E-ISSN: 2664-8857
P-ISSN: 2664-8849
www.anesthesiologyjournal.in
IJAR 2023; 5(1): 05-10
Received: 09-10-2022
Accepted: 22-12-2022

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Role of tranexamic acid in reducing blood loss in off pump coronary artery bypass surgery: A randomized, double blind study

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DOI: https://doi.org/10.33545/26648849.2023.v5.i1a.26

Abstract
Introduction: To reduce the morbidity associated with cardiopulmonary by-pass (CPB), off-pump coronary artery by-pass grafting (OPCAB) has gained popularity.
Methodology: A randomized double - blind study with patients undergoing off -pump coronary surgeries under anesthesia was carried out in Pondicherry Institute of Medical Sciences during October 2013 to April 2015. Sample size was 60 and those were patients randomized into two groups that is each group having 30 patients. Patient age group between 18 to 80 years were included.
Results: The study population included 63 patients with coronary artery disease-triple vessel disease coming for off pump coronary artery bypass surgery under anesthesia to Pondicherry Institute of Medical Sciences. Of the 63 patients, 30 were allotted to each group after randomization into – Group T-receiving Tranexamic acid 30mg/kg after heparin and 30 to Group S -receiving normal saline.
Discussion: Tranexamic acid significantly reduces intra as well post-operative bleeding in off pump coronary artery bypass (OPCAB) surgeries and also significantly reduces the requirement for allogeneic blood transfusion in patients undergoing OPCAB surgeries. There were no complications or adverse reactions related to the use of drug like hypotension, seizures, renal dysfunction, thrombosis or anaphylactic reactions.

Keywords: Tranexamic acid, pump coronary artery bypass surgery, cardiopulmonary by-pass, blood loss

Introduction
In 1953, John Gibbon performed the first successful open-heart operation on a human patient using a heart-lung machine, starting the age of open-heart surgery. Blood requirements per cardiac case in the early1950's were 20 to 30 units [1]. Despite continuous advances, cardiopulmonary by-pass is frequently associated with excessive bleeding where platelet dysfunction being the non-surgical cause of bleeding. To reduce the morbidity associated with cardiopulmonary by-pass (CPB), off-pump coronary artery by-pass grafting (OPCAB) has gained popularity. Off-pump coronary artery bypass (OPCAB) surgery is associated with a reduced frequency of hemorrhagic disorders [2]. But hemorrhagic complications are not completely eliminated and there is still a need for blood transfusion after OPCAB surgery. The protease inhibitors tranexamic acid is used to reduce blood loss after OPCAB. The defective hemostasis following cardiopulmonary bypass is a serious complication in open-heart surgery, which results in an increase in bleeding and the requirement for allogeneic blood transfusion in many patients. The mechanisms of bleeding during and after cardio pulmonary bypass (CPB) surgery are supposed to be related to hemodilution, heparin administration, impaired platelets function, and increased fibrinolytic activity. In order to reduce CPB associated morbidity, OPCAB procedures have gained popularity. Although postoperative bleeding seems to be attenuated by the avoidance of CPB, hemorrhagic complications are not completely eliminated and there is still a need for blood transfusion after OPCAB surgery. Despite the avoidance of CPB, there is still activation of the fibrinolytic pathway during off-pump procedures because of the surgical trauma (sternotomy, pericardiotomy, graft harvesting, manipulation of the heart) and exposure to heparin and protamine [2]. Allogeneic transfusions pose risks for adverse outcomes after cardiac surgery. Therefore, inhibiting therapies to reduce bleeding and allogeneic transfusions during OPCAB surgery are important.

Antifibrinolytic drugs are used to decrease perioperative bleeding. Reasons for blood conservation include the greater cost of red blood cells, reduced donation rates, concerns regarding the risks of receiving allogenic red blood cells and patient preference to avoid receiving blood transfusion [3]. A popular approach is to minimize peri-operative bleeding through the prophylactic use of the anti-fibrinolytic agents like aprotinin, tranexamic acid and epsilon aminocaproic acid to decrease perioperative bleeding [3].

Tranexamic acid is a synthetic derivative of the amino acid lysine which acts by forming a reversible complex with plasminogen and plasmin through the lysine binding sites, thus blocking the interaction with the specific lysine residues of fibrin. This process retards fibrinolysis because, although plasmin is still formed, it is unable to bind to fibrin.[4]Intravenous administration of tranexamic acid has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, scoliosis surgery, oral surgery, orthotopic liver transplantation, total hip or knee arthroplasty, and urinary tract surgery (5-30). Tranexamic acid has been shown to be very useful in reducing blood loss and incidence of blood transfusion in these surgeries. In this study, the efficacy of tranexamic acid in reducing the blood loss in Off pump coronary artery surgery was investigated. And the objectives were to assess the efficacy of tranexamic acid in reducing blood loss in Off-Pump coronary artery surgeries, to compare the blood loss between the two groups**,** to compare the requirement of allogenic blood transfusion between the two groups and to assess complications, if any.

Materials and Method

A randomized double - blind study with patients undergoing off -pump coronary surgeries under anesthesia was carried out in Pondicherry Institute of Medical Sciences during October 2013 to April 2015. Sample size was 60 and those were patients randomized into two groups that ids each group having 30 patients. Patient age group between 18 to 80 years were included in this study. Patients with known drug allergies, pre-operative anemia (hemoglobin < 10g/dl), history of bleeding disorders, left main coronary artery disease, chronic renal insufficiency (serum creatinine > 2mg/dl), active chronic hepatitis or cirrhosis, myocardial infarction < 30 days, and stoppage of clopidogrel <5 days before surgery. Inj. Tranexamic acid. Drug is approved by the Drug controller, India. Patients were randomized into two groups after obtaining institutional and ethical committee clearance. T group - tranexamic acid 30 mg/kg and S group – saline.

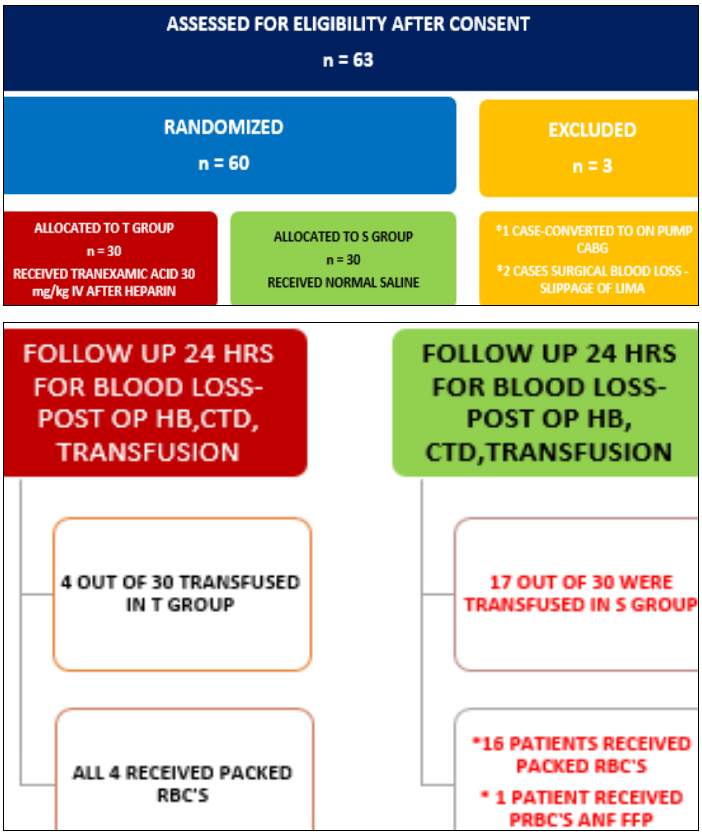


Fig 1: Consort diagram showing the flow of participants through each stage of the study comparing tranexamic acid with saline

Anaesthetic and surgical protocol

Pre-anaesthetic assessment was done the evening prior to surgery. Informed and written consent will be obtained after explaining the procedure to the patients in the language they understood. Pre-operative investigations will be done and reports will be reviewed. Tab. lorazepam 1mg and Tab. Ranitidine 150 mg will be given night before surgery. All patients will be kept nil per oral for six hours prior to surgery. Patient will be shifted to the O.T complex. Non-invasive monitors like electrocardiogram, non-invasive blood pressure and pulse oximeter will be connected. Patient is then cannulated with 16G iv cannula (Venflon). Following which patient are premedicated with injection glycopyrrolate 10mcg/kg, injection midazolam 0.05mg/kg, injection fentanyl 5mcg/kg. The left radial artery is then cannulated using 20G venflon for invasive BP monitoring. Patient is then induced with sleep dose of injection thiopentone 2 to 4 mg/kg and then intubated after adequate

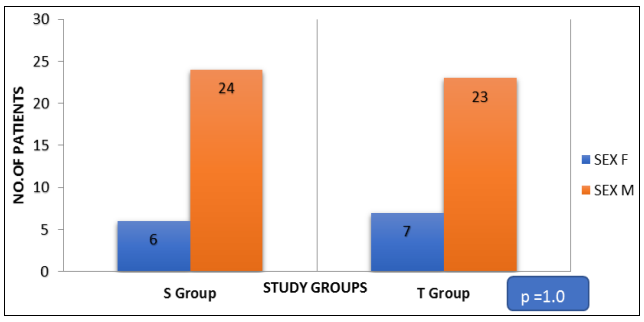
muscle relaxation is provided by intubation dose of Vecuronium 0.1mg/kg. EtCO2 monitor is connected to endotracheal tube. Central venous catheter is placed and CVP monitored. Anesthesia is maintained with 50% oxygen, 50% of nitrous oxide and isoflurane 0.8-1%.

All patients are operated on through a median sternotomy. The left internal thoracic artery is harvested routinely. When required a tract of the great saphenous vein is also harvested through a standard open approach. A heparin dose of 1-1.5 mg/kg will be administered to obtain an activated clotting time of more than 250 seconds before clamping the mammary. Then the study drug is given by the operator. Intra-operatively blood loss is assessed using gravimeteric method to weigh the soaked gauze and the amount of blood collected in the suction. Post-operatively blood loss is assessed by chest tube drainage, hemoglobin and serial ABG taken every 4 hours for the first 24 hours. Patient is taken off the study if there is excess chest tube drainage of more than 200 ml hourly for the first 3hours. Blood and additional products are transfused based on the outcome by measuring parameters like HB, Hct, PT, INR and aPTT. Transfusion trigger post-operatively for all patients will be 8g m/dl.

Statistical analysis was done using repeated measures ANOVA, Mann- Whitney test, independent t test, Chi square test, post hoc analysis was done using Bonferroni correction. All tests were two sided and p value of less than 0.05 was taken as statistically significant.

Results and Observations

The study population included 63 patients with coronary artery disease-triple vessel disease coming for off pump coronary artery bypass surgery under anesthesia to Pondicherry Institute of Medical Sciences. Of the 63 patients, 30 were allotted to each group after randomization into – Group T-receiving Tranexamic acid 30mg/kg after heparin and 30 to Group S -receiving normal saline. Three patients were withdrawn from the study after randomization because of conversion to on pump surgery due to acute MI and the other two due to surgical blood loss due to ligature slippage of left internal mammary artery (LIMA).



Graph 1: Gender comparison between s and t group

The above graph shows no difference in sex distribution between the two groups which is statistically insignificant (p = 1.0).

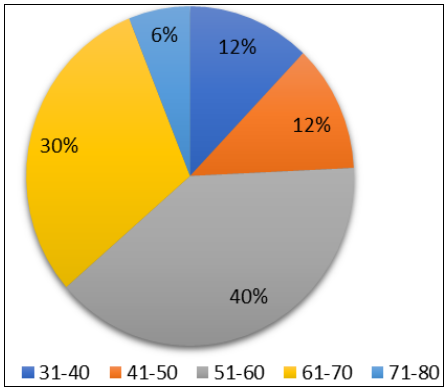
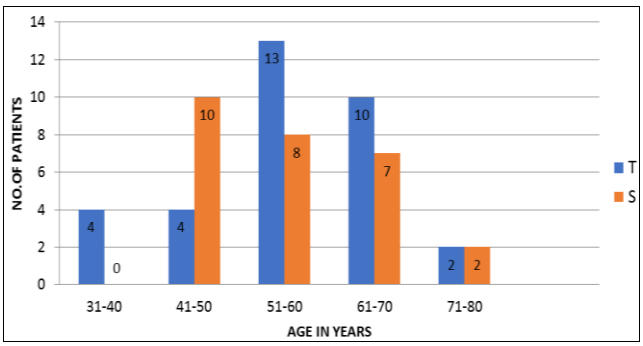


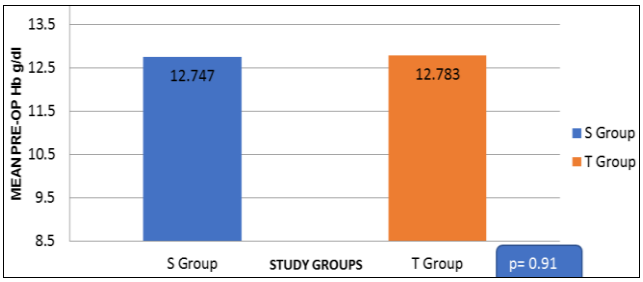
Fig 2: Percentage of age distribution in both s and t group

The above pie diagram shows that majority (40%) of patients fall between the age group of 51-60 years.



Graph 2: Mean age distribution between the s group and t group

The above graph shows that the majority of patients fall between 51-60 years with 56.3 ± 10.7 as the mean age distribution in both groups which is statistically insignificant

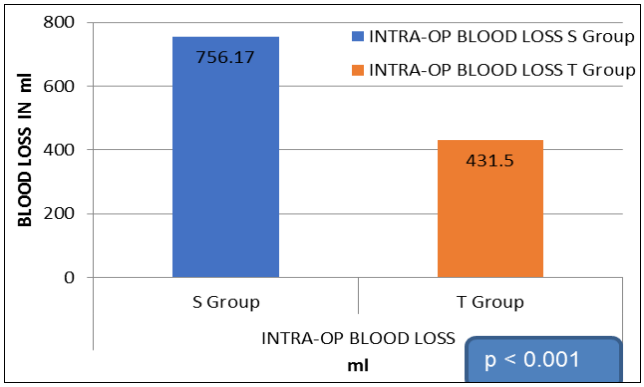


Graph 3: Mean pre-op hemoglobin in both s and t group

The above graph shows that the mean pre-operative hemoglobin in S group was 12.7 ± 1.3 g/dl and in T group was 12.8 ± 1.1 g/dl which was not significant (p= 0. 91)

Intra op blood loss

Intra operatively blood loss was assessed by measuring the weight of blood soaked gauze using Gravimetric method and by measuring the amount of blood in suction excluding the saline used. Mean blood loss intra operatively was 756.2 ± 320.0 ml in S Group and 431.5 ± 145.8 ml blood loss in T Group which was significant (p < 0.001). (Graph 4)

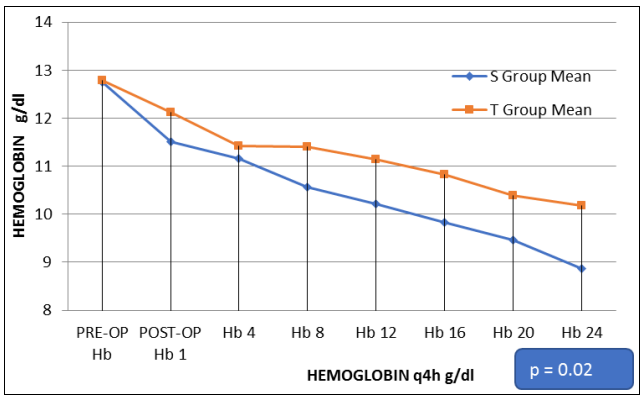


Graph 4: Mean intra-operative blood loss in s and t group

The above graph shows that the mean intra-operative blood loss (mean weight of blood soaked gauze and amount of blood in suction) in S group was more than that of T group (ie) 756.17 ml versus 431.5 ml which was statistically significant ($p< 0.001$)

Post OP 4th hourly hemoglobin values

There was a significant decline in hemoglobin levels of patients in S group (p = 0.02) when compared to T group for every 4 hrs in post-operative period (ie) 50% of patients in S group had decline in hemoglobin than 16.67% patients in T group and this decline was more at 12th,16th and 24th hour respectively (Graph 5). Transfusion was given if hemoglobin dropped below 8 gm /dl.

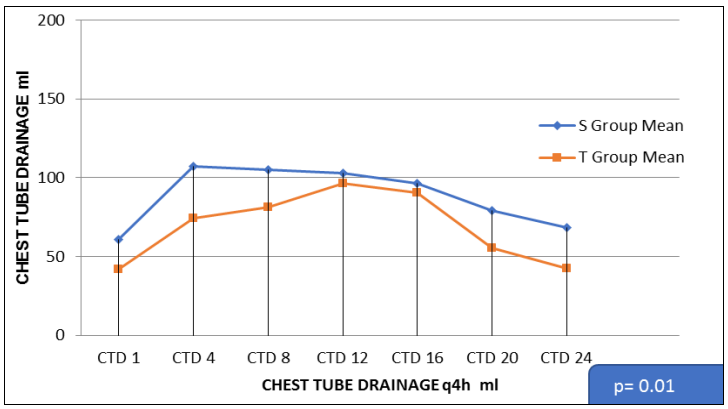


Graph 5: Mean drop in post op Hb every 4th hourly

The above graph shows that there is significant drop in post op hemoglobin in S group when compared to the T group. This difference was statistically significant p= 0.02.

Post op chest tube drainage

There was significant reduction in chest tube drainage at 0th (p = 0.03), 4th (p = 0.01), 8th(p = 0.02), 16th (p = 0.02), 20th (p = 0.03) and 24th (p = 0.007) hour in the T group when compared to the S group except for the 12th hour which was not significant(p=0.10) (Graph 6)



Graph 6: Mean chest tube drainage every 4th hourly for the first 24 hours

The above graph shows that there is significant reduction in chest tube drainage (p = 0.01) in T group when compared to S group except at the 12th hour which was not significant (p=0.10).

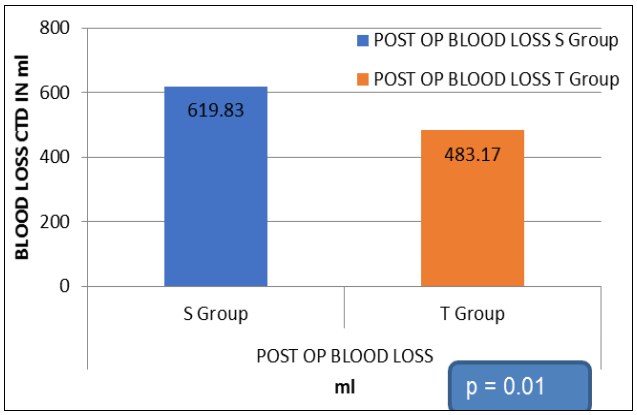
Post op blood loss and transfusion

There was 619.8 ± 247.9 ml blood loss in S group when compared to 483.2 ± 238.3 ml in T group which was significant (p= 0.01). (graph 7)

Transfusion was given if the chest tube drainage was > 200 ml in the first 3 hours and if so patient was excluded from the study. There was also significant decrease in amount of packed red cell and fresh frozen plasma transfused in the post-operative as well as frequency of transfusion in patients receiving tranexamic acid. Of the 60 patients, 35% of the patients received transfusion (figure 7).

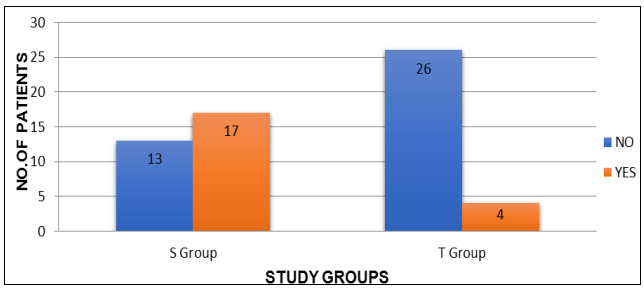
No platelets were transfused in either group.

No FFP was transfused in T group. Only PCV was used for transfusion in both groups (total-35% patients were transfused in both groups) that is only 4 out of 30 patients in T group received transfusion when compared to 17 out of 30 patients in S group (graph 8). Of all the 17 patients except one patient in S group received 4 units of packed cells (PCV) and 2 units of fresh frozen plasma(FFP).



Graph 7: Mean post-operative blood loss in s and t group

The above graph shows that there was significant reduction in blood loss through chest tube drainage in T group when compared to S group (ie) 483.2 ± 238.3 ml Vs 619.8 ± 247.9 ml which was significant (p= 0.01).



Graph 8: Comparison of post op blood transfusion between s and t-group

The above graph shows that there is significant reduction in allogenic blood transfusion in T group when compared to S group where only 4 patients in T group received transfusion when compared to 17 patients in S group- thereby reducing transfusion related complications.

Discussion

The synthetic lysine-analogues tranexamic acid was first described in 1957 by Okamoto. The activity of the trans-isomer of tranexamic acid was first described in 1964, since which time the drug has been used in a variety of clinical settings.[5] It acts by reversibly blocking the lysine binding sites of plasminogen, thus preventing its activation to plasmin, and therefore stopping the lysis of polymerized fibrin.[6] In our study two groups were compared based on age, sex, preoperative haemoglobin, intra operative blood loss, post op drop in hemoglobin, chest tube drainage and requirement of post op blood transfusion and the complications.

In our study results showed that tranexamic acid group had mean intra-operative blood loss of 431.5 ± 145.8 ml and saline group had 756.2 ± 320.0 ml and p value was < 0.001 and the mean blood loss in post-operative period was 619.8 ± 247.9 ml in S group when compared to 483.2 ± 238.3 ml in T group which was significant with p value of 0.01. Blood loss was lower in tranexamic acid group compared to the saline group and it was statistically significant. Similar to our study in 1997, Brown RS, Thwaites BK, *et al* patients received placebo or tranexamic acid 15mg/kg bolus followed by 1mg/kg/hr infusion before cardiopulmonary bypass and after cardiopulmonary bypass. In their study they found that tranexamic acid administered before and during the operation was effective in decreasing both bleeding and transfusion.[7] In 2006, A.T.L. Santos, R.A.K. Kalil, C. Bauemann, J.B. Pereira and I.A. Nesralla conducted a randomized, double-blind and placebo-controlled study with tranexamic acid after primary coronary artery bypass grafting and found that the post-op blood loss after 12 hour and 24hour surgery was 540 vs 300ml and 800 vs 500ml in the placebo versus tranexamic acid group[8] whereas in our study at 24 hours between saline and tranexamic acid group was 619.8 ± 247.9 ml vs in 483.2 ± 238.3 ml which was similar.

Guyan Wang tried tranexamic acid and placebo on patients for off pump coronary artery bypass graft and found that the patients receiving tranexamic acid had significant reduction in chest tube drainage at 6hrs and 24 hrs, 270±118 and 654 ± 224ml whereas in our study chest tube drainage at 8 hrs and 24 hrs was 105.0± 43.21 and 619.8 ± 247.9 ml which was almost similar. In his study, there was also a significant reduction in allogenic red blood cell transfusions between tranexamic acid and saline 47% vs 31.9%[9] and in our study it was 65% vs 35%.

In our study results showed that the total mean blood loss was lower in tranexamic acid group when compared to saline group that is 705.2 ± 259.9 ml in the T group compared to mean of 1441.8 ± 574.1 in the S group and this was statistically significant with p value of 0.01.

RW Reid, AA Zimmerman *et al*. gave pediatric patients either tranexamic acid 100 mg/kg followed by 10 mg/kg/kg/hr or saline placebo for cardiac surgery. They found that children who were treated with tranexamic acid had 24% less total blood loss compared with children who received placebo [10]. In 2002, Hilde Pleym *et al*. gave the tranexamic acid before cardiopulmonary bypass and concluded that tranexamic acid reduces post-operative bleeding after coronary surgery in patients treated with aspirin until surgery. Results showed that a single dose of tranexamic acid given before cardiopulmonary bypass significantly reduces post-operative bleeding in Coronary artery bypass graft surgery. Tranexamic acid reduces the morbidity as well mortality in patients who underwent coronary artery bypass graft. They have concluded that tranexamic acid is effective in cardiac surgery [4].

Our study results showed that the post-operative requirement for blood transfusion in tranexamic acid group was much lower that of saline group and overall there was only 35% of patients that required transfusion(packed red cells) in both groups and 65% of patients did not receive any blood transfusion and only 4 out of 30 patients in tranexamic acid group received blood transfusion post operatively compared to 17 out of 30 patients in saline group- showing that tranexamic acid significantly reduces the amount and frequency of blood transfusion directly and indirectly by reducing transfusion-related complications.

In our study results showed that only PCV was used for transfusion in both the groups. Out of the 35% of the patients that received transfusion in both the groups around 25% of the patients required more than two units of packed red cells. Only one patient received 4 units of packed red cells and 2 units of fresh frozen plasma as that patient INR was more than 1.2.

In 2005, Cochrane collaboration reviewed several studies on use of anti-fibrinolytics and conducted many trials to reduce blood transfusions due to transfusion associated complications. Tranexamic acid reduced the rate of pack cell volume transfusion by a relative 34%. This represented an absolute risk reduction of 17.2%. Tranexamic acid use resulted in a saving of 1.03 units of pack cell volume in those requiring transfusion and this was similar to our study [8]. A Systematic Review and Meta-analysis carried out by S.C. Adler Ma, William Brindle *et al* included 8 trials which is a meta-analysis of 24 hour blood loss, post-operative allogenic transfusion and thromboembolic events. Tranexamic acid significantly reduced the overall risk of allogeneic blood component transfusion ($p < 0.0001$) and packed red blood cell transfusions ($p = 0.0001$). No association was found between tranexamic acid and myocardial infarction, stroke or pulmonary embolism [11]. Cochrane Database Syst Rev. in 2013 conducted three studies comparing all three anti fibrinolytics with placebo.

Two studies reported red cell transfusion requirements and one study found a reduction in red cell transfusion usage [12].

Conclusion

Tranexamic acid significantly reduces intra as well post-operative bleeding in off pump coronary artery bypass (OPCAB) surgeries and also significantly reduces the requirement for allogeneic blood transfusion in patients undergoing OPCAB surgeries. There were no complications or adverse reactions related to the use of drug like hypotension, seizures, renal dysfunction, thrombosis or anaphylactic reactions. For future studies, low dose 15 mg / kg tranexamic acid can be tried and hence, tranexamic acid is safe to be used in practice in patients undergoing off pump coronary artery bypass graft surgeries.

Conflict of Interest

Not available

Financial Support

Not available

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How to Cite This Article
Krishna SDJ, Manikandan, Raj MVS, Ramachandran TR. Role of tranexamic acid in reducing blood loss in off pump coronary artery bypass surgery: A randomized, double blind study. International Journal of Anesthesiology Research. 2023;5(1):05-10.