



OUTCOMES OF MULTIMODAL COCKTAIL VS TRANEXAMIC ACID ON POST OPERATIVE PAIN AND BLOOD LOSS IN TOTAL KNEE REPLACEMENT PATIENTS: A PROSPECTIVE RANDOMIZED STUDY

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Abstract:

Background: Osteoarthritis is the most common form of arthritis and a leading cause of disability. Total knee replacement (TKR) is one of the most effective surgical procedures, providing improvement in function and relief of pain for the majority of patients. Intra-articular tranexamic acid [TXA] and multimodal cocktail (mixture of ketorolac, tramadol and bupivacaine) are commonly used drugs which help to reduce postoperative bleeding and pain respectively, improving outcome of surgery.

Objective: To compare the postoperative blood loss and pain with or without Intra-articular tranexamic acid and multimodal cocktail respectively in patients undergoing total knee replacement

Material and Methods: A total of 96 patients of either gender presenting to Orthopaedics department of Government Medical College, Amritsar, with knee osteoarthritis and planned to undergo total knee replacement were enrolled. Patients were divided into 3 groups. Group A being the control group was not given tranexamic acid [TXA] but only standard drugs for anesthesia. Group B patients were given 3gm intra-articular injection of tranexamic acid. Group C patients were given a multimodal cocktail (mixture of ketorolac, tramadol and bupivacaine). TKR was done and patients were followed-up for 72 hours. Blood loss and pain score after every 24 hours for 72 hours were noted. Intra-articular injections were given just before wound closure.

Results: The mean age of patients in control group was 48.92±13.22years, in TXA group was 52.31±14.69 years and in cocktail group was 50.22±9.63years. The male to female ratio was 11:21, 14:18 and 10:22 in three groups respectively. The total blood loss during first 72 hours was 1030.1±177.27ml in control group, 453.7±80.4ml in TXA group while 607.7±122.5ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p < 0.05$). The mean postoperative pain score during first 72 hours was 4.4±2.3in control group, 2.4±1.5 in TXA group while 1.8±1.0in cocktail group. The difference was significant in all three groups ($p < 0.05$) but insignificant between TXA and cocktail group ($p > 0.05$).

Conclusion: Results showed that intra-articular injection of TXA is beneficial in reducing blood loss and postoperative pain in comparison to control group. While pain was better controlled with the multimodal cocktail compared to TXA group and control group.

Keywords: Post-operative blood loss, Intra-articular injection, tranexamic acid, cocktail, total knee replacement

Introduction:

Osteoarthritis [OA] is the most common form of arthritis and a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease. The pain experienced in knee osteoarthritis transitions over time from intermittent weight-bearing pain to a more persistent, chronic pain.¹ Overall prevalence of osteoarthritis in some population studies was 14.8%, where 10.5% of individuals reportedly having knee osteoarthritis and 8.5% reportedly having hip osteoarthritis. Differences in prevalence were found for males and females across age categories for both knee and hip Osteoarthritis.²

Pathological changes in the late stage of OA include softening, ulceration, and focal disintegration of the

articular cartilage. Synovial inflammation also may occur in chronic cases even though it's classified as non inflammatory arthritis. Typical clinical symptoms are pain, particularly after prolonged activity and weight-bearing; whereas stiffness is experienced after inactivity. It is a degenerative arthritis, which may also affect the hands, feet, spine, and large weight-bearing joints, such as the hips and knees.³

Total knee replacement (TKR) is one of the most effective surgical procedures, providing improvement in function and relief of pain for the majority of patients.⁴ The development of TKR is characterized by the manufacturing of appropriate interposition materials, clinical application of knee biomechanics and the use of secure and reliable methods of component fixation. From the introduction of resection and interposition arthroplasty procedures to the

introduction of polycentric and geometric knees, significant improvements and important innovations have been made.⁵ Soft tissue balancing is crucial to the success of TKR and for creating a rectangular flexion joint gap, the rotation of the femoral component is important.⁶

Intravenous tranexamic acid is commonly used in a severely bleeding patient requiring massive transfusion protocols or when hyper-fibrinolysis is demonstrated. Various studies have found tranexamic acid to improve survival when administered within three hours of the injury in a patient population with significant hemorrhage. It should be noted that tranexamic acid is an anti-fibrinolytic and not a pro-coagulant.^{7, 8} Tranexamic acid has been used to reduce blood loss and the subsequent need for transfusion in orthopedic, spinal, cardiac and orthognathic surgery.⁹

TXA is a synthetic reversible competitive inhibitor to the Lysine receptor found on plasminogen. The binding of this receptor prevents plasmin (activated form of plasminogen) from binding to and ultimately stabilizing the fibrin matrix. TXA used for hereditary angioedema works by its indirect effect of reducing complement activation. By reducing plasmin activity, it reduces the consumption of C1 esterase inhibitor.¹⁰

The aim of this study was to find the more beneficial regimen to reduce the blood loss as well as postoperative pain after TKR. Some work has been done in this regard and no trial has been found in which TXA and a multimodal cocktail of ketorolac, tramadol and bupivacaine were compared. So this study would add information regarding efficacy of different regimens.

Objective:

To compare the postoperative blood loss and pain with or without Intra-articular tranexamic acid and a multimodal cocktail in patients undergoing total knee replacement.

Material and Methods

Study Design: Randomized Controlled Trial

Setting: Department of Orthopedics, Govt. Medical College, Amritsar.

Study Duration: Six months i.e. from August 2019 to January 2020.

Sample Size: Sample Size of 96 cases with 3 groups, 32 subjects in each group was calculated with 95% confidence level, 80% power of study and taking magnitude of mean blood loss i.e. 1131±336ml without TXA and 921±252ml with TXA in patients undergoing TKA.

Sampling technique: Non-probability consecutive sampling

Inclusion Criteria: Patients of age 40-70 years of either gender presenting with knee osteoarthritis and planned to undergo total knee replacement.

Exclusion Criteria: Patients with INR > 2 or PT > 15 sec, taking statins or aspirin, cardiac disease, Systemic lupus erythematosus, anemia (hH < 10g/dl), IV drug abuser, alcohol user, thalassemia or leukemia, thrombocytopenia, idiopathic thrombocytopenic purpura were excluded.

Data Collection Procedure: All the patients who meet inclusion criteria of this study, were enrolled from Department of Orthopedics, GMC, Amritsar. Informed consent was taken from the parents. Then patients were divided randomly in three groups. Group A was given only standard drugs for anesthesia. Group B, patients were given 3gm intra-articular injection of tranexamic acid. Group C patients were given intra-articular cocktail (mixture of ketorolac 30mg in 1mL, tramadol 100mg in 1mL and bupivacaine 0.5% 5mL). The surgeries were done under general anesthesia by a single surgical team with assistance of a researcher with use of tourniquet. After surgery, patients were moved to post-surgical care unit. Patients were followed-up for next 72 hours. Blood loss and VAS pain score after every 24 hours were noted.

Data Analysis: Data was analyzed by using SPSS Version 22. Mean and standard deviation were calculated for age, blood loss and pain. Frequency and percentage were tabulated for gender, diabetes and hypertension. ANOVA was applied to compare mean blood loss and pain score in all three groups setting p-value ≤ 0.05 as significant.

Results:

The mean age of patients in control group was 48.92±13.22 years, in TXA group was 52.31±14.69 years and in cocktail group was 50.22±9.63 years. The male to female ratio was 11:21, 14:18 and 10:22 in three groups respectively. The mean BMI of patients was 30.25±12.36 kg/m², 28.56±9.41 kg/m² and 27.44±5.69 kg/m², respectively. There were 27 (84.4%) hypertensive patients in control group, 24 (75.0%) in TXA group while 29 (90.6%) in cocktail group. There were 24 (75.0%) diabetic patients in control group, 21 (65.6%) in TXA group while 25 (78.1%) in cocktail group. Table 1

The mean blood loss during first 24 hours was 320.1±25.97 ml in control group, 147.2±23.2 ml in TXA group while 203.6±33.6 ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group (p < 0.05). The mean blood loss during first 48 hours was 489.7±88.4 ml in control group, 210.9±49.6 ml in TXA group while 296.3±79.1 ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group (p < 0.05). The mean blood loss during first 72 hours was 220.3±62.9 ml in

control group, 95.6±7.6ml in TXA group while 107.8±9.8ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p<0.05$). The mean total blood loss during first 72 hours was 1030.1±177.27ml in control group, 453.7±80.4ml in TXA group while 607.7±122.5ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p<0.05$). The mean postoperative pain score during first 24 hours was 1.9±0.4 in control group, 0.6±0.2 in TXA group while 0.5±0.1 in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p<0.05$). The mean postoperative pain score after 48 hours was 3.2±1.4 in control group, 2.1±1.1 in TXA group while 1.7±0.8 in cocktail group. The difference was significant in all three groups ($p<0.05$) but insignificant between TXA and cocktail group ($p>0.05$). The mean postoperative pain score after 72 hours was 4.4±2.3 in control group, 2.4±1.5 in TXA group while 1.8±1.0 in cocktail group. The difference was significant in all three groups ($p<0.05$) but insignificant between TXA and cocktail group ($p>0.05$). Table 2

Table 1: Demographics of patients

	Control	TXA	Cocktail
N	32	32	32
Age (years)	48.92±13.22	52.31±14.69	50.22±9.63
Male	11 (34.4%)	14 (43.8%)	10 (%)
Female	21 (65.6%)	18 (56.2%)	22 (%)
BMI	30.25±12.36	28.56±9.41	27.44±5.69
Hypertension	27 (84.4%)	24 (75.0%)	29 (90.6%)
Diabetes	24 (75.0%)	21 (65.6%)	25 (78.1%)

Table 2: Comparison of outcome in groups

Outcome	Control	TXA	Cocktail	p-value
N	32	32	32	
Blood loss (ml)				
24 hour	320.1±25.97	147.2±23.2*	203.6±33.6	<0.0001
48 hour	489.7±88.4	210.9±49.6*	296.3±79.1	<0.0001
72 hour	220.3±62.9	95.6±7.6*	107.8±9.8	<0.0001
Total blood loss (ml)	1030.1±177.27	453.7±80.4*	607.7±122.5	<0.0001
Pain score (VAS)				
24 hour	1.9±0.4	0.6±0.2*	0.5±0.1	<0.0001
48 hour	3.2±1.4	2.1±1.1!	1.7±0.8	<0.0001
72 hour	4.4±2.3	2.4±1.5!	1.8±1.0	<0.0001

* showed significant difference in TXA and cocktail group ($p<0.05$)

! Showed insignificant difference in TXA and cocktail group ($p>0.05$)

Discussion:

TKR is among the most commonly performed orthopedic procedures. With the ageing of the population, increase in life expectancy and our ability to more effectively manage comorbidities in the perioperative period, the number of

people undergoing joint replacement surgery has been steadily increasing over the last decades and that trend is going to continue into the foreseeable future. Only in the US it is estimated that by the year 2030 almost 3.5 million total knee arthroplasties will be performed annually.¹¹

Multiple analgesic techniques have been used for patients undergoing TKR like intrathecal morphine, epidural or femoral nerve block, intraarticular drug infusion, and periarticular multimodal drug injection (anesthetic cocktail). Periarticular multimodal drug injection is being used more frequently and several studies showed its ability to provide postoperative pain control and reduced narcotic-related side effects by minimizing narcotic consumption.¹²

Various "cocktails" have been suggested for the local injections. Most include a long-acting local anesthetic along with epinephrine and other additives such as opioids or ketorolac, corticosteroids, and various antibiotics¹³⁻¹⁵. Previous clinical trials showed a blood conservation level of 15% upon intravenous administration of TXA in minimally invasive TKR patients¹⁶. However, the efficacy in terms of reducing blood loss by topical application of TXA in minimally invasive TKR patients is still unclear. Moreover, the patients in most of the studies that have analyzed the blood conservation effect of topical TXA administration in TKR were not receiving modern oral anticoagulants for thromboprophylaxis.¹⁷

Blood transfusion after orthopaedic surgery accounts for 10% of all packed red blood-cell transfusions, but use varies substantially across hospitals and surgeons. Transfusions can cause systemic complications, including allergic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, graft-versus-host disease, and infections. TXA is a new cost-effective blood management tool to reduce blood loss and decrease the risk of transfusion after total joint arthroplasty. Current clinical evidence does not justify transfusions for a hemoglobin level of >8 g/dL in the absence of symptoms. Studies have also supported the use of this trigger in patients with a history or risk of cardiovascular disease.¹⁸

In our trial, the mean blood loss during first 24 hours was 320.1±25.97ml in control group, 147.2±23.2ml in TXA group while 203.6±33.6ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p<0.05$). The mean blood loss during first 48 hours was 489.7±88.4ml in control group, 210.9±49.6ml in TXA group while 296.3±79.1ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p<0.05$). The mean blood loss during first 72 hours was 220.3±62.9ml in control group, 95.6±7.6ml in TXA group while 107.8±9.8ml in cocktail group. The difference was significant in all three

groups and also between TXA and cocktail group ($p < 0.05$). The mean total blood loss during first 72 hours was 1030.1 ± 177.27 ml in control group, 453.7 ± 80.4 ml in TXA group while 607.7 ± 122.5 ml in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p < 0.05$).

Yen t al., found that the mean blood loss was 1131 ± 336 ml in placebo group while 921 ± 252 ml with intravenous TXA while 795 ± 231 ml with topical TXA. The difference was significant ($p < 0.01$). Authors concludes that an equal efficacy of TXA in blood conservation when administered intravenously or topically in minimally invasive TKA patients receiving rivaroxaban for thromboprophylaxis.¹⁷

The mean postoperative pain score during first 24 hours was 1.9 ± 0.4 in control group, 0.6 ± 0.2 in TXA group while 0.5 ± 0.1 in cocktail group. The difference was significant in all three groups and also between TXA and cocktail group ($p < 0.05$). The mean postoperative pain score after 48 hours was 3.2 ± 1.4 in control group, 2.1 ± 1.1 in TXA group while 1.7 ± 0.8 in cocktail group. The difference was significant in all three groups ($p < 0.05$) but insignificant between TXA and cocktail group ($p > 0.05$). The mean postoperative pain score after 72 hours was 4.4 ± 2.3 in control group, 2.4 ± 1.5 in TXA group while 1.8 ± 1.0 in cocktail group. The difference was significant in all three groups ($p < 0.05$) but insignificant between TXA and cocktail group ($p > 0.05$).

Recent reviews and meta-analyses have found no increased risk of thromboembolic events and renal failure with systemic TXA administration.¹⁹ The largest such analysis in orthopedic patients was recently published by Poeran and colleagues. In a retrospective cohort study encompassing over 870,000 cases of elective total knee or hip arthroplasty in 510 US hospitals perioperative intravenous TXA administration was not associated with increased risk of complications including a composite of thromboembolic complications, acute renal failure, cerebrovascular events, myocardial infarction and in-hospital mortality. Besides adding incremental evidence of safety of TXA use in orthopedic patients this study is also significant because patients receiving intravenous TXA were stratified into groups according to dose categories (none, $\leq 1,000$, 2,000 and $\geq 3,000$ mg). TXA use was significantly associated with a decreased need for allogeneic or autologous blood transfusions [odds ratio (OR) varying from 0.31-0.38 by dose category], and allogeneic blood transfusions (OR, 0.29-0.37), with no significantly increased risk for complications: thromboembolic complications (OR, 0.85-1.02), acute renal failure (OR, 0.70-1.11), combined complications (OR, 0.75-0.98), and admission to an intensive care unit (OR, 0.73-1.01). The authors concluded that 2,000 mg TXA seemed to have the best effectiveness and safety profile.²⁰

In a recently published meta-analysis of 14 randomized controlled trials which investigated the effect of TXA on blood loss, it was observed that indirect comparison of placebo-controlled trials of topical and intravenous TXA indicates that topical administration is even superior to the intravenous route without any significant difference in complication rates.²¹

In a prospective randomized controlled study investigating various TXA routes of administration and dosage regimens Maniar and colleagues found a single topical dose of TXA to be more effective compared to a single systemic dose. However, the same study concluded that the most effective TXA dosage regimen consists of two intravenous doses, a preoperative one followed by an intraoperative one.²²

In 2013, Kim et al., performed another RCT to analyze the efficacy of TXA in reducing blood loss and transfusion rates in unilateral TKA and bilateral TKA. They included 180 patients who underwent unilateral TKA and 146 patients who underwent bilateral TKA. The results showed that TXA use decreased the total blood loss, but its effects on transfusion rate may vary; the transfusion rate decreased when TXA was used during bilateral TKA, but there was no effect in unilateral TKA.²³

Like Kim et al.²³, Kakar et al.²⁴ conducted a similar study, but with 24 patients who underwent unilateral TKR and 26 patients who underwent bilateral TKR. This aspect differs from the conclusion by Kim et al.,²³ which only demonstrated this reduction in patients who underwent the bilateral procedure. This divergence may be related to sample size. The protocol for application and dosage of TXA also differed significantly between the studies.²⁴

Shi et al., conducted a trial on TXA alone versus cocktail of 3g TXA plus 0.25mg diluted-epinephrine; 1:200,000. It was found that the topical administration of cocktail wine significantly reduced total blood loss ($P = 0.007$) and blood loss ($P = 0.000$). Therefore, the hemostatic effect of topical TXA plus diluted-epinephrine was better than TXA alone. Their combination does not produce severe adverse reactions, and can be used as an important method to reduce blood loss after TKR.²⁵

Conclusion:

Results showed that application of intraarticular injection of TXA is more beneficial in reducing blood loss when compared to the control group. Pain was more controllable with cocktail of ketorolac, tramadol and bupivacaine. In future, we can use the TXA with a bipronged aim for reduction of blood loss per operative and in drain post operatively and cocktail (ketorolac, tramadol and bupivacaine) for effective post operative pain relief.

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