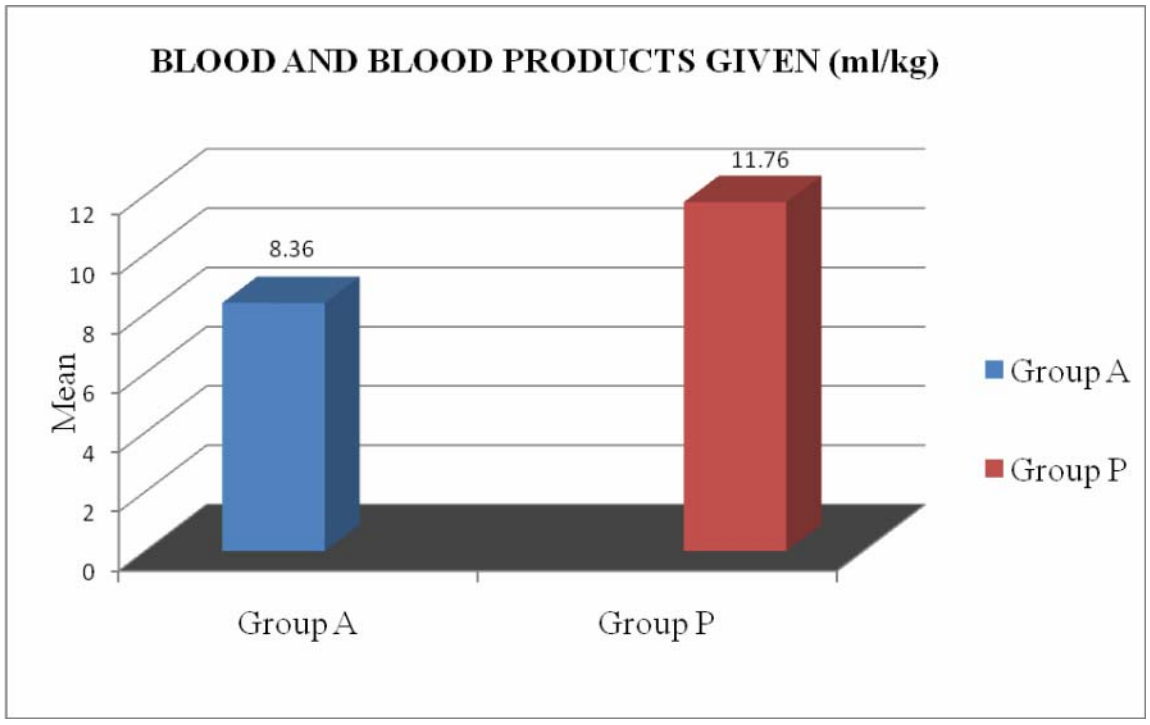
From this study, it is observed that in children undergoing open heart surgery using cardiopulmonary bypass, aprotinin is effective in improving clinical outcomes of the patients, by reducing postoperative blood transfusion requirements and duration of the surgery. There is a decreased requirement of banked blood and donor exposures. Aprotinin recipients have a significantly dry operative field after protamine reversal, aiding in early hemostasis and skin closure, thereby it shortens the duration of surgical procedure. Hence it is concluded that aprotinin is useful in anaesthetic management of the children undergoing open heart surgery.

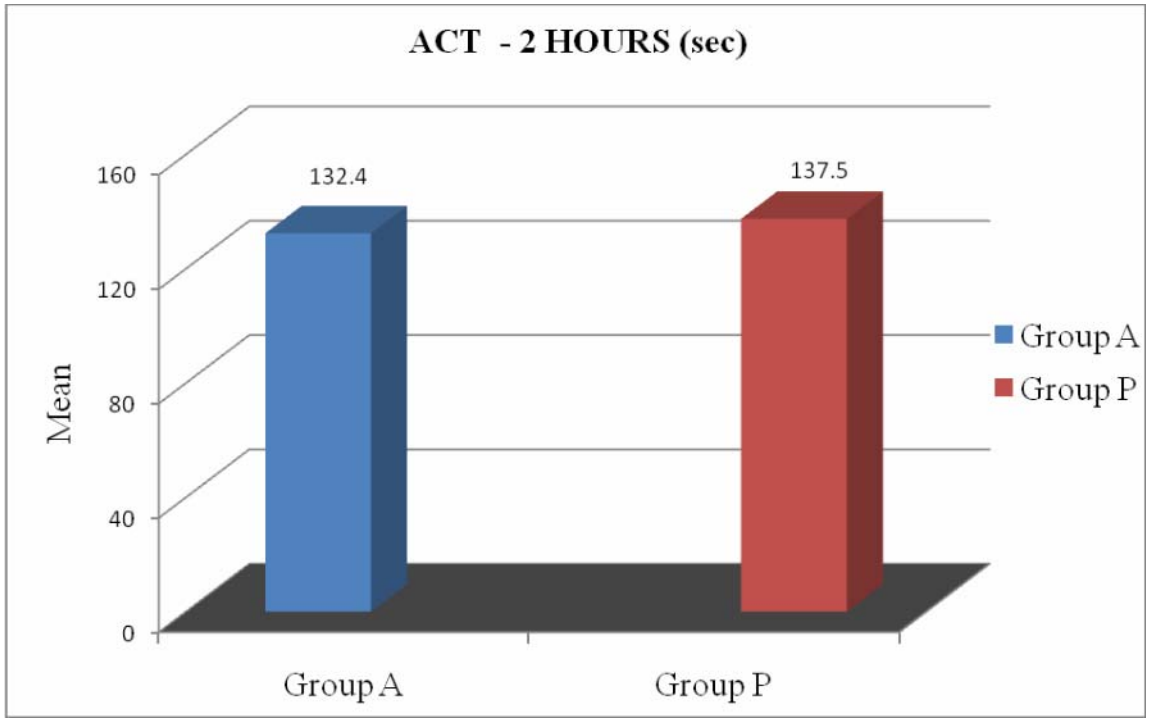

DEMOGRAPHIC PROFILE
Mean
20
15
10
5
0
16.85
16.95
7.15
7.6
Age (years)
Weight (kgs)
Group A
Group P

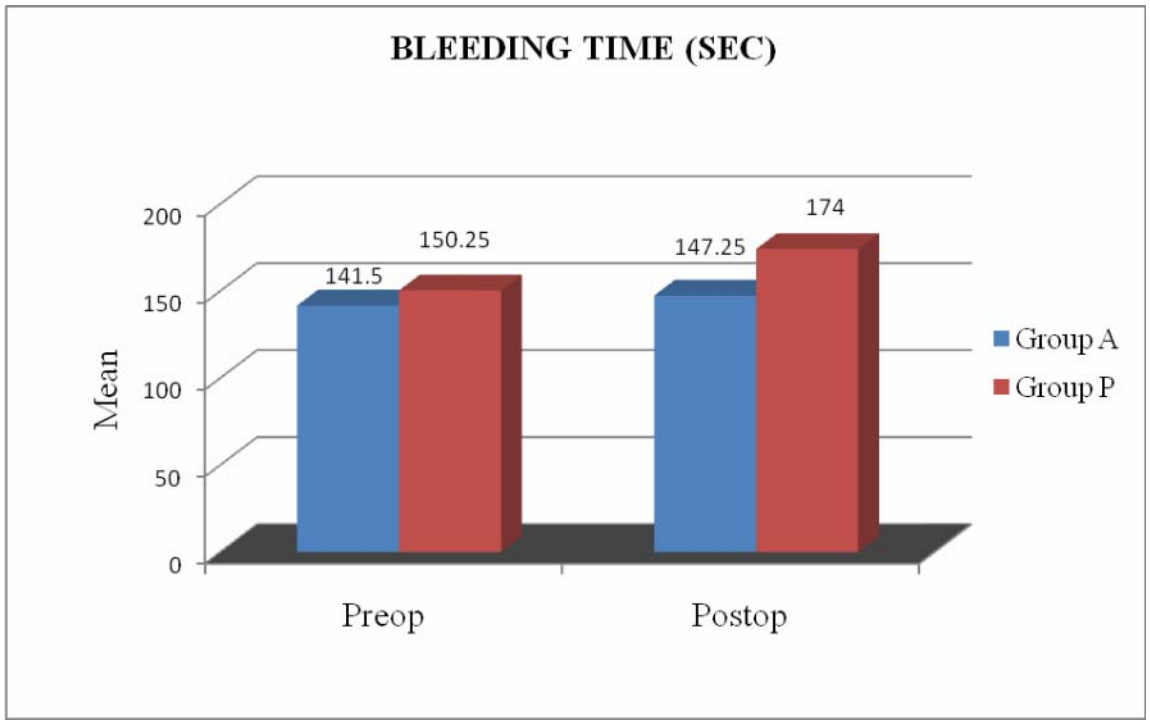

SEX PROFILE
No. of patients
0
2
4
6
8
10
12
14
14
11
6
9
Male
Female
Group A
Group P

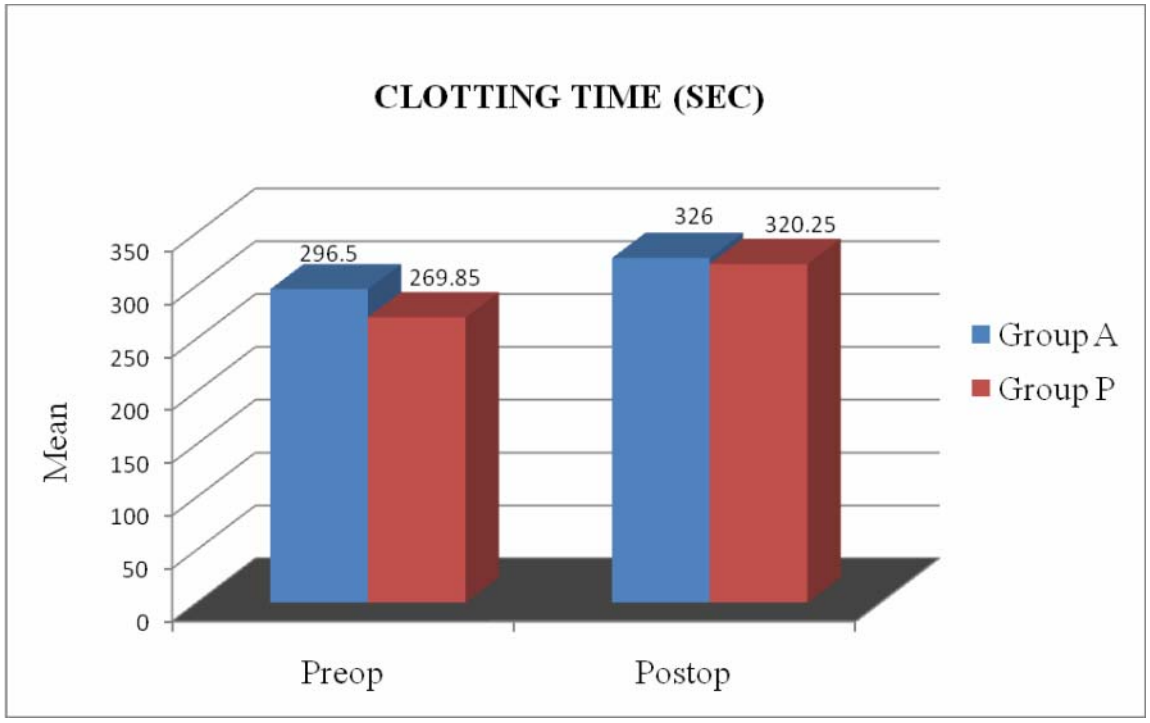

TIME INTERVAL FROM PROTAMINE ADMINSTRATION TO SKIN CLOSURE (min)
Mean
60
50
40
30
20
10
0
31.45
52.05
Group A
Group P
Group A
Group P

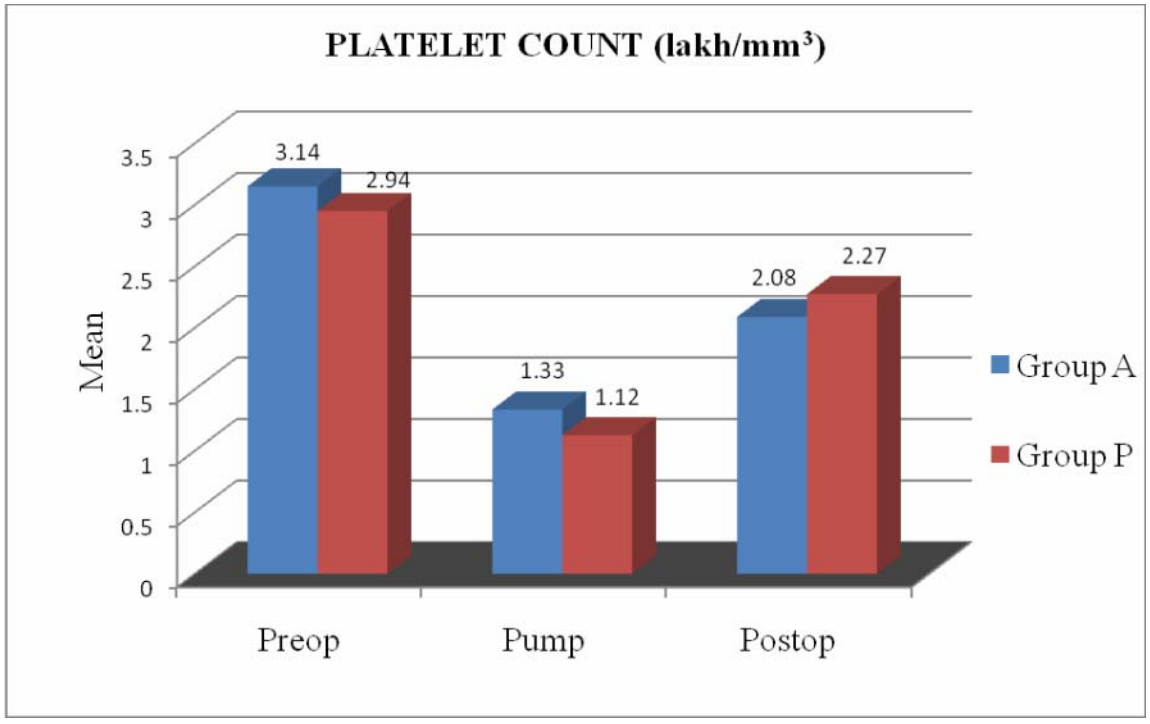

BLOOD LOSS (ml/kg)
Mean
9
8
7
6
5
4
3
2
1
0
7.01
8.72
Group A
Group P
Group A
Group P

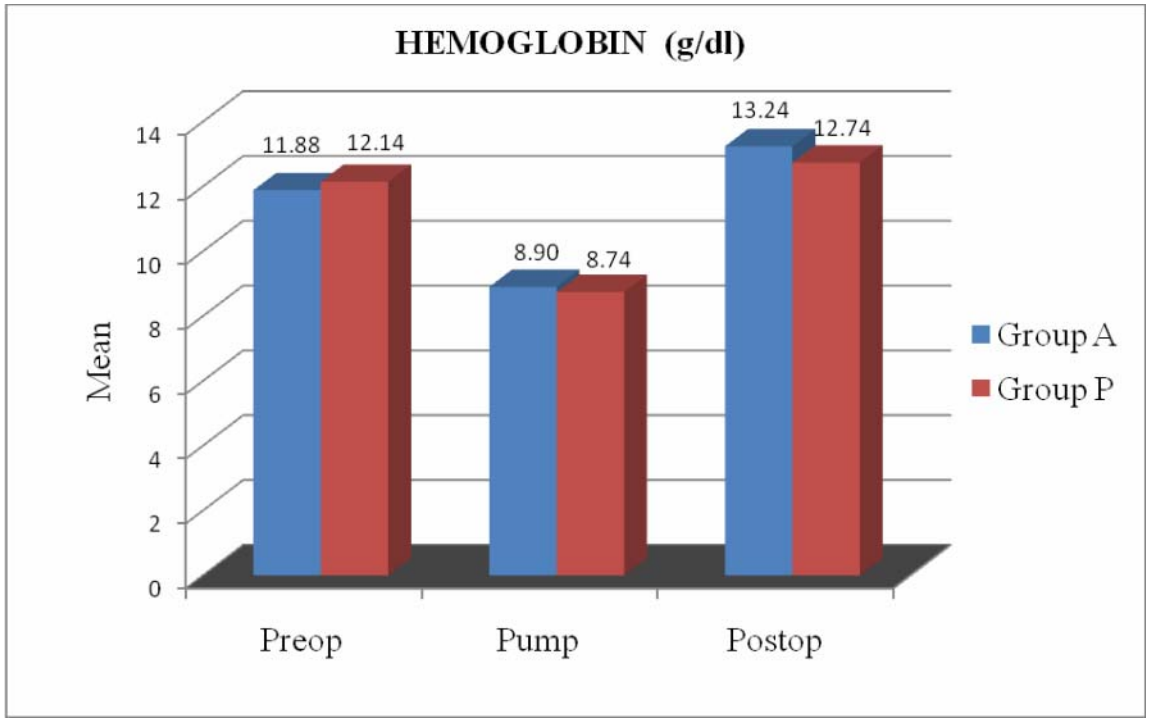

BLOOD AND BLOOD PRODUCTS GIVEN (ml/kg)
Mean
12
10
8
6
4
2
0
8.36
11.76
Group A
Group P
Group A
Group P

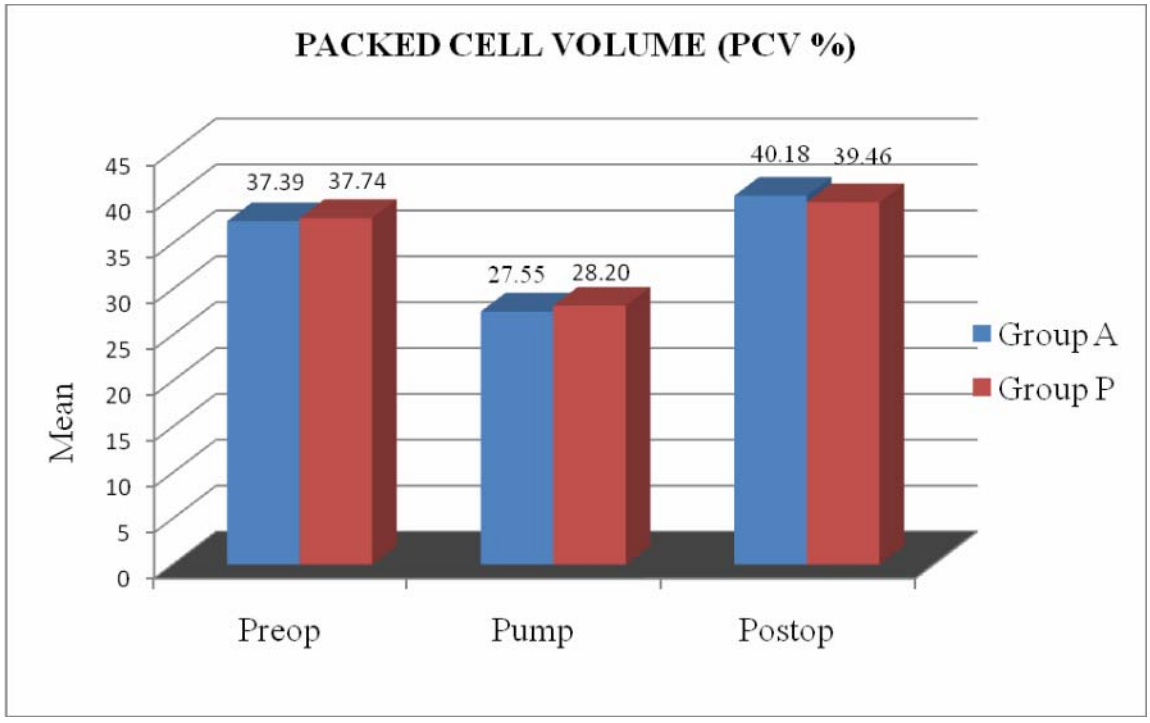

ACT - 2 HOURS (sec)
160
120
80
40
0
Mean
132.4
137.5
Group A
Group P
Group A
Group P


BLEEDING TIME (SEC)
Mean
200
150
100
50
0
141.5
150.25
147.25
174
Preop
Postop
Group A
Group P


CLOTTING TIME (SEC)
Mean
350
300
250
200
150
100
50
0
296.5
269.85
326
320.25
Preop
Postop
Group A
Group P


PLATELET COUNT (lakh/mm³)
Mean
3.5
3
2.5
2
1.5
1
0.5
0
3.14
2.94
1.33
1.12
2.08
2.27
Preop
Pump
Postop
Group A
Group P


HEMOGLOBIN (g/dl)
Mean
14
12
10
8
6
4
2
0
11.88
12.14
8.90
8.74
13.24
12.74
Preop
Pump
Postop
Group A
Group P


PACKED CELL VOLUME (PCV %)
Mean
45
40
35
30
25
20
15
10
5
0
37.39
37.74
27.55
28.20
40.18
39.46
Preop
Pump
Postop
Group A
Group P

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***PROFORMA***

Name :

Age :

Sex :

Height :

Weight :

ASA :

Study Group :

Informed consent :

Hospital No :

Date :

Diagnosis :

Operative procedure :

Co morbid illness :

General Examination :

PR -

BP -

CVS -

RS -

GIT -

CNS -

Airway - MPC

**Preop:-**

Hb -

PCV -

TC - DC-P % L %E % ESR:

Platelet count -

Blood Urea -

Blood Sugar -

Serum Creatinine -

Electrolytes in meq- Na K HCO3

Inj.Glycopyrrolate- (10µg/kg)

Inj.Midazolam- (0.15mg/kg)

Inj.Fentanyl- (2-5µg/kg)

Inj.Methyl prednisolone- (30mg/kg)

**Induction:-**

Inj.Thiopentone sodium- (5µg/kg)

Inj.Vecuronium bromide- (0.1mg/kg)

**Maintenance:-**

O2(50%)/N2O(50%)

Inj.Vecuronium bromide- (0.02mg/kg/30min)

Inj.Fentanyl - (maximum of 20µg/kg)

Inj.Morphine- (maximum of 0.1 mg/kg)

Inj.Midazolam- (0.2mg/kg/hour)

**Intraop:-**

**Group (A)-**

Aprotinin dose

After induction- (20,000KIU/kg)

Pump prime- (20,000KIU/kg)

Maintenance- (10,000KIU/kg/hr)

**Group(P)-**

Equal volume of Ringer Lactate solution

After induction-

Pump prime-

Maintenance-

Total heparin dose-

Baseline ACT-

Total protamine dose-

Protamine time-

Skin closure time-

**Intraoperative Hemodynamics:-**

| Time | HR(min) | BP(mmHg) | $SPO_2$% | ACT-1/2 hourly(secs) |
|---|---|---|---|---|
| 0 Min | | | | |
| 1 Min | | | | |
| 2 Min | | | | |
| 3 Min | | | | |
| 4 Min | | | | |
| 5 Min | | | | |
| 10 Min | | | | |

| | | | | |
|---|---|---|---|---|
| 15 Min | | | | |
| 20 Min | | | | |
| 25 Min | | | | |
| 30 Min | | | | |
| 35 Min | | | | |
| 40 Min | | | | |
| 45 Min | | | | |
| 50 Min | | | | |
| 55 Min | | | | |
| 60 Min | | | | |

| | | | | |
|---|---|---|---|---|
| ↓ till end of surgery | | | | |
| | | | | |
| | | | | |
| | | | | |

Hb -

PCV -

Platelet Count -

Blood transfused -

Intravenous fluids -

Total urine output -

Anaphylaxis - ABSENT(A)/PRESENT(P)

**Post op:-**

| **Time** | **b** | **CV** | **Platelet Count** | **Blood Sugar** | **S.Urea** | S.C | **$a^+$** | **$^+$** | **$CO3^-$** |
|---|---|---|---|---|---|---|---|---|---|
| 6 hours | | | | | | | | | |
| 24hours | | | | | | | | | |

TC- DC- P %, L %, E %, ESR:

ACT (2 hours after skin closure)-

Renal dysfunction- ABSENT(A)/PRESENT(P)

Blood and blood products transfused-

24 hour total intravenous fluids-

24 hour chest drain blood loss-

24 hour urine output-

| S.No | I.P.NO | AGE (yrs) | SEX (M/F) | Wt (kgs) | PROTAMINE TO SKIN CLOSURE TIME (min) | 24 HOUR DRAIN BLOOD LOSS(ml/kg) | BLOOD PRODUCTS GIVEN (ml/kg) | ACT(Sec) | | BLEEDING TIME (min:sec) | | CLOTTING TIME (min:sec) | | PLATLET COUNT (lakh/mm$^3$) | | | Hb g/dl | | | PCV % | | | ANAPHYLAXIS | RENAL DYSFUNCTION |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Group P | | | | | | | | BASELINE | 2 Hours | PREOP | POSTOP | PREOP | POSTOP | PREOP | PUMP | POSTOP | PREOP | PUMP | POSTOP | PREOP | PUMP | POSTOP | | |
| 1 | 611909 | 9 | F | 17 | 45 | 8.82 | 5.88 | 103 | 134 | 3:00 | 4:10 | 5:20 | 5:50 | 2.30 | 1.40 | 1.80 | 11.80 | 9.80 | 12.20 | 35.00 | 28.00 | 44.70 | A | A |
| 2 | 613987 | 5 | F | 12 | 48 | 6.66 | 4.17 | 145 | 160 | 2:45 | 3:15 | 4:55 | 4:30 | 2.90 | 1.00 | 1.60 | 12.40 | 8.90 | 15.10 | 39.00 | 28.00 | 45.00 | A | A |
| 3 | 615621 | 6 | F | 14 | 55 | 7.14 | 16.07 | 110 | 140 | 2:45 | 5:00 | 4:00 | 5:50 | 1.70 | 1.10 | 2.50 | 12.90 | 8.50 | 13.20 | 40.00 | 27.50 | 47.00 | A | A |
| 4 | 616069 | 7 | M | 20 | 62 | 7.50 | 10.00 | 123 | 136 | 3:15 | 3:10 | 4:00 | 5:50 | 3.40 | 0.90 | 2.30 | 11.70 | 8.20 | 13.20 | 35.00 | 26.00 | 40.00 | A | A |
| 5 | 615655 | 5 | M | 14 | 52 | 3.57 | 14.29 | 113 | 132 | 2:15 | 2:45 | 4:10 | 6:10 | 3.10 | 1.10 | 2.35 | 11.32 | 9.30 | 13.00 | 35.30 | 29.00 | 40.00 | A | A |
| 6 | 615326 | 10 | M | 18 | 38 | 13.88 | 13.89 | 128 | 128 | 2:50 | 3:15 | 5:00 | 5:15 | 3.60 | 1.00 | 2.40 | 10.80 | 8.20 | 13.40 | 38.00 | 28.00 | 40.00 | A | A |
| 7 | 610093 | 9 | M | 14 | 44 | 12.86 | 14.29 | 114 | 135 | 2:15 | 2:50 | 4:15 | 5:30 | 3.73 | 0.90 | 2.10 | 15.00 | 9.40 | 12.20 | 43.60 | 30.00 | 36.00 | A | A |
| 8 | 614891 | 5 | M | 12 | 58 | 8.33 | 12.50 | 123 | 125 | 1:05 | 2:00 | 5:20 | 5:00 | 2.60 | 1.30 | 2.20 | 14.40 | 8.10 | 11.20 | 44.00 | 26.00 | 34.00 | A | A |
| 9 | 618523 | 5 | M | 13 | 45 | 7.69 | 11.54 | 100 | 140 | 1:45 | 2:15 | 4:02 | 5:10 | 4.10 | 1.10 | 2.40 | 13.20 | 8.80 | 11.50 | 40.00 | 28.00 | 35.30 | A | A |
| 10 | 617845 | 6 | F | 15 | 40 | 8.00 | 10.00 | 132 | 160 | 2:00 | 2:20 | 3:50 | 5:05 | 3.82 | 1.20 | 1.90 | 10.80 | 8.00 | 11.40 | 35.00 | 26.30 | 35.00 | A | A |
| 11 | 615431 | 6 | F | 13 | 65 | 10.77 | 13.85 | 102 | 122 | 2:15 | 3:15 | 4:20 | 4:50 | 2.60 | 1.30 | 1.90 | 11.60 | 9.40 | 13.20 | 36.00 | 30.00 | 38.20 | A | A |
| 12 | 617530 | 10 | F | 20 | 42 | 9.00 | 15.00 | 98 | 134 | 2:45 | 3:15 | 5:10 | 5:50 | 1.70 | 1.00 | 2.30 | 12.00 | 8.30 | 14.00 | 38.00 | 28.00 | 40.30 | A | A |
| 13 | 616876 | 8 | M | 19 | 55 | 7.87 | 18.42 | 114 | 155 | 2:50 | 3:10 | 4:45 | 5:10 | 2.30 | 1.10 | 2.60 | 12.40 | 9.20 | 11.40 | 38.30 | 29.00 | 36.00 | A | A |
| 14 | 617518 | 11 | F | 25 | 62 | 9.20 | 14.00 | 130 | 143 | 2:55 | 2:00 | 3:50 | 5:00 | 3.20 | 1.50 | 2.90 | 13.30 | 9.60 | 14.20 | 42.00 | 32.00 | 42.30 | A | A |
| 15 | 615164 | 11 | M | 24 | 62 | 6.25 | 10.41 | 102 | 132 | 2:45 | 3:00 | 4:10 | 5:10 | 3.30 | 1.30 | 2.60 | 11.80 | 8.40 | 11.20 | 35.20 | 28.00 | 35.80 | A | A |
| 16 | 618154 | 5 | F | 14 | 50 | 7.14 | 5.55 | 99 | 128 | 1:50 | 2:30 | 5:00 | 5:30 | 2.40 | 1.00 | 1.90 | 10.40 | 8.00 | 12.20 | 33.00 | 26.00 | 35.40 | A | A |
| 17 | 614892 | 9 | F | 24 | 48 | 6.25 | 4.16 | 119 | 143 | 2:10 | 2:20 | 5:00 | 6:10 | 2.80 | 1.20 | 2.10 | 13.20 | 9.40 | 13.50 | 41.00 | 32.00 | 42.00 | A | A |
| 18 | 618298 | 6 | M | 15 | 65 | 17.33 | 20.00 | 93 | 118 | 2:50 | 2:20 | 4:30 | 5:15 | 4.10 | 1.00 | 3.20 | 11.80 | 8.10 | 14.00 | 38.00 | 27.30 | 44.00 | A | A |
| 19 | 618156 | 10 | M | 20 | 45 | 10.00 | 15.00 | 107 | 155 | 2:20 | 2:00 | 4:20 | 5:10 | 3.10 | 1.20 | 2.60 | 11.60 | 9.20 | 13.20 | 35.40 | 29.00 | 40.20 | A | A |
| 20 | 610604 | 9 | M | 16 | 60 | 6.25 | 6.25 | 116 | 130 | 3:30 | 3:10 | 4:00 | 4:30 | 2.20 | 0.90 | 1.80 | 10.50 | 8.00 | 11.50 | 33.00 | 26.00 | 38.00 | A | A |
| Group A | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | 610097 | 9 | M | 20 | 25 | 4.00 | 7.50 | 110 | 130 | 2:20 | 2:00 | 3:45 | 4:20 | 4.10 | 1.10 | 1.90 | 11.70 | 9.20 | 13.50 | 35.00 | 27.00 | 42.00 | A | A |
| 2 | 611410 | 6 | M | 15 | 30 | 3.33 | 3.33 | 89 | 110 | 2:20 | 2:15 | 4:15 | 4:45 | 4.10 | 1.40 | 2.20 | 11.60 | 8.40 | 13.00 | 35.20 | 25.00 | 41.10 | A | A |
| 3 | 611890 | 5 | M | 10 | 27 | 10.00 | 15.00 | 113 | 126 | 1:30 | 1:45 | 4:45 | 5:15 | 3.10 | 1.30 | 1.70 | 10.90 | 8.40 | 11.80 | 35.00 | 25.00 | 36.00 | A | A |
| 4 | 611220 | 2 | F | 10 | 30 | 11.00 | 12.50 | 112 | 125 | 2:15 | 2:30 | 4:00 | 5:10 | 4.05 | 1.29 | 2.30 | 11.30 | 10.80 | 10.80 | 35.40 | 29.00 | 38.00 | A | A |
| 5 | 610684 | 11 | M | 20 | 35 | 2.50 | 7.50 | 109 | 121 | 2:10 | 2:30 | 5:15 | 6:10 | 2.80 | 1.30 | 2.10 | 9.60 | 8.20 | 14.70 | 36.00 | 26.00 | 41.00 | A | A |
| 6 | 613537 | 5 | M | 13 | 25 | 4.23 | 7.69 | 87 | 103 | 2:15 | 2:00 | 5:30 | 6:10 | 3.48 | 1.10 | 2.30 | 10.80 | 8.00 | 11.80 | 33.70 | 26.00 | 37.00 | A | A |
| 7 | 614221 | 10 | F | 20 | 32 | 5.00 | 10.00 | 101 | 122 | 2:10 | 2:30 | 4:30 | 5:25 | 2.60 | 2.00 | 2.73 | 12.80 | 8.80 | 14.90 | 40.00 | 28.00 | 44.90 | A | A |
| 8 | 606658 | 9 | F | 20 | 30 | 5.75 | 7.50 | 112 | 136 | 2:05 | 2:15 | 5:00 | 5:30 | 2.20 | 1.00 | 2.10 | 12.00 | 9.00 | 11.80 | 40.00 | 27.00 | 37.00 | A | A |
| 9 | 608351 | 9 | M | 15 | 30 | 10.00 | 0.00 | 135 | 160 | 1:50 | 2:00 | 5:45 | 6:00 | 1.92 | 1.60 | 1.80 | 13.50 | 9.80 | 14.80 | 40.40 | 35.00 | 41.40 | A | A |
| 10 | 609640 | 5 | M | 15 | 33 | 8.33 | 6.66 | 123 | 154 | 2:35 | 1:45 | 5:30 | 5:10 | 2.30 | 1.40 | 1.57 | 11.20 | 8.40 | 11.40 | 42.00 | 26.20 | 37.00 | A | A |
| 11 | 610794 | 4 | F | 16 | 25 | 9.37 | 9.38 | 109 | 137 | 1:50 | 2:10 | 4:45 | 5:10 | 3.12 | 1.30 | 1.80 | 13.10 | 8.80 | 14.00 | 40.30 | 25.00 | 42.00 | A | A |
| 12 | 604158 | 2 | M | 10 | 45 | 12.50 | 20.00 | 124 | 145 | 2:00 | 1:45 | 5:10 | 5:15 | 2.75 | 1.34 | 2.10 | 12.20 | 10.00 | 12.20 | 40.80 | 30.00 | 34.00 | A | A |
| 13 | 609352 | 10 | M | 20 | 35 | 10.00 | 5.00 | 140 | 154 | 2:20 | 2:30 | 5:15 | 5:30 | 2.39 | 1.40 | 2.40 | 15.10 | 10.30 | 14.30 | 43.10 | 32.00 | 42.00 | A | A |
| 14 | 610984 | 11 | M | 25 | 34 | 3.20 | 2.00 | 133 | 138 | 2:55 | 3:00 | 4:45 | 5:15 | 3.10 | 0.95 | 1.73 | 10.80 | 8.00 | 14.50 | 34.00 | 26.00 | 45.00 | A | A |
| 15 | 612593 | 5 | M | 15 | 32 | 8.00 | 10.00 | 139 | 155 | 2:30 | 2:45 | 5:15 | 6:00 | 3.10 | 1.50 | 1.60 | 11.10 | 8.50 | 12.10 | 33.00 | 27.00 | 35.00 | A | A |
| 16 | 614692 | 9 | M | 24 | 38 | 6.25 | 0.00 | 112 | 123 | 3:00 | 3:30 | 4:45 | 5:15 | 4.20 | 1.40 | 2.45 | 12.90 | 9.20 | 14.50 | 38.00 | 28.00 | 44.10 | A | A |
| 17 | 611417 | 6 | M | 16 | 40 | 8.75 | 18.75 | 109 | 130 | 2:50 | 3:10 | 4:45 | 5:00 | 3.20 | 1.40 | 2.36 | 12.00 | 8.70 | 13.50 | 36.70 | 28.40 | 40.10 | A | A |
| 18 | 611876 | 7 | F | 15 | 20 | 10.00 | 13.33 | 112 | 124 | 2:30 | 2:55 | 4:50 | 5:10 | 3.83 | 1.10 | 1.90 | 12.70 | 8.40 | 13.10 | 37.30 | 26.40 | 41.00 | A | A |
| 19 | 610195 | 6 | M | 18 | 38 | 5.55 | 6.11 | 97 | 117 | 2:45 | 2:40 | 5:25 | 6:00 | 3.34 | 1.20 | 2.40 | 12.60 | 8.80 | 14.40 | 38.00 | 26.10 | 43.00 | A | A |
| 20 | 612595 | 12 | F | 20 | 25 | 2.50 | 5.00 | 132 | 138 | 3:00 | 3:10 | 5:40 | 6:10 | 3.30 | 1.60 | 2.30 | 9.80 | 8.40 | 13.70 | 34.00 | 28.00 | 42.00 | A | A |