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ROLE OF TRANEXAMIC ACID IN JOINT REPLACEMENT SURGERIES: A RANDOMISED DOUBLE BLIND PLACEBO CONTROL STUDY.

Anaesthesiology

Dr. R. Vinoth Kumar M.D. (Anaesthesia), Assistant Civil Surgeon, Government Headquarters Hospital, Ramanathapuram, Tamilnadu.

Dr. A. L. Shahjahan* M.D. (Anaesthesia), Assistant Professor of Anaesthesia, Institute of Child Health and Hospital for Children, Egmore, Chennai-600008. *Corresponding Author

ABSTRACT

Joint replacement surgeries are one of the most common and highly prevalent surgical procedures as of date. Blood transfusion comes with its own set of complications and hence the search for a complementary solution to minimize the quantum of blood transfusion. Tranexamic acid has been shown to be very useful in reducing blood loss and incidence of blood transfusion in a variety of surgeries. A randomized prospective double blind placebo controlled study was conducted on 40 American Society of Anaesthesiologists (ASA) physical status I and II patients, between the age group of 18-60 years of either sex undergoing either Total Hip replacement or Hemiarthroplasty. The patients were separated into two groups, Group I and Group II, consisting of 20 patients each and were randomized in such a way that each group had 10 Hemiarthroplasties and 10 Total Hip Replacements. Two doses of 15mg/kg of Tranexamic acid in 10ml syringe was given intravenously to the Test group (Group I) at spaced intervals whereas the Control group received Placebo intravenously – 10ml of normal saline in 10ml syringe (Group II) at spaced intervals. Peri-operative blood loss and blood transfusion requirements were measured. Statistical Analysis was done using the independent T Test. Tranexamic acid significantly reduced the peri-operative blood loss and post-operative transfusion requirements.
Its use was not associated with any complications or side effects. Hence tranexamic acid can be used effectively in replacement surgeries.

KEYWORDS

Tranexamic acid (TXA), peri-operative blood loss, blood transfusion.

INTRODUCTION :

Replacement surgery is one of the most commonly performed elective orthopaedic procedures in the world(1). But hip replacement surgery is not without any complications(1). Replacement surgery is commonly associated with significant blood loss which sometimes requires blood transfusion(1). Primary fibrinolysis occurs in case of trauma as well as replacement surgical procedures which is integral in the pathogenesis of the acute coagulopathy of trauma and replacement surgery(1).

Recently published studies have shown that patients undergoing revision hip replacement surgery frequently require red blood cell transfusions at higher rates than the other high volume orthopedic procedures(2). So there has been increased interest in peri-operative blood conservation for orthopedic surgery in recent years and lowering red blood cell use for surgery is increasingly considered as a quality marker(2). 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 patients' preference to avoid receiving blood transfusion(2).

Transfusion of blood products exposes the patients to develop transfusion-associated side effects like febrile non-hemolytic reactions and blood-borne infections(3). A popular approach is to minimise peri-operative bleeding through the prophylactic use of anti-fibrinolytic agents such as aprotinin, TXA, and epsilon aminocaproic acid(3).

TXA is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules(4,5). Intravenous administration of TXA 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(9,11). TXA has been shown to be very useful in reducing blood loss and incidence of blood transfusion in these surgeries.

Hence, owing to the reported efficacy of TXA in curtailing blood loss in several earlier studies, we proposed to evaluate the efficacy of TXA in reducing blood loss during and after joint replacement surgeries.

METHODS:

This was a randomized, prospective, double blind placebo controlled study conducted in a tertiary care hospital after prior approval from the Institute's Ethics Committee. Written and informed consent was obtained from all the patients after explaining about the objective of the study, the drug that was used for the study and its related complications.

Forty patients under ASA I and II category and between the age group of 18-60 years and belonging to either sex, posted for either Hemiarthroplasty or Total Hip Replacement under spinal anaesthesia were enrolled in this study. All these forty patients were selected from the study population using computer generated random table [https://www.randomizer.org/]. The patients were randomly allocated into one of the two study groups using sealed envelope technique. Group I received 10ml of TXA (Cyklokapron 5ml ampoule – Pfizer – 100mg/ml) in a 10ml syringe and Group II received 10ml of normal saline in 10ml syringe.

Patients with history of allergy to TXA, cardiac, hepatic or renal impairment, stroke or deep vein thrombosis and patients with hypercoagulable state such as pregnant women and breast feeding mothers and patients with history of polytrauma were excluded from this study. Moreover patients were also excluded if they came under ASA class III and IV.

Patients were randomized into two groups and each group comprised twenty patients, out of which ten patients were posted for hemiarthroplasty and ten patients were posted for total hip replacement in each group. Group I was administered two 15mg/kg doses of TXA at spaced intervals and the Group II was treated as the placebo group.

A thorough preoperative assessment was conducted a day before surgery and all the patients were kept NPO as per standard ASA guidelines. All patients were premedicated with Oral Lorazepam 1mg and oral Ranitidine 150mg on the night before surgery. Baseline vital parameters such as respiratory rate, heart rate, non-invasive blood pressure, peripheral oxygen saturation (SpO2) and electro cardiography (ECG) were recorded and continuous monitoring was started. Intravenous access was secured using an 18G cannula over the non-dominant hand and 0.9% normal saline solution was started as slow infusion. The first injection of TXA was administered at the dose of 15mg/kg intravenously slowly at the rate of 1ml/min to avoid hypotension in the preoperative holding area. Patients were shifted into the operation theatre 30 minutes after administration of TXA. Same standard monitoring protocol was observed once the patient was transferred to the operating table.

Patients were preloaded with 10ml/kg of Ringer's Lactate solution and under strict aseptic precautions and after the administration of local

anaesthetic skin infiltration, sub-arachnoid block was given in L3-L4 space. Hemodynamic status was assessed at the following intervals of 10, 20, 30, 40, 50, 60, 75 and 90 minutes. The second injection of TXA was administered

intravenously slowly over 10 minutes, 3 hours after the first injection, at the dose of 15mg/kg intra-operatively in a 10ml syringe. The study drug was prepared in similar 10ml syringes keeping the drug volume constant by an anaesthesiologist, who then handed over the syringe to another anaesthesiologist who was unaware of the contents of the syringe and performed the spinal anaesthesia and also monitored all the patients' variables.

During surgery blood loss was replaced with ringer lactate solution in a 1:3 ratio or with hydroxyethyl starch 130/0.4 in a 1:1 ratio. Blood loss was calculated by weighing soaked gauze packs, blood collected in the suction apparatus and wound drain. Packed red blood cells (PRBC) was transfused intra-operatively if blood loss was more than 20%. Transfusion trigger for all the patients was 9gm/dl.

In the postoperative unit, patients were monitored for hemodynamic parameters every 30 mins until the sensory and motor variables were back to normal. Haemoglobin and haematocrit values were measured on days 2, 4, 6 and after each post-operative transfusion. Transfusion with PRBCs was given when the hemoglobin dropped below 9gm/dl.

The primary outcome of the study was to compare the two groups, viz. TXA group and the placebo group, in terms of intra-operative and postoperative blood loss and blood transfusion requirements. The secondary outcome was to assess the hemoglobin and haematocrit values

between the two groups postoperatively. Intra-operative hemodynamic effects were also assessed between the groups.

Statistical analysis was done using the Independent T test. P value less than 0.05 was considered as clinically significant.

RESULTS:

In the present study, both groups were comparable with respect to demographic characteristics as shown in Table 1. There were no significant differences between the two groups with respect to the type of surgery, baseline haemodynamic parameters or American Society of Anaesthesiologists classification.

It was observed that the mean pre-operative hemodynamics between group 1 and group 2 was found to be statistically insignificant. The mean value of heart rate changes recorded in group 1 and group 2 were almost similar and statistically insignificant (p=0.130). The difference in the average of the pre-operative systolic and diastolic blood pressure readings in both the groups were also found to be statistically insignificant (p=0.496).

As seen in Table 2, the mean peri-operative blood loss between group 1 and group 2 was found to be statistically significant (p= 0.006, 0.001, 0.001).

Table 3 shows the no of patients who required blood transfusion in the peri-operative period. Intra-operative transfusion between group 1 and group 2 was found to be statistically insignificant(p=0.34), but post-operative transfusion between group 1 and group 2 was found to be statistically significant(p=0.02).

Table 4 shows the comparison of post-operative haemoglobin level between group 1 and group 2. In this period, the 2nd and 4th day haemoglobin levels were found to be statistically significant between group 1 and group 2.

Table 1 : Comparison of demographic characteristics of patients among groups.

Characteristics	Group 1 N=20 (Mean± SD)	Group 1N=20 (Mean± SD)	p value
Age (years)	56.05± 3.74	57.3±2.4	0.217
Weight (Kgs)	65.85± 4.96	68.5±5.21	0.108
ASA Grade 1 Grade 2	 8 12	 9 11	1.0

Table 2: Comparison of peri-operative blood loss between group I and group II.

Blood loss	Group 1 N=20 (Mean ± SD)	Group 2 N=20 (Mean ± SD)	p value
Intraop blood loss	435.25 ±124.15	566.25±156.59	0.006
Postop blood loss	206.25±29.77	274.75±34.96	0.001
Total blood loss	641.0±141.18	841.0±183.78	0.001

Table 3: Comparison of number of patients requiring blood transfusion between groups.

Blood transfusion	Group 1 N=20	Group 2 N=20	p value
Intraop transfusion	1	4	0.34
Postop transfusion	8	15	0.02

Table 4 : Comparison of postoperative haemoglobin levels between groups I and II.

Post op values	Group 1 N=20 (Mean ± SD)	Group 2 N=20 (Mean ± SD)	p value
Haemoglobin 2nd day	9.93±0.92	8.7±0.79	0.011
Haemoglobin 4th day	9.51±0.55	8.6±1.55	0.024
Haemoglobin 6th day	9.28±0.42	9.0±0.24	0.108

DISCUSSION:

Replacement surgery is commonly associated with significant blood loss which exposes the patients to develop post-operative anaemia. Severity of anaemia is directly related to reduced patient's functional recovery and increased morbidity and mortality(8). Blood transfusion, particularly in replacement surgeries, is associated with its own complications. Apart from non-pharmacological techniques such as maintaining normothermia, pharmacological measures are also available for reducing blood loss both during intra-operative as well as post-operative periods(15). An array of antifibrinolytics are commonly used during the peri-operative period and comprise drugs such as aprotonin, epsilon aminocaproic acid (EACA) and TXA.

TXA, a well-known fibrinolytic inhibitor, has been shown to reduce blood loss in surgical procedures in several studies conducted across the world. The antifibrinolytic effect of tranexamic acid results from the formation of a reversible complex of the drug with plasminogen(6). TXA does not bind to serum albumin and seems to be fully accounted for by its binding to plasminogen(7). Only a small fraction of the drug is metabolized in the human body(8). TXA is generally well tolerated and the same effect that makes it help to prevent or stop bleeding also may cause blood clots that could be dangerous(12,13).

Cochrane et al. conducted a review study comparing TXA with aprotinin as antifibrinolytics used for minimising peri-operative allogenic blood transfusion in 2005. They found that aprotinin reduced the rate of packed cell volume transfusion by a relative 30% and TXA by a relative 34%. They also found that epsilon aminocaproic acid use resulted in a statistically nonsignificant reduction in red blood cell transfusion(17).

Orpen NM, Little C et.al conducted a prospective, randomized, double blind, controlled trial study on the effect of TXA on total knee arthroplasty in 2006. They found that TXA significantly reduced the amount of blood loss in the early post-operative period. They also concluded that TXA was effective in reducing the post-operative blood loss(18).

Role of TXA on hip replacement surgeries became popular because of its antifibrinolytic activity and reduction in surgical blood loss. Rajesparan K, et.al studied the effect of an intravenous bolus of TXA on blood loss in total hip replacement in 2009. They concluded that TXA reduced the early post-operative blood loss and total blood loss but not the intra-operative blood loss. The TXA group required fewer transfusions and had no increased incidence of deep-vein thrombosis(19).

Jansen A.J et al. conducted a randomized double blind placebo controlled trial of TXA in total knee arthroplasty in 1999. They studied 42 patients who underwent unilateral bicondylar knee arthroplasty. Average blood loss measured at 72 hrs was 678 ml (range 40-1560ml) in the TXA group and 1419 ml (range 675ml - 3020ml) in the placebo group. Blood loss on discharge was reduced to 58% in the TXA group (p<0.001). Need for blood transfusion was greater in the control group with 13 out of 21 patients receiving a mean of 1.5 units of blood transfusion, compared with only two out of 21 patients receiving blood

transfusion in the TXA group(16).

Benoni G et al. conducted a randomized double bind placebo control study of blood conservation with TXA in total hip replacement in 2001. Totally 40 patients were included in their study. Total average blood loss was 745ml in the TXA group and 996ml in the placebo group. They concluded that prophylactic administration of TXA reduces the total blood loss in hip replacement surgeries and reduces the transfusion requirements by upto 60%(10).

In hip fracture surgery, transfused patients are at a higher risk of post operative infection and use of TXA reduces the transfusion requirements. Zufferey P.J et al, conducted a randomized controlled trial on TXA in hip fracture surgery in 2009. In their study, 57 patients were randomized to receive TXA and 53 patients to receive placebo. Totally 24 out of 57 patients received transfusion in TXA group and 32 out of 53 patients received transfusion in placebo group. They concluded that in hip fracture surgery, TXA reduces erythrocyte transfusion requirements and had no increased incidence of deep-vein thrombosis (14).

Considering the limitations of our study, we have not included elderly patients above the age of 60 years as they are more prone to haemodynamic instability, as well as patients belonging to ASA III and IV category in our study.

CONCLUSION:

TXA significantly reduced the amount of blood loss during & after the joint replacement surgeries. Moreover TXA use was not associated with any adverse drug reaction like nausea, vomiting, diarrhoea, hypotension, seizure or thrombosis in our study patients which encourages its safe use in such surgeries.

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Conflicts of interest:
There are no conflicts of interest.

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