Efficacy of tranexamic acid as compared to aprotinin in open heart surgery in children

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**ABSTRACT**

**Background:** Coagulopathy is a major issue in children undergoing high-risk pediatric cardiac surgery. Use of anti-fibrinolytics is well documented in adults, but recently there are questions raised about safety and effectiveness of their use on routine use. Tranexamic acid is a potent anti-fibrinolytic, but its role is not fully understood in children. This study aims to study the benefits tranexamic acid in controlling postoperative bleeding in pediatric cardiac surgical patients. **Methods and Results:** Fifty consecutive children who underwent cardiac surgery were randomized prospectively to receive either aprotinin (Group A; \(n = 24\)) or tranexamic acid (Group B; \(n = 26\)) from September 2009 to February 2010 were studied. Primary end points were early mortality, postoperative drainage, reoperation for bleeding and complications. Mean age and body weight was smaller in Group A (Age: 48.55 vs. 64.73 months; weight 10.75 vs. 14.80 kg) respectively. Group A had more cyanotic heart disease than Group B (87.5% vs. 76.92%). Mean cardiopulmonary bypass time (144.33 vs. 84.34 min) and aortic cross-clamp time (78.5 vs. 41.46 min) were significantly higher in group A. While the blood and products usage was significantly higher in Group A, there was no difference in indexed postoperative drainage in first 4, 8 and 12 h and postoperative coagulation parameters. Mean C-reactive protein was less in Group A than B and renal dysfunction was seen more in Group A (25% vs. 7.6%). Mortality in Group A was 16.66% and 7.6% in Group B. **Conclusion:** Anti-fibrinolytics have a definitive role in high-risk children who undergo open-heart surgery. Tranexamic acid is as equally effective as aprotinin with no additional increase in morbidity or mortality. **Ultramini Abstract:** Coagulopathy has been a major issue in pediatric cardiac surgery, and anti-fibrinolytics have been used fairly regularly in various settings. This study aims to evaluate the efficacy of tranexamic acid as compared against that of aprotinin in a randomized model. Tranexamic acid proves to be equally effective with less toxicity with no added mortality.

**Key words:** Aprotinin; Bleeding; Cardiopulmonary bypass; Paediatric open-heart surgery; Tranexamic acid

**INTRODUCTION**

Coagulopathy and bleeding are not uncommon following open-heart surgeries in children. It can be life-threatening at times, and does not always depend on the duration of cardiopulmonary bypass (CPB) for the procedure. Many factors are employed in controlling a difficult coagulopathic state, and use of aprotinin has been controversial more recently. While there are consensus opinions on guidelines to use aprotinin in adults, there exists none of such kind in children. There is also a paucity of evidence for the use of tranexamic acid in children. We designed a randomized study to see the efficacy of each of these to control a coagulopathic state in children following open-heart surgery and report our results.

**MATERIALS AND METHODS**

This is a randomized controlled study using tranexamic acid and aprotinin in 50 consecutive children undergoing open-heart surgeries. Institutional ethics committee clearance was obtained, and an informed consent was obtained from parents. A single
surgeon performed all the operations during the study period.

All open-heart operations were randomized prior, using a statistical model, for the use of either one of tranexamic acid or aprotinin. The uses of these were blinded till reaching operating room and were known to the anesthetists only just before giving the test dose for reactions. Though aimed to recruit a larger group, study was stopped at 50 patients, in view of the difficulty in proceeding with funding structure. The patients were self-funded for surgery, and it precluded use of additional agents at surgery without substantive proof of its use.

The exclusion criteria were either known allergic reactions or refusal to consent to take part in the study, as mentioned above.

Tranexamic acid was used in the dose of 10 mg/kg body weight as a loading dose (reduced to 5 mg/kg if creatinine is >200 mmol), and another bolus of 10 mg/kg was used at the time of initiation of CPB. Final dose of tranexamic acid 10 mg/kg was given at the time of administration of protamine during heparin reversal.

Aprotinin was used in the dose of 500 u/kg body weight intravenously as a test dose, and was given at least 10 min prior to its loading dose. A loading dose of 35000 u/kg was given after induction but prior to sternotomy, and an infusion of 10000 u/kg/h was continued until surgery was complete. An additional pump prime dose of 35000 u/kg was added to the recirculating priming fluid of CPB circuit prior to its institution. Both were continued postoperatively at corresponding dose (aprotinin: 10000 u/kg/h; tranexamic acid: 10 mg/kg/h) for 4 h before stopping them.

All the children were tested for routine coagulation studies at the end of the procedure, and renal function test 4 h following surgery. The bleeding rate was assessed, and repeat renal function test, CRP and coagulation tests were performed again at 24 h and 48 h period. Primary end points were early mortality, postoperative drainage, reexploration for bleeding and complications. Secondary end points included death, renal failure and secondary hemorrhage.

At the study size of 50 and a coefficient of 0.3, the power in this study to detect a significant result is slightly above 0.6.
There were 6 early deaths. The deaths were primarily related to pulmonary hypertensive crises in all of them. There were 7 re-explorations in total, 5 in Group A and 2 in Group B, though 4 of them had an open chest following complex totally anomalous pulmonary venous connection repair in neonates. The re-explorations were guided by the conventional criteria based on either the estimated volume of chest drain losses or rise in filling pressures with hemodynamic compromise, or both. Otherwise, the blood loss was statistically comparable between each group, though there was observational increase in the amount of blood loss in Group A as compared to Group B.

Follow-up was complete at 6 months, and there were no late deaths. 3 children from Group A had renal substitution in the form of peritoneal dialysis in the postoperative period, and two of them recovered well subsequently. None of the children from Group B had renal toxicity. There was no other organ dysfunction in any of the groups, and the inflammatory markers were comparable between the groups.

Initial randomization was done using a statistical model in a blinded way. Further statistical calculations were made using Microsoft excel (Microsoft, CA, USA) worksheet and SPSS-12 (SPSS Inc, Illinois, USA) software.

**DISCUSSION**

Bleeding remains a major and important issue in the management of children with open-heart surgery. When the complexity is increased, the operative time and the CPB time increase, making coagulopathy a part of common postoperative scenario. Various factors were attributed to the cause of this, including consumption of coagulation factors and activation of inflammatory cytokines.[1] There is also an inverse relation to the weight of children with the extent of coagulopathy.

Many steps were advocated in preventing and rather treating this coagulopathy following surgery. Elective use of blood products is simplistic, but also is both detrimental, and not cost-effective. Transfusion of large volume of blood products may not always be clinically feasible and in many situations, one would prefer to restrict the amount of colloid use in the immediate postoperative period. Though isolated factor administration in extreme situations is preferred, the management comes down to reducing the inflammatory response to CPB initially.[2]

Aprotinin is a serine protease inhibitor, and has been tested for its anti-inflammatory property and also for its efficacy in reducing bleeding postoperatively. Though serious concerns were raised recently about its toxic effects, with subsequent prevention from routine clinical usage,[2] its pediatric use has continued because of its efficacy. Allergic reactions are known, and toxicity on kidneys is well reported in the literature. Tranexamic acid is a glycoprotein IIb-IIIa inhibitor and is equally effective in controlling bleeding in open-heart surgery patients in adults. Though sparingly used in children, as compared to aprotinin, its routine use has not been matched against it on a randomized manner in children.[3,4]

Our study demonstrates the efficacy of tranexamic acid in a small group of children who undergo open-heart surgery without any undue postoperative complications. Schindler et al. had shown a similar profile of result in an observational study, with only a specific increase in platelet use intraoperatively in the group receiving tranexamic acid. The result is entirely reproducible irrespective of the profile, though there are more complex procedures in the group receiving aprotinin as evidenced by a longer CPB and cross-clamp time.

The dose at which tranexamic acid is effective is controversial and is related to the plasma level.[6] In the absence of ability to check plasma level periodically, we opted to use a standard dose of tranexamic acid and aprotinin, and renal parameters were checked periodically, not only to exclude a potential renal complication, but also to ensure a correct dose is

| Table 3: Postoperative coagulation and drainage status |
|-----------------------------------------------|
| **Group A** | **Group B** | **P** |
| INR | 1.37 | 1.29 | NS |
| Activated partial thromboplastin time (control:29) | 46.08 | 42.38 | NS |
| Serum fibrinogen (mg) | 216.85 mg | 204.57 | NS |
| Haemoglobin (g/dl) | 11.4 | 11.4 | NS |
| Packed cell volume | 35.87 | 34.73 | NS |
| Urea (mg) | 28.37 | 29.34 | NS |
| Creatinine (mg) | 0.4 | 0.41 | NS |
| Platelet count (mean) | 74,000 | 1,04,333 | 0.04 |
| Whole blood use (ml) | 124.34 | 73.07 | 0.03 |
| Fresh frozen plasma (ml) | 62.60 | 22.5 | 0.01 |
| Platelets (ml) | 11.52 | 8.7 | NS |
| Re-exploration | 5/24 | 2/26 | 0.04 |

NS: Not significant, INR: International normalized ratio
matched against the renal function and estimated glomerular filtration rate.

The coagulation parameters are comparable to aprotinin in the entire profile of patients, so also the indexed drain volume in the postoperative period. Aprotinin had established its role in preventing postoperative reactionary hemorrhage, and has been used as a standard prophylactic measure in many complex and reoperations. When matched against this principle, one would not deviate much from the fact that tranexamic acid does prove its role in its efficacy in preventing a similar episode of reactionary bleeding in children, though there were observational studies showing greater efficacy of aprotinin.[5]

Jaquiss et al. had shown an increased profile of thrombotic episodes in the use of aprotinin,[6] but we did not encounter any such effect with either of aprotinin or tranexamic acid. The reexplorations were related to postoperative hemorrhage, and only one patient had a surgically identifiable source for bleeding and the other neonates had negative exploration.

Complications are similarly low in this group, and dose-specific renal complications are very rare as compared to aprotinin.[7,8] Though aprotinin is known to offer anti-inflammatory properties, it is not uncommon to see a similar effect with tranexamic acid, but is not proven in our study.[9] The indirect measure of C-reactive protein this group offers some insight into this, though considered entirely nonspecific.

There were 4 deaths in aprotinin group and 2 in tranexamic acid group, with them being directly related to age (all of them neonates) and presentation being an emergency surgery for obstructed total anomalous pulmonary venous drainage with severe pulmonary hypertension. In the absence of extra-corporeal support, there were limitations to salvage this difficult group of patients, and there were not any direct indications towards any factor from use of either aprotinin or tranexamic acid in them causing any untoward effect for the final result.

Though a small study in a developing pediatric cardiac center, this study throws much insight into the fact that, with raising controversy surrounding the use of aprotinin, tranexamic acid offers an effective and equal alternative for a perioperative use to prevent bleeding complications in children undergoing open-heart surgery.

Study limitations: Though randomized, there were only a small group of recruits due to the center being a developing pediatric cardiac center. There was no extracorporeal support available to salvage certain difficult and severe complex cardiac conditions and further limited by the availability of parameters that can be checked to study the efficacy of these two products.

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