Impact of Tourniquet During Total Knee Arthroplasty when Tranexamic Acid was used: A Meta-analysis of Randomized Controlled Trials

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Abstract

Introduction: The efficacy of tourniquet use during primary total knee arthroplasty (TKA) is thought to reduce intraoperative blood loss, improve surgical exposure, and optimize cement fixation. Tranexamic acid (TXA) use can decrease postsurgical blood loss and transfusion requirements. This review aimed to appraise the effects of tourniquet use in TKA for patients with tranexamic acid use.

Methods: A meta-analysis was conducted to identify relevant randomized controlled trials involving TXA plus a tourniquet (TXA-T group) and use of TXA plus no tourniquet (TXA-NT group) in TKA. Web of Science, PubMed, Embase, Cochrane Controlled Trials Register, Cochrane Library, Highwire, CNKI, and Wanfang database were searched from 2010 through October 2021.

Results: We identified 1720 TKAs (1690 patients) assessed in 14 randomized controlled trials. Compared with the TXA-NT group, the TXA-T group resulted in less intra-operative blood loss (P < 0.00001) and decreased duration of surgery (P < 0.00001), however more hidden blood loss (P = 0.0004) and less knee range of motion (P < 0.00001). No significant differences were found between two groups in terms of decrease in hemoglobin (P = 0.84), total blood loss (P = 0.79), transfusion rate (P = 0.18), drainage volume (P = 0.06), Visual Analogue Scale (VAS) at either the day of surgery (P = 0.2), day 1 (P = 0.25), day 2 (P = 0.39), day 3 (P = 0.21), day 5 (P = 0.21), day 7 (P = 0.06), or 1 month after surgery (P = 0.16), Hospital for Special Surgery (HSS) score at either 7 day (P = 0.10), 1 month (P = 0.08), 3 month (P = 0.22) or 6 month after the surgery (P = 0.92), Knee circumference (P = 0.28), length of hospital (P = 0.12), and complications such as intramuscular venous thrombosis (P = 0.81), deep venous thrombosis (P = 0.10), superficial infection (P = 0.45), deep wound infection (P = 0.64) and delayed wound healing (P = 0.65).

Conclusion: No big differences could be found by using or not tourniquet when use the TXA, though some benefits are related to operation time and less intra-operative blood loss by using tourniquet and TXA. Using the tourniquet was related to more hidden blood loss and less knee range of motion. More adequately powered and better-designed randomized controlled trials (RCTs) studies with long-term follow-up are required to validate this study.

1. Introduction

Tourniquet use has been considered an essential element of the total knee arthroplasty (TKA). Many surgeons apply a tourniquet during TKA to reduce blood loss and operative times, improve surgical exposure, optimize cement fixation, and increase tissue concentrations of antibiotic drugs through intraosseous regional administration (1–5). However, the once highly regarded advantages of tourniquet use have come under great scrutiny in light of its potential disadvantages. Issues which bring its use into question included reperfusion injury (6), patellar tracking issues (7), increased perioperative pain (8, 9), increased postoperative limb swelling (10, 11), decreased postoperative range of motion (ROM) (12), delayed rehabilitation (12), increased risk of thrombosis (13, 14), more frequent wound complications (15–17) and its negative effect on patients with vascular disease (18). More recently, as a new strategy for reducing blood loss, perioperative administration of tranexamic acid (TXA) has gained popularity during TKA, mitigating some of the adverse effects of tourniquet use. Several studies have confirmed that TXA significantly reduces blood loss and transfusion requirements without increasing venous thrombotic events (19–21). Although there are many systematic reviews and meta-analysis comparing tourniquet use and non-tourniquet use during TKA. There was no meta-analysis comparing the effects of TXA plus a tourniquet and the use of TXA plus no tourniquet. Therefore, we compare the impact of TXA plus a tourniquet
and use of TXA plus no tourniquet in TKA. This review aimed to appraise the effects of tourniquet use in TKA for patients with tranexamic acid use.

2. Methods

2.1. Protocol and registration

The study protocol was registered with International prospective register of systematic reviews (PROSPERO), and the registration number was CRD42020185403. This meta-analysis was performed using a predetermined protocol following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to assess the results' quality to make sure our meta-analysis's results reliable and veritable.

2.2. Search strategy

A meta-analysis was conducted to identify relevant randomized controlled trials involving TXA plus a tourniquet (TXA-T group) and use of TXA plus no tourniquet (TXA-NT group) in TKA. Web of Science, PubMed, Embase, Cochrane Controlled Trials Register, Cochrane Library, Highwire, CNKI, and Wanfang database were searched from 2010 through October 2021. The keywords used were "total knee replacement," "total knee arthroplasty," "tourniquet," "tranexamic acid," "TXA," "randomized controlled trials" in conjunction with Boolean operators 'AND' or 'OR.' We used Review Manager Software for MAC to perform the meta-analysis.

2.3. Inclusion criteria

Studies were eligible if 1. The intervention was patients undergoing primary TKA using TXA and a tourniquet (TXA-T group); 2. The comparator was patients undergoing primary TKA using TXA and without tourniquet use (TXA-NT group); 3. The design of the study was a randomized controlled trial (RCTs); 4. The clinical outcome data were intra-operative blood loss (IBL), hidden blood loss (HBL), total blood loss (TBL), drainage volume, decrease in hemoglobin level, transfusion rate, Visual Analogue Scale (VAS) score, Hospital for Special Surgery (HSS) score, knee circumference, knee range of motion (ROM), length of stay (LOH), complications including intramuscular venous thrombosis (IMVT), deep venous thrombosis (DVT), superficial infection, deep wound infection, delayed wound healing. 5. The studies were required to contain at least one clinical outcome data; The exclusion criteria were as follows: 1. Observational studies; 2. non-RCTs; 3. studies with insufficient clinical outcome data.

2.4. Data extraction process

Two reviewers (C.J.S and Q.M.) used a standardized form to extract data. A third reviewer (X.C) was used to resolve disagreements in eligibility, data extraction, or quality assessment. Extracted data included the primary data based on the following: first author, year of publication, participants, age, gender, body mass index, diagnosis, anesthesia, prosthesis, patellar resurfacing, tourniquet pressure, tourniquet realizing time, TXA administration, drainage, thromboprophylaxis.

2.5. Assessment of studies

The studies' methodological quality was assessed following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions

2.6. Statistical Analysis
RevMan software (version 5.4; The Cochrane Collaboration) was used for the analysis. The statistical heterogeneity was tested with the $X^2$ test and $I^2$ test. $I^2 < 25\%$ was considered low statistical heterogeneity, $I^2 < 50\%$ moderate statistical heterogeneity, and $I^2 < 75\%$ high statistical heterogeneity. If the P value of heterogeneity was less than 0.1, heterogeneity would exist. Then, the random-effects model was used for meta-analysis. Data were summarized as the ratio of relative risk (transfusion rate, complications including the rate of IMVT, DVT, superficial infection, deep wound infection, delayed wound healing.) or the difference between means (IBL, HBL, TBL, drainage volume, decrease in hemoglobin level, VAS score, HSS score, knee circumference, knee ROM and LOH). For studies that did not report standard deviations (SDs), it was calculated from p values, confidence intervals, or standard errors. The results were considered as a statistically significant difference when P values were less than 0.05.

3. Results

The search strategy identified 259 studies, of which 245 were excluded after screening in Fig. 1. The literature search identified 259 citations. Of these, 164 duplicates were removed. After examining the titles and abstracts of the 95 remaining articles, we excluded 77 papers according to the inclusion and exclusion criteria; the full text of 18 articles was retrieved. Because we could not acquire sufficient data in one article, and four studies were non-RCTs. Hence four studies were excluded. Fourteen articles were assessed for eligibility. In Palanne’s (22) article, there were two subgroups comparing TXA+ tourniquet group with TXA+ NT group. One is the spinal anaesthesia subgroup, The other is the general anaesthesia subgroup. So we divided the study into two groups, Palanne 2020(1) and Palanne 2020(2). Finally, we identified 1720 TKAs (1690 patients) assessed in 15 randomized controlled trials(2, 22–34). Study baseline characteristics and general intervention information are summarized in Table 1-table 4.
| Author/year       | Patients | Knees | Mean age(years) | Female gender(%) | BMI | Diagnosis            |
|------------------|----------|-------|-----------------|------------------|-----|----------------------|
| Alexandersson 2018 | 38/43    | 38/43 | 68/69.7         | 52.6/48.8        | 28.6/27.9 | 38OA/43OA           |
| Concina 2019     | 50/50    | 50/50 | NA              | NA               | NA | NA                   |
| Eraz 2014        | 33/31    | 33/31 | 68/68           | 45.5/45.2        | 25/25 | 33OA/31OA           |
| Huang 2017       | 50/50    | 50/50 | 66.2/65.1       | 64/68            | 25.1/24.4 | 50OA/50OA          |
| Ma 2017          | 31/32    | 31/32 | 66.8/67.2       | 61.3/65.6        | 24.38/24.02 | 31OA/32OA         |
| Palanne 2020^1   | 101/99   | 101/99 | 64/63           | 72.3/58.6        | 30.7/30.8 | 101OA/99OA         |
| Palanne 2020^2   | 99/96    | 99/96 | 63/65           | 62.6/61.5        | 30.5/29 | 99A/96OA            |
| Wang 2017        | 30       | 30/30 | 65.9/65.9       | 86.7/86.7        | 26.6/26.6 | 30OA/30OA          |
| Wang 2019        | 30/30    | 30/30 | 62.8/64.1       | 90/73.3          | 23.48/23.68 | 30OA/30OA       |
| Xie 2017         | 45/45    | 45/45 | 66.2/66.1       | 85/75            | 26.1/25.9 | NA                  |
| Xu 2018          | 30/30    | 30/30 | 68.2/69.1       | 60/53.3          | NA | 30OA/30OA           |
| Yu 2017          | 40/40    | 40/40 | 60.65/62.6      | NA               | NA | 40OA/400A           |
| Zak 2021         | 161/166  | 161/166 | 66.5/67.6     | 57/66            | 30.55/30.63 | 161OA/166OA     |
| Zeng 2021        | 50/50    | 50/50 | 68.44/68        | 84/86            | 25.34/26.13 | 50OA/50OA        |
| Zhou 2017        | 72/68    | 72/68 | 66.8/69.1       | 81.9/89.7        | 26.1/25.7 | 50OA/52OA;22RA/16RA |

The detailed baseline characteristics information, including the number of TKAs, age, gender, BMI, and two groups' diagnosis.

Abbreviations: OA=osteoarthritis; RA=rheumatoid arthritis; BMI=body mass index; TXA= Tranexamic acid
| Author/year | Anesthesia | Prothesis | patellar resurfacing | Drainage |
|------------|------------|-----------|----------------------|----------|
| Alexandersson 2018 | spinal/general anesthesia, | NexGen fixed bearing (Zimmer) | No | No |
| Concina 2019 | NA | Triathlon® (Stryker) and Attune® (DePuy) | NA | No |
| Ejaz 2014 | spinal anesthesia | NexGen fixed bearing (Zimmer) | Yes | No |
| Huang 2017 | general anesthesia | NA | NA | Yes |
| Ma 2017 | general anesthesia and FNB | PS, PFC (DePuy) | NA | Yes |
| Palanne 2020¹ | spinal anesthesia | Triathlon® (Stryker) | Yes | No |
| Palanne 2020² | general anesthesia | Triathlon® (Stryker) | Yes | No |
| Wang 2017 | general anesthesia | GenesisII (Smith&Nephew) or NexGen (Zimmer) | No | Yes |
| Wang 2019 | general anesthesia | PS Haixing (Weihai) | NA | Yes |
| Xie 2017 | general anesthesia | PS (Depuy) | No | Yes |
| Xu 2018 | general anesthesia | NA | No | Yes |
| Yu 2017 | spinal anesthesia | NA | Yes | Yes |
| Zak 2021 | NA | NA | NA | No |
| Zeng 2021 | | PS, PFC (DePuy) | NA | Yes |
| Zhou 2017 | general anesthesia | PS, PFC (DePuy) | NA | Yes |

The detailed information of surgery including anesthesia, prosthesis, patellar resurfacing, and drainage of two groups

Abbreviations: FNB= femoral nerve block; PS=Posterior Cruciate-Stabilizing; CR=Cruciate Retaining.
Table 3
The detailed information of tourniquet use

| Author/year | Tourniquet pressure | Tourniquet realizing Time | TXA administration |
|-------------|---------------------|---------------------------|--------------------|
| Alexandersson 2018 | 300mmHg | After bandage applied | Intravenously, 1g, 10 min before surgery |
| Concina 2019 | 300mmHg | Before wound closure | Intravenously, 15mg/kg, 20 minutes before surgery and after 4 hours |
| Ejaz 2014 | 250mmHg | After bandages applied | Orally, 1g, before surgery; Orally, 0.5g 3 h after surgery |
| Huang 2017 | 100 mm Hg above systolic pressure | NA | Intravenously, 20 mg/kg, 5 to 10 minutes before the skin incision; Intravenous, 10 mg/kg, 3, 6, 12, and 24 hours after operation; Topical, 1 g, intraoperatively |
| Ma 2017 | 100 mm Hg above systolic pressure | NA | Intravenously, 20mg/kg, anesthesia induction; Topical, 1g, intraoperatively; Intravenous, 10 mg/kg, 3, 6, 12, 24h after anesthesia induction. |
| Palanne 2020¹ | 250mmHg | After bandages applied | Intravenously, 1g, 5 min before surgery; Topical, 1g, intraoperatively; 1g, 3h, 6h after surgery |
| Palanne 2020² | 250mmHg | After bandages applied | Intravenously, 1g, 5 min before surgery; Topical, 1g, intraoperatively; 1g, 3h, 6h after surgery |
| Wang 2017 | 300mmHg | After bandages applied | Intravenously, 1g, 15 min before surgery; Topical, 1g, intraoperatively |
| Wang 2019 | NA | After bandages applied | Intravenously, 1g, 15 min before surgery; Topical, 1g, intraoperatively; Intravenously, 1g, 3h after surgery |
| Xie 2017 | 100 mm Hg above systolic pressure | After bandages applied | Intravenously, 20 mg/kg, 10 min before surgery; Topical, 60ml, intraoperatively |
| Xu 2018 | 100 mm Hg above systolic pressure | After fascia layer closed | Intravenously, 1kg, 30 min before surgery |
| Yu 2017 | 300mmHg | After bandages applied | Topical, 1g, intraoperatively |
| Zak2021 | NA | NA | Intravenously, two dose of 1g, before surgery and during wound closure |

The detailed information of Tourniquet pressure, Tourniquet inflation time, tourniquet realizing time of two groups.
| Author/year | Tourniquet pressure | Tourniquet realizing Time | TXA administration |
|-------------|---------------------|--------------------------|-------------------|
| Zeng 2021   | 100 mmHg above systolic blood pressure | After bandages applied | Intravenously, 1kg, before surgery |
| Zhou 2017   | NA                  | NA                       | Intravenously, 1g, at the initiation of the surgery and just before closure |

The detailed information of Tourniquet pressure, Tourniquet inflation time, tourniquet realizing time of two groups.
Table 4
The detailed information of TXA and Thromboprophylaxis drugs

| Author/year | TXA administration | Thromboprophylaxis drugs |
|-------------|--------------------|--------------------------|
| Alexanderson 2018 | Intravenously, 1g, 10 min before surgery | Low-molecular weight heparin |
| Concina 2019 | Intravenously, 15mg/kg, 20 minutes before surgery and after 4 hours | Enoxaparine 4000 IU |
| Ejaz 2014 | Orally, 1g, before surgery; Orally, 0.5g 3 h after surgery | Rivaroxaban (10 mg/day) |
| Huang 2017 | Intravenously, 20 mg/kg, 5 to 10 minutes before the skin incision; Intravenous, 10 mg/kg, 3, 6, 12, and 24 hours after operation; Topical, 1 g, intraoperatively | Enoxaparine 4000 IU |
| Ma 2017 | Intravenously, 20 mg/kg, anesthesia induction; Topical, 1 g, intraoperatively; Intravenous, 10 mg/kg, 3, 6, 12, 24h after anesthesia induction. | Enoxaparine 4000 IU |
| Palanne 2020¹ | Intravenously, 1g, 5 min before surgery; Topical, 1g, intraoperatively; 1g, 3h, 6h after surgery | NA |
| Palanne 2020² | Intravenously, 1g, 5 min before surgery; Topical, 1g, intraoperatively; 1g, 3h, 6h after surgery | NA |
| Wang 2017 | Intravenously, 1g, 15 min before surgery; Topical, 1 g, intraoperatively | Rivaroxaban (10 mg/day) |
| Wang 2019 | Intravenously, 1g, 15 min before surgery; Topical, 1 g, intraoperatively; Intravenously, 1g, 3h after surgery | Enoxaparine 4000 IU |
| Xie 2017 | Intravenously, 20 mg/kg, 10 min before surgery; Topical, 60ml, intraoperatively | Enoxaparine 4000 IU |
| Xu 2018 | Intravenously, 1kg, 30 min before surgery | Rivaroxaban (10 mg/day) |
| Yu 2017 | Topical, 1g, intraoperatively | Rivaroxaban (10 mg/day) |
| Zak 2021 | Intravenously, two dose of 1g, before surgery and during wound closure | NA |
| Zeng 2021 | Intravenously, 1kg, before surgery | Rivaroxaban (10 mg/day) |
| Zhou 2017 | Intravenously, 1g, at the initiation of the surgery and just before closure | Rivaroxaban (10 mg/day) |

The detailed information of TXA and Thromboprophylaxis drugs of two groups. Abbreviations: h=hour; min=minute; IU= international unit; kg= kilogram; g= gram; mg=milligram; ml=millilitre.

The risk of bias summary and bias graph for RCTs is shown in Figs. 2 and 3. Fourteen studies adequately described the correct randomization. Thirteen studies demonstrated sufficient allocation concealment. Four studies described the blinding of participants and personnel. No studies described the blinding of outcome assessment. All thirteen articles retained complete outcome data and avoided selective reporting. We rated as
unclear risk of other bias because we can’t ignore other potential dangers of biases. As a result, there is low or moderate risk of bias in most of the articles reviewed (Fig. 2).

3.1. Blood loss

Nine RCTs reported IBL; Three RCTs reported HBS and Seven RCTs reported total blood loss. The pooled data showed that the TXA with tourniquet group had significantly decreased IBL (MD=-109.89, 95% CI [-148.04,-71.74], P<0.0001 Fig. 4). However, the TXA without tourniquet group has significantly increased HBL (MD=117.64, 95% CI [52.4,182.88], P=0.0004 Fig. 4). Both groups experienced similar TBL (MD=7.13, 95% CI [-46.23,60.49], P=0.79 Fig. 4).

3.2. Drainage volume

Five RCTs reported drainage volume. The forest plot showed that the drainage volume was not significantly different between the two groups (MD=69.50, 95% CI [-3.91,142.9], P=0.06 Fig. 5).

3.3. Decrease in hemoglobin

Four RCTs reported a decrease in hemoglobin. The pooled data revealed that the reduction in hemoglobin was not significantly different between the two groups (MD=7.90, 95% CI [-5.44,6.68], P=0.84 Fig. 6).

3.4. Transfusion rate

Seven RCTs reported the transfusion rate. The forest plot revealed that the transfusion rate was not significantly different between the two groups (RD=0.07, 95% CI [-0.02,0.04], P=0.18 Fig. 7).

3.5. Duration of surgery

Five RCTs reported duration of surgery, TXA with tourniquet group have significantly decreased time of surgery compared with TXA-NT group (MD=-1.05, 95% CI [-1.46,-0.64], P<0.0001 Fig. 8).

3.6. VAS

Four RCTs reported VAS on the day of surgery. Ten RCTs reported VAS on the first day after surgery. Six RCTs reported VAS on the third day after surgery. Two RCTs reported VAS on the second and fifth day after surgery. Three RCTs reported VAS on the seventh day after surgery. Two RCTs reported VAS at one month after surgery. The results of random-effects meta-analysis showed no significant differences between the two groups in the postoperative VAS score at either the day of surgery (MD=1.56, 95% CI [5.0,3.62], P=0.20 Fig. 9), first day (MD=0.42, 95% CI [0.29,1.13], P=0.25 Fig. 9), second day (MD=0.16, 95% CI [0.21,0.54], P=0.39 Fig. 9), third day (MD=0.20, 95% CI [-0.12,0.53], P=0.21 Fig. 9), fifth day (MD=0.95, 95% CI [-0.52,2.42], P=0.21 Fig. 9), seventh day (MD=0.89, 95% CI [-0.04,1.83], P=0.06 Fig. 9) or 1 month after surgery (MD=0.16, 95% CI [-0.06,0.39], P=0.16 Fig. 9).

3.7. HSS

Three RCTs reported HSS 7 day, 1 month, 3 month after surgery. Two RCTs reported HSS 6 month after surgery. The pooled results showed that both groups experienced similar HSS scores at either 7 day (MD=-10.11, 95% CI [-21.98,1.76], P=0.10; Fig. 10), 1 month (MD=-2.93, 95% CI [-6.22,0.35], P=0.08; Fig. 10), 3 month (MD=-0.73, 95% CI [-1.89,0.43], P=0.22; Fig. 10) or 6 month after the surgery (MD=-0.08, 95% CI [-1.84,1.67], P=0.92; Fig. 10).

3.8. Knee circumference
Two RCTs reported Knee circumference. We detected a similar knee circumference between two groups (MD=5.86, 95% CI -4.72,16.44], P=0.28; Fig. 11).

3.9. Knee ROM

Six RCTs reported Knee ROM. TXA with tourniquet group have significantly decreased knee ROM compared with TXA-NT group (MD=-2.68, 95% CI -3.30, -2.07], P=0.00001; Fig. 12)

3.10. LOH

Nine RCTs reported LOH. No significant difference was found for LOH between both groups (MD=0.40, 95% CI -0.1, -0.9], P=0.12; Fig. 13)

3.11. Complications

Five RCTs reported intramuscular venous thrombosis. Six RCTs reported Deep venous thrombosis. Five RCTs reported superficial infection, Four RCTs reported Deep wound infection. Four RCTs reported Delayed wound healing. We detected no significantly difference in terms of intramuscular venous thrombosis(RD=0.01, 95% CI -0.04,0.05], P=0.81; Fig. 14), deep venous thrombosis(RD=0.03, 95% CI -0.00,0.05], P=0.10; Fig. 14), superficial infection(RD=0.01, 95% CI -0.02,0.05], P=0.45; Fig. 14), deep wound infection(RD=0.01, 95% CI -0.02,0.04], P=0.64; Fig. 14), delayed wound healing(RD=0.01, 95% CI -0.03,0.04], P=0.65; Fig. 14) between two groups.

4. Discussion

Our study is the first meta-analysis to identify relevant randomized controlled trials involving TXA plus a tourniquet and use of TXA plus no tourniquet during TKA. This meta-analysis of 15 RCTs that evaluated a total of 1720 TKAs shows that TXA plus tourniquet group can decrease intraoperative blood loss and surgery duration however increase hidden blood loss and decrease the knee ROM. Our findings suggested that there were no significant differences in terms of total blood loss, decrease in hemoglobin, transfusion rate, drainage volume, VAS, HSS, Knee circumference, Knee ROM, LOH, and complications between the two groups. The result showing that the use of a tourniquet plus TXA effectively reduced intraoperative blood loss was consistent with the outcome of previous meta-analysis (35–37). However, we found the TXA-T group has more hidden blood loss. An explanation for these conflicting results of IBL and HBL indicates that hidden blood loss plays a key role. Tourniquet release can result in ongoing bleeding from cut cancellous bone (38), blood extravasated into the knee joint and adjacent soft tissues(39), or blood loss from hemolysis(40) because of tourniquet-induced ischemia(41, 42). Furthermore, there are no differences in drainage volume and total blood loss between the two groups, which is inconsistent with the previous meta-analysis. At an earlier meta-analysis(13, 37, 43), they found total blood loss to be significantly lower with a tourniquet. We think the reason for the difference between our study and previous meta- analysis(13, 37, 43) is the TXA used in all RCT studies included in our meta-analysis.

Hemoglobin level and transfusion rate have been recognized as the most objective indicators of actual blood loss. The decrease in hemoglobin and transfusion rate was similar in the TXA-NT group compared with the TXA-T group in our study. Blood transfusion is associated with adverse effects, including hemolytic reactions, infections, morbidity, immunologically mediated diseases, and cost (44). The result of similar transfusion rate in both groups
is consistent with Cai’s recent meta-analysis(45). They found no significant difference between the tourniquet group and the non-tourniquet group.

A tourniquet will provide surgeons with a bloodless surgery field to facilitate the clear identification of anatomical structures with less electrocoagulation and wound irrigation during surgery, which might help shorten the operation time. Our result showed tourniquet with TXA use reduced surgery duration, which was consistent with previous studies (2, 35, 38). So a reduction of course of surgery is a potential benefit of tourniquet use with TXA in TKA.

Pain relief in the early postoperative period after TKA is crucial in facilitating early recovery. Whether the use of tourniquets will increase postoperative pain remains controversial. Theoretically, tourniquet use may increase thigh pain and swell due to lower limb blood flow occlusion and ischemia-reperfusion injury. Our study identified no difference in pain intensity at either the day of surgery, first day, second day, the third day, fifth day, the seventh day, or one month after surgery. Although tourniquet pressure, time, and time of postoperative pain evaluation were variable across studies, we found that these factors of all included RCTs were comparable between experimental and control groups, so endpoints like VAS, ROM, and LOS could still be properly assessed. We also have tried our best to evaluate VAS based on time points. Our results of VAS were inconsistent with previous studies (25, 46, 47). It may be related to the tourniquet pressure in our tourniquet group. In our study, lower or personalized tourniquet pressure was used in 5 of the 11 RCTs. Worland et al. (48) showed an essential correlation between higher tourniquet pressure and more thigh pain in the immediate postoperative period.

Knee flexion ROM is often used to evaluate short-term effectiveness. Besides, discharge from the hospital is dependent on the mobility of patients following TKA. We found significantly decreased knee ROM in TXA-T group compared with TXA-NT group, which is inconsistent with the previous systematic review of 26 RCTs (13). We think the reason is that some studies in the previous analysis didn’t use TXA, and we included studies with TXA use, which may make the advantage of hemostasis effect with tourniquet less obvious compare with non-tourniquet group, So the impact on the knee range of motion appears more obvious compared with non-tourniquet group. No significant difference was also found in terms of knee circumference between the two groups. These findings seem logical, given that we found no significant difference in terms of VAS.

The analysis of the postoperative HSS at either seven days ± one-month ± three months or six months after the surgery also did not reveal a difference. HSS might be affected by many factors such as pain, ROM, function, muscle force, and flexion deformity. Moreover, the effect of a tourniquet application plus TXA on HSS needs to be further confirmed by more high-quality studies.

As for complications, we observed no significant difference in terms of IMVT, DVT, superficial infection, deep wound infection, delayed wound healing between the two groups. Although TXA use in TKA didn’t increase thromboembolic events (49–52), perhaps one of the more significant clinical concerns regarding tourniquet use plus TXA is its association with thromboembolism. No significant difference was found between groups regarding the rate of intramuscular venous thrombosis and deep venous thrombosis in our study. Several studies have investigated the incidence of venous thrombosis with the use of the tourniquet (3, 13, 14, 36, 53). However, the evidence is mixed because of heterogeneous study groups and designs, making it difficult to compare. Nonetheless, we cannot underscore the importance of chemoprophylaxis following TKA regardless of tourniquet use. DVT was detected in 81% of patients when all the patents only received mechanical compression but no chemoprophylaxis following TKA of tourniquet use(54).
The current meta-analysis has several limitations: First, there is a high heterogeneity of blood loss caused by the different methods for measuring blood loss, separate application of a tourniquet, different operative techniques, and different perioperative management as the drain and anticoagulant therapy. The reliability of results maybe influenced by this heterogeneity. Second, the studies' comparability was complicated through the different measurement methods and follow-up examination time points; however, we have tried our best to evaluate results based on time points. Third, the tourniquet time, the time for loosening the tourniquet, and the cuff pressure used were also not uniform. Fourth, there are no worldwide uniform guidelines for performing total knee arthroplasty. Different surgical techniques (such as the selection of approach, anesthesia methods, patellar resurfacing, and type of prosthesis) were used in the individual studies.

5. Conclusion

No big differences could be found by using or not tourniquet with TXA. Some benefits are related to operation time and less intra-operative blood loss by using tourniquet and TXA, however using the tourniquet and TXA was also related to more hidden blood loss and less knee range of motion. These are obvious conclusions that are confirmed after this meta-analysis. Given our meta-analysis's relevant possible biases, we required more adequately powered and better-designed RCT studies with long-term follow-up to reach a firmer conclusion.

Abbreviations

Cis=Confidence intervals; RCTs= randomized controlled trials; RR= Risk ratio; OR= odds ratio; VMD= Weighted mean difference; TXA= Tranexamic acid; TKA= total knee arthroplasty; OA= osteoarthritis; RA= rheumatoid arthritis; BMI= body mass index; VAS= Visual Analogue Scale; HSS= Hospital for Special Surgery; ROM= range of motion; IBL= intra-operative blood loss; HBL= hidden blood loss; TBL= total blood loss; LOH= length of stay; IMVT= intramuscular venous thrombosis; DVT= deep venous thrombosis.

Declarations

Ethics approval

Ethical approval is not required, because this study is based on existed literature.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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None.

**Author contribution**

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Figures

![Diagram of the search results and selection procedure]

The literature search identified 259 citations. Of these, 164 duplicates were removed. After examining the titles and abstracts of the 95 remaining articles, we excluded 77 papers.
according to the inclusion and exclusion criteria; the full text of 18 articles was retrieved. Fourteen articles were assessed for eligibility. In Palanne’s article, there were two subgroups comparing TXA+ tourniquet group with TXA+ NT group. So we divided the study into two groups. Finally, we identified 1720 TKAs (1690 patients) assessed in 15 randomized controlled trial.

Risk of bias summary: +: no bias; -: bias; ?: bias unknown. Fourteen studies adequately described the correct randomization. Thirteen studies demonstrated sufficient allocation concealment. Four studies described the blinding of participants and personnel. No studies described the blinding of outcome assessment. All thirteen articles retained complete outcome data and avoided selective reporting. We rated as unclear risk of other bias.
because we can't ignore other potential dangers of biases. As a result, there is low or moderate risk of bias in most of the articles reviewed.

**Figure 3**

Risk of bias graph The overall quality of the included studies was considered adequate.

| Study or Subgroup | TXA with a tourniquet | TXA without a tourniquet | Mean Difference Mean Difference IV, Random, 95% CI |
|-------------------|-----------------------|--------------------------|-----------------------------------------------|
| **1.1.1 Intra-operative (ml)** | | | |
| Concina 2019      | 168.42                | 101.67                   | 50 607.14 171.13 50 5.6% -438.72 [-493.89, -383.55] |
| Ejaz 2014         | 140                   | 32.7                     | 33 280 52 31 6.6% -140.00 [-161.44, -118.56] |
| Huang 2017        | 244.8                 | 80.1                     | 50 150.6 86 50 6.4% -5.80 [-32.38, 26.78] |
| Ma 2017           | 81.45                 | 35.94                    | 31 259.84 97.55 32 6.2% -178.39 [-234.48, -122.30] |
| Wang 2017         | 39.5                  | 20.7                     | 30 71.8 24.4 30 6.8% -32.30 [-43.75, -20.85] |
| Xie 2017          | 32.7                  | 9.4                      | 45 94.5 23.6 45 6.8% -61.80 [-69.22, -54.38] |
| Xu 2018           | 242.6                 | 26.5                     | 30 342.6 37.5 30 6.7% -100.00 [-116.43, -83.57] |
| Zeng 2021         | 70.2                  | 36.62                    | 50 159.8 28.32 50 6.8% -89.60 [-102.41, -76.77] |
| Zhou 2017         | 77.2                  | 14.5                     | 72 82 12.7 68 6.9% -6.40 [-9.31, -0.29] |
| **Subtotal (95% CI)** | 391                   | 386                      | 58.8% -109.89 [-148.04, -71.74] |

Heterogeneity: Tau² = 3327.02; Ch² = 713.88, df = 8 (P < 0.00001); I² = 99%
Test for overall effect: Z = 5.65 (P < 0.00001)

| **1.1.2 Hidden blood loss (ml)** |
|---------------------------------|
| Huang 2017                      | 421.2                 | 230.3                   | 50 293.9 176.9 50 4.6% 127.30 [46.81, 207.79] |
| Ma 2017                         | 770.81                | 564.45                  | 31 471.58 334.55 32 1.4% 299.23 [69.19, 529.27] |
| Xu 2018                         | 564.9                 | 78.9                    | 30 475.8 78.9 30 6.1% 89.10 [49.17, 129.03] |
| **Subtotal (95% CI)**           | 111                   | 112                     | 12.1% 117.64 [52.40, 182.88] |

Heterogeneity: Tau² = 1497.71; Ch² = 3.60, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 3.53 (P = 0.0004)

| **1.1.3 Total blood loss (ml)** | | | |
|---------------------------------| | | |
| Huang 2017                      | 734.5                 | 274.2                   | 50 627.7 198.1 50 4.1% 106.80 [51.04, 200.56] |
| Ma 2017                         | 837.7                 | 366.7                   | 31 1118.2 584.41 32 1.3% -280.30 [-520.63, -40.37] |
| Wang 2017                       | 251.5                 | 124.9                   | 30 272.5 107.4 30 5.4% -21.00 [-79.95, 37.95] |
| Xie 2017                        | 896.1                 | 245.4                   | 45 804.3 215.9 45 4.1% 91.80 [3.70, 187.30] |
| Xu 2018                         | 1044.4                | 113.8                   | 30 1005.7 102.8 30 5.6% 34.70 [20.18, 49.58] |
| Zeng 2021                       | 611.02                | 299.22                  | 50 693.1 333.43 50 3.2% -84.98 [108.26, 40.10] |
| Zhou 2017                       | 374.5                 | 165.3                   | 72 389.2 178.3 68 5.5% -14.70 [-71.74, 42.34] |
| **Subtotal (95% CI)**           | 308                   | 305                     | 29.1% 7.13 [-46.23, 60.49] |

Heterogeneity: Tau² = 3015.02; Ch² = 17.30, df = 6 (P = 0.008); I² = 65%
Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Ch² = 38.22, df = 2 (P < 0.00001); I² = 94.8%

**Figure 4**

A forest plot diagram showing blood loss Nine RCTs reported IBL; Three RCTs reported HBS and Seven RCTs reported total blood loss. The pooled data showed that the TXA with tourniquet group had significantly decreased
IBL (MD = -109.89, 95% CI [-148.04, -71.74], P = 0.00001). However, the TXA without tourniquet group has significantly increased HBL (MD = 117.64, 95% CI [52.4, 182.88], P = 0.0004). Both groups experienced similar TBL (MD = 7.13, 95% CI [-46.23, 60.49], P = 0.79).

Figure 5
A forest plot diagram showing drainage volume. Five RCTs reported drainage volume. The forest plot showed that the drainage volume was not significantly different between the two groups (MD = 69.50, 95% CI [-3.91, 142.9], P = 0.06).

Figure 6
A forest plot diagram showing decrease in hemoglobin. Four RCTs reported a decrease in hemoglobin. The pooled data revealed that the reduction in hemoglobin was not significantly different between the two groups (MD = 7.90, 95% CI [-5.44, 6.68], P = 0.84).

Figure 7
A forest plot diagram showing transfusion rate. Seven RCTs reported the transfusion rate. The forest plot revealed that the transfusion rate was not significantly different between the two groups (RD = 0.07, 95% CI [-0.02, 0.04], P = 0.18)
**Figure 8**

A forest plot diagram showing time of surgery. Five RCT reported duration of surgery, TXA with tourniquet group have significantly decreased time of surgery compared with TXA-NT group (MD=-1.05, 95% CI [-1.46, -0.64], P=<i>0.00001</i>)
Table 1: Comparison of VAS between groups with and without a tourniquet

| Study or Subgroup | TXA with a tourniquet | TXA without a tourniquet | Mean Difference IV | Random, 95% CI |
|-------------------|-----------------------|--------------------------|------------------|---------------|
| Ma 2017           | 1.79 ± 0.22           | 1.69 ± 0.43              | 0.16 (0.08, 0.34)| P = 0.01       |
| Ma 2018           | 1.86 ± 0.20           | 1.76 ± 0.42              | 0.10 (0.01, 0.19)| P = 0.02       |
| Wang 2019         | 2.17 ± 0.33           | 2.08 ± 0.54              | 0.09 (0.00, 0.18)| P = 0.05       |
| Xie 2017          | 2.2 ± 0.36            | 2.12 ± 0.55              | 0.08 (0.00, 0.16)| P = 0.07       |
| Subtotal (95% CI) |                       |                          |                  |               |

Figure 9

A forest plot diagram showing VAS. Four RCTs reported VAS on the day of surgery. Ten RCTs reported VAS on the first day after surgery. Six RCTs reported VAS on the third day after surgery. Two RCTs reported VAS on the second and fifth day after surgery. Three RCTs reported VAS on the seventh day after surgery. Two RCTs reported VAS at one month after surgery. The results of random-effects meta-analysis showed no significant differences between the two groups in the postoperative VAS score at either the day of surgery (MD = 1.56, 95% CI [-5.0, 3.62], P = 0.20), first day (MD = 0.42, 95% CI [-0.29, 1.13], P = 0.25), second day (MD = 0.16, 95% CI [-0.21, 0.54], P = 0.39), third day (MD = 0.20, 95% CI [-0.12, 0.53], P = 0.21), fifth day (MD = 0.95, 95% CI [-0.52, 2.42], P = 0.21), seventh day (MD = 0.89, 95% CI [-0.04, 1.83], P = 0.06) or 1 month after surgery (MD = 0.16, 95% CI [-0.06, 0.39], P = 0.16).
Table 2

| Study or Subgroup | TXA with a tourniquet | TXA without a tourniquet | Mean Difference | Mean Difference |
|-------------------|-----------------------|--------------------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| 6.1.2 7 day        |       |    |       |       |    |       |         |                |                |
| Wang 2019         | 58.2 | 8.2| 30    | 46.3 | 5.7| 30    | 8.3%  | -6.10 [-9.61, -2.59] |
| Xu 2018           | 58.3 | 6.8| 30    | 81.7 | 10.7| 30    | 7.3%  | -23.40 [-27.94, -18.86] |
| Zhou 2017         | 65.4 | 7.4| 72    | 66.6 | 8.1| 68    | 9.3%  | -1.20 [-3.72, 1.37] |
| Subtotal (95% CI) | 132 |    |        | 128  |    |        | 24.9% | -10.11 [-21.98, 1.76] |

Heterogeneity: Tau² = 106.55; Chi² = 69.64, df = 2 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.67 (P = 0.10)

6.1.3 1 month

| Study or Subgroup | TXA with a tourniquet | TXA without a tourniquet | Mean Difference | Mean Difference |
|-------------------|-----------------------|--------------------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Wang 2017         | 78.3 | 4.9| 30    | 79.1 | 4.7| 30    | 9.4%  | -0.80 [-3.23, 1.63] |
| Wang 2019         | 78.5 | 6.8| 30    | 80.5 | 6.2| 30    | 8.6%  | -2.00 [-5.29, 1.29] |
| Xu 2018           | 77.4 | 6.7| 30    | 83.7 | 5.9| 30    | 8.7%  | -6.36 [-9.49, -3.11] |
| Subtotal (95% CI) | 90  |    |        | 90   |    |        | 26.7% | -2.93 [-6.22, 0.35] |

Heterogeneity: Tau² = 6.11; Chi² = 7.39, df = 2 (P = 0.02); I² = 73%
Test for overall effect: Z = 1.75 (P = 0.08)

6.1.4 3 month

| Study or Subgroup | TXA with a tourniquet | TXA without a tourniquet | Mean Difference | Mean Difference |
|-------------------|-----------------------|--------------------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Xu 2018           | 86.9 | 8.7| 30    | 90.8 | 8.9| 30    | 7.4%  | -3.90 [-8.35, 0.55] |
| Zeng 2021         | 83.96| 3.2| 50    | 84.16| 2.92| 50    | 10.4% | -0.20 [-1.41, 1.01] |
| Zhou 2017         | 81.6 | 4.4| 72    | 82.5 | 4.5| 68    | 10.2% | -0.90 [-2.38, 0.58] |
| Subtotal (95% CI) | 152 |    |        | 148  |    |        | 27.0% | -0.73 [-1.80, 0.34] |

Heterogeneity: Tau² = 0.20; Chi² = 2.69, df = 2 (P = 0.26); I² = 26%
Test for overall effect: Z = 1.23 (P = 0.22)

6.1.5 6 month

| Study or Subgroup | TXA with a tourniquet | TXA without a tourniquet | Mean Difference | Mean Difference |
|-------------------|-----------------------|--------------------------|----------------|----------------|
|                   | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | IV, Random, 95% CI |
| Huang 2017        | 90.3 | 3.2| 50    | 91.2 | 2.5| 50    | 10.4% | -0.93 [-2.03, 0.23] |
| Zhou 2017         | 90.7 | 4.5| 72    | 89.8 | 4.9| 68    | 10.1% | 0.90 [0.06, 2.31] |
| Subtotal (95% CI) | 122 |    |        | 118  |    |        | 20.5% | -0.08 [-1.84, 1.67] |

Heterogeneity: Tau² = 1.14; Chi² = 3.36, df = 1 (P = 0.07); I² = 70%
Test for overall effect: Z = 0.99 (P = 0.32)

Heterogeneity: Tau² = 11.44; Chi² = 120.71, df = 10 (P < 0.00001); I² = 92%
Test for overall effect: Z = 3.18 (P = 0.001)

Test for subgroup differences: Chi² = 4.64, df = 3 (P = 0.20), I² = 35.4%

Figure 10

A forest plot diagram showing HSS Three RCTs reported HSS 7 day, 1 month, 3 month after surgery. Two RCTs reported HSS 6 month after surgery. The pooled results showed that both groups experienced similar HSS scores at either 7 day MD = -10.11, 95% CI [-21.98, 1.76], P = 0.10, 1 month MD = -2.93, 95% CI [-6.22, 0.35], P = 0.08, 3 month MD = -0.73, 95% CI [-1.89, 0.43], P = 0.22 or 6 month after the surgery MD = -0.08, 95% CI [-1.84, 1.67], P = 0.92.

Figure 11

A forest plot diagram showing Knee circumference Two RCTs reported Knee circumference. We detected a similar knee circumference between two groups (MD = 5.86, 95% CI [-4.72, 16.44], P = 0.28).

Figure 12

A forest plot diagram showing Knee ROM: Six RCTs reported Knee ROM. TXA with tourniquet group have significantly decreased knee ROM compared with TXA-NT group (MD = -2.68, 95% CI [-3.30, -2.07], P < 0.00001)
Figure 13

A forest plot diagram showing LOH Nine RCTs reported LOH. No significant difference was found for LOH between both groups (MD=0.40, 95% CI [-0.1, -0.9], P=0.12)
Figure 14

A forest plot diagram showing complications. Five RCTs reported intramuscular venous thrombosis. Six RCTs reported deep venous thrombosis. Five RCTs reported superficial infection. Four RCTs reported deep wound infection. Four RCTs reported delayed wound healing. We detected no significantly difference in terms of intramuscular venous thrombosis (RD=0.01, 95% CI [-0.04, 0.05], P=0.81), deep venous thrombosis (RD=0.03, 95% CI [-0.00, 0.05], P=0.10), superficial infection (RD=0.01, 95% CI [-0.02, 0.05], P=0.45), deep wound infection (RD=0.01, 95% CI [-0.02, 0.04], P=0.64), delayed wound healing (RD=0.01, 95% CI [-0.03, 0.04], P=0.65) between two groups.