DOI: 10.7860/JCDR/2023/60311.17837

Original Article

Anaesthesia Section

Comparison of Intravenous Tranexamic Acid versus Combined Intravenous and Local Infiltration of Tranexamic Acid in Reducing Perioperative Blood Loss in Patients Undergoing Primary Unilateral Total Hip Arthroplasty: A Randomised Clinical Study

T SITA RAO[1], MONU YADAV[2], AKHYA KUMAR KAR[3], D PADMAJA[4]

ABSTRACT

Introduction: The use of Tranexamic Acid (TXA) in primary unilateral Total Hip Arthroplasty (THA) is well documented. However, considering the potential side effects including deep vein thrombosis and pulmonary embolism, the ideal route of administration of TXA to patients undergoing THA is still not known.

Aim: To compare the efficacy of single dose intravenous (i.v.) TXA administration versus combined intravenous and local infiltration of TXA in reducing the perioperative blood loss in primary unilateral THA patients.

Materials and Methods: This prospective, randomised clinical study, was conducted in the Department of Anaesthesiology and Critical Care at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, between October 2020 to May 2021. 60 patients were randomly allocated into two groups: the combined group C (i.v. administration of 10 mg/kg of TXA combined with local infiltration of 600 mg TXA diluted to 60 mL with normal saline) and the single i.v. group S (i.v. administration of 10 mg/kg of TXA). The perioperative blood loss was calculated in terms of three variables- intraoperative blood loss, drainage blood loss and total blood loss. The number of postoperative blood transfusions noted. Student's t-test and Fischer's-exact tests were applied for statistical analysis.

Results: A total of 60 patients scheduled to have primary unilateral THA. Both the groups were similar in demographic features, baseline biochemical values and procedural distribution. There was a statistically significant reduction in the (mean±SD) intraoperative blood loss (697.26±221.43 mL), drain blood volume (254.66±81.36 mL) and total blood loss (952.26±263.57 mL) in the combined group C when compared to the single group S. There was no statistically significant difference (p-value=0.671) in the postoperative blood transfusion rate between the two groups.

Conclusion: Intravenous combined with local infiltration of TXA significantly reduced the perioperative blood loss in patients undergoing primary unilateral THA when compared to single dose intravenous administration of TXA.

Keywords: Blood volume, Blood transfusions, Haemorrhage

INTRODUCTION

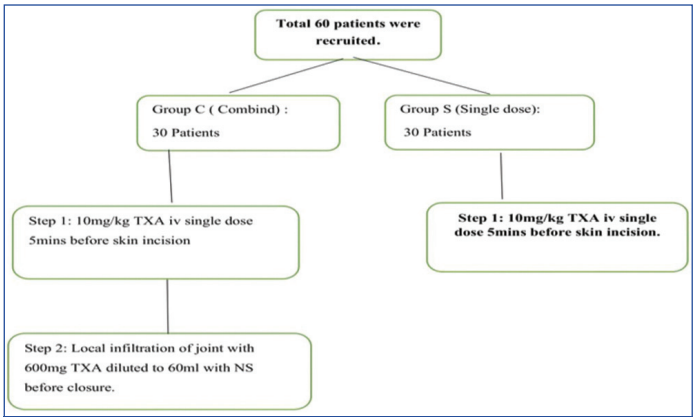
The total hip arthroplasty is the most common operative procedure for osteoarthritis of hip joint. It is associated with high perioperative blood loss, which leads to a longer hospital stay, impedes rehabilitation and may be poorly tolerated by patients with cardiovascular diseases. It is estimated that 65% of blood loss in THA occurs within the first eight hours after surgery and often leads to significant postoperative anaemia and many patients need peri and postoperative blood transfusion [1]. Different blood conserving techniques, such as autologous blood transfusion or autologous fibrin tissue application, have been used in clinical practice to reduce the postoperative blood transfusion rates. Autologous transfusion reduces the risks of infection, but is also expensive [2].

To minimise blood loss, hypotensive anaesthesia is also used. Another method for control of the perioperative blood loss is the application of antifibrinolytic agents including aprotinin, TXA and epsilon-aminocaproic acid. Among them TXA has been gaining popularity in recent years. TXA is an inhibitor of fibrinolysis and an activator of plasminogen that is known to inhibit blood loss in various surgical settings [1]. Many previous studies have demonstrated that the administration of TXA reduced postoperative blood loss and the transfusion rate after THA [1-3]. The majority of these studies utilised single or repeated intravenous administration of TXA [2]. Some researchers have recently shown that local application of TXA to the joint (such as wound irrigation or intra-articular injection or infiltration) at the time of surgery might be safer and easier route of administration that could achieve results similar to those of i.v. administration [4,5]. They proposed that the use of local TXA might be preferable because of the potential reduction in systemic side effects such as deep vein thrombosis and pulmonary embolism. In addition, local TXA administration might reduce joint swelling, improve wound healing, and permit rapid rehabilitation. The authors hypothesised that topical TXA administration could reduce intraoperative and drainage blood loss and the i.v. method could reduce hidden and systemic blood loss. Hence, this prospective randomised study was planned, to compare the effects of combined intravenous and local administration of TXA versus intravenous administration alone in primary THA patients in reducing the perioperative blood loss and need for post operative blood transfusion as primary and secondary outcome measures of the study.

MATERIALS AND METHODS

A randomised controlled study was conducted in Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India, between October 2020 to May 2021 on 60 patients undergoing unilateral THA, after

obtaining the approval of the Institutional Ethics Committee (IEC approval letter no. EC/NIMS/2509/2020). They were randomly allocated into 2 groups (30 each) by computer generated simple randomisation [Table/Fig-1]. Depending on the group the respective steps will be followed. Depending on the group the respective steps will be followed.



[Table/Fig-1]: Methodology.

Sample size calculation: Let δ be the smallest difference between the means of two samples and S be the combined standard deviation of the two samples. The desired sample size to compare the significant difference between the means of two samples at α% level of significance with the 1-β power of test is given by the formula: $n=f(\alpha,\beta)*2S2/\delta2$. In other words, it is assumed/derived from the previous articles [6] that the average blood loss in Group I (single i.v. group) is 1002.62±366.85 mL and in group II (placebo group) is 1221.11±386.25 mL. let δ=225 mL be the smallest difference between the means of two groups and sS=300 be the combined standard deviation of the two groups. The desired sample size to compare the significant difference between the means of two groups at α=5% level of significance with the 80% (1-β) power of test is given by:

n=7.9*{2*(300*300)}/(225*225)=7.9*{180000}/50625=7.9*3.5=28.08

Thus, the final sample size included in the present study was 30 [Table/Fig-1].

Inclusion criteria: Patients of either sex, age, aged 18-70 years, who gave written informed consent and fulfilled the criteria of American Society of Anesthesiologists (ASA) grade 1 and 2 were included.

Exclusion criteria: Subjects with acute infections, allergy to TXA, renal dysfunction, hepatic dysfunction, obese (body mass index >30 kg/m^2), patients with h/o epilepsy, hypercoagulation, haemophilia, deep vein thrombosis, or pulmonary embolism, stroke or cerebrovascular disease, myocardial infarction and h/o treatment with warfarin, heparin or oestrogen before surgery were excluded from the study.

Study Procedure

All the patients were premedicated with tab. ranitidine 150 mg and tab. alprazolam 0.25 mg (unless contraindicated) per orally on the night before and on the morning of surgery. After confirming NBM status, patients were shifted into operation theatre, standard monitors were connected and baseline vitals recorded. Two 18 G cannulas secured under strict aseptic precautions. Intravenous fluid was connected and antibiotic administered. After combined spinal epidural, patients were positioned. All the patients of group C and group S were given 10 mg/kg of TXA i.v. as single dose, five minutes before skin incision. Towards the end of the surgery only in group C patients' joint were infiltrated with 600 mg of TXA diluted to 60 mL with normal saline before closure.

Total blood loss was calculated as sum of intraoperative blood loss and drain blood volumes on postoperative days 1, 2 and 3. Intraoperative blood loss included blood loss in mops (weight of all the wet mops using digital weighing scale minus weight of the same number of dry mops), blood loss in suction apparatus (Total volume of fluid in suction apparatus minus volume of irrigation fluid used) and miscellaneous losses in drapes etc., Total volume of intraoperative fluids and blood administered was noted. Any episodes of hypotension were noted. In postoperative period also, any transfusion of blood or blood products were noted.

Blood transfusion protocol: Blood transfusion was indicated when the haemoglobin concentration was <100 g/L or when a patient developed any anaemia related organ dysfunction, such as alteration in mental status or palpitations or sustained hypotension (regardless of haemoglobin concentration).

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences (SPSS) version 22.0, and R environment version 3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in n (%). Significance is assessed at 5% level of significance. The assumptions made on data were, that dependent variables were normally distributed, samples were randomly drawn from the population. Student's t-test two-tailed, independent) was used to find the significance among the study parameters on continuous scale between two groups (Intergroup analysis) on metric parameters. Leven's test for homogeneity of variance was performed to assess the homogeneity of variance. Fisher's-exact test was used when cell samples were very small.

RESULTS

Were included in the study after the application of the inclusion and exclusion criteria and with the informed consent of the patients. These patients were randomly allocated to the combined group C and the single group S of 30 patients in each group. The data collected was analysed using the above mentioned statistical methods [Table/Fig-1].

Demographic parameters age and gender and procedure distribution [Table/Fig-2] were comparable in group C and group S, no statistical significance (p>0.05). Baseline biochemical parameters [Table/Fig-3] of group C and group S were comparable with no statistically significant difference (p>0.05).

There was statistically significant reduction in intraoperative blood

Variables		Group C	Group S	Total	p-value
Age in years	≤30	4 (13.3%)	0 (0%)	4 (6.7%)	0.436 (Student's t test- on mean values)
	31-40	9 (30%)	7 (23.3%)	16 (26.7%)	
	41-50	5 (16.7%)	13 (43.3%)	18 (30%)	
	51-60	7 (23.3%)	6 (20%)	13 (21.7%)	
	>60	5 (16.7%)	4 (13.3%)	9 (15%)	
	Total	30 (100%)	30 (100%)	60 (100%)	
	Mean±SD	45.80±12.55	48.03±9.27	46.91±11.00	
Gender	Female	13 (43.3%)	9 (30%)	22 (36.7%)	0.284 (Chi-square test)
	Male	17 (56.7%)	21 (70%)	38 (63.3%)	
	Total	30 (100%)	30 (100%)	60 (100%)	
Procedure	LT THR	12 (40%)	16 (53.3%)	28 (46.7%)	0.301 (Chi-square test)
	RT THR	18 (60%)	14 (46.7%)	32 (53.3%)	
	Total	30 (100%)	30 (100%)	60 (100%)	

[Table/Fig-2]: Distribution of patients according to age, gender and procedure.

Variables	Group C	Group S	Total	p-value
Hb (gm%)	13.68±1.46	13.82±1.69	13.75±1.56	0.745
Haematocrit (%)	41.03±4.08	40.80±5.07	40.91±4.56	0.845
Platelet count (lacs/mm^3)	287033.33±6432.18	260800.00±7644.90	273916.66±71386.34	0.156
PT (Seconds)	12.24±0.80	12.09±0.71	12.16±0.75	0.438
APTT (Seconds)	28.99±3.40	28.28±3.35	28.64±3.36	0.417
INR (Ratio)	1.07±0.11	1.06±0.09	1.06±0.10	0.625
Baseline SBP (mmHg)	141.83±13.96	141.23±13.82	141.53±13.77	0.868
Baseline DBP (mmHg)	81.20±8.64	80.60±9.76	80.90±9.14	0.802

[Table/Fig-3]: Comparison of clinical variables (Student's t-test).
Hb: Haemoglbin; PT: Prothrombin time; APTT: Activated partial thromoplastin time; INR: International normalised ratio; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

loss (p=0.013), drain volume (p=0.006) and total blood loss (p=0.004) in group C when compared to group S. There was no statistically significant difference (p=0.671) in the postoperative blood transfusion rate between the two groups [Table/Fig-4].

Variables	Group C (30 patients)	Group S (30 patients)	Total	p-value
Intraoperative BL	697.26±221.43	877.46±314.72	787.36±284.67	0.013*
Drain volume	254.66±81.36	314.00±79.37	284.33±85.12	0.006**
Total BL	952.26±263.57	1191.46±353.04	1071.86±331.59	0.004**
Patients required postoperative blood transfusion	2	4		
Transfusion rate	6.67%	13.34%		0.671 (Fisher's-exact test)

[Table/Fig-4]: Comparison of Intraoperative BL, Drain volume, Total BL (Student's t-test) and postoperative blood transfusion (Fisher's exact Test); BL: Blood loss

DISCUSSION

The potential mechanism and advantage of local TXA administration are that, it directly targets the site of bleeding and inhibits local fibrinolytic activity, which helps to prevent fibrin clot dissolution and increases the volume and strength of the TXA at the raw surgical surfaces [7,8]. Compared with i.v. TXA, local application has the advantages of being easier to administer, providing a maximum concentration of TXA at the bleeding site, lowering the absorption of TXA, reducing joint swelling, and improving wound healing [9,10]. It was reported that TXA could maintain a biological half life of 2 to 3 hours within joint fluid and enhance microvascular haemostasis [10]. The methods and effect of local TXA administration were unclear. Some authors have reported that, local administration of TXA reduces blood loss and the transfusion rate but not to a statistically significant extent, and they hypothesised that i.v. administration is a more predictable route for maximum efficacy [9]. Other researchers found a significant increase in the prevalence of deep vein thrombosis, pulmonary embolism, and cerebrovascular strokes in patients who received i.v. TXA during hemiarthroplasty surgery [11,12].

With the background mentioned above, a randomised clinical study was done to discover whether the combined i.v. and local TXA administration could reduce blood loss and the transfusion rate in patients undergoing primary unilateral THA. The results showed that, 600 mg local infiltration of TXA combined with 10 mg/kg of i.v. TXA was more efficacious in reducing perioperative blood loss than a single dose of 10 mg/kg i.v. TXA in patients undergoing a primary unilateral THA. With THA, the majority of the blood loss occurs from the acetabular preparation, broach preparation of the femoral canal, and wound surface haemorrhage. The present study and previous studies (showed local TXA administration to be a useful method in THA. Local TXA administration directly targets the bleeding site in a surgical wound and reduces the intraoperative and drainage blood loss. The routine dose of i.v. TXA in THA is 10 to 15 mg/kg of body weight, five minutes before the skin incision, and the concentration of TXA in the plasma was found to remain above the minimum therapeutic level for approximately three hours after such i.v. administration. The authors found that, the topical TXA administration could reduce intraoperative and drainage blood loss and the i.v. method could reduce hidden and systemic blood loss, Thus, accepting the hypothesis. In a randomised controlled trial of 101 patients, who underwent THA, Yue C et al., found that a high dose (3 g) of local TXA significantly reduced the transfusion rate from 22.4% (in a placebo group) to 5.8% without increasing complications [13]. Huang Z et al., performed a randomised controlled trial, in which 184 patients were enrolled, to determine the efficacy and safety of combined i.v. and topical application of TXA in unilateral total knee arthroplasty compared with the efficacy and safety of i.v. TXA only [14]. They found that adding 1.5 g of local TXA to 1.5 g of i.v. TXA was as effective as 3 g of i.v. TXA in reducing the transfusion rate and total blood loss without sacrificing safety. A network meta-analysis by Fillingham YA et al., also concluded that, irrespective of route, dosage or time of administration the use of TXA to reduce blood loss and risk of transfusion after primary THA [15].

In present study, also similar benefit, with significant reduction of total blood loss with i.v. as well as local filteration of TXA in THA surgery were noted. However, comparison of the postoperative blood transfusion rate in the two groups did not yield any statistically significant difference. Some authors recommended that, the dose of topically administered TXA be >2 g to play its role in reducing blood loss and the transfusion rate [9]. However, this recommendation was meant for a single-TXA-use strategy (i.v. or topical) and is not suitable for combined strategy. The maximum dose of TXA was approximately 2.5 g in the previous studies [7]. In present trial, 600 mg of TXA was used locally and 10 mg/kg was used for i.v. administration, a total dose of TXA of approximately 1.5 g. It was hypothesised that, it would be safer to use this lower dose, rather than 2.5 g, for the combined TXA strategy. Poeran J et al., studied if there is any association between TXA use and increased postoperative complications in high-risk patients and concluded that, TXA is effective in reducing postoperative blood transfusions, and is not associated with increased complications, even in high-risk patients undergoing hip or knee arthroplasty [16].

Limitation(s)

The limitation of the present study is that, it does not allow to reach conclusions regarding the comparative safety of the two regimens because of lack of long term follow-up for incidence of deep vein thrombosis and pulmonary embolism. Also, a larger sample size might demonstrate a statistically significant difference in the postoperative blood transfusion rate between the two groups.

CONCLUSION(S)

In conclusion, 10 mg/kg of i.v. TXA combined with 600 mg of local TXA in patients undergoing primary unilateral THA significantly reduced perioperative blood loss, compared with a single i.v. dose of TXA. The postoperative blood transfusion rate between the two groups were similar.

REFERENCES

[1] Xu HD, Zhou ZK, Pei FX, Hu X, Zhou Z, Pei F. Perioperative efficiency and safety of different regimen of tranexamic acid on total knee arthroplasty. Chin J Orthop. 2014;34:599-604.
[2] Zhou XD, Tao LJ, Li J. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. Arch Orthop Trauma Surg. 2013;133:1017-27.
[3] Zhang XC, Sun MJ, Pan S, Rui M, Zhao FC, Zha GC, et al. Intravenous administration of tranexamic acid in total hip arthroplasty does not change the blood coagulopathy: a prospective thrombelastography analysis. J Orthop Surg (Hong Kong). 2020;28(3):2309499020959516.

[4] Furqan A, Hafeez S, Khan F, Orakzai SH, Nur AN, Khan MA. Intra-articular Versus Intravenous Tranexamic Acid in Primary Total Knee Replacement. Cureus. 2022;14(1):e21052.
[5] Coelho M, Bastos C, Figueiredo J. Total knee arthroplasty: superiority of intra-articular tranexamic acid over intravenous and cell salvage as blood sparing strategy-a retrospective study. J Blood Med. 2022;13:75-82.
[6] Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P. Tranexamic acid administration in primary total hip arthroplasty: a randomized controlled trial of intravenous combined with topical versus single-dose intravenous administration. J Bone Joint Surg Am. 2016;98(12):983-91.
[7] Morrison RJM, Tsang B, Fishley W, Harper I, Joseph JC, Reed MR. Dose optimisation of intravenous tranexamic acid for elective hip and knee arthroplasty: The effectiveness of a single pre-operative dose. Bone Joint Res. 2017;(8):499-505.
[8] Gilbody J, Dhotar HS, Perruccio AV, Davey JR. Topical tranexamic acid reduces transfusion rates in total hip and knee arthroplasty. J Arthroplasty. 2014;29(4):681-84.
[9] Wind TC, Barfield WR, Moskal JT. The effect of tranexamic acid on transfusion rate in primary total hip arthroplasty. J Arthroplasty. 2014;29(2):387-89.
[10] Martin JG, Cassatt KB, Kincaid-Cinnamon KA, Westendorf DS, Garton AS, Lemke JH. Topical administration of tranexamic acid in primary total hip and total knee arthroplasty. J Arthroplasty. 2014;29(5):889-94.
[11] Emara WM, Moez KK, Elkhouly AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of postoperative bleeding in hemiarthroplasty. Anaesth Essays Res. 2014;8(1):48-53.
[12] Zufferey PJ, Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, et al. Tranexamic acid in hip fracture surgery: a randomized controlled trial. British Journal of Anaesthesia. 2010;104(1):23-30.
[13] Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthro- plasty. 2014;29(12):2452-56.
[14] Huang Z, Ma J, Shen B, Pei F. Combination of intravenos and topical appli- cation of tranexamic acid in primary total knee arthroplasty: a prospective random- ized controlled trial. J Arthroplasty. 2014;29(12):2342-46.
[15] Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total hip arthroplasty: a network meta-analysis. J Arthroplasty. 2018 Oct;33(10):3083-3089.
[16] Poeran J, Chan JJ, Zubizarreta N, Mazumdar M, Galatz LM, Moucha CS. Safety of tranexamic acid in hip and knee arthroplasty in high-risk patients. Anaesthesiology. 2021;135(1):57-68.

PARTICULARS OF CONTRIBUTORS:
1. Senior Resident, Department of Anaesthesiology and Critical Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
2. Additional Professor, Department of Anaesthesiology and Critical Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
3. Associate Professor, Department of Anaesthesiology and Critical Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
4. Professor and Head, Department of Anaesthesiology and Critical Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Monu Yadav,
Additional Professor, Department of Anaesthesiology and Critical Care,
Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
E-mail: monubalbir@yahoo.co.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Sep 30, 2022
- Manual Googling: Mar 22, 2023
- iThenticate Software: Apr 08, 2023 (17%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Sep 18, 2022**
Date of Peer Review: **Dec 08, 2022**
Date of Acceptance: **Apr 10, 2023**
Date of Publishing: **May 01, 2023**