Evaluation of Effect of Intra-articular Injection of Tranexamic Acid in Arthroscopic Anterior Cruciate Ligament Reconstruction.

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The Egyptian Orthopedic Journal; 2021 supplement (1), June, 56: 12- 18

Abstract:

Background:
Arthroscopic anterior cruciate ligament reconstruction (ACLR) often results in rapid recovery and return to preinjury activities; however, postoperative hemarthrosis and swelling can lead to pain, decreased range of motion, and delayed rehabilitation and return to work and sports activities.

Aim of the work:
To evaluate the effect of intra-articular injection of tranexamic acid (TXA) in patients receiving arthroscopic anterior cruciate ligament reconstruction (ACLR).

Study Design:
A prospective randomized controlled clinical trial, Level of evidence, II.

Patient and Methods:
50 patients who underwent arthroscopic ACL reconstruction (ACLR) were enrolled in this study in the period from October 2019 and April 2020. Single-bundle reconstructions using autologous hamstring tendon grafts were performed in all patients. Patients were randomized into two groups: Group one patients (TXA group) received the index procedure with a 10-mL intra-articular injection of TXA (100 mg/mL). Group two patients (control group) received the index procedure without TXA injections. An intra-articular suction drain was placed in the joint and clamped for 2 hours after the procedure. The volume of drainage was recorded 24 hours after surgery, The pre-operative condition of the patients, postoperative hemoglobin (Hb) levels, Clinical evaluations of the grade of hemarthrosis by Coupens and Yates (CY) value were performed on day 2, week 2 and at week 4 postoperatively were compared between these two groups.

Results:
Twenty-four hours after surgery, a significant decrease in the amount of drainage was observed in patients receiving intra-articular injections (TXA group, 182±84.01 mL, and control group, 392±144.83 mL; P <0.001). We found a statistically significant reduction in Hemoarthrosis grade (P <0.001) within the first 2 weeks in patients in the test group compared with those in the control group, The between-group difference in hemarthrosis after removing the drain was significant between the 2 groups until the end of week 4.

Conclusion:
Intra-articular injections of TXA reduce postoperative hemarthrosis and the amount of suction drainage blood volume in the early postoperative period in patients receiving arthroscopic ACLR. No systemic side effects or need for aspiration was noted during the follow-up period. Therefore, intra-articular injection of TXA could be considered an effective and relatively safe solution to reduce postoperative bleeding and pain in ACLR patients.

Keywords: tranexamic acid; ACL reconstruction; hemarthrosis.

Introduction:

Anterior cruciate ligament injury is a common athletic injury and one of the most commonly treated conditions of the knee. (1) As concepts and techniques advance, the number of anterior cruciate ligament reconstructions (ACLRs) is increasing, although ACLR is considered a relatively safe and minimally invasive procedure, it is not without potential complications.(2) In a cross-sectional study by Salzler et al.,9%of ACLR patients had complications, the most common complications were pain (6.7%) and tension hemarthrosis requiring arthrocentesis (4.4%).(2,3) Hemarthrosis creates many adverse joint effects including increased susceptibility to infection, potential toxic effects to the cartilage, possible subsequent synovitis, and increased scar formation with delayed rehabilitation.(2, 4) In the setting of anterior cruciate ligament (ACL) reconstruction, hemarthrosis has been shown to increase postoperative pain and delay rehabilitation and return to sport.(5, 6)

Therefore, minimizing postoperative intra-articular bleeding may be potentially advantageous to the recovery of function in ACLR patients. Previously published reports showed how Tranexamic acid (TXA) has a great

role in reducing blood loss and therefore reduces the need for transfusion after a major surgical procedure such as total knee or total hip replacement.(7, 8)

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, which exerts antifibrinolytic effects through reversibly blocking lysine-binding sites on plasminogen molecules and inhibiting the interaction of plasma fibrin.(9) TXA inhibits the activation of plasminogen to plasmin by blocking the lysine binding sites of plasminogen to fibrin. This results in a decrease in proteolytic action on fibrin monomers and fibrinogen, leading to clot stabilization .(10)

Previously published reports showed how TXA has a great role in reducing blood loss and therefore reduces the need for transfusion after a major surgical procedure such as total knee or total hip replacement.(7, 8) The use of TXA has been considered safe and has not been associated with an increased mortality rate; increased risk of myocardial infarction, stroke, deep venous thrombosis, pulmonary embolism, or renal failure; or prolonged hospital length of stay.(8, 11) Tranexamic acid (TXA) has gained popularity in orthopedic practice over the past decade after being shown to decrease blood loss in hip and knee arthroplasty. TXA in the setting of total knee arthroplasty has been shown to reduce postoperative swelling and drain output. In an RCT, Ishida et al(12) injected 2000 mg of TXA into the joint at closure and showed that this produced decreased knee swelling at 1 week.

The use of TXA in arthroscopic anterior cruciate ligament (ACL) reconstruction has been a topic of interest in the past years.(13) In 2015, a prospective double-blinded RCT in 105 patients undergoing arthroscopic ACL reconstruction showed that the use of intravenous TXA before tourniquet inflation and for 3 hours postoperatively led to decreased pain, reduced rates of hemarthrosis, and improved knee function in the early postoperative period, without an increased risk in infection or deep vein thrombosis.(5, 13)

TXA administration in arthroscopic ACL reconstruction may minimize postoperative hemarthrosis and related complications, thereby decreasing postoperative pain and producing better outcomes in the short-term period after the operation.(11, 13)

Patients and Methods:

Study Design: A prospective randomized controlled clinical trial was carried out in orthopedic departments of AL-Azhar University hospital, the Assiut branch to evaluate the hemostatic effect of intra-articular injection of tranexamic acid (TXA) in patients receiving arthroscopic anterior cruciate ligament reconstruction (ACLR). The study included 50 patients (48 males and 2 females). The age varied between 18 and 50 years with a mean age of (28.52). The research was conducted only by scientifically qualified and trained personnel, all data were confidentially kept. The research was reviewed by the Faculty Ethics Review Board, AL-Azhar University Assiut branch.

Patient selection:

Inclusion criteria: Age more than 18 years old, patients with torn ACL alone or with a meniscal tear.

Exclusion criteria: Patients with Previous knee procedures on the same side, Known hypersensitivity to tranexamic acid, renal insufficiency, history of known thromboembolic disease (DVT&PE), and refusal to participate in this study. All patients who agreed to participate in this study signed an informed consent document. A total of 50 patients were included in this study and were randomized into two groups: Patients in the TXA group (25) received ACLR and a 10-mL intra-articular injection of TXA after the procedure. Patients in the control group (25) only received ACLR without TXA injections. Randomization was performed on the day of the operation using the permuted block randomization technique by an independent investigator who was involved in enrolling or consenting study participants but did not participate in the surgical procedure.

Method of intervention:

All patients enrolled in this study were operated by a senior surgeon. Spinal anesthesia was administered in all patients, and a pneumatic tourniquet was routinely used and was not released until skin closure. Surgery was performed using a standard two-portal technique with anterolateral (AL) and anteromedial (AM) portals. The autologous hamstring tendons were harvested and prepared. The diameters of the folded tendons were determined by using sizing cylinders with incremental size changes of 0.5 mm. The femoral tunnel was created at the lateral femoral condyle through the anteromedial portal. The tibial tunnel was created with a tibial ACL guide. The tunnel diameters were created in the same manner as the diameter of the folded graft. At the femoral and tibial site, grafts were fixed with bioscrews. The screw and tunnel sizes were the same.

After completion of the procedure, a suction drain (16 F–sized) was placed at the anterolateral aspect of the joint. At the end of the operation, 10 mL of TXA (100 mg/mL) was injected into the joint in the TXA group, and all drains were clamped for 2 hours.

Postoperative Regimen:

All of the patients received a postoperative analgesic and prophylactic antibiotic twice daily. A compression bandage was routinely used postoperatively. The suction drain at the knee was removed 24 hours postoperatively, and the volume of drained blood was measured. The early reductions in Hb level were defined as the difference between the pre-operative value and the postoperative sample taken 48 hours after surgery. ACL braces were used. Patients were discharged from the hospital when postoperative pain was manageable with oral analgesics. Discharge usually occurred between hospital days 2 and 3.
Patients were enrolled in the ACL rehabilitation program as described by Shelbourne and Wilckens.(14) Weight-bearing was allowed as tolerated after surgery. Crutch-assisted walking with a range of motion (ROM) of 90° within the first 2 weeks after surgery was allowed. The ROM increased to 120° at 4 weeks after surgery. Muscular training included quadriceps, hamstring, and core stability at each stage.

Clinical and laboratory Evaluations:

The primary outcomes included the drainage output, the grade of hemarthrosis, and hemoglobin level. The drain was routinely removed and the volume of drainage was recorded 24 hours after surgery.
The grade of hemarthrosis, as described by Coupens and Yates,(15) was documented on day 2, week 2, and week 4 (table 1). All the objective measurements (hemarthrosis and ROM) were evaluated by an independent observer who was blinded to the study as well as the presence of any complications was documented.

Table (1) Clinical grading of hemarthrosis

Grade	
	tense hemarthrosis

"From Coupens and Yates.(15)

Statistical Analysis:

Data were analyzed using Statistics Package for Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA). The normality test (Kolmogorov-Smirnov & Shapiro-Wilk test) was performed and data (Hb pre & post) were normally distributed. In contrast, data for (Age, Drain volume) were not normally distributed. Continuous data were expressed as mean ± standard deviation (SD) or median (Interquartile range). Differences between the two groups were detected using independent samples T-test for parametric data and Mann-Whitney test for non-parametric data. Nominal data were expressed as percentages; differences between the two groups were detected using the Chi-square test. P-value of less than 0.05 was considered statistically significant. Statistical analysis was performed within the following variables: Sex, age, drain volume, drop in hemoglobin level, and Hemoarthrosis grade.

Results:

A total of 50 patients were available for follow-up (TXA group, n = 25; control group, n = 25) between October 2019 and April 2020. Patient demographic data are shown in (Table 2)

Table (2**)** Comparison between control and TXA groups as regards patient age & sex (demographic data).

	With Tranexamic ACID (n=25)		Without Tranexamic ACID (n=25)		P. value
	No.	%	No.	%	
Range	20 – 50		18 – 41		0.870
Mean ± SD	28.68±6.81		28.36±6.96		
Male	23	92.0	25	100.0	0.149
Female	2	8.0	0	0.0	

1) Drain

Postoperatively, patients receiving intra-articular injections of TXA showed a significant decrease in drainage within the first 24 hours (TXA group, 182±84.01 mL, and control group, 392±144.83 mL (Fig 1). and that was a statistically significant difference with P. value (<0.001) showing that the decrease in drainage volume was less in the TXA group than in the Control group (table 3).

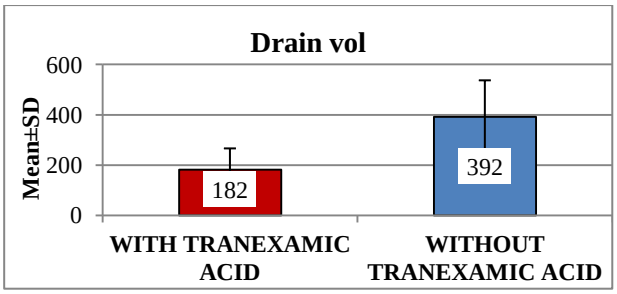

Figure (1): Clustered column chart showing (Mean±SD) of Drain volume distribution between two groups.

Table (3) Comparison between control and TXA groups as regards drain volume**.**

Drain volume	With Tranexamic ACID (n=25)	Without Tranexamic ACID (n=25)	P. value
Range	50 – 350	200 – 700	**<0.001 ****
Mean±SD	182±84.01	392±144.83	
Median(IQ)	200(100-250)	350(300-500)	**<0.001 ****

2) Hg level

The Mean difference in hemoglobin level was 2.3±0.74 (15.35 %) in the control group while it was 1.41±0.67 (9.76 %) in TXA group and that was a statistically significant difference with P. value (<0.001) showing that the decrease in HB level was less in TXA group than in the Control group (Table 4).

3) Hemarthrosis

Postoperatively, patients receiving intra-articular injections showed a significant decrease in mean hemarthrosis values within the first 2 weeks (TXA group, 0.24±0.47, and control group, 1.52±0.49. and that was a statistically significant difference with P. value (<0.001), The between-group difference in hemarthrosis after removing the drain was significant between the 2 groups until the end of week 4 (Table 5& Fig 2).

No patients exhibited postoperative complications such as infection, arthrofibrosis, or the need for aspiration.

Table (4) Comparison between control and TXA groups as regards decrease in HB level.

Hb	With Tranexamic ACID (n=25)	Without Tranexamic ACID (n=25)	P. value
Range	12 - 16.6	12 – 17	0.150^{ns}
Mean±SD	14.44±1.21	14.98±1.1	
Range	10.8 - 14.9	10.2 - 14.8	0.285^{ns}
Mean±SD	13.03±0.97	12.69±1.26	
P. value	<0.001**	<0.001**	

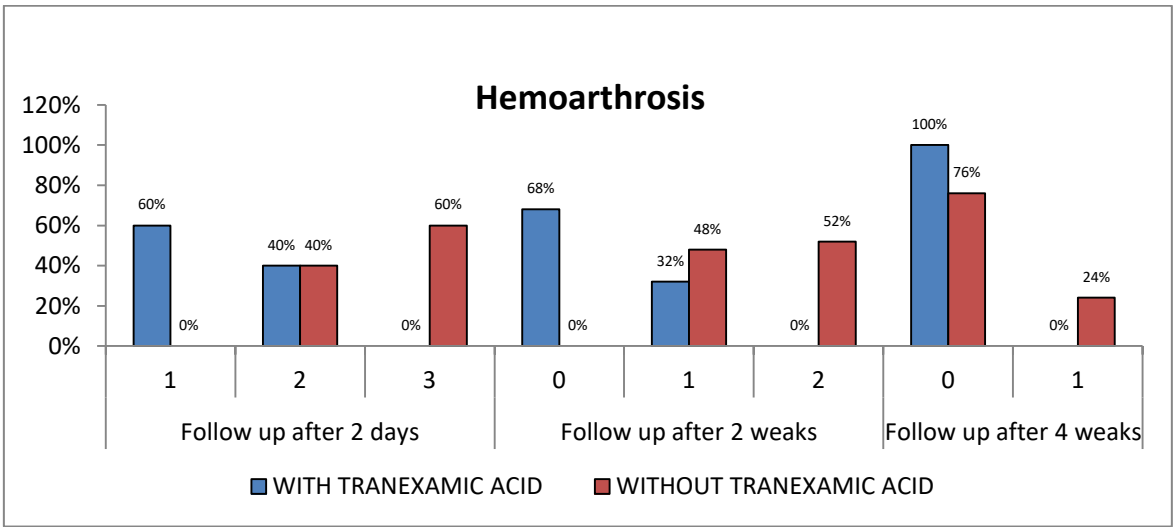

Figure (2): Clustered column chart showing the percentage of Hemoarthrosis distribution between two groups.

Table (5) Comparison between control and TXA groups as regards the decrease in hemarthrosis value.

Hemoarthrosis	WITH TRANEXAMIC ACID (n=25)		WITHOUT TRANEXAMIC ACID (n=25)		P-value
	No.	%	No.	%	
Follow up after 2 days					
1	15	60.0	0	0.0	**<0.001****
2	10	40.0	10	40.0	
3	0	0.0	15	60.0	
Follow up after 2 weeks					
0	17	68.0	0	0.0	**<0.001****
1	8	32.0	12	48.0	
2	0	0.0	13	52.0	
Mean±SD	0.24±0.47		1.52±0.49		
Follow up after 4 weeks					
0	25	100.0	19	76.0	**0.009****
1	0	0.0	6	24.0	

Discussion:

Arthroscopically assisted ACL reconstruction is a common and reproducible procedure. Different strategies have been established to decrease the complication rate in these patients, and hemarthrosis is one of these undesired complications.(13, 16)

Postoperative hemarthrosis having a 3% to 10% incidence after ACL reconstruction and accounting for 60% of all complications in arthroscopic knee surgical procedures.(6) Hemarthrosis can lead to temporary changes in cartilage and synovial histology, causing fever, pain, and a growing susceptibility to infection.(17, 18)

These aspects negatively affect the patient's outcome, with increased morbidity and loss of knee ROM resulting in growing costs and loss of resources to manage these conditions.(4, 19, 20)

Small(21) found that 60.1% of all complications of arthroscopic surgery are due to hemarthrosis. Although postoperative hemarthrosis is usually associated with immediate morbidity, it can ultimately lead to poor results.(22) In contrast, repeated aspiration of fluid during the first 3 postoperative days (to relieve pain and achieve full knee extension during the early postoperative period) is more distressing for patients than removing the drain.(13, 16)

TXA administration is another promising means for reducing postoperative complications. The therapeutic effect of tranexamic acid is apparent when the fibrin clot gets prematurely dissolved by proteolysis of plasmin. The tranexamic acid molecule works at an active bleeding site of the wound and not within the blood vessels. Thus, its presence within the clot may be considered effective irrespective of the route of administration. While at therapeutic concentration, the antifibrinolytic action of tranexamic acid involves competitive inhibition of fibrinolysis, at a higher concentration it also acts as a weak non-competitive inhibitor of fibrinolysis.(23) This study was specifically designed to investigate the efficacy of intra-articular administration of tranexamic acid.

The route of administration of TXA in orthopedic surgical procedures is a topic of controversy. Several systematic meta-analyses have shown that topical administration of TXA has comparable effectiveness to TXA delivered intravenously in reducing blood loss in orthopedic surgical procedures.(24-26) However, the potential benefit of local drug administration includes allowing its use at a higher local concentration, which may prevent the risk of adverse systemic effects. Therefore, in their study, Alshryda et al.(27) concluded that topical TXA provides a greater benefit in decreasing postoperative blood loss and transfusion rates than IV TXA in arthroplasty. In ACLR patients, Karaaslan et al.(13) Have shown that IV administration of TXA may significantly reduce the amount of postoperative drainage in the first 24 hours, as well as the need for aspiration after ACLR. Moreover, significantly decreased hemarthrosis values with a minimal decrease in hematocrit levels were observed in patients receiving TXA.(13)

In this study, we assessed the hemostatic effect of intra-articular injection of TXA after ACLR on various parameters related to drain output, hemoglobin level, and hemarthrosis grade. We found that all parameters are lower with the use of the tranexamic acid group as opposed to the control group as decrease postoperative drain output on the first day. The hemarthrosis grade and drop in hemoglobin levels were also significantly reduced in the early postoperative period. This difference was statistically significant.

TXA role in reducing blood loss reduces the need for transfusion after a major orthopedic surgical procedure such as total knee replacement or total hip replacement.(7, 28) In the previous literature, TXA has been administrated during many orthopedic surgical procedures to reduce perioperative bleeding and postsurgical hemorrhage. In 1 systematic review, TXA reduced the risk of transfusion by 87% and 58% in total knee replacement patients and total hip replacement patients, respectively.(29, 30) TXA has been shown to have similar effects in patients who underwent spinal surgery.(31, 32) These studies have shown the safety and efficacy of TXA for controlling perioperative and postoperative bleeding in major orthopedic surgery. However, it remained elusive whether TXA is advantageous in a procedure in which the soft tissue is relatively preserved, such as arthroscopic surgery.

Evidence regarding the clinical benefits of administrating TXA during ACLR is limited. In one prospective randomized study, a total of 105 patients were enrolled (53 in the TXA group, and 52 in the control group), the results of this study show that intravenous TXA reduced the amount of suction drainage and postoperative hemarthrosis and reduced the need for aspiration of the knee in patients who underwent arthroscopic ACL reconstruction. Consequently, TXA reduced pain and improved knee ROM in the early postoperative period without side effects.(2, 13) In another prospective randomized study, evaluated 80 patients (40 in the TXA group

and 40 in the control group), the main finding of this randomized trial is that a single IV administration of TXA 20 to 30 minutes before tourniquet release in patients who underwent ACL reconstruction surgery reduced the blood volume in suction drainage, amount of hemarthrosis, and postoperative pain during the first 2 weeks. TXA use improved early phase outcomes in the postoperative period after ACL reconstruction.(11)

In another prospective randomized study, a total of 300 patients were enrolled (151 in TXA group and 149 control group,) the results of this prospective, randomized study show that intraarticular injection of TXA could significantly reduce postoperative intra-articular bleeding in the first 24 hours after ACL reconstruction. TXA injection also decreases pain and the grade of hemarthrosis in the early postoperative period.(2)

In the aforementioned study, about 35% of the patients underwent aspiration in the early postoperative period.(13). However, none of the patients in our study required aspiration for hemarthrosis, with ROM being comparable between the 2 groups after 4 weeks.

In our study, we showed that the topical use of TXA could significantly decrease intra-articular bleeding during the first postoperative day. Also, a significant decrease in the grading of hemarthrosis was noted, and none of our patients required aspiration during the follow-up period. Previous studies have concluded that, although TXA may penetrate large joints efficiently after IV administration, it has a relatively short half-life (2 hours) and might remain just above the effective plasma concentration for only 4 to 6 hours.(33-35)

Therefore, we believe that the local administration of TXA exerts its effect in the early postoperative period without systemic risks. However, the optimal dosage, route, and timing of TXA application in ACLR surgery remain to be investigated. Further comparative studies are needed to clarify these issues.

Limitations

There were several limitations to this study. First, the follow-up period was only 6 weeks after surgery, which was relatively short in terms of clinical evaluations. Also, this short period might not be able to allow examination of the adverse effects of TXA. Second, the sample size was small, and there is a risk of accidental bias during the treatment allocation process and with the randomization method. Third, the treatment was not allocated evenly to each sex because there were substantially more men than women in this study and men were more likely to undergo ACL reconstruction. Finally, only a single observer recorded the objective measurements without a validation study, which might increase the risk of errors.

Conclusion

The results of this prospective, randomized study show that Intra-articular injection of TXA could significantly reduce the amount of suction drainage in the first 24 hours postoperative and reduced the need for aspiration of the knee in patients who underwent arthroscopic ACL reconstruction. TXA injection may also decrease pain and the grade of hemarthrosis in the early postoperative period Consequently, TXA reduced pain and improved knee ROM in the early postoperative period. No systemic side effects or need for aspiration was noted during the follow-up period. Therefore, intra-articular injection of TXA could be considered an effective, efficient, and reproducible method for reducing blood loss and hemarthrosis, with the potential to reduce patient discomfort after arthroscopic ACL reconstruction (ACLR).

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