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Systematic Review

The outcomes of intra-articular injection of tranexamic acid in arthroscopic anterior cruciate ligament reconstruction: a systematic review

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ABSTRACT

Arthroscopy is the gold standard for anterior cruciate ligament (ACL) rupture nowadays. Although minimal invasive, this procedure carries the risk of hemarthrosis. Hemarthrosis and pain can interfere with the patient's rehabilitation process and can develop into arthrofibrosis. The administration of antifibrinolytic agents such as tranexamic acid (TXA) has long been developed but it had various results. Compared with intravenous administration, intra-articular (IA) injection of TXA in ACL reconstruction cases is still rarely done. The purpose of this study was to assess the outcomes of intra-articular administration of TXA in ACL reconstruction cases. Identification of relevant studies was developed with a comprehensive search strategy. The eligibility of each study was assessed based on predetermined inclusion and exclusion criteria. The inclusion criteria were studies that discussed the outcomes of giving IA TXA in ACL reconstruction, randomized controlled trial study design comparing IA TXA with control, and full-text English-language journals from 2019-2024. IA administration of TXA is given immediately after the arthroscopy procedure. This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Four studies comprising 550 patients who were treated with IA TXA were included. Assessed from postoperative bleeding, patients who underwent IA TXA tended to have less bleeding than the control group with most studies showed a significant difference in the amount of bleeding (<0,05). Most studies represented that administration of IA TXA was able to significantly reduce postoperative pain. No patients presented with systemic side effects or complications such as infection, deep vein thrombosis, retears, or revisions through the administration of this procedure. IA administration of TXA can be considered as a safe modality with good tolerance to overcome bleeding or pain in ACL patients undergoing arthroscopy.

Keywords: ACL, Intra-articular, Randomized controlled trial, Tranexamic acid

INTRODUCTION

The anterior cruciate ligament (ACL) is a ligament that runs from the posterior medial aspect of the lateral femoral condyle from the intercondylar notch to the anterior side of the intercondylar eminence of the tibia. The ACL is a ligament that is often ruptured in athletes compared to other ligaments.[1] Along with the development of technology and knowledge, arthroscopy is the gold standard in ACL cases. Arthroscopy has dual clinical techniques for both accurate examination and management.[2] Although it is an effective and minimally

invasive procedure, arthroscopy is a risky procedure for hemarthrosis. Hemarthrosis and pain can interfere with the patient's rehabilitation process and can develop into arthrofibrosis.[3] This incident has been reported to increase to 60% of all arthroscopy procedures on the knee. As a result, patients will experience pain, swelling, and decreased range of motion after surgery, which will result in decreased quality of life for patients.[3,4]

To overcome the occurrence of hemarthrosis, patients are generally given an antifibrinolytic agent, which is tranexamic acid. Tranexamic acid (TXA) is a group of lysine-based plasminogen with an inactive precursor of plasmin which is a protease involved in blood clot formation. TXA is able to provide hemodynamic stability and reduce the incidence of preoperative bleeding.[5,6] Administration of TXA in cases of arthroscopy on ACL has been carried out for a long time. Generally, intravenous administration gives promising results with good early function and pain relief, thus providing information on its effective efficacy and safety. Although more often done intravenously, TXA can also be given intraarticularly.[7,8]

Previous studies have shown that intra-articular administration of TXA can also reduce the risk of hemarthrosis, reduce pain, improve rehabilitation, and improve the outcome of patients after ACL reconstruction.[8,9] However, other studies have shown that intra-articular injection has no effect in reducing blood loss or postoperative pain.[10] Given the differences in these results, intra-articular administration of TXA still requires consideration. Research that focuses on discussing the outcomes of intra-articular TXA in ACL reconstruction is not widely conducted. The purpose of this systematic review is to assess the effectiveness of intra-articular administration of TXA in ACL reconstruction cases.

METHODS

Literature search

A comprehensive search strategy was developed to identify relevant studies. Electronic databases including Science Direct, Pubmed, and Google Scholar were systematically searched for the earliest data in 2019-2024. The following search terms, both individually and in combination, were used: “intra articular”, “tranexamic acid”, "TXA", "anterior cruciate ligament", “ACL”, “arthroscopic”, dan “reconstruction”.

The search strategy was adapted to each specific database using appropriate search operators and medical subject headings (MeSH) terms to ensure comprehensive coverage of relevant articles.

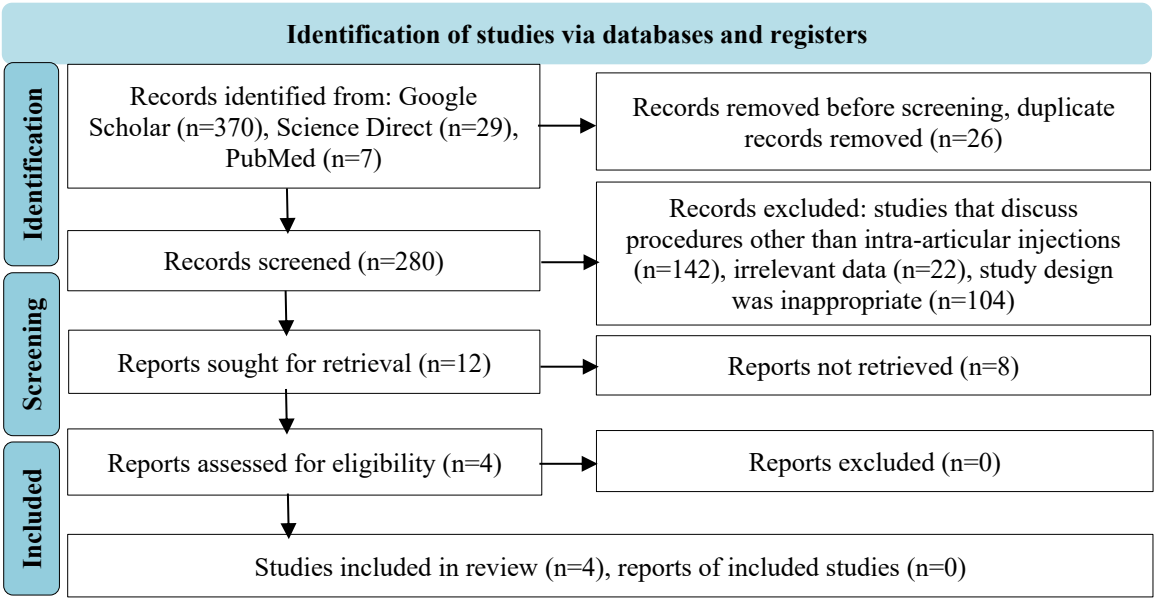

Figure 1: PRISMA flowchart.

Study selection

After conducting the initial search, duplicate articles were removed using reference management software. The remaining studies underwent a two-step screening process: title/abstract screening and full-text screening. The eligibility of each study was assessed based on predetermined inclusion and exclusion criteria. The inclusion criteria were: studies that discussed the outcomes of giving intra-articular TXA in ACL reconstruction; samples aged >18 years who were diagnosed with ACL injury; randomized controlled trial study design; and full-text English-language journals from 2019-2024. The exclusion criteria were: studies that do not focus on discussing intra-articular TXA in ACL reconstruction; inappropriate study designs such as review articles, case reports, conference abstracts, and editorials; and studies lacking relevant results or data related to intra-articular

TXA in ACL reconstruction. Intra-articular (IA) administration of TXA is given immediately after the arthroscopy procedure.

Data extraction

Data extraction was performed independently using a standard data extraction form. Data extracted from each study included: author, year of publication, study location, study objectives, study design, sample size, sample age range, main findings, and relevant statistical data.

Data synthesis

A narrative synthesis of the included studies was performed. Findings are organized and presented according to the stated study objectives, highlighting the implementation of intra-articular TXA in ACL reconstruction. Any significant associations, trends, or inconsistencies observed across studies are thoroughly discussed.

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were used to ensure transparent and comprehensive reporting of systematic reviews.

RESULTS

Characteristic of the included studies

This systematic review consisted of 4 studies in the last 5 years. Each RCT study met the inclusion criteria. In this study, there were 551 participants who had ACL rupture and underwent arthroscopic reconstruction. A total of 276 participants were given IA TXA while 275 participants were included in the control group. Most of the patients were male. The following are the characteristics of the studies listed in Table 1.

Outcomes of the studies

Most studies found that IA TXA administration was able to significantly reduce bleeding rates ($p<0.01$) compared to the control group. In addition, based on the pain scale obtained, IA TXA also had better pain outcomes compared to the control group. Early post-operative outcomes in the form of the amount of bleeding and pain scale based on VAS can be seen in Table 2. Not only assessing the amount of bleeding and pain scale, but several studies also provided additional information in the form of hemarthrosis degree, range of motion (ROM), patellar circumference, Lysholm score, and hemoglobin level which can be seen in Table 3. No patients presented with systemic side effects or complications such as infection, deep vein thrombosis, retears, or revisions through the administration of this procedure.

Risk of bias

The risk of bias is depicted in Figure 2.

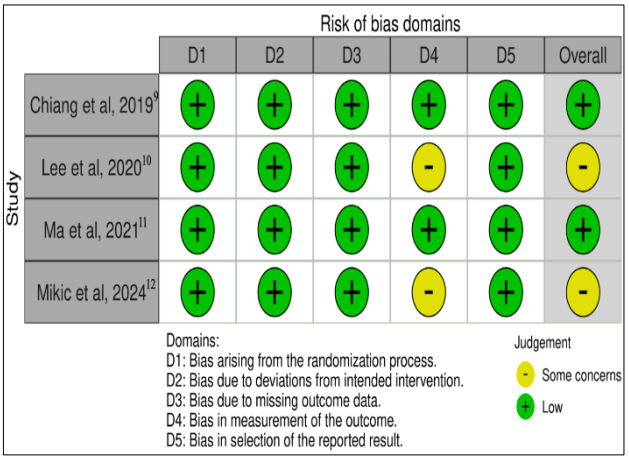

Figure 2: The risk of bias.

Table 1: Study characteristics.

Study	Country	Number of patients		Age (mean±SD)		Sex, male (%)	
		IA TXA	Control	IA TXA	Control	IA TXA	Control
Chiang et al, 2019[9]	Taiwan	151	149	25.7±8.4	27.6±6.9	82.3	79.9
Lee et al, 2020[10]	Korea	23	24	30.3±9.0	25.1±8.1	87	87.5
Ma et al, 2021[11]	China	40	40	32.7±8.5	30.3±8.0	65	57.5
Mikic et al, 2024[12]	Serbia	62	62	29.37±7.93	26.76±7.93	82	82

Table 2: Early post-operative outcomes.

Study	Post-operative bleeding (ml)		P value	VAS score		P value
	IA TXA	Control		IA TXA	Control	
Chiang et al, 2019[9]	56.1±34.1	80.1±48	<0.05	3.2±1.0	6.7±2.5	<0.001
Lee et al, 2020[10]	467±242	558±236	0.20	3.3±1.3	4.2±1.8	0.07
Ma et al, 2021[11]	63.3±31.8	120.1±57.4	<0.005	2.4±1.1	3.5±0.9	<0.005
Mikic et al, 2024[12]	71.29±40.76	154.35±81.45	<0.001	3.98±3.31	5.26±3.15	0.030

Table 3: Other results.

Study	Results
Chiang et al, 2019[9]	The amount of drainage was significantly reduced in the IA TXA group who also underwent different meniscal procedures (p<0.001). On the third day, the hemarthrosis grade between the IA TXA and control groups was significantly different (p<0.001) but at the fourth week there was no significant difference between the two groups (p=0.163). After the fourth week, there was no significant difference between the ROM of patients who received IA TXA and the control group (p=0.502).
Lee et al, 2020[10]	There was no significant difference in ROM of post-operative patients at week 6 between the IA TXA group and the control group (p=0.61). There was no significant difference in patellar circumference between the IA TXA and control groups on the second and fifth days (p=0.75 and p=0.84, respectively). There was no significant difference in hemoglobin levels of patients undergoing IA TXA and the control group on postoperative days 1, 2, and 5 (p=0.72, p=0.89, p=0.32 respectively).
Ma et al, 2021[11]	There was a significant difference in patellar circumference between IA TXA and control groups in the first and second weeks (p<0.001, respectively). In the first- and second-week follow-up, the hemarthrosis grade was higher in the control group and significantly different from the IA TXA group (p<0.05). However, in the fourth week follow-up, there was no significant difference in the hemarthrosis grade. The Lysholm score of IA TXA was higher than the control group (82.1±11.1 versus 78.6±10.6).
Mikic et al, 2024[12]	After follow-up in the first, third, and sixth weeks, the IA TXA pain scale was found to be lower than the control group but not significant at week 6 (p=0.018, p<0.001, p=0.073 respectively). At the end of the sixth week of follow-up, the control group had a higher number of hemarthosis events than the IA TXA group.

DISCUSSION

TXA is an antifibrinolytic agent derived from lysine and binds to the lysine receptor on plasminogen which can then inhibit the formation of plasmin, thereby inhibiting the breakdown of fibrin and ultimately reducing active bleeding. TXA has a role in reducing postoperative bleeding and the need for postoperative knee transfusion without increasing the risk of surgery performed.[13] TXA can be given intravenously (IV) or intraarticularly (IA). Studies report that intraarticular administration of TXA can significantly reduce postoperative intraarticular bleeding and has a low risk of systemic side effects.[9] Physiologically, IA TXA can be rapidly absorbed by the body locally with a physiological half-life of TXA in the joint gap of around 3 hours so that local hemostasis will be achieved.[11]

Most studies have found that IA TXA is effective in reducing the amount of bleeding in arthroscopy ACL reconstruction. The study from Chiang et al confirmed that administration of 10 ml of TXA (100 mg/ml) can significantly reduce postoperative bleeding in the drain. The study conducted by Ma et al found that the administration of 15 mg/kg in 100 ml of saline solution has also significantly reduce postoperative bleeding. The same result from Mikic et al that was given 20 ml solution of TXA.[9,11,12] However, this is different from the study conducted by Lee et al who found that IA TXA 30 mg/ml did not effectively reduce bleeding in ACL reconstruction and was not significantly different from the control group. However, in their study, no drain was installed so that the estimated blood loss was assessed using the indirect method, as one of the limitations of their study.[10] The maximum dose of TXA is 1 gram.[14] In fact, there have been many studies that have assessed the effectiveness of TXA in various arthroscopy cases, not only in ACL cases. TXA is considered effective because it can reduce blood loss of the knee, regulate fibrinolytics function, and reduce inflammatory reactions. The study also stated that TXA does not pose a thromboembolic risk. The ability of IA TXA to reduce blood loss rates will also reduce the patient's need for blood transfusions.[15]

TXA has been shown to not only reduce the effects of blood loss but also reduce pain. This is associated because TXA has an anti-inflammatory effect that can increase postoperative analgesia.[16] Chiang et al found that the VAS value was significantly lower on the 3rd day after ACL arthroscopy, indicating an early benefit of TXA use. However, the difference between the control and IA TXA groups was different at week 4, indicating that the effect of TXA may decrease after the postoperative period.[9] This is different from the study of Lee et al, which stated that there was no significant comparison of pain between IA TXA and the control group. His study stated that the level of pain will be influenced by analgesia, anesthesia protocol, and surgical technique used.[10]

Chiang et al found that there were no cases of hemarthrosis in their study.[9] Studies by Chiang et al and Lee et al also found no difference in ROM between the IA TXA group and the control group.[9,10] In cases of hemarthrosis, patients generally require aspiration or arthrocentesis procedures. This procedure will cause discomfort to the patient and can be a source of infection.[12] Another study by Karaaslan et

al provided evidence that TXA is effective in reducing drainage, reducing hemarthrosis, and reducing the need for knee aspiration.[8] However, in the study by Mikic et al, there were cases of hemarthrosis that required aspiration in cases of IA TXA. His study added that additional research is needed to confirm the late effect of IA TXA on the incidence of hemarthrosis.[12] Prevention of hemarthrosis can help minimize joint fibrosis after injury so that it can maintain joint ROM and maintain short-term function. The hemarthrosis process can also affect the healing of ligaments or menisci so it should be prevented.[10] Hemarthrosis can be associated with patellar circumference. As found by Ma et al, there was a significant difference in patellar circumference given IA TXA (Ma et al, 2021). In contrast to the study conducted by Nugent et al who found that patellar circumferences were not significantly different from IA TXA on arthroscopy. Although not significant, patellar circumferences were found to be lower with IA TXA compared to the control group.[17]

The effectiveness of the ACL reconstruction procedure was also assessed using the Lysholm score. This scoring is one of the instruments used to assess the outcome of patients with knee-related problems and is generally also used to determine the functional status of patients after ACL reconstruction.[18] Ma et al found that the Lysholm score was significantly different between the IA TXA group and the control group, where IA TXA had a better Lysholm score. His study stated that the difference in Lysholm score could be caused by differences in the dose and frequency of TXA administration. To achieve a good score, because the average duration of the TXA effect is around 3 hours, several studies suggest giving a second dose to extend the effect during the first 6 hours, when the most bleeding occurs.[11]

The chondrotoxic effect after IA TXA administration is an important but controversial issue. It is currently unclear whether TXA can damage the joint environment which is potentially said to cause apoptosis of chondrocytes and tenocytes. Several studies have shown that TXA given at high doses can cause detrimental effects on human or animal chondrocytes in vitro.[19,20] Previous studies have shown that TXA at an appropriate dose (concentration up to 40 mg/ml) has no effect on chondrocytes after 6 hours of exposure. Considering that ACL reconstruction will be filled with irrigation fluid and hemarthrosis, the concentration of TXA will decrease. Therefore, the dose of IA TXA needs to be reviewed further.[21]

However, in addition, considering the benefits obtained by IA TXA in ACL reconstruction cases, it can be assessed that the use of IA TXA can reduce drainage output and the risk of knee swelling, hemarthrosis incidence, pain intensity, and the need for aspiration in the postoperative period. Although through the same route, intraarticularly, the dose of TXA given can be different and can affect patient outcomes so this needs to be considered.[12] The potential benefits of IA TXA given locally even with higher local concentration have good results because they can prevent the risk of adverse systemic effects such as infection, deep vein thrombosis, retears, or revisions through the administration of this procedure. Previous studies have found that there are no systemic side effects produced by IA TXA in ACL reconstruction.[9] The absence of side effects caused by IA TXA indicates that the use of IA TXA is a safe solution and can be beneficial in ACL arthroscopy.[9,12]

CONCLUSION

IA administration of TXA can be considered as a safe modality with good tolerance to overcome bleeding or pain in ACL patients undergoing arthroscopy. Not only reducing the risk of bleeding and pain, IA TXA also provides a decrease in the risk of hemarthrosis, good Lysholm scores, and minimal systemic side effects in patients. Therefore, IA TXA has good benefits in ACL arthroscopy and can be used clinically.

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