The efficacy and safety of tranexamic acid in lumbar surgery: A meta-analysis of randomized-controlled trials

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With the improvement of human life expectancy and changes in lifestyle, the number of patients undergoing lumbar surgery for lumbar diseases is increasing. In lumbar surgery, extensive muscle tissue stripping can lead to spinal canal decompression, bone graft fusion, a large wound, and internal fixation may injure the long segment of the intraspinal venous plexus, and these factors are expected to cause more postoperative bleeding. The amount of pre- and postoperative bleeding is closely related to the complexity of the operation and is directly related to the time of the drainage tube removal and the need for postoperative blood transfusion. Reducing the exudation of incision blood and removing the drainage tube as soon as possible is not only necessary for postoperative rehabilitation, but it is also essential to minimize the risk of lower-extremity deep venous thrombosis (DVT). Concurrently, minimizing quantity of blood loss from the wound following the surgery may help to eliminate the necessity for a blood transfusion. Therefore, reducing perioperative blood loss is important to ensure the safety of surgery.

ABSTRACT

Objectives: This meta-analysis aims to assess tranexamic acid (TXA) effectiveness and safety in lumbar surgery.

Patients and methods: Renewals of randomized-controlled trials (RCTs) were conducted utilizing databases of medical literature such as PubMed, China Science and Technology Journal Database, Cochrane Library, China National Knowledge Infrastructure (CNKI), and EMBASE to compare principal and safety endpoints. The risk ratio (RR), standard mean difference (SMD), and 95% confidence intervals (CIs) were calculated. For the evaluation of the quality of the included studies, the Cochrane risk of bias criteria were utilized by two authors.

Results: In total, 49 articles were enrolled that included 4,822 patients. Of the patients, 2,653 were administered TXA and 2,169 were in the control group. The findings indicated that TXA was capable of significantly lowering postoperative blood loss (PBL), transfusion rate, transfusion volume, total blood loss (TBL), intraoperative blood loss (IBL), and drainage compared to the control group. Besides, hemoglobin (Hb) and hematocrit (Hct) values were higher in the TXA group compared to the control group. As the safety endpoints, TXA significantly reduced D-dimer levels compared to the control group; however, both TXA and control groups had no significant variations in deep venous thrombosis (DVT). Subgroup analysis was administrated according to the administration method of TXA and the operation type and intravenous and topical TXA were combined in the meta-analysis.

Conclusion: This meta-analysis showed that TXA had the potential to significantly lower PBL, transfusion rate, transfusion volume, TBL, IBL, and drainage compared to the control group. As the safety endpoints, TXA significantly reduced D-dimer levels compared to the control group; however, both TXA and control groups had no significant variations in deep venous thrombosis (DVT). Subgroup analysis was administrated according to the administration method of TXA and the operation type and intravenous and topical TXA were combined in the meta-analysis.

Keywords: Lumbar surgery; meta-analysis, tranexamic acid.
To minimize perioperative blood loss, physicians have utilized a variety of techniques, such as controlled hypotension, blood dilution, autologous blood transfusion, and application of hemostatic drugs.[7] Currently, in orthopedic surgery, hemostatic medications with various hemostatic routes have been widely utilized, but due to the need for immobilization, DVT risk exists and, therefore, the application of hemostatic drugs is still controversial.[8] As a common hemostatic drug, tranexamic acid (TXA) is a lysine synthetic derivative and an antifibrinolytic agent.[9] Its pharmacological action is to bind competitively to the lysine binding sites on the source of fibrinolytic enzyme, tissue type plasminogen activator, and plasmin to prevent the dissolution of thrombi.[10-12] Numerous studies have reported that TXA has no effect on enhancing the incidence of DVT, but most of them are routinely used for chemical thromboprophylaxis and, thus, the risk of thrombosis is still not clear.[13-16]

The application of TXA in lumbar surgery is relatively common, but it is still controversial and ambiguous about its safety and effectiveness.[17] Therefore, our study aimed to discover the safety and effectiveness of TXA in lumbar surgery to reinforce the hemostatic medicines clinical application.

**PATIENTS AND METHODS**

**Search strategy**

A literature search utilizing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were carried out by two authors[18] for papers assessing the safety and effectiveness of TXA in lumbar operation. We searched in PubMed, the Cochrane Library, EMBASE, the China National Knowledge Infrastructure (CNKI), and the China Science and Technology Journal Database (commonly known as “VIP”) comprehensively for randomized-controlled trials (RCTs). The language choice is restricted to English or Chinese, and the date of publication was set to begin on January 1st, 2003 to June 30th, 2021. “Tranexamic Acid” and “Lumbar” were utilized as key words, Other meta-analyses and reviews were used to retrieve additional relevant literature. For incomplete or missing data, we contacted the original research authors through electronic mail. Two authors reviewed the retrieved literature. In case of disagreements, a third author was invited to review the paper and render a final decision. No written consent or ethical approval was required, as all data in this meta-analysis were derived from previously published research.

**Inclusion and exclusion criteria**

**Inclusion criteria:**

1. The study was an RCT;
2. Evaluated TXA effectiveness and safety in lumbar surgery;
3. The subjects of study were patients who underwent lumbar surgery;
4. On basis of TXA, at least one of groups were assessed;
5. TXA had no dosage or use restrictions;
6. Language options were restricted to English or Chinese;
7. The papers included give sufficient data for analysis.

**Exclusion criteria:**

1. Animal experiments;
2. Non-randomized trials or semi-randomized controlled trials;
3. Case reports, non-clinical trials, or series;
4. Papers containing wrong or missing data or articles from which data could not be collected.

**Endpoints**

Total blood loss (TBL) and transfusion rate were the initial endpoints of the study. Secondary endpoints were postoperative drainage, transfusion volume, intraoperative blood loss (IBL), postoperative blood loss (PBL), hemoglobin (Hb) and hematocrit (Hct). Safety endpoints were DVT, and D-dimer (a fibrin degradation product that is traditionally used as a biomarker of DVT).[19,20]

**Data extraction**

The retrieved studies contents were reviewed by two authors independently. A third author validated the primary endpoints derived by the two authors. The following information were included in extracted data: author's first name, publication year, country conducted in, body mass index (BMI), the size of the sample, sex ratio, intervention, average age, operation type, follow-up time and the endpoints computed in each study. If the study's contents required clarifying, the study's primary author was called up. Conflicts were resolved via prevailing opinion or by calling up a third author who ultimately took the decision.
Risk of bias assessments

Two authors independently appraised the studies’ methodological quality using the Cochrane risk of bias criteria. Each item was classified as having a low risk, a high risk, or no obvious risk. The guideline for detecting limitations of this study (risk of bias) in Cochrane Reviews is shown in Table I, along with the corresponding GRADE evaluation of the quality of evidence. Every trial’s bias assessment checklist involved seven items: randomization sequence generation, allocation concealment, blinding of participants and personnel, findings appraisal blinding, inadequate data findings, selective reporting, as

| Risk of bias | Across studies | Interpretation | Considerations | GRADE assessment of study limitations |
|--------------|----------------|---------------|----------------|---------------------------------------|
| Low          | Most information is from studies at low risk of bias. | Plausible bias unlikely to seriously alter the results. | No apparent limitations. | No serious limitations, do not downgrade. |
| Unclear      | Most information is from studies at low or unclear risk of bias. | Plausible bias that about the results. | Potential limitations are unlikely to lower confidence in the estimate of effect. | No serious limitations, do not downgrade. |
| High         | The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results. | Plausible bias that seriously weakens confidence in the results. | Potential limitations are likely to lower confidence in the estimate of effect. | Serious limitations, downgrade one level. |

TABLE II

Study limitations in randomized-controlled trials: Explanation

| Explanation |
|-------------|
| Lack of allocation concealment | Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (a major problem in “pseudo” or “quasi randomized trials with allocation by day of week, birth date, chart number, etc.). |
| Lack of blinding | Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial). |
| Incomplete accounting of patients and outcome events | Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available. The significance of particular rates of loss to follow-up, however, varies widely and is dependent on the relation between loss to follow-up and number of events. The higher the proportion lost to follow-up in relation to intervention and control group event rates, and differences between intervention and control groups, the greater the threat of bias. |
| Selective outcome reporting | Incomplete or absent reporting of some outcomes and not others on the basis of the results. Stopping trial early for benefit. Substantial overestimates are likely in trials with fewer than 500 events and that large overestimates are likely in trials with fewer than 200 events. Empirical evidence suggests that formal stopping rules do not reduce this bias. |
| Other limitations | | | | |
well as additional biases. We evaluated publication bias according to the guidance shown in Table II.

**Statistical analysis**

The individual study results were analyzed and pooled using the Stata version 12.0 software (Stata Corp., College Station, TX, USA). Risk ratios (RRs), standardized mean differences (SMDs), and 95% confidence intervals (CIs) with two-sided p values were estimated in the pooled results. A p value of <0.05 was considered statistically significant. The I² test was utilized to assess heterogeneity. In case of I²<50%, heterogeneity was deemed to be minor; but, in case of I²>50%, heterogeneity was deemed to be substantial. If the I² was <50%, the fixed-effects model was utilized; when the I² was >50%, the random-effects model was utilized. If more than 10 studies were involved in the analysis of this endpoint, a funnel plot was constituted to scrutinize publication bias, as well as discovering the heterogeneity sources. We conducted a subgroup analysis of the indicators including the patients’ TBL, transfusion rates, DVT, and D-dimer level. Subgroup analyses were performed on the basis of administration and operation type.

**RESULTS**

**Studies retrieved and characteristics**

Relying on the (PRISMA) guideline, a total of 2,963 studies were registered. The research titles and abstracts were reviewed to preclude studies that were not pertinent. Then, we excluded research that were not suitable by scanning articles full text. Ultimately, relying on the inclusion and exclusion criteria, 49 studies [21-69] including a total of 4,822 patients were enrolled (Figure 1). [70] At length, 2,653 patients (55.0%) and 2,169 patients (45.0%) were allotted to the experimental and the control groups, respectively. The researches involved were all RCTs in the meta-analysis. The participants’ baseline characteristics in the RCTs are fully revealed in Table III.

**Literature quality evaluation**

Since studies included were all RCTs, two authors were saddled with the responsibility of assessing the retrieved studies quality relying on the Cochrane risk of bias criteria. In 49 studies, random sequence generation and allocation concealment were performed. Twenty-four studies verified
| Authors                  | Year  | Country     | Sample size | Female, No (%) | Average age (years) | BMI | Intervention                                                                 | Follow-up | Operative type   | Endpoints                                                                 |
|-------------------------|-------|-------------|-------------|----------------|---------------------|-----|------------------------------------------------------------------------------|-----------|-----------------|--------------------------------------------------------------------------|
| Elmose et al.[21]       | 2019  | Denmark     | 117         | 116 (0.49)     | 48.9±15.4           | 51.1±14.9 | TXA, 10 mg/kg, IV, Equivalent normal saline (0.9%), IV                        | 28 days   | Minor lumbar spine surgery | Total blood loss, Intraoperative blood loss, Postoperative blood loss |
| Kim et al.[22]          | 2017  | South Korea | 24          | 24 (0.67)      | 63.3±7.6            | 65.2±7.0 | TXA, 5 mg/kg, IV, preoperation; A maintenance dosage of 1 mg/kg/h, until 5 h after surgery | 7 days    | PLIF             | Total blood loss, Intraoperative blood loss, Postoperative blood loss, postoperative drainage, Hb, Hct |
| Kim et al.[22]          | 2017  | South Korea | 24          | 24 (0.50)      | 61.0±9.0            | 65.2±7.0 | TXA, 10 mg/kg, IV, preoperation; A maintenance dosage of 2 mg/kg/h, until 5 h after surgery | 7 days    | PLIF             | Total blood loss, Intraoperative blood loss, Postoperative blood loss, postoperative drainage, Hb, Hct |
| Liang et al.[23]        | 2016  | China       | 30          | 30 (0.50)      | 51.1±10.7           | 53.8±11.2 | Gelfoam was soaked in TXA (2,000 mg: 20 mL), topical, intraopration           | 3 days    | Lumbar spine surgery | Transfusion volume, postoperative drainage, Hb, Hct                      |
| Mu et al.[24]           | 2019  | China       | 45          | 42 (0.40)      | 54.2±7.4            | 52.6±6.7 | TXA, 15 mg/kg, IV, preoperation; A maintenance dosage of 1 mg/kg/h, intraoperation | 84 days   | PLIF             | Transfusion rate, Intraoperative blood loss, Postoperative blood loss, postoperative drainage, Hb, Hct |
| Mu et al.[24]           | 2019  | China       | 39          | 42 (0.44)      | 51.8±8.1            | 52.6±6.7 | Gelfoam was soaked in TXA (1 g: 50 mL), intraoperation                        | 84 days   | PLIF             | Transfusion rate, Intraoperative blood loss, Postoperative blood loss, postoperative drainage, Hb, Hct |
| Nagabhushan et al.[25]  | 2017  | India       | 25          | 25 (0.64)      | 49.6±9.8            | 51.7±9.7 | TXA, 10 mg/kg, IV, preoperation; A maintenance dosage of 1 mg/kg/h, until closure | NA       | Lumbar Spinal Fusion Surgery | Intraoperative blood loss, Postoperative drainage, Hb                   |
| Ou et al.[26]           | 2018  | China       | 59          | 59 (0.47)      | 64.2±4.6            | 64.0±5.1 | Gelfoam was soaked in TXA (1 g: 10 mL), topical, intraoperation               | 30 days   | Lumbar decompression and fusion surgery | Total blood loss, Total blood loss, postoperative drainage, Hb, Hct, D-dimer |
| Authors          | Year | Country | Sample size | Female, No (%) | Average age (years) | BMI | Intervention | Follow-up | Operative type | Endpoints                                                                                     |
|------------------|------|---------|-------------|----------------|-------------------|-----|--------------|-----------|----------------|--------------------------------------------------------------------------------------------|
| Shi et al.[27]   | 2017 | China   | 50          | 25 (0.50)     | 53.8±12.1        | 55.8±13.1 | TXA, 30mg/kg, IV, preoperation; A maintenance dosage of 2 mg/kg/h, until the end of the operation | 35 days   | Posterior lumbar surgery for stenosis or spondylolisthesis | Total blood loss, transfusion rate, Intraoperative blood loss, postoperative drainage, Hb, Hct |
| Wang et al.[28]  | 2013 | China   | 30          | 14 (0.47)     | 63.1±4.0         | 62.0±4.6 | Equivalent normal saline (0.9%), IV | 2 days    | Posterior approach lumbar surgery | Total blood loss, intraoperative blood loss, postoperative blood loss |
| Wong et al.[29]  | 2008 | Canada  | 73          | 52 (0.71)     | 56.8±16.2        | 50.0±16.2 | TXA, 10 mg/kg, IV; A maintenance dosage of 1 mg/kg/h, until the end of the operation | 90 days   | PLIF/PTIF | Transfusion rate, Hb, D-dimer, |
| Xu et al.[30]    | 2017 | China   | 40          | 21 (0.525)    | 53.1±2.8         | 57.4±10.7 | TXA (1g/100ml), topical, intraoperation | 30 days   | Posterior spinal fusion surgery | Total blood loss, transfusion rate, postoperative drainage, Hct |
| Shi[59]          | 2016 | China   | 55          | 24 (0.44)     | 54.6±12.2        | 52.3±12.1 | TXA, 30 mg/kg, IV, preoperation; The maintenance dose of 2 mg/kg/h, until the end of the operation | 3 days    | PLIF | Total blood loss, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer |
| Shi[59]          | 2016 | China   | 54          | 26 (0.48)     | 55.6±11.8        | 52.3±12.1 | TXA, 20 mg/kg, IV, preoperation; the maintenance dose of 1 mg/kg/h, until the end of the operation | 3 days    | PLIF | Total blood loss, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer |
| Shi[59]          | 2016 | China   | 55          | 32 (0.58)     | 54.5±11.2        | 52.3±12.1 | TXA, 10 mg/kg, IV, preoperation; the maintenance loss of 0.5 mg/kg/h, until the end of the operation | 3 days    | PLIF | Total blood loss, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer |
| Huang and Yang[57]| 2011 | China   | 34          | 20 (0.59)     | 75.8±3.4         | 73.6±4.2 | TXA, 1 g, IV; the same dosage of TXA, 2 h after the first administration | 7 days    | Multi-level lumbar spinal stenosis surgery | Transfusion rate, Intraoperative blood loss, postoperative drainage, Hb |
| Bu et al.[30]    | 2014 | China   | 133         | 31 (0.23)     | 54.2±13.1        | 52.6±16.3 | TXA, 1g, topical, after the deep fascia was closed | 90 days   | PUF | Transfusion volume, transfusion rate, postoperative drainage, Hb |
| Authors        | Year | Country | Sample size | Female, No (%) | Average age (years) | BMI | Intervention | Follow-up | Operative type | Endpoints                                                                 |
|--------------|------|---------|-------------|----------------|------------------|-----|--------------|-----------|----------------|-----------------------------------------------------------------------------|
| Zhang et al. | 2015 | China   | 35 38       | 20 (0.57) 21 (0.55) | 52.3±9.7 51.6±10.4 | 23±1.2 23.8±3.2 | Gelfoam was soaked in TXA (5 mL: 0.5 g), topical, intraoperation | 30 days   | Two-segment lumbar posterior decompression and intervertebral fusion | Total blood loss, transfusion rate, intraoperative blood loss, postoperative bleeding drainage |
| Zhang et al. | 2015 | China   | 46 46       | 21 (0.46) 20 (0.43) | NA NA NA NA NA | TXA, 2 g, topical, after laminotomy; TXA, 1 g, topical, intraoperation | 15 days   | PLIF with cage | Transfusion volume, intraoperative blood loss, postoperative blood loss, D-dimer |
| Yan          | 2015 | China   | 35 33       | 15 (0.43) 13 (0.39) | 58.4±6.6 56.6±9.4 | 20.6±3.2 22.8±4.1 | TXA, 15 mg/kg, IV, preoperation | 2 days    | PLIF/TLIF | Total blood loss, intraoperative blood loss, transfusion volume, D-dimer |
| Huang et al. | 2015 | China   | 30 30       | 5 (0.17) 7 (0.23) | 56.1±4.9 56.9±4.8 | NA NA | TXA, 30 mg/kg, IV, before operation; The maintenance dose of 1 mg/kg, intraoperation | 3 days    | PLIF | Transfusion volume, intraoperative blood loss, Hb, DVT |
| Feng         | 2016 | China   | 60 60       | 24 (0.4) 26 (0.43) | 74.5±16.2 76.3±14.8 | NA NA | TXA (100 mL: 1 g), 15 mg/kg, IV, preoperation | 90 days   | lumbar spinal stenosis surgery | Intraoperative blood loss, postoperative drainage, Hb, D-dimer |
| Nian, et al. | 2016 | China   | 30 30       | 13 (0.43) 11 (0.37) | 54.6±10.9 52.1±11.0 | 24.6±3.2 25.7±3.3 | TXA (100 mL: 1 g), topical, intraoperation | 7 days    | PLIF | Total blood loss, transfusion rate, postoperative drainage, Hb, D-dimer |
| Wang et al.  | 2016 | China   | 25 25       | 10 (0.4) 12 (0.48) | 64.7±8.0 66.3±9.8 | 23.5±4.0 21.8±3.5 | TXA, 100 mg/kg, IV, preoperation; The maintenance dose is 10 mg/kg/h, until the end of the operation | NA       | ALSS | Transfusion volume, intraoperative blood loss, postoperative drainage |
| Jia et al.   | 2016 | China   | 30 30       | 14 (0.47) 12 (0.40) | 63.1±4.0 62.0±4.6 | 21.7±1.9 22.2±1.9 | TXA, 15 mg/kg, IV, preoperation | 2 days    | Posterior approach lumbar surgery | Total blood loss, intraoperative blood loss |
| Meng et al.  | 2017 | China   | 40 40       | 16 (0.4) 20 (0.2) | 61.1±5.8 62.7±6.1 | 27.5±4.7 26.1±4.9 | TXA, topical | 2 days    | Lumbar spine surgery | Transfusion volume, transfusion rate, intraoperative blood loss, postoperative blood loss, DVT |
| Meng et al.  | 2017 | China   | 40 40       | 17 (0.425) 20 (0.2) | 62.3±5.4 62.7±6.1 | 25.2±5.3 26.1±4.9 | TXA, 15 mg/kg, IV, preperation | 7 days    | Lumbar spine surgery | Transfusion volume, transfusion rate, intraoperative blood loss, postoperative blood loss, DVT |
| Authors         | Year | Country | Sample size | Female, No (%) | Average age (years) | BMI | Intervention                                                                 | Follow-up | Operative type                        | Endpoints                                      |
|-----------------|------|---------|-------------|----------------|---------------------|-----|-------------------------------------------------------------------------------|-----------|---------------------------------------|------------------------------------------------|
| Song et al.     | 2017 | China   | 16 16       | NA  NA         | 18–65 18–65        | NA  NA | TXA, 1g, IV, preoperation; A maintenance dosage of 10 mg/kg/h, until the end of the operation | Equivalent normal saline (0.9%), IV | 1 day | Transpedicular vertebral osteotomy | Total blood loss, transfusion volume, postoperative drainage |
| Chang et al.    | 2017 | China   | 29 29       | 15 (0.52) 17 (0.59) | 51.1±13.7 52.8±14.6 | NA  NA | Gelfoam was soaked in TXA, 500 mg Gelfoam | 7 days | PLIF |                             | Intraoperative blood loss, postoperative drainage, Hb, DVT |
| Zhang et al.    | 2017 | China   | 41 41       | 18 (0.44) 22 (0.54) | 49.6±8.7 46.8±10.7 | NA  NA | TXA, 10 mg/kg, IV, preoperation TXA, 10 mg/kg, IV, preoperation | Equivalent normal saline (0.9%), IV | 7 days | PLIF |                             | Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, DVT |
| Zhang et al.    | 2017 | China   | 41 41       | 22 (0.54) 22 (0.54) | 49.0±9.1 46.8±10.7 | NA  NA | TXA, 15 mg/kg, IV, preoperation Equivalent normal saline (0.9%), IV | 7 days | PLIF |                             | Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, DVT |
| Liu and Liu     | 2018 | China   | 39 39       | 15 (0.38) 18 (0.46) | 66.3±5.6 64.2±4.8 | 25.4±3.1 24.7±2.6 | TXA, 1g, topical, intraoperation Equivalent normal saline (0.9%), topical | 3 days | PLIF |                             | Intraoperative blood loss, postoperative drainage, Hb, DVT |
| Zhang et al.    | 2018 | China   | 54 50       | 32 (0.59) 20 (0.4) | 45.8±10.6 44.1±9.9 | 22.2±2.4 22.3±2.7 | TXA, 15 mg/kg, IV, preoperation Equivalent normal saline (0.9%), IV | 3 days | PLIF | Percutaneous pedicle screw fixation for thoracolumbar fractures | Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer |
| Hu et al.       | 2018 | China   | 40 40       | NA  NA         | 67.0±10.5 64.5±10.1 | NA  NA | TXA, 10 mg/kg, IV, preoperation A maintain dose of 2 mg/kg/h, until the end of the operation Equivalent normal saline (0.9%), IV | 3 days | PLIF | Surgery for spinal metastatic tumors | Transfusion rate, Intraoperative blood loss, postoperative drainage, Hb |
| Chen et al.     | 2018 | China   | 100 100     | 35 (0.43) 43 (0.43) | 55.7±15.8 53.9±13.6 | 23.8±4.7 23.7±5.1 | TXA (5 mL: 0.5g), 1 g IV, preperation; A maintenance dose of 10 mg/kg/h Equivalent normal saline (0.9%), IV | 2 days | PLIF | Multilevel lumbar inter-body fusion | Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, Hct, DVT |
| Liu et al.      | 2019 | China   | 35 35       | 19 (0.54) 20 (0.57) | 76.8±4.3 77.4±4.2 | 25.4±2.8 25.3±3.9 | TXA, 10 mg/kg, IV, preperation; A maintenance dose of 1 mg/kg/h, intraoperation Equivalent normal saline (0.9%), IV | 90 days | PLIF | Posterior lumbar surgery of 3 segments | Transfusion rate, Intraoperative blood loss, postoperative drainage, Hb |
| Wang et al.     | 2017 | China   | 39 41       | 18 (0.46) 19 (0.46) | 41.2±10.3 42.5±9.5 | NA  NA | TXA, 10 mg/kg, IV; The maintenance dose of 1 mg/kg/h, until the end of the operation Equivalent normal saline (0.9%), IV | 12 weeks | PLIF | Transforaminal thoracic inter-body fusion (TTIF) | Total blood loss, Intraoperative blood loss, postoperative drainage, D-dimer, DVT |
| Authors          | Year | Country | Sample size | Female, No (%) | Average age (years) | BMI | Intervention                                                                 | Follow up | Operative type | Endpoints                                                                 |
|------------------|------|---------|-------------|----------------|--------------------|-----|-------------------------------------------------------------------------------|-----------|----------------|---------------------------------------------------------------------------|
| Wang et al.[32]  | 2019 | China   | 30          | 28 (0.47)     | 60.5±6.3           | 24.7±2.6 | TXA, 15 mg/kg, IV; The maintenance dose of 15 mg/kg                             | 12 months | PLIF           | Total blood loss, Intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer, DVT |
| Deng et al.[31]  | 2019 | China   | 50          | 49 (0.98)     | 62±2.0             | 25±2.5  | TXA, IV                                                                      | 3 months  | TLIF           | Intraoperative blood loss, postoperative drainage, Hb                      |
| Xia[37]          | 2019 | China   | 20          | 21 (0.55)     | 50.2±12.5          | 54.0±12.8 | TXA saline, 800 mL, topical                                                   | NA       | NA             | Postoperative drainage, Hb, D-dimer                                      |
| Xu et al.[34]    | 2019 | China   | 30          | 21 (0.7)      | 49.6±12.8          | 50.6±16.2 | TXA saline, 1 g in 100 mL, topical                                             | 72 hours  | PLIF           | Postoperative drainage, Hb, D-dimer                                      |
| Yang et al.[35]  | 2019 | China   | 18          | 16 (0.89)     | 72.5±6.3           | 73.7±6.1  | TXA, 1 g in 100 mL, IV; TXA saline, 1 g in 100 mL, topical                   | 3 days    | PLIF           | Total blood loss, transfusion volume, transfusion rate, postoperative drainage, Hb, Hct |
| Zhao et al.[36]  | 2019 | China   | 43          | 43 (0.99)     | 71.3±4.4           | 71.1±4.3  | TXA, 30 mg/kg, IV; TXA saline, 0.5 g in 10 mL, topical                       | 4 days    | Other          | Intraoperative blood loss, postoperative drainage, Hb, D-dimer            |
| Zhu[38]          | 2019 | China   | 39          | 22 (0.56)     | 64.4±3.6           | 64.1±4.1  | TXA, 20 mg/kg, IV; The maintenance dose of 2 mg/kg, until the end of the operation | 12 weeks  | PLIF/TLIF      | Total blood loss, transfusion rate, postoperative drainage, intraparoperative blood loss |
| Zhu[38]          | 2019 | China   | 40          | 22 (0.55)     | 63.9±4.0           | 64.1±4.1  | TXA saline, 0.1 g/mL, topical                                                | 12 weeks  | PLIF/TLIF      | Total blood loss, transfusion rate, postoperative drainage, intraparoperative blood loss |
| Ding et al.[41]  | 2020 | China   | 15          | 15 (0.5)      | 64.3±5.6           | 66.2±5.0  | TXA, 5 mg/kg, IV; The maintenance dose of 2 mg/kg, until the end of the operation | 1 week    | PLIF           | Total blood loss, postoperative drainage, intraparoperative blood loss, postoperative blood loss, Hb, Hct |
| Authors     | Year | Country | Sample size | Female, No (%) | Average age (years) | BMI | Intervention Details                                                                                                                                                                                                 | Follow-up | Operative type | Endpoints                                                                                   |
|------------|------|---------|-------------|----------------|--------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------------|---------------------------------------------------------------------------------------------|
| Ding et al. [47] | 2020 | China   | 15, 15      | NA, NA          | 62.0±7.0, 66.2±5.0 | 26.5±2.8, 26.1±2.3 | TXA, 10 mg/kg, IV; The maintenance dose of 2 mg/kg/h, until the end of the operation                                                                                                                                         | 1 week    | PLIF           | Total blood loss, postoperative drainage, intraoperative blood loss, postoperative blood loss, Hct |
| He et al. [46]  | 2020 | China   | 20, 20      | 12 (0.6), 9 (0.46) | 58.0±12.4, 57.9±11.8 | 25.0±5.2, 24.8±4.4 | TXA, 10 mg/kg, IV; The maintenance dose of 6-8 mg/kg/h up to a total dose of 15 mg/kg during the surgery                                                                                                                     | NA        | TLIF           | Transfusion rate, intraoperative blood loss, postoperative blood loss, postoperative drainage, Hb |
| Li et al. [49] | 2020 | China   | 70, 70      | 46 (0.66), 47 (0.67) | 66.7±3.3, 65.6±3.2 | 24.0±3.3, 22.8±2.4 | TXA, 15 mg/kg, IV; TXA saline, 2 g in 20 mL, injected into the incision                                                                                                                                                    | 3 months  | Other          | Total blood loss, intraoperative blood loss, postoperative blood loss, Hb, DVT |
| Xia et al. [46] | 2020 | China   | 46, 44      | 26 (0.57), 20 (0.45) | 51.2±10.4, 56.3±13.9 | NA, NA              | TXA, 1 g in 100 mL, topical; Equivalent normal saline (0.9%)                                                                                                                                                           | 7 days    | Other          | Transfusion volume, transfusion rate, D-dimer, postoperative drainage, postoperative blood loss |
| Yang et al. [43] | 2020 | China   | 33, 32      | 13 (0.39), 14 (0.44) | 62.9±5.5, 65.6±7.2 | 30.3±6.5, 24.4±3.6 | TXA, 15 mg/kg, IV; TXA saline, 1 g in 10 mL, topical; the maintenance dose of 15 mg/kg/h, until the end of the operation                                                                                                                                 | 72 hours  | Other          | Intraoperative blood loss, postoperative blood loss, D-dimer |
| Yang et al. [41] | 2020 | China   | 32, 32      | 15 (0.47), 14 (0.44) | 65.6±7.5, 65.6±7.2 | 28.2±5.9, 24.4±3.6 | TXA, 1 g in 100 mL, topical; Equivalent normal saline (0.9%)                                                                                                                                                              | 72 hours  | Other          | Intraoperative blood loss, postoperative blood loss, D-dimer |
| Yang et al. [39] | 2020 | China   | 30, 30      | 17 (0.57), 15 (0.5) | 66.8±5.3, 67.6±7.0 | 25.8±2.1, 25.4±1.1 | TXA, 10 mg/kg, IV; The maintenance dose of 2 mg/kg/h, until the end of the operation                                                                                                                                         | 72 hours  | Other          | Total blood loss, transfusion volume, intraoperative blood loss, postoperative drainage, D-dimer |
| Zhang et al. [39] | 2020 | China   | 151, 138    | 94 (0.62), 91 (0.66) | 54.7±9.9, 57.0±10.2 | 25.8±3.3, 25.2±3.5 | TXA, 1 g, IV; TXA 1.0 g in 10 mL, topical; the maintenance dose of 15 mg/kg/h, until the end of the operation                                                                                                                                 | 35 days   | PLIF           | Total blood loss, transfusion rate, intraoperative blood loss, postoperative blood loss |
| Liu et al. [41] | 2021 | China   | 40, 40      | 23 (0.58), 21 (0.53) | 50.2±12.2, 49.3±11.6 | 24.9±1.7, 25.2±1.6 | TXA, 1 g in 100 mL, IV; Equivalent normal saline (0.9%)                                                                                                                                                                    | 1 week    | PLIF           | Total blood loss, intraoperative blood loss, postoperative blood loss, D-dimer |
**TABLE III**  
Continued

| Authors       | Year | Country | Sample size | Female, No (%) | Average age (years) | BMI | Intervention | Follow-up | Operative type | Endpoints                                                                                     |
|---------------|------|---------|-------------|----------------|---------------------|-----|--------------|-----------|----------------|---------------------------------------------------------------------------------------------|
| Mi et al.[44] | 2021 | China   | 50          | 24 (0.48)     | 56.5±16.8           | NA  | NA           | 7 days    | TLIF           | Transfusion rate, intraoperative blood loss, postoperative drainage, D-dimer, DVT          |
| Yuan et al.[41] | 2021 | China   | 39          | 22 (0.56)     | 64.1±6.7            | NA  | TXA saline, 2 g in 100 mL, IV before surgery | NA       | PLIF           | Hb, Hct, total blood loss, intraoperative blood loss, D-dimer, transfusion rate, postoperative drainage |
| Yuan et al.[41] | 2021 | China   | 36          | 20 (0.56)     | 65.5±6.8            | NA  | TXA saline, 2 g in 100 mL, IV; the maintenance dose of 10 mg/kg/h, until the end of the operation | NA       | PLIF           | Hb, Hct, total blood loss, intraoperative blood loss, D-dimer, transfusion rate, postoperative drainage |
| Zhang et al.[45] | 2021 | China   | 40          | NA            | NA                  | NA  | TXA; 1-2 g, IV; TXA, 1 g, topical | NA       | Other          | Total blood loss, transfusion volume, transfusion rate, intraoperative blood loss, postoperative drainage, Hb, Hct, D-dimer |

BMI: Body mass index; PTIF: Posterior thoracic interbody fusion; TLIF: Transforaminal lumbar interbody fusion; DVT: Deep venous thrombosis; E: Experimental group; C: Control group; TXA: Tranexamic acid; PLIF: Posterior lumbar interbody fusion; PTIF: Posterior thoracic interbody fusion; TLIF: Transforaminal lumbar interbody fusion; ALSS: Adult lumbar scoliosis; TBL: Total blood loss; IBL: Intraoperative blood loss; PBL: Postoperative blood loss; Hb: Hemoglobin; Hct: Hematocrit; IV: Intravenous; Htc: Hematocrit.
| Study               | Random allocation | Hidden distribution | Blind method | Incomplete outcome data | Selective reporting of results | Other bias | Quality grade |
|--------------------|-------------------|---------------------|--------------|-------------------------|-------------------------------|------------|---------------|
| Wong et al. [29]   | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Huang and Yang [57]| Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Wang et al. [28]   | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low B         |
| Bu et al. [93]     | Randomized        | No clear            | Single-blind | Low                     | Low                           | Low        | Low C         |
| Huang et al. [84]  | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Yan [50]           | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Zhang et al. [85]  | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Zhang et al. [84]  | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Liang et al. [23]  | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low B         |
| Feng [59]          | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Jia et al. [83]    | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low B         |
| Nian et al. [84]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Shi et al. [27]    | Randomized        | No clear            | Triple-blind | Low                     | Low                           | Low        | Low B         |
| Wang et al. [84]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Chang et al. [85]  | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Kim et al. [22]    | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low B         |
| Nagabhushan et al. [25] | Randomized    | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Shi [80]           | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low B         |
| Song et al. [84]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Xu et al. [83]     | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low A         |
| Meng et al. [87]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Zhang and Yang [89] | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low B         |
| Chen et al. [83]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Hu et al. [81]     | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Liu and Liu [82]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Mua et al. [24]    | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low A         |
| Ou et al. [26]     | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low A         |
| Zhang et al. [89]  | Randomized        | No clear            | Single-blind | Low                     | Low                           | Low        | Low B         |
| Elmose et al. [21] | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Liu et al. [86]    | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Wang et al. [83]   | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Wang et al. [83]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Deng et al. [81]   | Randomized        | No clear            | Single-blind | Low                     | Low                           | Low        | Low B         |
| Xia [87]           | Randomized        | No clear            | Single-blind | Low                     | Low                           | Low        | Low B         |
| Xu et al. [34]     | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Yang et al. [35]   | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Zhao et al. [36]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Zhu [38]           | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Ding et al. [47]   | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| He et al. [48]     | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Jianjiang et al. [49] | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Xia et al. [49]    | Randomized        | No clear            | Double-blind | Low                     | Low                           | Low        | Low A         |
| Yang et al. [49]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Yang et al. [48]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Zhang et al. [39]  | Randomized        | No clear            | Single-blind | Low                     | Low                           | Low        | Low B         |
| Liu et al. [40]    | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Mi et al. [44]     | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Yuan et al. [41]   | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
| Zhang et al. [45]  | Randomized        | No clear            | No clear     | Low                     | Low                           | Low        | Low C         |
participant and personnel blinding, while 24 studies demonstrated outcome assessment blinding. Other biases were not mentioned in any of the studies. Table IV summarizes the quality score of the literature.

Primary effective endpoints

Total blood loss (mL)

Total blood loss was reported in 27 studies (35 trial comparisons). In all, 2,841 patients were assessed for TBL, with 1,623 and 1,218 allotted to the experimental and the control groups, respectively. The results demonstrated that the control group’s TBL were significantly higher than that of the experimental group (SMD: -1.15, 95% CI: -1.37 to -0.92, I²=87.9%, p=0.000) (Figure 2). We utilized the random-effects model.

Transfusion rate (%)

There were 14 studies (18 trial comparisons) covered the transfusion rate. In all, 172 of 1,366 individuals in the experimental group required blood transfusion, and 337 of 1,039 individuals in the control group required concurrently. The results indicated that TXA significantly reduced blood transfusions incidence compared to the control group (12.6% vs. 31.4%) (RR: 0.41, 95% CI: 0.34 to 0.49 I²=1.7%, p=0.434) (Figure 3). The fixed-effects model was done.

Secondary effective endpoints

Transfusion volume (mL)

Thirteen studies (14 trial comparisons) reported the transfusion volume. In the aggregate, 1,136 patients were contained to evaluate the transfusion volume.
rate, 588 and 548 in the experimental and control groups, respectively. Based on findings, compared to the control group, transfusion volume seems to be significantly lower in the experimental group’s transfusion volume (SMD: -2.42, 95% CI: -3.24 to -1.60, I²=96.9%, p=0.000) as illustrated in Supplementary Figure 1. The random-effects model was done.

Intraoperative blood loss (mL)

Thirty-nine studies (51 trial comparisons) reported IBL. The number of patients was 3,881, with 2,180 allotted to the experimental group and 1,701 to the control group. The statistical findings revealed that, compared to the control group, the experimental group’s IBL was significantly lower (SMD: -0.83, 95% CI: -1.05 to -0.61, I²=91.3%, p=0.000) as illustrated in Supplementary Figure 2. The random-effects model was done.

Postoperative blood loss (mL)

Eleven studies (15 trial comparisons) reported PBL. A total of 1,385 patients were evaluated for PBL. Of them, 761 and 624 were allotted to the experimental and control groups, respectively. Compared to the control group, the experimental PBL was significantly lower (SMD: -2.13, 95% CI: -2.68 to -1.57, I²=94.9%, p=0.000) as illustrated in Supplementary Figure 3. The random-effects model was done.

Postoperative drainage (mL)

Thirty-five studies (44 trial comparisons) reported postoperative drainage. In all, 3,109 patients were assessed for postoperative drainage, with 1,704 and 1,405 allotted to the experimental and control groups, respectively. The findings revealed that the experimental had significantly lower postoperative drainage than the control group (SMD: -1.55, 95% CI: -1.83 to -1.26, I²=92.2%, p=0.000) as illustrated in Supplementary Figure 4. The random-effects model was done.

Hemoglobin (g/dL)

Thirty-two studies (42 trial comparisons) reported Hb content. A total of 3,326 patients were involved to evaluate Hb content, of whom 1,863 were in the experimental group and 1,463 in the control group. The findings indicated that the experimental group’s Hb content was significantly higher than the control group (SMD: 0.53, 95% CI: 0.36 to 0.71, I²=83.9%, p=0.000) as illustrated in Supplementary Figure 5. The random-effects model was done.
Hematocrit (%)

Eighteen studies (24 trial comparisons) reported Hct. A total of 1,844 patients were evaluated for Hct, of whom 1,052 and 792 in the experimental and control groups, respectively. The results demonstrated that the TXA group had a greater level of Hct than the control group (SMD: 0.39, 95% CI: 0.08 to 0.70, I²=91.0%, p=0.000) as illustrated in Supplementary Figure 6. The random-effects model was done.

Safety endpoints

Deep venous thrombosis

Eight studies (11 trial comparisons) covered DVT, of which 19 out of 581 in the experimental group and 23 out of 432 in the control group experienced DVT. There was no significant variation among the TXA and control groups (3.2% vs. 5.3%) (RR: 0.78, 95% CI: 0.48 to 1.28, I²=0.0%, p=0.926) as illustrated in Figure 4. The fixed-effects model was done.

D-dimer (mg/L)

The concentration of D-dimer can be used in blood tests to help to diagnose thrombosis. Negative results can rule out thrombosis, while positive results suggest thrombosis probability, even so other potential reasons were not excluded. Therefore, its fundamental usage is to exclude thromboembolic diseases with a low probability. D-dimer was evaluated in 19 studies (24 trial comparisons), enrolling 1,837 participants for D-dimer assessment. The experimental group composed of 1,014 participants, whereas the control group composed of 823 participants. The results revealed that, compared to the control group, the experimental group's D-dimer levels were significantly lower (SMD: -0.35, 95% CI: -0.70 to -0.01, I²=92.5%, p=0.000) as illustrated in Figure 5. The random-effects model was done.

Publication bias and sensitivity analysis and subgroup analysis

According to the TXA administration method and the type of operation, subgroup analysis was done. Subgroup analysis results are listed in Supplementary Figures 7-14. The patients' TBL in the posterior lumbar surgery (PLS) group, posterior lumbar interbody fusion (PLIF) group, other operative type group and PLIF/transforaminal lumbar interbody fusion (TLIF) group was significantly lower compared to the control group (SMD: -0.84, 95% CI: -1.39 to -0.28, I²=89.4%, p=0.000; SMD: -1.14, 95% CI: -1.42 to -0.86, I²=79.9%, p=0.000; SMD: -1.21, 95% CI: -1.67 to -0.75, I²=92.0%, p=0.000; SMD: -1.94, 95% CI: -2.32 to -1.56, I²=87.9%, p=0.799) as illustrated in Supplementary Figure 7. The findings revealed that patients' TBL in the intravenous administration group, topical application group, and intravenous administration before the operation group was significantly lower compared to the control group.
group, whereas there were no significant variations in the intravenous administration group + topical application group (SMD: -0.06, 95% CI: -1.32 to -0.81, I²=87.7%, p=0.000; SMD: -1.46, 95% CI: -1.95 to -0.97, I²=87.8%, p=0.000; SMD: -1.55, 95% CI: -2.09 to -1.01; SMD: -0.29, 95% CI: -0.97 to 0.39) as illustrated in Supplementary Figure 8. The transfusion rates in the PLIF group, the other operative type group, and the topical application group were all significantly lower compared to the control group. There were no significant variations between the TLIF group and the control group (RR: 0.40, 95% CI: 0.33 to 0.48, I²=18.3%, p=0.269; RR: 0.60, 95% CI: 0.39 to 0.92, I²=0.0%, p=0.855; RR: 0.27, 95% CI: 0.11 to 0.70, I²=0.0%, p=0.658; RR: 0.11, 95% CI: 0.01 to 2.01) as illustrated in Supplementary Figure 9. The transfusion rates in the topical application group, intravenous administration group, and intravenous administration before the operation group were all significantly lower compared to the control group, whereas there were no significant variations while comparing intravenous administration with topical application (RR: 0.40, 95% CI: 0.30 to 0.54, I²=0.0%, p=0.440; RR: 0.41, 95% CI: 0.32 to 0.53, I²=0.0%, p=0.684; RR: 0.21, 95% CI: 0.06 to 0.69) as illustrated in Supplementary Figure 10. There were no significant variations in DVT in the PLIF group patients, other operative type group, transforaminal thoracic interbody fusion (TTIF), TLIF, and the control group (RR: 1.00, 95% CI: 0.29 to 3.41, I²=0.0%, p=0.764; RR: 0.47, 95% CI: 0.13 to 1.64, I²=0.0%, p=0.805; RR: 0.98, 95% CI: 0.53 to 1.80; RR: 0.33, 95% CI: 0.04 to 3.10) as illustrated in Supplementary Figure 11. There were no significant variations in the intravenous administration group's DVT patients, topical application group, and control group (RR: 0.85, 95% CI: 0.50 to 1.46, I²=0.0%, p=0.856; RR: 0.54, 95% CI: 0.15 to 1.94, I²=0.0%, p=0.719) as illustrated in Supplementary Figure 12. Patients in the PLS group had significantly lower D-dimer levels compared to the control group (SMD: -0.31, 95% CI: -0.53 to -0.09, I²=0.0%, p=0.698) as illustrated in Supplementary Figure 13; however, there were no significant variations in the patients' D-dimer levels in the PLIF group, other operative type group, TLIF...
Tranexamic acid in lumbar surgery

Our results revealed that TXA might significantly reduce TBL, transfusion rate, transfusion volume, IBL, PBL, drainage, and D-dimer compared to the control group. While comparing to the control group, TXA could significantly improve Hb and Hct and there

Currently, there are many articles studying TXA in lumbar surgery. In terms of its efficacy, Du and Feng\cite{87} conducted a meta-analysis to show that TXA had an important ability to minimize IBL and length of hospital stay following lumbar spinal fusion surgery. According to Lu et al.,\cite{79} TXA usage significantly decreased perioperative blood loss and the needs of red blood cell transfusions, but other surgical and clinical outcomes were not significantly different. On the other hand, some scholars put an opposed opinion that TXA might be incapable to reduce blood transfusion rate. Gong et al.,\cite{80} performed a meta-analysis and concluded that intravenous TXA had the ability to significantly minimize surgical blood loss. However, TXA treatment did not result in a significant reduction in the transfusion rates in treated patients. Endres et al.,\cite{81} performed a retrospective, case-control study and suggested that, when TXA was used in PLS, the Hb concentration was higher and the amount of blood loss was reduced. It lacked the capability to demonstrate a variation in transfusion rates. Furthermore, the safety of the TXA is also under study and some have offered the opinion that it has not any effect on enhancing thrombotic events risk. Bai et al.,\cite{82} performed a meta-analysis and proposed that TXA can minimize Hb loss, TBL, intraoperative and PBL, and it does not enhance thrombotic events risk following posterior lumbar fusion. However, there was no significant variation in blood transfusion rates. A retrospective, non-randomized, case-cohort study was performed by Sun et al.,\cite{83} and reported that TXA efficiently lowered perioperative blood loss, tube drainage durations, and length of hospitalization and it had no impact on increasing the risk of complications. Ren et al.,\cite{84} also carried out a retrospective, case-control study and concluded that TXA significantly minimized PBL, shortened the time to withdrawal of drainage tubes and the length of hospitalization in patients receiving PLS fusion surgery, although it did not increase the complication incidence. In contrast, Baldus et al.,\cite{85} conducted a comparative study with controls and found that the TXA group had less blood loss and received fewer blood transfusions than the aprotinin treatment group without any significant differences in the intraoperative or postoperative complications. As a result, it is yet unclear if TXA is safe and effective enough to be utilized in the clinic.

Recently, with the maturity of lumbar surgical techniques and the improvement of surgical equipment, bleeding during lumbar surgery has been effectively controlled.\cite{86} However, lumbar surgery is still one of the surgical procedures that causes extensive blood loss and, thus, surgeons are concerned about how to reduce perioperative blood loss.\cite{87} The TXA has been approved by the United States Food and Drug Administration (FDA) for more than 30 years and was added to the World Health Organization (WHO) Essential Drugs List in 2011.\cite{88} It shows excellent tolerance, with only rare dose-dependent adverse reactions, including nausea, vomiting, diarrhea, headache, upright reaction, blurred vision, and vertigo.\cite{89} Many original studies and reviews have suggested that TXA is safer than placebo and does not increase the incidence of DVT or pulmonary embolism.\cite{90} Additionally, clinical findings indicate that TXA usage in cardiac valve replacement and total hip arthroplasty can significantly minimize intraoperative blood transfusion volumes without enhancing the risk of thrombosis.\cite{91} Even so, TXA's effectiveness and safety in lumbar surgery still remain controversial.
were no significant variations in DVT among the TXA group and the control group. We did subgroup and sensitivity analyses after assessing that the endpoints had a high degree of heterogeneity. There were no restrictions on the usages or dose of TXA in our inclusion criteria and, therefore, we performed a subgroup analysis according to the method of administration of TXA (intravenous injection or local injection) and compared their postoperative drainage. Both routes could significantly reduce the patients’ TBL postoperative drainage compared to the control group. Nonetheless, there were no significant variations in postoperative drainage among the two subgroups, and these results cannot explain the heterogeneity. We speculated that this might be because the articles we included had a limited sample size and the patients were relatively heterogeneous. The disunity of the control group and the different dosages used in the TXA group might be also causes of heterogeneity.

To the best of our knowledge, the safety of TXA has been a bigger issue than studies of its efficacy, on account of its hemostatic mechanism that through the abnormal hyperactive fibrinolytic enzyme, causing platelet agglutination and inhibiting the decomposition of coagulation factors, and playing a hemostatic role. Until now, several studies have found that TXA is not associated with the increasing risk of complications; but the patients enrolled in these studies are also routinely prophylaxis with antithrombotic drugs after surgery which may cover the potential increased risk of TXA in venous thromboembolism. Besides, these vast majority of studies also exclude patients with comorbidities and patients who may be at risk for thromboembolism. The result in the meta-analysis suggests that the level of D-dimer decreases in TXA group than the control group. After reviewing the included literatures, we found that, in some of them, the D-dimer levels in the experimental group were somewhat less than in the control group, and there were non-significant variations. Others showed that TXA attenuated the increase of D-dimer after surgery. We can speculate that it is related to its anti-fibrinolytic effect: fibrinolytic enzymes, plasminogen, and fibrin binding may be inhibited by TXA by blocking lysine binding sites on plasminogen molecules, thus inhibiting the fibrinolytic decomposition caused by fibrinolytic enzyme. Theoretically, the risk of thrombosis is low after TXA use.

The potential clinical implications are as follows: (i) Thirty RCTs were identified, which comprised 3,042 subjects, more than in previous meta-analyses. The larger, population-inclusive, evidence-based review we conducted summarized the data and might provide a theoretical basis for future clinical drug use; (ii) Subgroup analyses were carried out based on the type of operation and administration route to account for the impact of several parameters on the overall effect; (iii) To determine the source of heterogeneity, we performed a sensitivity analysis to indicate the impact of sample size on the overall effect; and (iv) Ten indicators were assessed including TBL, transfusion rate, transfusion volume, IBL, PBL, drainage Hb, Hct, D-dimer, and DVT, which seemed to be more comprehensive than previous articles. Nonetheless, this study has some limitations: (i) We did not examine the interactions among the subgroup analyses due to the inherent limitations of the enrolled studies; (ii) The impact of the baseline features on the results could not be determined, since the outcome events documented in the enrolled studies were utilized; (iii) As most of the included articles did not report this information, we could not extract relevant data for some baseline features, such as other drug use, hypertension, or diabetes, which may cause some mixed bias. In addition, subgroup analysis according to the dose of TXA, the age of the adults and the safety endpoints, such as the risk of cerebrovascular accident, heart disease, or pulmonary embolism could not be performed; (iv) The outcomes of the various interventions in the control group may show significant heterogeneity. Even so, for ethical issues, we realize that it is unrealistic to compel the original author to refrain from using any hemostatic or anticoagulant interventions; hence, we incorporated all of these articles; (v) Since the limitation of the number of safety events such as cardiac problems or pulmonary embolism in published RCTs, the more safety endpoints could not be included; and (vi) Since there were no obvious findings were found in sensitivity analysis we conducted, it was not detailed in the paper. Moreover, although the results from this meta-analysis did not find an increased risk for DVT, RCTs included almost all exclude patients with comorbidities for this reason and consisted of patients with a low risk. It is still not clear that the safety of TXA in patients with risk factors. Further comprehensive studies with more data are needed to confirm these findings.

In conclusion, this meta-analysis demonstrates that TXA has the potential to significantly minimize TBL, transfusion rate, transfusion volume, IBL, PBL, drainage compared to the control group. Besides, the Hb and Hct values were higher in the TXA group than the control group. Its hemostatic potential
Tranexamic acid in lumbar surgery

after lumbar spine surgery is trustworthy. Besides, it is still controversial in safety endpoints that TXA can significantly reduce D-dimer compared to the control group, whereas there were no significant variations in DVT between the TXA and the control groups.

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SUPPLEMENTARY FIGURE 1. Comparison of Transfusion volume between the tranexamic acid group and the control group.

SUPPLEMENTARY FIGURE 2. Comparison of intraoperative blood loss between the tranexamic acid group and the control group.

SUPPLEMENTARY FIGURE 3. Comparison of Postoperative blood loss between the TXA group and the control group.

SUPPLEMENTARY FIGURE 4. Comparison of Postoperative drainage between the TXA group and the control group.
SUPPLEMENTARY FIGURE 5. Comparison of Hb between the TXA group and the control group.
SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 6. Comparison of Hct between the TXA group and the control group.
SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 7. Comparison of TBL between the TXA group and the control group. (Subgroup analysis according to operative type).
SMD: Standardized mean difference; CI: Confidence interval; TBL: Total blood loss; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 8. Comparison of TBL between the TXA group and the control group. (Subgroup analysis according to administration).
SMD: Standardized mean difference; CI: Confidence interval; TBL: Total blood loss; TXA: Tranexamic acid.
### SUPPLEMENTARY FIGURE 9. Comparison of Transfusion rate between the TXA group and the control group. (Subgroup analysis according to operative type).

RR: Risk ratio; CI: Confidence interval; TXA: Tranexamic acid.

### SUPPLEMENTARY FIGURE 10. Comparison of Transfusion rate between the TXA group and the control group. (Subgroup analysis according to administration).

RR: Risk ratio; CI: Confidence interval; TXA: Tranexamic acid.

### SUPPLEMENTARY FIGURE 11. Comparison of DVT between the TXA group and the control group. (Subgroup analysis according to operative type).

RR: Risk ratio; CI: Confidence interval; TXA: Tranexamic acid; DVT: Deep venous thrombosis.

### SUPPLEMENTARY FIGURE 12. Comparison of DVT between the TXA group and the control group. (Subgroup analysis according to administration).

RR: Risk ratio; CI: Confidence interval; DVT: Deep venous thrombosis; TXA: Tranexamic acid.
SUPPLEMENTARY FIGURE 13. Comparison of D-dimer between the TXA group and the control group. (Subgroup analysis according to operative type).

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 14. Comparison of D-dimer between the TXA group and the control group. (Subgroup analysis according to administration).

SMD: Standardized mean difference; CI: Confidence interval; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 15. Comparison of TBL between the TXA group and the control group. (Funnel plot)

SMD: Standardized mean difference; TBL: Total blood loss; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 16. Comparison of Transfusion rate between the TXA group and the control group (Funnel plot).

RR = Risk ratio; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 17. Comparison of Transfusion volume between the TXA group and the control group. (Funnel plot)

SMD: Standardized mean difference; TXA: Tranexamic acid.
SUPPLEMENTARY FIGURE 18. Comparison of IBL between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; IBL: Intraoperative blood loss.

SUPPLEMENTARY FIGURE 19. Comparison of PBL between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; PBL: Postoperative blood loss.

SUPPLEMENTARY FIGURE 20. Comparison of Postoperative Drainage between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 21. Comparison of Hb between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.
SUPPLEMENTARY FIGURE 22. Comparison of Hct between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 23. Comparison of DVT between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; DVT: Deep venous thrombosis; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 24. Comparison of D-dimer between the TXA group and the control group. (Funnel plot)
SMD: Standardized mean difference; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 25. Comparison of Transfusion rate between the TXA group and the control group. (Sensitivity analysis)
RR: Risk ratio; TXA: Tranexamic acid.
SUPPLEMENTARY FIGURE 26. Comparison of Transfusion volume between the TXA group and the control group. (Sensitivity analysis)
SMD: Standardized mean difference; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 27. Comparison of IBL between the TXA group and the control group. (Sensitivity analysis)
SMD: Standardized mean difference; IBL: Intraoperative blood loss; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 28. Comparison of PBL between the TXA group and the control group. (Sensitivity analysis)
SMD: Standardized mean difference; PBL: Postoperative blood loss; TXA: Tranexamic acid.

SUPPLEMENTARY FIGURE 29. Comparison of Hct between the TXA group and the control group. (Sensitivity analysis)
CI: Confidence interval; Hct: Hematocrit; TXA: Tranexamic acid.
SUPPLEMENTARY FIGURE 30. Comparison of D-dimer between the TXA group and the control group (Sensitivity analysis).

CI: Confidence interval; TXA: Tranexamic acid.