Combination Of Oral Versus Intravenous Formulation Of Tranexamic Acid And Ethamsylate In Controlling Postoperative Bleeding Of Cardiac Surgeries Done Under CPB

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ABSTRACT
Background and Objective: The aim of the study is to evaluate efficacy of Tranexamic acid and Ethamsylate in oral and intravenous forms in ‘reduction of post cardiopulmonary bypass bleeding’ in patients undergoing mitral valve replacement surgery. Methods: All patients with rheumatic heart valvular disease are enrolled serially and decided to study up to 100 consecutive patients that meets inclusion criteria. Patients are randomly divided into 2 groups, ‘oral’ and ‘intravenous’, containing 50 patients in each group using card method. Results: Bleeding time, Clotting time, Activated clotting time and Platelet count are the observed parameters in both the groups in the pre bypass, post bypass and postoperative period for 24 hrs. The respective values are statistically analyzed to compare the efficacy of oral and intravenous drug combination of Ethamsylate and Tranexamic acid in mitral valve replacement surgeries. Blood collected in the mediastinal and pleural drains is measured to assess the postoperative bleeding for next 24 hrs and quantified to compare with oral and intravenous formulations. Conclusion: A Combination of Ethamsylate and Tranexamic acid are quite effective both in the parenteral and oral forms in reducing post CPB and post-operative bleeding in valve replacement surgeries for rheumatic heart disease. The oral form when started 24 hours prior to surgery is as effective as intravenous formulation.

Key words: Activated clotting time (ACT), Cardiopulmonary bypass (CPB), Ethamsylate, mitral valve replacement surgery, Tranexamic acid,

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INTRODUCTION
Excessive hemorrhage after cardiac surgery contributes to post-operative morbidity and mortality. Platelet dysfunction is considered to be a major cause of bleeding after cardiac surgery followed by Cardiopulmonary bypass (CPB), resulting in an increased need for transfusions. CPB results in a systemic inflammatory response produced by the Kinin, Kallikrein, the fibrinolytic, coagulation and complement system that generate pro-inflammatory mediators through a series of consecutive proteolytic cleavages. Moreover, increased plasma concentration of plasmin and thrombin leads to platelet dysfunction after CPB.

Anti-fibrinolytic drugs reduce bleeding and post-operative transfusion requirements. Two different classes have been developed, the Lysine analogues, including Aminocaproic acid and Tranexamic acid (TA), and serine protease inhibitors namely Aprotinin. Lysine analogues inhibit fibrinolysis by attaching themselves to the lysine binding sites on
Plasminogen and Plasmin, and prevent fibrinolysis by blocking engagement of these fibrinolytic proteins with fibrinogen and fibrin. Tranexamic acid, a synthetic anti-fibrinolytic, is a lysine derivative that competitively inhibits the activation of plasminogen, thereby reducing the conversion of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, and other plasma proteins, including the pro-coagulant factors V and VIII. At higher doses, Tranexamic acid directly inhibits plasmin activity. Tranexamic acid thus inhibits fibrinolysis, a putative mechanism of bleeding, after cardiopulmonary bypass. Hence, this compound is routinely used during cardiac surgery procedures involving CPB, to reduce blood loss. Tranexamic acid, therefore, is considered to have a proven safety profile.

Ethamsylate acts by inhibiting the activity of prostacyclin synthetase and thromboxane synthetase thereby by reducing capillary bleeding and achieving hemostasis especially in thrombocytopenia and thrombasthenia. Ethamsylate is very popular in Obstetric, Gynecological, Dental, Pediatric, and ENT surgeries. It is the drug of choice to prevent or reduce the bleeding in to the cerebral ventricles in premature children and neonates, who are considered to be at high risk. Ethamsylate is seldom used to control bleeding, as far as open heart surgeries are concerned. In India, tablets of Ethamsylate and Tranexamic acid are available in combination, and are widely used by Gynecologists, Dental and ENT surgeons. Ethamsylate and Tranexamic acid are perfectly synergistic and complement each other very well. They are readily available, highly affordable and cost effective making it a very economically viable choice. The present study attempts to explore the advantage of using combination of Ethamsylate and Tranexamic acid in reducing bleeding during CPB, through oral administration in comparison with intravenous route.

MATERIAL & METHODS

A total number of 100 patients with rheumatic heart disease undergoing mitral valve replacement surgery at Osmania General Hospital, a tertiary care teaching hospital were taken into the present study. The study was approved by ethical committee and research council of Osmania medical college. The patients were divided into two groups of 50 each, at random. One group was called “Oral” group were given a combination tablets of Ethamsylate (250mg) and Tranexamic acid (500mg) started 24 hours prior to surgery at eighth hourly intervals with the last dose given 2 hours before surgery, with sips of water. The other group was called the “Parenteral” group, and patients were given injections of Ethamsylate (250mg) and Tranexamic acid (500mg) before the incision and also in the pre-bypass, during Bypass (CPB), post CPB at scheduled intervals. Baseline ACT (Normal: 70-120 seconds) levels were taken prior to administering the drugs and giving incision. Standard protocols, treatment and techniques were followed in both groups. Bleeding time, Clotting time, Platelet count and the bleeding in the post CPB period up to first 24 hours were assessed in both the groups before and after the administration of drugs in both the groups. Post operative bleeding was assessed by counting soaked swabs, measuring bleeding from pleural and pericardial drains, and ascertaining the need for transfusion of blood and blood products. Patients with bleeding diathesis and those requiring re-exploration due to bleeding from a surgical cause were excluded from the study. The results were analyzed for further evaluation and arriving at a conclusion. Modified paired student T test was used for statistical
analysis of the data.

RESULTS

Statistical analysis is done by Paired T-test. The mean age of Oral group is 35.3±3.45 and Parenteral group is 33.5±2.16. There was no statistically significant variation between the two groups age-wise (p value >0.005). The male, female ratio of Oral group is 26:24 and Parenteral group is 22:28. There was no statistically significant variation between two groups gender-wise (p value >0.005).

The mean weight of Oral group is 46.3±6.45 and parenteral group is 49.2±5.66. There was no statistically significant variation between the two groups weight-wise ((p value >0.005). Blood samples were collected before starting oral drugs i.e., one day prior to surgery. Blood samples for parenteral group were collected before giving drugs, on the day of the surgery and in postoperative period. Post-operative bleeding is collected in mediastinal and pleural drains for next 24 hours. Post-operative blood samples were collected after 24 hours from both the groups. Bleeding time, Clotting time, Activated clotting time, Platelet count, Post-operative bleeding for 24 hours are assessed and tabulated for statistical analysis.

STATISTICAL ANALYSIS

Pre-operative parameters for bleeding

No statistically significant difference was noticed for the two groups as measured by the parameters of bleeding as depicted in the graph.

Bleeding time: Bleeding time in Oral group was 96.2±3.2 seconds and Parenteral group was 97.08±1.14 seconds.

Clotting time: Clotting time in Oral group was 302.24±2.2 seconds and Parenteral group was 301.74±1.9 seconds.

Activated clotting time: Activated clotting time in Oral group is 122.9±1.3 seconds and Parenteral group was 125.64±1.5 seconds.

Platelet count: Platelet count in Oral group is 208.4±0.62 thousands/cu.mm and Parenteral group was 212±0.43 thousands/cu.mm.

Figure 1: Pre-Operative parameters (bleeding, Clotting, Activated Clotting and Platelet count) in Oral and Parenteral groups.

Post operative parameters for bleeding:

No statistically significant difference was found between the two groups as measured by the parameters of bleeding during post-operative period.

Bleeding time: Bleeding time in Oral group was 110.66±5.3 seconds and Parenteral group was 122.44±5.2 seconds.

Clotting time: Clotting time in oral group was 325.3±3.4 seconds and Parenteral was 361±8.5 seconds.

Activated clotting time: Activated Clotting time in Oral group was 130.62±5.6 seconds and Parenteral group was 142.68±6.2 seconds.

Platelet count: Platelet count in Oral group was 163±0.02 thousands/cu.mm and Parenteral group was 143±0.08 thousands/cu.mm.

Postoperative bleeding: Post-operative bleeding in first 24hrs in Oral group was 402.86±35ml and Parenteral group was 502.62±38.4ml.
Naive conclusions
Null hypothesis: There is no difference between post-operative bleeding and lab parameters in both the groups. Statistical significance was tested by Paired T-test. As there is no statistical difference in the pre-operative lab values between the two groups, we used only post-operative data for testing the significance. Paired T-test results of post-operative metrics are tabulated in Table 1 below:

Table 1: Paired T-test results of Oral and Intravenous post-operative parameters

<table>
<thead>
<tr>
<th>Oral vs Intravenous</th>
<th>Mean difference</th>
<th>Standard deviation</th>
<th>Standard error of mean</th>
<th>'T' Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>11.9</td>
<td>6.72</td>
<td>0.95</td>
<td>12.52</td>
</tr>
<tr>
<td>Clotting time</td>
<td>35.84</td>
<td>17.714</td>
<td>2.504</td>
<td>14.306</td>
</tr>
<tr>
<td>Activated Clotting time</td>
<td>14.84</td>
<td>10.17</td>
<td>1.43</td>
<td>10.3</td>
</tr>
<tr>
<td>Platelet count</td>
<td>0.324</td>
<td>0.263</td>
<td>0.037</td>
<td>8.7</td>
</tr>
<tr>
<td>Post op bleeding</td>
<td>57.4</td>
<td>34.68</td>
<td>4.905</td>
<td>11.7</td>
</tr>
</tbody>
</table>

The standard T value at Probability of 0.05 with 49 degrees of freedom is 2.01. As calculated T value for all the parameters is greater than the standard T value, Null hypothesis is rejected.

DISCUSSION
Bleeding is the most important problem in a patient undergoing an open heart surgery under cardiopulmonary bypass. There are many factors involved in the etiology of bleeding; the most important are the damage to platelets, red blood corpuscles and other cellular components of the blood, due to the trauma subjected by the heart lung machine. There is a depletion of clotting factors due to the heart lung machine, when the prime is circulated. Diseases like rheumatic heart disease associated with raised Anti-Streptolysin O titers, anti-coagulants use and drugs like Aspirin, Clopidogrel in the pre-operative period also result in significant loss in the operative and post CPB period. The patients with right heart failure and chronic passive congestion of liver also bleed more than the normal, during the CPB and the post CPB period.

One of the methods adopted by us in our institute is administration of autologous blood drawn from the femoral vein of the patient in the pre bypass period in a dosage of 5-10ml/Kg body weight. The advantage of the autologous blood transfusion is that it gives back fresh RBCs, platelets and clotting factors to the patients in the post CPB period after reversal with protamine. Drugs like Epsilon-aminocaproic acid, Protamine and Tranexamic acid have been used
during open heart surgeries, to minimize bleeding, in the post CPB period with varying results. Of the above mentioned drugs, Tranexamic acid is the most popular drug used to prevent CPB bleeding in coronary artery bypass surgeries and used all-over the world. For it to be effective, Tranexamic acid injection should be given before incision and should be continued by infusion in the pre CPB and post CPB period. Tranexamic acid helps by decreasing the fibrinolysis and helps in the formation of a firm organized clot.

Ethamsylate acts by inhibiting the activity of prostacyclin synthetase, endoperoxide reductase, endoperoxide isomerase, and thromboxane synthetase there by reducing capillary bleeding and achieving hemostasis especially in conditions associated with platelet dysfunction. In India, combination of Ethamsylate and Tranexamic acid in the tablet form and as injections are very popular in the field of gynecology to control menorrhagia. They are also used in ENT, dental and general surgeries to reduce bleeding. Ethamsylate has not been much evaluated in open heart surgeries. Ethamsylate has a unique mechanism of action where it is known to stabilize the platelets and maintain their integrity and functions. It is the drug of choice in premature children, who bleed into the cerebral ventricles. In these children, prophylactic administration of Ethamsylate has been shown to reduce the incidence of the intra ventricular bleed. Ethamsylate is perfectly synergistic with Tranexamic acid, both in tablet and injectable forms. The end result with this synergistic combination has dual advantage of minimizing the damage to platelets due to CPB and forming firm clots following reversal with Protamine.

In this study the following observations were made when the patient was administered Ethamsylate and Tranexamic acid 24 hours prior to surgery.

- The activated clotting time (ACT) done in the pre bypass period with the use of oral Ethamsylate and Tranexamic acid combination showed a reduction by about 10-20 seconds. For example the ACT, which was between 130 and 140 seconds before starting the tablets, came down to 110-120 seconds.

- The ACT values reached the pre bypass values in a significantly short period of the time after the administration of the Protamine. The value of the ACT did not again increase up to 4 hours after reversal with Protamine. This point is highly beneficial because at this point, the anti-coagulant action of heparin naturally fades away. In very few cases we noted rebound heparinisation after complete reversal with Protamine.

- “Ethamsylate and Tranexamic acid in the oral form was comparable to parenteral form in our study”. In both groups the mops fully soaked with blood were not more than 3-4 for a surgery of 6 hours duration. In our study a fully soaked pack accounts for around 20ml of blood loss.

- In both the oral and intravenous groups, the bleeding from the drain was significantly less when compared to the control group. The post CPB bleeding for the first 24 hours of post-operative period was as high as one liter in the control group where as in the Ethamsylate and Tranexamic acid group, the bleeding ranged from 300-600 ml for the first 24 hours post-operative period.

The combination of Ethamsylate and Tranexamic acid appears to be more promising than the solitary use of Tranexamic acid, which is usually the case.
in most of the centers. In our study, the results were equally satisfactory in both the oral and the parenteral groups. Here we have to remember that the oral group is very effective from the point of view of economy and there is no need to use the injection up to 6 hours as most of the open heart surgeries are finished by 6 hours. By this time, even the heparin action fades away and there are very minimal chances of rebound bleeding due to heparin. The only way by which the bleeding can occur in the post-operative period is due to damage to platelets, RBC, and clotting factors. Hence selecting and using drugs like Ethamsylate and Tranexamic acid in combination will go a long way in establishing the satisfactory haemostasis in the post-operative period. If needed, this drug can also be continued in the post-operative period without compromising the haemodynamic parameters in the injectable form up to 24-48 hours.

The post CPB bleeding for the first 24 hours of post-operative period was 1000ml in the CPB conducted without any administration of hemostatics, where as in the study group, the bleeding was around 300-600 ml.9 The cause for post-operative bleeding is Heparin administration, Platelet dysfunction, fibrinolysis and decrease in coagulation factors. Acute acquired platelet dysfunction is the main cause of post CPB bleeding and decrease in platelet count and adhesion, and aggregation is significantly reduced post CPB and this is taken care of by Ethamsylate which specifically reduce micro vascular bleeding whereas tranexamic acid averts clot lysis.

CONCLUSIONS
1. Ethamsylate and Tranexamic acid are quite effective both in the parenteral and oral forms in combination in reducing post CPB and post-operative bleeding in valve replacement surgeries for rheumatic heart disease.
2. Ethamsylate and Tranexamic acid in combination effectively brings down the requirements for blood and blood product transfusion in the post CPB period in both the oral and parenteral groups.
3. The combination of Ethamsylate and Tranexamic acid brings down the baseline ACT levels in the oral group especially after treatment. Hence Heparin and Protamine dosages should be planned as per the baseline ACT record before giving incision for sternotomy.
4. Ethamsylate and Tranexamic acid in combination effectively brings down the requirements for blood and blood product transfusion in the post CPB period in both the oral and parenteral groups.

The oral group when started 24 hours prior to surgery is quite effective, simple and economical when compared to Parenteral group and obviates the need for continuously priming patients with Tranexamic acid and Ethamsylate throughout the surgery. This is because most of surgeries get over by 4 to 6 hours and the oral drugs will still be effective during that period.

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