Effect of tranexamic acid in arthroscopic anterior cruciate ligament repair: A systematic review and meta-analysis of randomised clinical trials

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Abstract
Purpose: Perioperative blood loss remains a major challenge to surgeons in anterior cruciate ligament reconstruction (ACLR) surgery, despite of the introduction of minimally invasive approach. Tranexamic acid (TXA) is believed to reduce blood loss, which may minimise the complication of postoperative haemarthrosis with insufficient evidence on its effectiveness in ACLR. The primary aim of this study was to examine the effect of TXA on postoperative blood loss and other secondary outcomes in patients undergoing arthroscopic ACLR surgery. Method: PUBMED, EMBASE, MEDLINE and CENTRAL database were systematically searched from its inception until November 2020. All randomised clinical trials (RCTs) comparing TXA (intravenous or intra-articular) versus placebo in the arthroscopic ACLR surgery were included. Case series, case report and editorials were excluded. Results: Five RCTs comprising of a total of 580 patients (291 in TXA group, 289 in control group) were included for qualitative and quantitative meta-analysis. In comparison to placebo, TXA group was significantly associated with lower postoperative blood loss (mean difference (MD): −81.93 ml; 95% CI −141.80 to −22.05) and lower incidence of needing knee aspiration (odd ratio (OR): 0.19; 95% CI 0.08 to 0.44). Patients who randomised to TXA were also reported to have better range of movement (MD: 2.86; 95% CI 0.54 to 5.18), lower VAS Pain Score (MD: −1.39; 95% CI −2.54 to −0.25) and higher Lysholm Score (MD: 7.38; 95% CI 2.75 to 12.01). Conclusion: In this meta-analysis, TXA reduced postoperative blood loss with lesser incidence of needing knee aspiration along with better range of knee movement and Lysholm score in patients undergoing arthroscopic ACLR surgery.

Keywords
anterior cruciate ligament repair, blood loss, meta-analysis, pain score, tranexamic acid

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Introduction
The arthroscopic-guided anterior cruciate ligament reconstruction surgery (ACLR) has replaced the approach of open incision due to better anatomical visualisation and minimal trauma impact on delicate structures surrounding the knee.¹ As a result, arthroscopic approach offers better recovery rate with shorter rehabilitation period and early return to work.¹ Thus, the number of patients undergoing ACLR surgery is on the rise every year.² Despite of its minimally invasive technique, it still comes with complications, namely postoperative haemarthrosis and pain, which

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could delay the recovery and rehabilitation process. Bahl and colleagues reported that the duration of first 3 months postoperatively is a critical period for rehabilitation and recovery to restore full range of knee movement. Two common bleeding sources were identified mainly from intra-articular femoral or tibial tunnels and harvested graft sites. Some surgeons advocate placing a drain at the surgical site prior to skin closure but multiple randomised controlled trials (RCTs) have proven this technique to be ineffective in the reduction of haemarthrosis in ACLR surgery.

Tranexamic acid (TXA) is a synthetic analogue of lysine, which acts as a competitive inhibitor at the plasminogen lysine-binding site to reduce postoperative bleeding. It is believed that the use of TXA reduced postoperative blood loss and incidence of severe haemarthrosis in patients undergoing ACLR surgery. Several studies have also reported lower incidence of blood transfusion in patients randomised to TXA in orthopaedic surgery. Furthermore, TXA has proven to be effective in reducing blood loss in other surgeries, such as transplant surgery, orthopaedic surgery and cardiac surgery. However, the use of TXA comes with its fatal adverse effect of thromboembolic events. The administration of TXA can either be given intravenously or direct intra-articular injection. McCormack reported that the plasma concentration of topical TXA was 90% lower than intravenous TXA, which may minimise its adverse events.

A recent meta-analysis and systematic review comprising of 71 RCTs with 7539 patients showed that topical TXA is effective in reducing postoperative blood loss and incidence of blood transfusion without any significant TXA’s adverse events in patients undergoing any surgical procedures. Several recent RCTs investigating the use of intravenous or intra-articular TXA in arthroscopic ACLR surgery were published with conflicting findings. Thus, a systematic review and meta-analysis is warranted to summarise the evidence use of TXA (intravenous or intra-articular) in arthroscopic ACLR surgery before any recommendation is made.

We hypothesised that the use of TXA reduced postoperative blood loss in patients undergoing arthroscopic ACLR surgery. The primary aim of this systematic review and meta-analysis was to examine the effect of TXA on postoperative blood loss in arthroscopic ACLR surgery. Secondary aims were to investigate the effect of TXA on pain score, Lysholm score, severity of haemarthrosis, range of knee movement and incidence of needing for knee aspiration.

Materials and methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards. The protocol was published on PROSPERO (CRD42020219757) before the literature search was conducted.

Search methods

Databases of OVID MEDLINE, OVID EMBASE, CENTRAL and PUBMED were systematically searched from their starting date until November 2020 for any RCTs comparing TXA versus placebo in arthroscopic ACRL surgery using autograft with or without meniscal surgeries. Keywords utilised for the search included ‘Tranexamic Acid [MeSH] OR Tranexamic Acid (All Text)’ and ‘Control Groups [MeSH] OR Control Group (All Text) OR Placebo Group (All Text)’ and ‘Anterior Cruciate Ligament Reconstruction [MeSH] OR Anterior Cruciate Ligament (All Text) OR Anterior Cruciate Ligament Reconstruction (All Text) OR Anterior Cruciate Ligament Repair (All Text) OR Arthroscopic Anterior Cruciate Ligament Reconstruction OR Orthopedics’. Any ongoing clinical trials of the relevant topic were also searched on the ClinicalTrials.gov.my. The search approach and search strategy are outlined in the Online Supplementary Tables 1 and 2, respectively. Observational studies, review papers, case series and case reports were excluded from this review and no language restriction was applied. Patients less than 18 years old or those with coagulative disorder or anti-coagulant therapy or thrombophilia were also excluded. All references of relevant articles were manually checked for any additional studies. Emails were sent to the relevant authors to request for any unclear data or missing information.

Based on the inclusion and exclusion criteria, the titles and abstracts of articles were independently screened by two authors (TKT and HJL). Any disagreement was resolved by a third author (RR). Subsequently, full text articles were screened by two authors (TKT and HJL) independently. Any conflicts were resolved by a third author (RR). The final included articles were discussed among all the authors to reach a general consensus. Primary outcome was postoperative blood loss (ml) in arthroscopic ACLR surgery. Secondary outcomes included pain visual analogue score (VAS), severity of haemarthrosis, range of knee movement, incidence of needing for knee aspiration and Lysholm score.

An online data extraction form was piloted prior to the process of data extraction. Two authors (TKT and HJL) independently extracted data from the included studies. A third author (RR) cross-checked the accuracy of the extracted data. Apart from the measured outcomes, other data namely name of author, year of publication, mode of administration TXA, total sample size and baseline demographic data were also extracted. Any values presented as median with range or interquartile range or 95% confidence interval (CI) were converted into mean ± standard deviation. Any discrepancies encountered were resolved by consulting a third author (RR).
The risk of bias assessment was conducted independently by two authors (TKT and HJL) using the Cochrane Risk of Bias Assessment tool. The criteria of assessment included selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential sources of bias. For all the domain of criteria, all the included RCTs were classified into low, unclear, and high risk of bias. Any disagreement was resolved via a discussion with a third author (RR).

**Data analysis**

Review Manager 5.3 software was utilised for data analysis. Mean difference (MD) was calculated as summary measure for continuous outcomes while odd ratio (OR) was calculated as the summary measure for dichotomous outcomes with 95% confidence interval. p-value of <0.05 was denoted as statistically significant difference for all the reported outcomes. The I-square ($I^2$) statistical test was used to evaluate degree of heterogeneity across studies. Value of $I^2$ less than 40%, 40–60% and more than 60% were considered as low, moderate and substantial degree of heterogeneity, respectively. Fixed-effect model was used for all the measured outcomes. If substantial heterogeneity was observed, a random-effect model was utilised. A subgroup analysis was performed based on different route of TXA administration for all the reported outcomes if adequate data was available.

**Results**

The PRISMA flow is displayed in the Figure 1. Searching four databases (OVID MEDLINE, OVID EMBASE, CENTRAL and PUBMED) identified 630 articles for titles/abstracts screening after the removal of duplicates. Applying inclusion and exclusion criteria, 15 articles were included for full text screening. Among all, 10 studies were excluded, which is showed in the Online Supplementary Table 3. The final five included RCTs (a total sample size of 580 patients) were included for qualitative and quantitative analysis. Searching of trial registry identified two ongoing study and one completed study as shown in the Online Supplementary Table 4.

**Study characteristics**

The publication dates of all the included studies ranged from 2015 to 2020. Two RCTs adopted the route of intra-articular injection and the remaining three RCTs gave intravenous injection of TXA. Among all the five included trials, four RCTs reported operative time of less than an hour for arthroscopic ACLR surgery. Of all the included five RCTs with a total of 580 patients, 291 patients were assigned to the TXA group and 289 patients were assigned to the control group. The dosage of TXA ranged from 1 to 3 gram across all the included RCTs.
The clinical characteristics, dosage of TXA, route of administration and baseline characteristics of the included studies are outlined in Table 1. All the findings of primary and secondary outcomes are reported in Table 2.

**Risk of bias in included studies**

The risk of bias assessment for all the included studies are summarised in Figure 2. All the five studies demonstrated low risk of bias in the domains of random sequence generation and incomplete outcome data. High risk of allocation concealment was detected in Felli 2019 as they acknowledged the risk of accidental bias during the treatment allocation process.19

**Primary outcome**

Four RCTs with a total sample size of 532 patients examined the postoperative blood loss in the arthroscopic ACRL surgery.11,19–22 Our analysis demonstrated that the use of intra-articular or intravenous TXA reduced approximately 80 ml of postoperative blood loss in comparison to the placebo group (MD: −81.93 ml [95% CI −141.80 to −22.05], p = 0.007). However, statistical heterogeneity was observed as substantial (I² = 95%).

**Secondary outcomes**

In comparison to the placebo, the TXA group was associated with a significant lower postoperative VAS score (studies = 5, patients = 580, MD: −1.39 [95% CI, −2.54 to −0.25], p = 0.02).19–22 Heterogeneity was assessed as substantial (I² = 96%). All the included RCTs reported on the number of patients requiring postoperative knee aspiration.11,19–22 Our pooled data revealed that patients randomised to TXA was associated with lower incidence of needing knee aspiration than the placebo group (studies = 5, patients = 580, OR: 0.19 [95% CI, 0.08 to 0.46], p = 0.0002; I² = 0%).

In term of range of knee movement, patients who received TXA were associated with greater degree of knee movement than the placebo group (studies = 5, patients = 580, MD: 2.86 [95% CI, 0.54 to 5.18]; p = 0.02; I² = 0%).11,19–22 The TXA group was also significantly associated with higher Lysholm score as compared to the placebo group (studies = 3, participants = 233, MD: 7.38 [95% CI 2.75 to 12.01], p = 0.002; I² = 69%).11,19,21

Two RCTs (a total number of 405 patients) investigated the use of TXA in the severity of haemarthrosis.11,20 In comparison to the placebo group, our analysis showed that the TXA group was significantly associated with higher incidence of the lowest severity of haemarthrosis grade 0 (OR: 4.58 [95% CI, 3.86 to 35.12, p < 0.0001]) and 1 (OR: 11.64 [95% CI, 2.82 to 7.45, p < 0.0001]; and lower incidence of severe haemarthrosis grade 2 (OR: 0.61
Table 2. Summary of findings for primary and secondary outcomes.

| No | Outcomes                        | Trials | N   | I² (%) | Effect Model | MD/OR (95% CI)         | p-value |
|----|---------------------------------|--------|-----|--------|--------------|------------------------|---------|
| 1  | Estimated Blood Loss (mL)       | 4      | 532 | 95     | REM          | –81.93 (–141.80, –22.05) | 0.007   |
|    | Subgroup analysis by type of surgeries |       |     |        |              |                        |         |
|    | Intra-articular injection       | 2      | 347 | 0      | REM          | –25.04 (–42.10, –7.99)  | 0.004   |
|    | Intravenous administration      | 2      | 185 | 95     | REM          | –109.56 (–180.40, –38.72) | 0.002   |
|    | Heterogeneity: Tau² = 3053.37; Chi² = 58.37; df = 3 |       |     |        |              |                        |         |
|    | (p < 0.0001); I² = 95%          |        |     |        |              |                        |         |
|    | Test for overall effect: Z = 2.68 (p = 0.007) |       |     |        |              |                        |         |
|    | Test for subgroup differences: Chi² = 5.17, df = 1 (p = 0.02), I² = 80.7% |       |     |        |              |                        |         |
| 2  | Postoperative VAS Pain Score    | 5      | 580 | 96     | REM          | –1.39 (–2.54, –0.25)    | 0.02    |
|    | Subgroup analysis by type of surgeries |       |     |        |              |                        |         |
|    | Intra-articular injection       | 2      | 347 | 96     | REM          | –2.23 (–4.78, 0.32)     | 0.09    |
|    | Intravenous administration      | 3      | 233 | 77     | REM          | –0.97 (–1.59, –0.34)    | 0.01    |
|    | Heterogeneity: Tau² = 1.59; Chi² = 101.21; df = 4 |       |     |        |              |                        |         |
|    | (p < 0.00001); I² = 96%        |        |     |        |              |                        |         |
|    | Test for overall effect: Z = 2.38 (p = 0.007) |       |     |        |              |                        |         |
|    | Test for subgroup differences: Chi² = 0.89, df = 1 (p = 0.34), I² = 0% |       |     |        |              |                        |         |
| 3  | Postoperative Range of Motion (°) | 5      | 580 | 0      | FEM          | 2.89 (0.54, 5.18)       | 0.02    |
|    | Subgroup analysis by type of surgeries |       |     |        |              |                        |         |
|    | Intra-articular injection       | 2      | 347 | 0      | FEM          | 0.92 (–5.24, 7.09)      | 0.77    |
|    | Intravenous administration      | 3      | 233 | 0      | FEM          | 3.18 (0.68, 5.68)       | 0.01    |
|    | Heterogeneity: Chi² = 1.18, df = 4 (p = 0.88); I² = 0% |       |     |        |              |                        |         |
|    | Test for overall effect: Z = 2.42 (p = 0.02) |       |     |        |              |                        |         |
|    | Test for subgroup differences: Chi² = 0.44, df = 1 (p = 0.51), I² = 0% |       |     |        |              |                        |         |
| 4  | Incidence of Joint Aspiration  | 5      | 580 | 0      | FEM          | 0.19 (0.08, 0.44)       | 0.0001  |
|    | Subgroup analysis by type of surgeries |       |     |        |              |                        |         |
|    | Intra-articular injection       | 2      | 347 | NA     | FEM          | 0.19 (0.08, 0.44)       | 0.0001  |
|    | Intravenous administration      | 3      | 233 | 0      | FEM          | 0.19 (0.08, 0.44)       | 0.0001  |
|    | Heterogeneity: Chi² = 0.92, df = 2 (p = 0.63); I² = 0% |       |     |        |              |                        |         |
|    | Test for overall effect: Z = 3.79 (p = 0.0001) |       |     |        |              |                        |         |
|    | Test for subgroup differences: Not applicable |       |     |        |              |                        |         |
| 5  | Haemarthrosis Grade 0           | 2      | 405 | 23     | FEM          | 11.64 (3.86, 35.12)     | <0.0001 |
| 6  | Haemarthrosis Grade 1           | 2      | 405 | 0      | FEM          | 4.58 (2.82, 7.45)       | <0.00001|
| 7  | Haemarthrosis Grade 2           | 2      | 405 | 0      | FEM          | 0.61 (0.39, 0.96)       | 0.03    |
| 8  | Haemarthrosis Grade 3           | 2      | 405 | 25     | FEM          | 0.41 (0.25, 0.67)       | 0.0003  |
| 9  | Haemarthrosis Grade 4           | 2      | 405 | 55     | FEM          | 0.13 (0.06, 0.29)       | <0.00001|
| 11 | Postoperative Lysholm Score     | 3      | 233 | 69     | FEM          | 7.38 (2.75, 12.01)      | 0.002   |

MD: mean difference; OR: odds ratio; REM: random-effect model; FEM: fixed-effect model; NA: not applicable; NE: not estimated.

[95% CI, 0.39 to 0.96, p = 0.03), grade 3 (OR: 0.41 [95% CI, 0.25 to 0.67, p = 0.003) and grade 4 (OR: 0.13 [95% CI, 0.06 to 0.29, p < 0.00001).

**Subgroup analysis**

In the subgroup analysis based on the route of TXA administration, the outcomes of VAS pain score (studies = 2, patients = 347, MD: –2.23 [95% CI, –4.78 to 0.32, p = 0.09) and range of knee movement (studies = 2, patients = 347, MD: 0.92 [95% CI, –5.24 to 7.09, p = 0.77) became non-significant in the intra-articular TXA group as compared to the intravenous TXA group. The results of these interactions may be skewed due to limited studies of small sample size. For our primary outcome (postoperative blood loss), both the findings of intra-articular (studies = 2,
patients = 347, MD: \(-25.04\) [95% CI, \(-42.10\) to \(-7.99\), \(p = 0.004\)] and intravenous TXA (studies = 2, patients = 347, MD: \(-109.56\) [95% CI, \(-180.40\) to \(-38.72\), \(p < 0.0001\)] groups remained significant.

Discussion

Our meta-analysis demonstrated that the use of TXA reduced postoperative blood loss and incidence of needing knee aspiration with lower pain score. Patients who randomised to TXA were also noted to have significant lower incidence of severe haemarthrosis than the placebo group. However, the present systematic review needs to be interpreted with caveats due to small sample size, high risk of bias in some of the included studies, substantial degree of heterogeneity and non-standardised dosage of TXA. Due to the limited available RCTs in the literature, the present review included both intravenous and intra-articular route of administration of TXA. It is believed that the intra-articular administration of TXA will be associated with lower plasma TXA level than intravenous injection of TXA, resulting in lower systemic adverse events (incidence of thromboembolism or stroke) of TXA.\(^{27-30}\) A recently published meta-analysis of 71 RCTs (7539 patients) also concluded that topical use of TXA reduced intraoperative blood loss and blood transfusion in surgical patients without any notable adverse events associated with TXA.\(^{18}\)

The present meta-analysis reported that TXA reduced postoperative blood loss (approximately 80 ml) in patients undergoing arthroscopic ACLR surgery. This seems like a negligible amount of blood loss to an adult, however the accumulation of such amount of blood loss in the operated knee joint will result in severe joint complications, such as haemarthrosis and septic arthritis.\(^{31}\) The finding in this study was similar to other meta-analyses examining the use of intravenous TXA in the reduction of postoperative blood loss, incidence of blood transfusion without any notable thromboembolic risk.\(^{14,32-35}\) However, it remains unclear regarding the optimal safe dose of TXA for intra-articular joint injection. Parker and colleagues reported that intra-articular TXA injection >20 mg/ml or more than 3 g into joint could be cytotoxic to the chondrocytes, which may impair recovery process of joint postoperatively.\(^{36,37}\) Substantial heterogeneity was also observed in this measured outcome due to limited trials of small sample size and inclusion of different route of TXA administration. Different route of TXA administration in orthopaedic surgeries is still debatable. A meta-analysis by Montroy and co-workers demonstrated no significant difference in term of postoperative blood loss and incidence of blood transfusion between both the intravenous TXA and topical TXA groups.\(^{38}\) The subgroup analysis in the present review demonstrated similar positive effects of intra-articular and intravenous injection of TXA in the reduction of postoperative blood loss. However, no data of adverse events associated with intra-articular or intravenous TXA was available for data analysis. In contrast, the most updated systematic review and meta-analysis by Li and colleagues comparing intravenous versus intra-articular TXA in total knee replacement surgery reported greater reduction of intraoperative blood loss and incidence of blood transfusion in those who received intra-articular TXA.\(^{39}\) Thus, future adequately powered RCTs are warranted to fill knowledge gap with regard to the efficacy and safety of different route of TXA administration in arthroscopic ACLR surgery. Of note, the threshold of blood transfusion varies from one study to another, which may potentially introduce variances to the finding.

The present systematic review found that TXA patients were associated with lower incidence of needing knee aspiration and lower severity of haemarthrosis than the placebo group. Haemarthrosis is defined as bleeding into the joint cavity due to intra-articular injury.\(^{31}\) It is one of the most common postoperative complication seen in an arthroscopic orthopaedics surgery.\(^{40}\) It can cause severe postoperative pain, joint infection or damage to articular cartilage, which impair the process of healing. A recent review based on level 1 and level 2 evidences by Belk and
colleagues demonstrated that the introduction of TXA is beneficial in improving severity of haemarthrosis in arthroscopic assisted orthopaedics surgery, and their results were consistent with our findings. In low grade haemarthrosis, joint aspiration is required to withdraw effusion and prevent tissue adhesion in the knee joint. However, knee arthrocentesis or knee washout is required for severe haemarthrosis. Pain secondary to the complication of haemarthrosis can lead to muscle wasting as a result of an ineffective strengthening exercise after surgery.

The present review showed that patients who randomised to TXA were associated with lower postoperative VAS pain score than those receiving placebo. The finding was consistent with a trial conducted by Guerreiro and co-workers where the TXA group was reported to have lower postoperative pain score. However, our finding needs to be interpreted with caution due to substantial degree of heterogeneity and limited RCTs of small sample size. The subgroup analysis also revealed that the data inclusion of intra-articular group with non-significant postoperative VAS score may introduce variances to the findings. VAS pain score is a numerical subjective measurement of pain intensity. It can be varied across different individuals given the same type of pain stimulus, depending on their pain threshold and perception of pain. Several studies showed that VAS score is effective in the assessment of acute pain score in patients undergoing knee surgery.

Two RCTs demonstrated lower level of inflammatory markers (IL-6 and C-reactive protein) in the TXA group when compared to the placebo group in hip replacement surgery. We postulate that good postoperative pain control can lead to greater degree of knee movement and hasten recovery process. In the present meta-analysis, it is demonstrated that TXA group was also reported to have greater range of knee movement and better Lysholm score (knee function assessment) after surgery. However, Belk and colleagues reported no significant difference in the range of knee movement between the TXA and control groups with substantial heterogeneity.

There were some limitations to our review. The protocol of TXA administration (dosage and route of TXA) varied across all the included RCTs. All the included RCTs of small sample size were not powered for our primary outcome (postoperative blood loss). Different RCTs adopt different methods in estimating postoperative blood loss. Three studies measured the amount of blood loss from the drainage bottle. In contrast, Lee and colleagues used haemoglobin-balance method to predict amount of blood loss as no intra-articular drain was inserted in their patients. In term of postoperative pain, there was no standardised analgesia protocol among all the included RCTs, which can contribute to high degree of heterogeneity. Two review articles suggested that the route of intra-articular TXA injection can be an alternative to intravenous TXA due to lower risk of systemic adverse effects of TXA. Future adequately powered trials are warranted to examine the efficacy and safety of intravenous versus intra-articular injection of TXA in the arthroscopic ACLR surgery.

**Conclusion**

In this meta-analysis, TXA reduced postoperative blood loss with lesser incidence of needing knee aspiration along with better range of knee movement and Lysholm score in patients undergoing arthroscopic ACLR surgery.

**Author contributions**

TKT: Protocol/project management, Data collection or management, Data analysis, Manuscript writing/editing. KTN: Manuscript writing/editing. HJN: Data collection or management. SBH: Manuscript writing/editing. RR: Manuscript writing/editing.

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**Supplemental material**

Supplemental material for this article is available online.

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