นิพนธ์ต้นฉบับ
Original Article

ประสิทธิภาพของยา Tranexamic acid ขนาดต่ำทางหลอดเลือดดำในการลดปริมาณการเสียเลือดจากการผ่าตัดส่องกล้องสร้างเอ็นไขว้หน้าในข้อเข่า

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บทคัดย่อ

วัตถุประสงค์: วัตถุประสงค์หลักคือการศึกษาประสิทธิภาพของยา Tranexamic acid (TXA) ขนาดต่ำทางหลอดเลือดดำในการลดปริมาณการเสียเลือดจากการผ่าตัดส่องกล้องสร้างเอ็นไขว้หน้าที่ข้อเข่า และมีวัตถุประสงค์รองเป็นการศึกษาประสิทธิภาพของยาในการลดระดับความเจ็บปวดหลังการผ่าตัด พิสัยการงอข้อเข่า การเกิดเลือดออกในข้อเข่า และศึกษาถึงภาวะแทรกซ้อนที่เกิดจากการใช้ยา TXA

วิธีการศึกษา: เป็นการศึกษาแบบไปข้างหน้า โดยการสุ่มตัวอย่างแบบ double blind ในผู้ป่วยทั้งหมด 60 รายที่ได้รับการผ่าตัดส่องกล้องสร้างเอ็นไขว้หน้าที่ข้อเข่า แบ่งออกเป็น 2 กลุ่ม คือกลุ่มที่ได้รับยา TXA จำนวน 30 ราย และกลุ่มควบคุมจำนวน 30 ราย ขนาดยา TXA ที่ให้คือ 10 มก./กก. ฉีดเข้าหลอดเลือดดำ10 นาทีก่อนการผ่าตัด ส่วนกลุ่มควบคุมฉีดน้ำเกลือปกติในปริมาณเท่ากัน ประเมินผลทางคลินิกโดยการวัดปริมาตรของเลือดที่ระบายออกทางสายระบายเลือดที่ 3 และ 24 ชั่วโมงหลังการผ่าตัด, ระดับการเกิดเลือดออกในข้อเข่า วัดในสัปดาห์ที่ 1 และ 2 หลังผ่าตัด, ประเมินระดับความเจ็บปวดโดยใช้ visual analog scale (VAS)ในวันที่ 1, สัปดาห์ที่ 1 และ 2 หลังผ่าตัด, บันทึกพิสัยการงอข้อเข่าในช่วงสัปดาห์ที่ 2 และ 4 หลังผ่าตัด

ผลการศึกษา: การลดลงของระดับฮีโมโกลบินหลังการผ่าตัด (กลุ่ม TXA 1.10 ± 0.52, เทียบกับกลุ่มควบคุม 1.80 ± 0.71, p<0.001) และการลดลงของความเข้มข้นเลือดหลังการผ่าตัด (กลุ่ม TXA 3.42 ± 1.74 เทียบกับกลุ่มควบคุม 5.41 ± 2.04, p<0.001) ในกลุ่มผู้ป่วยที่ได้รับ TXA ต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ค่าเฉลี่ยของระดับความเจ็บปวดหลังผ่าตัด พิสัยการงอข้อเข่า และระดับการเกิดเลือดออกในข้อเข่าไม่แตกต่างกัน โดยทั้ง 2 กลุ่มไม่พบภาวะแทรกซ้อนหลังการผ่าตัด

สรุป: ผลการศึกษานี้แสดงให้เห็นว่ายา TXA ขนาดต่ำทางหลอดเลือดดำมีประสิทธิภาพในการลดการสูญเสียเลือดหลังการผ่าตัดส่องกล้องสร้างเอ็นไขว้หน้าที่ข้อเข่าอย่างมีนัยสำคัญ แต่ไม่มีผลต่อการลดความเจ็บปวดหลังการผ่าตัด พิสัยการงอข้อเข่า และการเกิดเลือดคั่งในข้อเข่าหลังการผ่าตัด

คำสำคัญ : ทรานเนกซามิค แอซิด, การผ่าตัดส่องกล้องข้อเข่า, การผ่าตัดสร้างเอ็นไขว้หน้าข้อเข่า, ภาวะเลือดออกในข้อ

The Efficacy of Low – Dose Intravenous Tranexamic Acid in Reducing Postoperative Blood Loss in Arthroscopic Anterior Cruciate Ligament Reconstruction

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Abstract

Purpose: This prospective, randomized, double-blind study aimed to assess the efficacy of single intravenous administration of low-dose tranexamic acid (TXA) in arthroscopic anterior cruciate ligament reconstruction (ACLR) for minimizing postoperative blood loss. Secondary objectives included assessing early postoperative pain levels, range of knee flexion, knee joint hemarthrosis, and TXA-associated complications.

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Methods: Sixty patients undergoing arthroscopic ACLR were randomly assigned to either the treatment group (n = 30), receiving a single bolus dose of 10 mg/kg TXA intravenously 10 minutes before surgery, or the control group (n = 30), receiving an equal volume of normal saline via the same route. The volume of drained blood was measured at 3 and 24 hours postoperatively. Hemarthrosis grade was assessed in postoperative weeks 1 and 2. Pain levels were evaluated using a visual analog scale (VAS) at postoperative day 1, week 1, and week 2. Knee flexion range was recorded at the end of postoperative week 2 and week 4.

Results: Patient demographics were comparable between the two groups. Postoperative reductions in hemoglobin (TXA group 1.10 ± 0.52, control group 1.80 ± 0.71, p<0.001) and hematocrit (TXA group 3.42 ± 1.74, control group 5.41 ± 2.04, p<0.001) were statistically significant in favor of the TXA group. The mean postoperative VAS scores, range of knee flexion, and hemarthrosis grades were similar between the groups. No postoperative complications were reported.

Conclusion: Single intravenous administration of low-dose TXA effectively reduces postoperative blood loss in arthroscopic anterior cruciate ligament reconstruction (ACLR) surgery. However, this intervention did not demonstrate clinical benefits in terms of pain levels, range of motion, or knee hemarthrosis during the early postoperative period. Additional research may be warranted to explore optimal TXA dosing strategies and its impact on functional outcomes in ACLR patients.

Keywords : Tranexamic acid, arthroscopy, ACL reconstruction, hemarthrosis

Introduction

Tranexamic acid (TXA) is a synthetic lysine analog known for its anti-fibrinolytic properties, achieved through competitive and reversible blockage of lysine binding sites on plasminogen molecules, thereby inhibiting fibrinolysis[1]. This mechanism makes TXA a promising agent in reducing perioperative blood loss and mitigating the need for blood transfusion and its associated complications. Extensive research in hip and knee arthroplasty has established the efficacy of TXA in minimizing blood loss without significantly increasing thromboembolic risks[2-5]. Recent attention has focused on its potential benefits in arthroscopic procedures, particularly in lowering the incidence of postoperative hemarthrosis. The accumulation of intraarticular blood following surgery can lead to pain, toxic effects on articular cartilage, heightened infection susceptibility, synovitis, restricted range of motion, and delayed recovery[6-7]. Despite these concerns, literature supporting TXA's use in arthroscopic anterior cruciate ligament reconstruction (ACLR) regarding perioperative blood loss, knee hemarthrosis, and pain remains inadequate. While some reports suggest TXA's efficacy in reducing post-ACLR blood loss and hemarthrosis, variations in study protocols—including TXA dosage, administration route (intravenous, intra-articular, or combined), dosage interval (single or repeated doses), and clinical evaluation methods—contribute to conflicting findings.

Although TXA's side effects are typically mild to moderate, dose-related serious adverse effects such as thrombotic events and seizures have been sporadically reported[8]. Thus, this study aims to evaluate the effects of low-dose, single intravenous administration of TXA in ACLR primarily concerning postoperative blood loss. Additionally, secondary objectives include assessing postoperative pain levels, knee flexion range, hemarthrosis and potential TXA-related complications.

Materials and methods

Study Approval and Patient Selection

This study (31/63/R/h1) received approval from the Chonburi Hospital Institutional Review Board. Patients scheduled for anterior cruciate ligament reconstruction (ACLR) at our institution between January 2020 to December 2022 were considered for inclusion in this prospective, randomized controlled trial. Exclusion criteria comprised a history of bleeding or clotting disorders, abnormal coagulation profile, ischemic heart disease, preoperative anticoagulant

therapy, prior pulmonary embolism or venous thrombosis, malignancies, known allergy to tranexamic acid (TXA), and ACLR revision cases. A total of 60 patients meeting the inclusion and exclusion criteria and the calculated sample size were enrolled during the study period.

Tranexamic Acid Administration

Considering the potential chondrotoxic effects associated with intra-articular injection of high-concentration TXA (>20 mg/ml)[9-10], we opted for intravenous (IV) administration in this study. Patients were randomly assigned using block randomization into one of two groups: the TXA group, receiving a single intravenous dose of 10 mg/kg of TXA (Transamine, 250 mg/2.5 mL; Windlas Biotech), and the control group, receiving normal saline solution. TXA and saline solutions were prepared separately by the hospital pharmacist in identical saline bottles for injection, each assigned a random code number to ensure blinding of patients, anesthetists, surgeons, and postoperative observers regarding TXA use.

Surgical Procedure

Arthroscopic ACL reconstruction procedures were conducted by one of the senior authors (K.T. or S.S.) under spinal anesthesia with tourniquet control. Single-bundle reconstruction using semitendinosus tendon with or without gracilis tendon grafts was performed in both TXA and control groups. Graft fixation was achieved using metallic interference screws in femoral and tibial tunnels. Other necessary procedures were performed as indicated by each patient's pathology such as meniscus resection or repair. Prophylactic cefazolin was administered in 4 sequential doses over 24 hours perioperatively. Intraarticular suction drainage and a compressive knee dressing were applied postoperatively.

Postoperative Protocol

Patients received intravenous morphine sulfate for analgesia on the first day, along with oral naproxen until postoperative day 5. Compressive dressing and suction drainage were removed 24 hours postoperatively, and a standardized rehabilitation program was initiated, including range of motion and quadriceps exercises. Patients were allowed to toe-touch weight-bearing ambulation with axillary crutches and discharged on the second postoperative day with a hinged knee brace.

Clinical Assessments

Demographic data, operative details, including graft type, concomitant procedures, and intraoperative parameters, were recorded. Outcome measures encompassed drain output at 3 and 24 hours postoperatively, pre- and 24 hours-postoperative hemoglobin (Hb) and hematocrit (Hct) differences, hemarthrosis grade based on the Coupens and Yates classification[11](Table 1) at postoperative weeks 1 and 2, pain assessed using a Visual Analog Scale (VAS) at postoperative day 1, week 2, and week 4, knee flexion range at weeks 2 and 4 postoperatively, and any complications observed.

Table 1: Clinical grading of hemarthrosis*

Grade	Description
0	No detectable fluid
1	Fluid present with fluid wave
2	Palpable fluid in suprapatellar space
3	Ballotable patella
4	Tense hemarthrosis

* **From Coupens and Yates**[11]

Statistical Analysis

The sample size for this study was determined following the methodology of Turgut Akgül et al.12, considering a significance level of alpha = 0.05 and power (1- ß) of 90%. Based on these parameters, the minimum total number of patients required for this study was calculated to be 60. Descriptive statistics were presented as mean ± SD or median for continuous variables and percentages for categorical data. Statistical significance was assessed using independent t-tests for normally distributed data and the Mann-Whitney U test for non-normally distributed data. A power analysis was conducted, with $p < 0.05$ considered statistically significant. Data analysis was performed using SPSS (IBM SPSS Statistics 25).

Results

A total of 60 patients were enrolled in the study, with 30 patients each allocated to the TXA and control groups. The demographic characteristics including sex distribution, mean age, body mass index (BMI), smoking and alcohol habits, as well as comorbidities, were comparable between the two groups (Table 2). Surgical procedures involved the use of either solitary semitendinosus or combined semitendinosus plus gracilis tendon grafts in equal proportions across both groups. There were no significant differences observed in mean operative time, drain output volume, or concomitant procedures between the TXA and control groups.

Table 2 : Patient characteristics

	TXA group (n=30)	**control group (n=30)**
Sex		
Male: Female	25: 5	23: 7
Age (years)		
Mean ± SD	27.93 ± 8.55	29.47 ± 9.07
Median (range)	27 (16 - 58)	27 (16 - 49)
BMI (kg/m2)	25.63 ± 4.00 (24.1 - 27.13)	25.37 ± 4.12 (23.83 - 26.90)
Smoking		
Yes: No	7: 23	9: 21
Alcohol		
Yes: No	14: 16	12: 18
Comorbidities		
Yes: No	4: 26	3: 27
Type of hamstring graft		
Semi T: Semi T + Gracilis	5: 25	3: 27
Concomitant procedures		
Partial meniscectomy	6	5
Meniscus repair	3	4
Synovial fold resection	1	0
Operative time (min)	84.83 ± 21.97 (53 - 175)	79.97 ± 14.22 (55 - 109)

Data are presented as number of patients or mean ± standard deviation (range).
Semi T = Semitendinosus

Postoperative hemoglobin level was higher in the TXA group compared to the control group (13.38 ± 0.67 vs 12.43 ± 1.14, p<0.001). Furthermore, statistically significant reductions were observed in both pre- and postoperative hemoglobin (TXA group: 1.10 ± 0.52; control group: 1.80 ± 0.71, p<0.001) and hematocrit (TXA group: 3.42 ± 1.74; control group: 5.41 ± 2.04, p<0.001) in favor of the TXA group (Table 3).

Table 3 : Drain output volume, hemoglobin and hematocrit difference

	TXA group	control group	*P* value*
Drain output volume (ml)			
3h post-operative	43.50 ± 32.41 (5 - 150)	41.67 ± 28.66 (10 - 120)	*0.817*
24 h post-operative	113.33 ± 42.13 (40 - 220)	126.0 ± 38.11 (70 - 200)	*0.227*
Hb (g/dL)			*0.299*
pre-operative	14.49 ± 0.81 (12.70 - 15.90)	14.24 ± 1.00 (12.10 - 16.40)	*<0.001*
24 h post-operative	13.38 ± 0.67 (11.20 - 14.50)	12.43 ± 1.14 (10.00 - 14.50)	*<0.001*
Hb reduction	1.10 ± 0.52 (0.30 - 2.30)	1.80 ± 0.71 (0.20 - 3.00)	
Hct (%)			
pre-operative	44.07 ± 2.38 (40.20 - 50.30)	43.27 ± 3.24 (37.30 - 51.60)	*0.276*
24 h post-operative	40.17 ± 2.09 (36.40 – 44.20)	37.40 ± 3.86 (29.80 – 45.20)	*0.001*
Hct reduction	3.42 ± 1.74 (0.70 - 7.70)	5.41 ± 2.04 (0.90 - 8.60)	*<0.001*

Data are presented as mean ± standard deviation (range).

* Independent t-test

Assessment of pain using the Visual Analog Scale (VAS) at postoperative day 1, week 1, and week 2, as well as evaluation of knee flexion range at the conclusion of week 2 and week 4, revealed comparable outcomes between the TXA and control groups (Table 4). Hemarthrosis grades at week 1 indicated that the majority of patients in both cohorts exhibited grade 0 or 1 hemarthrosis (93.3% in TXA and 90% in control group). By the end of week 2, most patients had attained grade 0 hemarthrosis (93.3% in TXA and 90% in control group), with no statistically significant differences noted between the groups (Table 5). Notably, there were no instances of infection, venous thrombosis, pulmonary embolism, myocardial infarction, or cerebrovascular accidents reported in either group at the conclusion of week 4.

Table 4 : Postoperative pain and range of knee flexion

	TXA group	control group	*P* value*
VAS score			
24 hr	4.93 ± 1.20 (3 - 10)	5.23 ± 1.17 (3 - 10)	*0.330*
1 wk	0.70 ± 0.84 (1 - 8)	0.80 ± 0.85 (2 - 10)	*0.647*
2 wk	0.13 ± 0.35 (0 - 5)	0.17 ± 0.38 (1 - 8)	*0.723*
Knee flexion (degrees)			
2 wk	67.00 ± 12.36 (30 - 95)	64.67 ± 10.50 (30 - 90)	*0.434*
4 wk	100.67 ± 12.71 (80 - 135)	93.17 ± 15.23 (30 - 135)	*0.043*

Data are presented as mean ± standard deviation (range).

* Mann-Whitney U test

Table 5 : Grading of postoperative hemarthrosis

Hemarthrosis	TXA	Control	*P* value*
Week 1			*0.751*
Grade 0	21 (70.0)	15 (50.0)	
Grade 1	7 (23.3)	12 (40.0)	
Grade 2	1 (3.3)	3 (10.0)	
Grade 3	1 (3.3)	0	
Grade 4	0	0	
Week 2			*1.000*
Grade 0	28 (93.3)	27 (90.0)	
Grade 1	2 (6.7)	3 (10.0)	
Grade 2	-	-	

Data are presented as number of patients (percentage).

*Fisher's exact test

Discussion

Arthroscopically assisted ACLR is a common, less invasive, and reproducible procedure in patients suffering traumatic ACL deficiency. Despite the excellent outcomes after the operation, there are concerns over postoperative complications and morbidity. The overall complication rates of this procedure in one study were 1.68%, of which hemarthrosis occurred in a frequency of 60.1%.[13] Postoperative hemarthrosis deteriorates the results of ACLR by scar formation, decreased range of motion, subsequent synovitis, and delayed rehabilitation.

TXA was approved by the US Food and Drug Administration (FDA) since 1986 only for bleeding prevention in hemophilic patients undergoing dental procedure and cyclic heavy menstrual bleeding[8]. In 2011 the World Health Organization (WHO) added TXA to its list of essential medicines since it has been shown that early TXA administration after severe trauma can significantly increase the rate of survival[1]. At present day, TXA has been evaluated in various orthopaedic clinical scenarios as a hemostatic agent, predominantly in joint replacement procedures[14]. Insufficient data are available to support routine use of TXA in arthroscopically assisted ACLR regarding route of administration, optimal dosage and interval, adverse effects and most importantly its hemostatic efficacy.

Our study was designed to explore the potential benefits of a single low-dose (10 mg/kg) intravenous tranexamic acid (TXA) regimen in patients undergoing anterior cruciate ligament reconstruction (ACLR). While we did observe a significant reduction in postoperative blood loss, we did not find corresponding clinical improvements in terms of postoperative pain, knee flexion range, or knee hemarthrosis. This contrasts with findings from other studies that utilized higher TXA dosages.

Not many well-designed randomized controlled trials have highlighted the hemostatic efficacy and improved outcomes associated with higher TXA dosage regimens in the early postoperative period. For instance, Karaaslan et al.[15] demonstrated reduction of drain output volume, reduced postoperative hemarthrosis, decreased need for knee aspiration, and improved pain scores and Lysholm knee scores after arthroscopic ACLR with a TXA bolus dose of 15 mg/kg followed by 10 mg/kg/h continuous infusion for 3 hours. Similarly, Felli et al.[16] reported reductions in hemarthrosis and drainage volume, along with improvements in range of motion and quadriceps strength, with a 15 mg/kg TXA infusion. Systematic review and meta-analysis[17,18] also support the role of TXA in lowering the blood loss and hemarthrosis after ACLR.

However, studies investigating high TXA doses have also reported nonsignificant impacts on blood loss and hemarthrosis. Lee et al.'s study[19] using 3 g of intra-articular TXA after ACLR and Fried et al.'s trial[20] with a 1 g bolus IV TXA regimen showed no significant

effects on blood loss, pain control, or opioid consumption. Worth noting is that both trials were conducted in the United States which postoperative suction drain after ACLR was typically omitted. The absence of postoperative suction drainage may allow the tamponade effect within the knee joint to contribute to a reduction in postoperative blood loss. This divergence in postoperative care protocols could potentially impact outcomes related to postoperative blood loss and hemarthrosis. Furthermore, Lee el at. use calculated blood loss based on hemoglobin (Hb) balance, which can be affected by hemodilution from intravenous fluid administration and may lead to higher value of blood loss.

The lower TXA dosage employed in our study may elucidate the absence of significant clinical benefits observed. Nonetheless, it is crucial to highlight that no adverse cardiovascular effects were observed, aligning with data from the National Danish Databases[21].

These findings collectively underscore the complexity of TXA's optimal dosage and its varying effects on postoperative outcomes in ACLR. Further research with standardized protocols and larger sample sizes is necessary to elucidate the ideal TXA regimen for maximizing benefits while minimizing potential risks in ACLR patients.

Limitations

It is important to interpret the content of our study with respect to its limitations. Firstly, the relatively small sample size may have limited the generalizability of our findings. Larger studies with more participants could provide a more robust assessment of the effects of low-dose intravenous tranexamic acid (TXA) in anterior cruciate ligament reconstruction (ACLR), especially in the clinical benefits. Secondly, our study included 2 orthopaedic surgeons which may introduce bias into the study. However, their method of ACLR with autogenous hamstring graft as well as postoperative protocol were similar. Additionally, the third group of patients without postoperative suction drains were not included in our study. This absence precludes assessment of the intra-articular tamponade effect, which may influence postoperative blood loss.

Addressing these limitations in future studies, such as increasing sample size, standardizing postoperative care protocols across institutions, utilizing consistent methods for blood loss measurement, and incorporate a group of patients without suction drains would contribute to a more comprehensive understanding of the efficacy and potential limitations of TXA in ACLR procedures.

Conclusion

Low dose intravenous tranexamic acid (TXA) administration in patients undergoing arthroscopically assisted single-bundle ACL reconstruction with hamstring autograft significantly reduces postoperative blood loss. However, our findings did not reveal any clinical benefit in terms of reducing postoperative pain, knee flexion range and knee hemarthrosis.

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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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