

Effectiveness of a standard protocol for tranexamic acid administration in total hip and knee arthroplasty - does it make a difference?

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Background: Intraoperative blood loss plays a key role in the outcome of any surgery and is most important during the immediate post-operative period in the management, for both the operating surgeon and the anesthetist. **Methods:** The primary aim of the study was to prove the efficiency of standardized tranexamic acid administration in reducing blood loss and need for blood transfusion in total knee and hip arthroplasty by comparing postoperative hemoglobin levels, peri-operative hemoglobin drop and frequency of blood transfusion in 2 groups one receiving and the other not receiving tranexamic acid during the peri-operative period. **Results:** The mean pre-operative hemoglobin in the tranexamic acid group was 13.45 and in the control group was 13.0 with a p-value of 0.267, The mean hemoglobin level as on a postoperative day 1 in the tranexamic acid group was 12.32 and in the control group was 10.78 with p-value <0.001. **Conclusion:** The use of standardized Tranexamic acid infusion during the perioperative period of Total Hip and Knee Arthroplasty reduced the perioperative blood loss which was evident by high mean postoperative hemoglobin levels and low mean postoperative hemoglobin drop and decreased need for blood transfusion in Tranexamic acid group when compared to the control group.

Keywords: Total Knee Arthroplasty, Total Hip Arthroplasty, Tranexamic Acid

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Introduction

The number of Total Knee Arthroplasty (TKA) and Total Hip Arthroplasty (THA) has been markedly increasing in the last few decades due to an increase in life expectancy [1]. The evolving nature of mankind in pursuing improved quality of life demands precision in the protocol for arthroplasty, and thus it emerged as the most performed surgery in the western world and India [1].

Total hip replacement has been widely acclaimed as the "Operation of the century" and Substantial blood loss in perioperative and postoperative periods is inevitable and it affects the outcome of surgery and may result in increased morbidity, mortality, and length of hospital stay [2]. Thus, it becomes mandatory to control the blood loss to improve the outcome of surgery and to decrease the disability days and the economic burden of patients. Several methods of conservation of blood have been used that include autologous blood transfusion, Intra-operative blood salvage, medical management by use of erythropoietin, and antifibrinolytic agents [3,4].

Blood transfusion can be accompanied by rare, life-threatening complications, including acute and delayed hemolytic reactions, acute lung injury, and disease transmission [5]. Several observational studies have raised concerns over the association of blood transfusion with poorer outcomes after surgery, such as including longer length of hospital stay, economic concerns, increased infections, and mortality [6]. Various studies have assessed the effectiveness of antifibrinolytics (Tranexamic acid TXA) in patients of Total Knee Arthroplasty and Total Hip Arthroplasty which showed promising results [7].

Anti-Fibrinolytic action of TXA and aprotinin has been proven to reduce blood loss in surgeries [8] and TXA is cheaper and more specific fibrinolytic inhibitor than aprotinin and has been shown to reduce blood loss in arthroplasties [9,10]. The efficacies of TXA in TKA and THA remains uncertain due to varied protocol of administration (time and dosage of administration of TXA) and have yielded contrasting results varying from decreased blood loss, decreased blood transfusion requirements to no difference in perioperative blood loss and even increased transfusion requirements [11-13].

This prompted us to evaluate the efficacy of TXA with a standardized protocol of administration.

Material and Methods

This prospective randomized study was conducted in the Department of Orthopaedics, Medical Trust Hospital, Ernakulam, Kerala from December 2016 to Dec.2017. Institutional Ethical committee permission was obtained for the Study. Written consent was obtained for the study.

Inclusion criteria

01. Patients age between 30-80 years who are undergoing THA and
02. Patients with weight 50-100
03. Patients with the ability to provide informed consent and to co-operate with the

Exclusion criteria

01. Patients with major co-morbidities.
02. Patients with renal
03. Patients with abnormal liver
04. Patients with a major neurological

The study interventions were perioperative standard 1gm intravenous Tranexamic acid infusion with 100ml NS (Tranexamic Acid Group/TXA group) versus No-tranexamic acid [Control group].

Patients will be included, evaluated, and studied after explaining the procedures in detail and after getting the patient's consent. A total of n=41 patients have been included in the study and were studied.

Patients are randomized using the numbers generated in the range from 0 to 99 by a computer software program (Microsoft Excel), each time when a patient is enrolled in the trial, a generated random number is allotted, such that patients with even numbers were taken for Tranexamic acid group (TXA Group) and odd numbers were taken for Control group.

Table 1: Blood transfusion protocol.

Hemoglobin levels	Blood transfusion
<8 mg/dl	Blood transfusion irrespective of signs and symptoms of low volume
8 mg/dl -10 mg/dl	Blood transfusion only if patients were symptomatic
>10 mg/dl	No transfusion

All patients undergoing TKA and THA were receiving a standard perioperative dose of 1gm of Tranexamic acid given intravenously with 100ml Normal saline

Immediately after spinal anesthesia, preoperative hemoglobin levels (at 12 hours prior to surgery) and postoperative hemoglobin levels are recorded (at 6 hours postoperatively, 24 hours and 72 hours thereafter) and compared with patients who have not received tranexamic acid, frequency of blood transfusion in both the groups were noted and compared. Standard institutional blood transfusion protocols were followed in all patients regardless of the diagnosis (Primary OA, RA, Post Traumatic OA), TKA is done by medial Parapatellar approach, a tourniquet was used for all patients, no drain was used in THA irrespective of diagnosis and was done through standard lateral approach in the lateral position without a drain, other perioperative interventions such as spinal anesthesia, prophylactic antibiotics, knee prostheses, and hip prostheses and thromboprophylaxis were kept similar in all patients. Post-operatively all patients will undergo the same standardized rehabilitation protocol.

Parameters observed

01. Preoperative hemoglobin levels of all the patients of Tranexamic acid group and control group (at 12 hours prior to surgery),
02. Postoperative hemoglobin levels of both the groups (at 6 hours postoperatively, 24 hours and 72 hours thereafter),
03. Frequency of blood transfusions in both the groups,
04. Complications if any in patients who were given Tranexamic acid and those who are undergoing blood transfusion (observed for a period of 30 days).

Patients did not receive any premedication. In both treatment groups, paracetamol 1 g iv infusion 8 hourly and after 48 hours converted to Oral tablet Aceclofenac 100 mg 12 hourly and capsule Omeprazole 20 mg once a day. Opioid (Tramadol Hydrochloride 50mg) with centrally acting anti-emetic Ondansetron 4 mg SOS is used as rescue analgesia. 2nd generation cephalosporin and aminoglycoside will be used as prophylactic antibiotics as intravenous (IV) perioperatively and for every 12 hours for the first 48 hours of surgery. For thromboprophylaxis, Injection Dalteparin 2500 IU subcutaneously once each evening (at 6 pm) will be given till the day of discharge from the postoperative day (POD)-0. Bilateral flowtron pumps were also used for all the patients. Range of movement exercises was started from day 1,

Patients are made to stand and walk on flat ground on POD 1 and climb steps on POD 2. Suture removal was done on the 14th postoperative day. Patients were followed on an outpatient basis after 1 month followed by every 2 months for one year. The technique of giving Tranexamic Acid: All the patients who included in the tranexamic acid group received a standard dose of 1 gm of tranexamic acid diluted in 100 ml of normal saline and given over 10 minutes, immediately after spinal anesthesia. Two vials of tranexamic acid each 500 mg were used. The statistical analysis will be performed by IBM SPSS Statistics 20 version Categorical variables will be described as frequency and percentage.

Results

A total of n=41 patients underwent THA and TKA during the study period and were eligible for inclusion in the study. N=20 patients in the group were given Tranexamic Acid prior to the commencement of surgery after spinal anesthesia, and n=21 patients were not given Tranexamic acid. The mean age of patients in Tranexamic Acid Group [TXA group] is 60.40±12 and the Control Group is 60.23±12.31. The difference between the two groups was not statistically significant (P = 0.967). The sex distribution among TXA Group and Control Group was comparable and there was no significant difference 0.09.

Table 2: Comparison of age between the two groups of the study.

Study Group	Mean ±S.D	P-Value
Control Group	60.23±12.31	0.967
TXA Group	60.40±12.84	

Table 3: Comparison of sex between the TXA group and the control group.

Study Group	Sex		Total
	Female	Male	
Control Group	13	8	21
TXA Group	17	3	20
Total	30	11	41

P-value = 0.09

Table-4: Distribution of surgical procedure in the study group.

Study Group	LEFT		RIGHT		TOTAL
	THR	TKR	THR	TKR	
Control group	3	4	5	9	21
TXA group	5	3	3	9	20
Total	8	7	8	18	41

In this prospective randomized controlled study, evaluation, and comparison of the efficiency of 'single, standard Intravenous dose of Tranexamic acid' in the group of 41 patients who underwent THA and TKA was done. There was no significant difference in the demographic profile including age, sex, and diagnosis of the subjects compared, ensuring comparability and matching between the two groups i.e. Tranexamic Acid Group and Control Group. Postoperative hemoglobin levels on a postoperative day [POD] 1 and postoperative day [POD] 3 were higher in subjects undergoing THA and TKA who were receiving Standard Intravenous dose of 1gm tranexamic acid than subject undergoing THA and TKA and not receiving tranexamic acid when compared individually, and their Mean implied the same results.

The hemoglobin decrease from preoperative level to postoperative day 1 and postoperative day 3 was less in subjects undergoing THA and TKA and receiving Standard intravenous dose of 1gm tranexamic acid than subjects undergoing THA and TKA and not receiving tranexamic acid when compared individually and their Mean implied the same results.

Table-5: Mean hemoglobin level of both the groups at POD 1 and POD 3.

Mean ±S.D		P-Value
Postoperative Day 1		
Control group	10.78±1.36	<0.001
TXA group	12.32±1.34	
Postoperative Day 3		
Control group	9.31±1.40	<0.001
TXA group	11.75±1.35	

Table-6: Requirements for blood transfusion in both groups.

Study Group	Blood Transfusion		Total
	No	Yes	
Control group	18	3	21
TXA group	20	0	20
Total	38	3	41

Discussion

The need for blood transfusion during the postoperative period in the group receiving tranexamic acid during the perioperative period was nil when compared with the control group not receiving perioperative tranexamic acid. The findings of the present study were in agreement with Hiippala S et al; [14] in their prospective,

Randomized, double-blind study, had investigated the effect of Tranexamic acid on blood loss and transfusion requirements associated with total knee arthroplasty group and concluded that tranexamic acid reduced perioperative blood loss and transfusion requirements associated with TKA.

Johansson T et al; [15] investigated the effects of a single bolus of 15 mg/kg IV TXA given at the start of the primary THA and found a significant reduction in both blood loss and the need for postoperative transfusion. Alvarez JC et al; [16] in a prospective, randomized, double-blinded study, assessed the effectiveness of IV TXA in patients undergoing primary TKA and receiving 10 mg/kg of IV TXA before tourniquet release, supplemented by a 1 mg/kg/h infusion for 6 hours postoperatively.

The TXA-administered group showed a significant reduction in blood loss and transfusion requirements. There were no significant differences in venous thromboembolic events in the TXA group compared with the control group. Similarly with Zufferey PJ et al; [17] conducted on a variety of hip fracture types, shows a decreased number of transfusions in the TXA group, however, this did not have statistical significance. Similarly with Alshryda S et al; [18] compared topical tranexamic acid versus normal saline administration in n=161 patients undergoing unilateral primary THA.

A total of n=81 patients received normal saline, and n=80 patients received 1g of topical TXA. The TXA group had a higher post-operative hemoglobin level and a significant decrease in the transfusion rate from 32.1% to 12.5% in the group receiving 1g of topical TA, though his study used topical tranexamic acid rather than Intravenous Tranexamic acid, the efficiency of tranexamic acid in reducing blood loss and hemoglobin decrease and Blood transfusion requirements can be confirmed.

In the present study, patients treated with TXA never required transfusions, and there were no differences in symptomatic thromboembolic events within 30 days of surgery between patients who received TXA and those who did not. And especially in high-risk patients, TXA was not associated with an increase in symptomatic thromboembolic events. Thus, it facilitated them to mobilize early and to return to normal daily activities faster, thereby reducing the duration of hospital stay and days of disability. Similar results were observed in blood loss and venous thromboembolic events by Wei Z et al; [19] who conducted a meta-analysis that

Combined all data from available randomized controlled trials, regardless of the methods of TXA administration, which included intravenous, intra-articular, topical or oral. CD Watts et al; [20] (2017) in their study 138 patients presented with a low-energy, isolated, Fracture neck of femur treated with either hemi or total hip arthroplasty. In the TXA group, patients received 2 doses of 15mg/kg intravenous TXA dissolved in 100 ml of saline; each administered over 10 minutes; 1 dose just before incision, and the second at wound closure.

In the placebo group, 100 ml of saline solution was administered similarly. There was a trend toward decreased transfusion rate in the TXA group (17% vs. 26%, $P = 0.22$). TXA was safe with no differences in adverse events at 30 and 90 days and concluded that the TXA administration safely reduces blood loss with a tendency for decreased transfusion rate and total blood product consumption for patients undergoing hip arthroplasty for acute fracture neck of femur. More studies are needed to further ascertain the role of TXA in the management of patients with Fracture neck of femur.

Conclusion

The use of a standard protocol and dose of intravenous tranexamic acid during the perioperative period of THA and TKA reduced the perioperative blood loss which was evident by higher mean postoperative hemoglobin levels and low mean hemoglobin drop thus decreasing the need for blood transfusion in the Tranexamic acid group when compared to the control group.

What does the study add to the existing knowledge?

Thus, the administration of Tranexamic acid greatly reduces the complications, morbidity, and duration of hospital stay and decreases the disability period thereby improving the standard of arthroplasty and quality of life.

Author's contribution

All the authors, **Dr. Ram Sudhan S., Dr. Srinivas Karthick, Dr. Vijetha Nagendra, Dr. Jithesh Asokan, Dr. Vinod George, Dr. Jacob J.** jointly collaborated during the study design, conduct of the study, statistical analysis and during the manuscript preparation.

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