Global Journal of Medicine & Public Health

A comparative study of effect of tranexamic acid (TXA) parenteral versus local administration in reducing blood loss in total knee replacement

Chiranjeevi Varudu[1]*, *Srikanth Matha*[1], *Paavan Kanoboyina*[1]

ABSTRACT

Background

Total knee arthroplasty (TKA) is a common orthopaedic surgery that results in significant blood loss due to extensive soft tissue release and bone cuts. The aim of this study is to compare blood loss between parenteral intravenous (IV) administration and local intra-articular (IA) administration of tranexamic acid (TXA), in patients undergoing primary total knee arthroplasty.

Methods

This present study was carried out at the Orthopaedics Department, Maharaja Institute of Medical Sciences and General Hospital (MIMS), Vizianagaram, India, between January 2019 and June 2020 using prospective observational study methods. Fifty patients who presented to the outpatient department with grade 3 and grade 4 Kellgren & Lawrence System of classification for osteoarthritis requiring surgical intervention were included: 25 in the intra-articular group (IA) and 25 in the intravenous group (IV). Chi-square tests and independent sample t-tests were used to calculate statistical significance of the results. Pre-operative haemoglobin levels were assessed using a haematocrit test. Haemoglobin and haematocrit levels were noted before surgery and 24 hours after surgery.

Results

No significant difference was observed between intra-articular vs intravenous TXA in terms of mean post-op haemoglobin, haematocrit and mean fall in haemoglobin using a haematocrit test in both groups ($p<.001$).

Conclusion

TXA can be given through local or parentral route during surgery. Both routes of administration are equally efficacious. The IA route is preferred over IV due to a lower risk of side effects, including deep vein thrombosis (DVT), cerebrovascular accidents (CVA), and pulmonary embolisms (PE), than with IV. Administration of intra-articular TXA after TKR is gaining in popularity and our study shows there is no statistically significant difference in efficacy noted between IA and IV routes.

Keywords: Tranexamic acid, Total knee arthroplasty, Osteoarthritis, Kellgren & Lawrence System, Haemocrit

GJMEDPH 2021; Vol. 10, issue 3 | OPEN ACCESS

[1] Orthopaedics Departments, Maharaja Institute of Medical Sciences and General Hospital (MIMS), Vizianagaram, India

***Corresponding author** Chiranjeevi Varudu, Room 508, Doctors Quarters, Besides Girls Hostel, Engineering Campus, Gitam, Yendada, Visakhapatnam, Andhra Pradesh, chiru.varudu@gmail.com

Conflict of Interest—none | Funding—none

INTRODUCTION

Total knee arthroplasty (TKA) is a prominent orthopedic surgery that involves significant blood loss due to extensive soft tissue release and bone cuts. Blood loss ranges from 800ml–1800ml,[1,3] making bleeding one of the main concerns in elective TKA. Total blood loss comprises visible blood loss from the surgical field as well as wound drainage and blood loss into the tissues, which is hidden. Excessive bleeding may lead to swelling, arthrofibrosis, haematoma and seroma formation, increased blood in the drain, post-operative pain, delayed healing and a requirement for increased blood transfusions.[2,4,5] Different strategies to minimize per-operative blood loss include peri-operative blood donation, peri-operative red cell salvage, fibrin sealants, deliberate hypotension, haemodilution and recombinant erythropoietin. The discovery of hyperfibrinolysis as the essential physiological mechanism behind excessive bleeding has led to the advent of several pharmacological approaches including the use of aprotinin, tranexamic acid (TXA), and aminocaproic acid.

The purpose of our study is to compare the efficacy of intravascular (IV) and intra-articular (IA) TXA administration in reducing the extent of peri-operative blood loss, as reflected by changes in parameters including haemoglobin concentration using a hematocrit test and the necessity for blood transfusions. TXA, a synthetic amino acid, functions by competitive inhibition of plasminogen conversion into plasmin, which helps clot stabilization.[6,7] It is a useful antifibrinolytic, helpful in reducing blood loss and the need for transfusions, and is not associated with increased thromboembolic complications.[8]

Senior surgeons can choose to administer tranexamic acid intravenously, topically or orally.[8] With regard to total knee arthroplasty involving TXA, the main focus of studies has been on the intravenous route, though spraying of topical TXA has proved to be equally productive and safer as far as common post-operative problems such as deep vein thrombosis (DVT), cerebrovascular accidents (CA) and pulmonary embolisms (PE) are concerned. The efficacy of existing evidence contains some controversy, however: some studies show no difference between parenteral IV and local IA routes in terms of blood loss.[8] Other studies show significant differences and advocate for IA application,[9-12] or report the IV route to be better and associated with significantly lower perioperative blood loss.[13-16]

Tranexamic Acid was first described in the 1960s[17] as a medication used to prevent excessive blood loss from major surgery, trauma, tooth removal and nose bleeds. It is an antifibrinolytic that can be administered by oral, IV (parenteral administration), or IA route (local administration). It inhibits plasmin formation and displaces plasminogen from the fibrin surface. At higher concentrations, it directly inhibits plasmin and partially inhibits fibrinogenolysis but has a contraindication of severe renal impairment, a history of arterio/venous thromboembolism, seizures, and allergic reactions as well as the DVT, CVA and PE side effects mentioned above. It can also cause nausea, headaches and vomiting.

METHODS AND MATERIALS

All patients with grade 3 and 4 Kellgren-Lawrence osteoarthritis, who presented to Maharaja Institute of Medical Sciences and General Hospital, Vizianagaram, India to undergo total knee arthroplasty between January 2019 and November 2020 (a period of 23 months) were included in this study. The study design is a prospective observational randomised clinical trial. Patients were randomised into two groups: Local administration (IA group), containing 25 patients, and parenteral administration (IV group), also containing 25 patients. Investigations such as X-ray of knee joint (standing); chest X-ray; anterior-posterior and lateral view; complete blood count; C-Reactive Protein; renal function test; random blood sugar levels; serum electrolytes, ECG, throat swab, cultures of blood/urine/sputum, and a gynaecological examination in the case of female patients, were carried out.

Patients were included if they were over 52 years of age, had an X-ray showing grade 3 and 4 arthritic changes with both or unilateral involvement and no relief of symptoms following at least six months of conservative treatment, had gross reduction in a

range of movements, displayed pain on a visual analogue Scale > 7/8 and were willing to undergo surgery and post-operative lifestyle modifications. Patients were excluded if they were under 52 years old, were medically unfit for surgery, had an active infection, existing cardiac disease, CVA or tumours.

All the patients were evaluated with AP and lateral view X-rays of knee joints, pre-operative haemoglobin (recorded using haematocrit test before surgery) and postoperative haemoglobin, (recorded using haematocrit test 24 hours after surgery). Two equal-sized treatment groups were made by random allocation of patients. In the IA group, patients received 2g of TXA in 20 ml solution injected into the joint and periarticular soft tissue by syringe after the prosthesis was inserted and cemented. In the IV group, patients received an intravenous dose of 1g TXA, administered 5–10 min before incision and 1g TXA before closure.

Pneumatic tourniquet inflation was carried out before administration. In all TKA replacement procedures under a high thigh tourniquet, a midline medial parapatellar approach was used, routine bone cuts were made, patella debulking and denervation was undertaken, and tibia and femoral components were cemented. PCL-sacrificing posterior stabilised knee prosthesis was used in all patients, either under spinal anesthesia or general anesthesia, always combined with an epidural. The tourniquet was deflated before the closure of the wound and haemostasis was achieved. A drain was not used in either group. After layered closure and intra-articular injection in the IA group, a compression bandage was given with the knee in extension; this stayed for about eight hours post-operatively. DVT prophylaxis comprised low molecular weight heparin, started 12 hours preoperatively and was continued for 30 days after the surgery was performed.

Outcome variables were mean post-operative haemoglobin levels, haematocrit test scores and mean a fall in haemoglobin and heamatocrit measured 24 hours after surgery. Numerical variables including age, BMI, haematocrit score, pre-operative and post-operative haemoglobin levels. The fall in haematocrit and haemoglobin levels are described as mean ± S.D. A p-value ≤0.05 was considered statistically significant for comparing the mean of variables in the study groups. An independent sample t-test was applied. Categorical variables such as gender are described in percentages and as a frequency. In order to minimize bias, a standard technique was used and a single orthopedic surgeon performed all the procedures.

Post-operative protocol

All the patients received a single dose of 3rd generation cephalosporin (injected ceftriaxone) just before incision and 3 oral doses of 3rd generation cephalosporin (tablet cefixime). DVT prophylaxis was also given to all patients. Wounds and dressings were checked on the first and second day following the operation for all patients. During the first post-operative day, patients were encouraged to undertake quadriceps strengthening exercises and active knee mobilization. Supportive ambulation using a walker was allowed. Suture removal was carried out between 10 and 12 days following the operation and patients were discharged.

RESULTS

Statistics and visualization were produced for the 50 patients, 25 in the IA group and 25 in the IV group. Chi-square test, independent sample t-tests were used for calculation. The age of study participants ranged from 52-78 years, with a mean age of 61.1 years. The mean age of the patient in the IA group was 60.7 years and in the IV group it was 61.4 years, p-value=0.658, which was not significant. The age of patients in both groups was thus comparable (Table 1).

Table 1 Age distribution of study participants

Group	n=50	Mean	Std. deviation	p value
Intra-articular	25	60.68	5.056	0.658
Intravenous	25	61.36	5.729	

Table 2 Comparing the pre-operative and post-operative HCT values (IA vs IV)

	Group	n	Mean	Std. deviation	p value
Pre-op HCT	Intra-articular	25	10.392	65	0.148
	Intravenous	25	10.0172	0.82511	
Post-op HCT	Intra-articular	25	34.57	1.02	0.785
	Intravenous	25	34.49	1.044	

Table 3 Comparing the pre-operative and post-operative Hb values (IA vs IV)

	Group	N	Mean	Std. deviation	p value
Pre-op Hb	Intravenous	25	12	0.8524	0.931
	Intravenous	25	12.02	0.7773	
Post-op Hb	Intra-articular	25	10.392	0.97165	0.148
	Intravenous	25	10.0172	0.82511	

Table 4 Outcome values of fall in HB and fall in HCT

	Group	N	Mean	Std. deviation	p value
Fall in Hb	Intravenous	25	1.608	0.5322	0.254
	Intravenous	25	1.768	0.4795	
Fall in HCT	Intra-articular	25	2.4604	0.81217	0.125
	Intravenous	25	2.272	0.58844	

Out of the 50 study participants, 19 were male, and 31 were female (9 males and 16 females in the IA group; 10 males and 15 females in the IV group). The p-value (p=0.771) of this is not significant.

Thirty-three of the patients had a right leg TKR, and 17 had the procedure on their left leg. This gave a p-value of 0.7652, which is also not significant for comparing the groups.

The BMI of the patients ranged from 24.3kg\m2 to 34.0kg\m2. The difference in mean BMI values of both groups was not significant (p=0.265).

The p-value for the difference between the pre-operative IA and IV groups for HCT is 0.148, which is not significant, nor is the p-value for the two groups post operation, at 0.785. The outcome values are therefore comparable (Table 2).

The p-value for pre-operative Hb differences between the two groups is 0.931, which is not significant; nor is the p-value for post-op Hb between the groups (p=0.148). Hence the outcome values are again comparable between the two groups (Table 3).

The p-value for the fall in Hb between the two groups is 0.254. This is not statistically significant. Nor is the p-value for fall in HCT, at 0.125, statistically significant. Hence the outcome values of fall in Hb and fall in HCT are comparable (Table 4).

DISCUSSION

Total knee replacement is a valuable surgical procedure to relieve pain and disability, by replacing the weight-bearing surface of the knee joint. It is mainly performed for osteoarthritis and also for other diseases including psoriatic arthritis and rheumatic arthritis. This surgery can carry a high risk of complications in patients with severe deformity from advanced osteoarthritis, trauma or long-standing rheumatoid arthritis. The most common indication for total knee replacement is osteoarthritis. Various factors are associated with the onset and progression of clinical osteoarthritis. Different measures to reduce operative blood loss have been employed in orthopedic surgery to reduce the need for transfusion. The standard technique is transfusion of autologous blood that reduces the risk of infection but it is expensive and is only available in a few centres in India that have the appropriate facilities.

Tranexamic acid has gained importance in total knee replacement surgery in recent years as it can be given through both intra-articular and intravenous routes during surgery; however, the selection of the route of administration is controversial as the available evidence is contradictory. It is therefore useful to compare our results to those of some of the previous studies that have been undertaken.

In the present study, we observed that the mean age of the patient was 61.04 ± 5.3 years. This is younger than in a study by Habib et al., which reported a mean age of 67.3 ± 8.2 years at the military hospital, Lahore, and also in a study by Suhail Amin et al, which recorded a similar mean age[18]. Khan et al. reported a mean age of 64 ± 3 years in Gurkhi Teaching Hospital, Lahore and Obaid-Ur-Rahman et al recorded 64 ± 8.4 years in TKR patients at the Military Hospital, Rawalpindi. Keyhani et al., and Sarzeem et al[19] reported mean ages of 67 ± 11.9 years and 67.5 ± 7.6 years in Iran; Seo et al[11] of 67.5 ± 6.6 years in Korea; Maniar et al[13] of 67 ± 7.96 years in India and Pinsornsal et al[20] of 67.63 ± 7.96 years in Thailand. The cohort in this study therefore seems somewhat younger than the global average, for which we offer no explanation. It was beyond the scope of the study.

We observed no significant difference between IA and IV routes of tranexamic acid administration in terms of mean post-operative Hb, HCT and mean fall in Hb and HCT. A similar result in mean post-operative HCT between an IA and IV TXA group was recorded by Suhail Amin et al,[18] [34.8±1.66 vs 34.73±1.27]. The value recorded in our study [34.58±1.02 vs 34.49±1.04] is similar to other studies such as one by Aguleria et al. [34.69±3.42 vs 34.05±4.53]. The difference between mean post-op HCT with intra-articular and intravenous tranexamic acid was not significant and is similar to results recorded by Tzatzairiuis et al [32.44±3.3 vs. 30.9±3.11], Drosos et al. [33.19±2.9 vs. 32.4±5.20] and Pinsornsat et al[20] [31.0±2.7 vs. 31.8±3.4].

We observed a 1:1 male:female ratio of patients undergoing TKR. Suhail Amin et al[18] recorded a male to female ratio of 1:3.7; Chen et al. of 1:4 in Singapore, Digas et al. of 1:3.3 and Drosos et al of 1:4 in Greece. Pinsornsak et al[20] reported a male to female ratio of 1:5, while Aggarwal et al reported a male predominance in India of 1.9:1. We offer no explanation for the differences recorded in these studies to ours: further research would be needed.

This is the first time a study of this type has been conducted in our region. We conclude that intra-articular and intravenous routes of TXA administration are equally efficacious. In our opinion, this means that the intra-articular route should be favoured as it avoids possible complications associated with IV administration of TXA including DVT, CVA, PE and myocardial infraction. IA TXA was found to be as effective and as safe as IV administration in reducing primary blood loss during TKR. It is easy and convenient to use IA administration of TXA in place of IV administration in TKR.

CONCLUSION

Tranexamic acid is a synthetic amino acid, which functions by competitive inhibition of plasminogen conversion to plasmin, thus promoting clot stabilization. The main aim of our study was to reduce peri-operative blood loss and to decrease the total number of blood transfusions needed as part of the surgical procedure process. The main method of controlling blood loss is the application of anti-fibrinolytic agents that include aprotinin, epsilon-amino caproic acid and tranexamic acid. Among these, TXA has gained the maximum attention amongst the medical profession. It can be given through local or parentral during surgery. Though both routes of administration are equally efficacious, IA is preferred over IV as it is less associated with side effects including PE, DVT and CVA.

We found no statistically significant difference between blood loss or clotting using IA or IV routes. We therefore recommend that IA administration of tranexamic acid after total knee arthoplasty should be preferred in future practice. We recognise that our study contains only a small number of cases and was conducted over a short time period, and therefore requires follow-up with further study.

REFERENCES

1. Cushner FD, Friedman RJ. Blood loss in total knee arthroplasty. Clin Orthop Relat Res. 1991;(269):98 101
2. Weiss A-PC, Krackow KA. Persistent wound drainage after primary total knee arthroplasty. J Arthroplasty. 1993;8:285-289.
3. Sehat KR, Evans R, Newman JH. How much blood is really lost in total knee arthroplasty? Correct blood loss management should take hidden loss into account. Knee. 2000;7:151–155.
4. Dennis DA. Wound Complications in Total Knee Arthroplasty. Knee Arthroplasty: Springer; 2001.
5. Spahn DR, Moch H, Hofmann A, et al. Patient blood management: the pragmatic solution for the problems with blood transfusions. Anesthesiology. 2008;109:951-953.
6. Danninger T, Memtsoudis SG (2015) Tranexamic acid and orthopedic surgery—the search for the holy grail of blood conservation. Ann Translat Med 3(6), 77.
7. Pabinger I, Fries D, Schöchl H, Streif W, Toller W (2017)Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr 129(9), 303–316.
8. May JH, Rieser GR, Williams CG, Markert RJ, Bauman RD,Lawless MW (2016) The assessment of blood loss during total knee arthroplasty when comparing intravenous versus intracapsular administration of tranexamic acid. J Arthroplasty 31(11),2452–2457.
9. Aggarwal AK, Singh N, Sudesh P (2016) Topical vs. intravenous tranexamic acid in reducing blood loss after bilateral total knee arthroplasty: a prospective study. J Arthroplasty 31(7), 1442–1448.
10. Digas G, Koutsogiannis I, Meletiadis G, Karamoulas V, BikosCh (2015) Intra-articular injection of tranexamic acid reduce blood loss in cemented total knee arthroplasty. Eur J Orthop Surg Traumatol 25(7), 1181–1188.
11. Seo JG, Moon YW, Park SH, Kim SM, Ko K.R. (2013) Thecomparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 21(8), 1869–1874.
12. Wang J, Wang Q, Zhang X, Wang Q (2017) Intraarticular application is more effective than intravenous application of tranexamic acid in total knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 32(11), 3385–3389.
13. Maniar RN, Kumar G, Singhi T, Nayak RM, Maniar PR (2012) Most effectve regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res 470(9), 2605–2612.
14. Lacko M, Cellar R, Schreierova D, Vasko G (2017) Comparisonf intravenous and intra-articular tranexamic acid in reducing blood loss in primary total knee replacement. Eklem Hastalik Cerrahisi 28(2), 64–71.
15. Sarzaeem MM, Razi M, Kazemian G, Moghaddam ME, RasiAM, Karimi M (2014) Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. J Arthroplasty 29(8), 1521– 1524.
16. Triyudanto AN, Lubis AM (2017) The effects of intra-articulartranexamic acid given intraoperatively and intravenous tranexamic acid given preoperatively on post surgical bleeding and transfusion rate post total knee arthroplasty. Med J Indonesia 25(4), 234–239
17. Sophia binz et al , Jonathan MC collester, Scott Thomas, Joseph miller, CRASH 2 Study of tranexamic acid to treat bleeding in trauma patients.
18. Amin MS, Habib KM & Rehman AU (2020) Comparison of blood loss between intra-articular and intra-venous administration of tranexamic acid in primary total knee arthroplasty. SICOT-J 6, 20
19. Keyhani S, Esmailiejah AA, Abbasian MR, Safdari F (2016) Which route of tranexamic acid administration is more effective to reduce blood loss following total knee arthroplasty? Arch Bone Jt Surg 4(1), 65–69.
20. Pinsornsak P, Rojanavijitkul S, Chumchuen S (2016) Periarticular tranexamic acid injection in total knee arthroplasty: a randomized controlled trial. BMC Musculoskelet Disord 17, 313.