

Safety of intravenous tranexamic acid in patients undergoing major orthopaedic surgery: a meta-analysis of randomised controlled trials

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Abstract

Among the various pharmacological options to decrease peri-operative bleeding, tranexamic acid appears to be one of the most interesting. Several trials have consistently documented the efficacy of this synthetic drug in reducing the risk of blood loss and the need for allogeneic blood transfusion in patients undergoing total hip and knee arthroplasty. The safety of intravenous tranexamic acid in major orthopaedic surgery, particularly regarding the risk of venous thromboembolism, was systematically analysed in this review. A systematic search of the literature identified 73 randomised controlled trials involving 4,174 patients and 2,779 controls. The raw overall incidence of venous thromboembolism was 2.1% in patients who received intravenous tranexamic acid and 2.0% in controls. A meta-analytic pooling showed that the risk of venous thromboembolism in tranexamic acid-treated patients was not significantly different from that of controls (risk difference: 0.01%, 95% confidence interval [CI]: -0.05%, 0.07%; risk ratio: 1.067, 95% CI: 0.760-1.496). Other severe drug-related adverse events occurred very rarely (0.1%). In conclusion, the results of this systematic review and meta-analysis show that intravenous tranexamic acid is a safe pharmacological treatment to reduce blood loss and transfusion requirements in patients undergoing major orthopaedic surgery.

Keywords: tranexamic acid, orthopaedic surgery, safety, thromboembolic events.

Introduction

Tranexamic acid (TXA) is a synthetic amino acid which competitively blocks the lysine binding sites on plasminogen, thereby slowing the conversion of plasminogen to plasmin^{1,2}. Thanks to its ability to inhibit fibrinolysis and clot degradation, TXA, which can be administered intravenously, orally or topically, has been successfully used to prevent or decrease blood loss in a variety of clinical conditions characterised by excessive

bleeding in patients with or without inherited bleeding disorders^{3,4}. For instance, the early administration of TXA has been found to confer a survival benefit in the settings of severe trauma^{5,6} and of post-partum haemorrhage without an increase in thromboembolic events⁷. In addition, this haemostatic agent has been used successfully to decrease blood loss in numerous surgical specialties, particularly cardiac surgery^{8,9}. More recently, TXA has been widely administered to minimise bleeding and exposure to allogeneic blood transfusion in major orthopaedic surgery and several large randomised clinical trials and meta-analyses have consistently confirmed that the intravenous administration of TXA could effectively and safely reduce perioperative blood loss and transfusion requirements in total hip and knee arthroplasty¹⁰⁻¹⁴. In spite of this sound evidence, however, some concerns still remain among physicians over the hypothetical increased risk of thromboembolic complications (i.e., venous thromboembolism [VTE], including deep vein thrombosis and pulmonary embolism) following the systemic infusion of this anti-fibrinolytic agent in the setting of orthopaedic surgery. Thus, to refute this unjustified, non-evidence-based perception, we conducted a systematic review and meta-analysis aimed at assessing the safety of intravenous TXA in patients undergoing major orthopaedic surgery.

Materials and methods

This systematic review was conducted according to the recommended PRISMA checklist guidelines¹⁵.

Search methods

A computer-assisted literature search of the Medline, Embase and Scopus electronic databases was performed to identify randomised clinical trials on the use of intravenous TXA in major orthopaedic surgery. The following search strategy was used to maximise the search specificity and sensitivity: "total knee arthroplasty OR total knee replacement OR total hip arthroplasty OR total hip replacement OR total shoulder arthroplasty

OR total shoulder replacement OR major orthopaedic surgery OR hip fracture surgery" and "tranexamic acid". In addition, we hand-searched the reference lists of the most relevant items (original studies and reviews) in order to identify potentially eligible studies not captured by the initial literature search.

Study selection

Study selection was performed independently by two reviewers (MF and CM), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (GML). The eligibility assessment was based on the title or abstract and on the full text if required. Articles were eligible if they reported either in the title or in the abstract the use of intravenous TXA in patients undergoing major orthopaedic surgery. Studies on the use of TXA given by other routes of administration (i.e., oral or topical) were considered for the analysis only if they included an arm using intravenous TXA. Only randomised clinical trials published in full in English between January 1990 and July 2017 were included in this systematic review and meta-analysis¹⁶⁻⁸⁸.

Data extraction

For each study included in the systematic review, the following data were extracted by two reviewers (MF and CM) independently: study design, type of intervention, sample size (TXA and control groups), protocol (dose administered of intravenous TXA), thromboprophylaxis and TXA-related adverse events (i.e., VTE and other drug-related severe adverse events). The follow-up period for each trial was also recorded, when available.

Outcome measures

According to the study design of the different trials, the primary outcome measured was the safety TXA administered intravenously in major orthopaedic surgical procedures. The safety included mainly the incidence of venous thromboembolic complications (i.e., pulmonary embolism and deep vein thrombosis) following the intravenous administration of the anti-fibrinolytic agent. All the other drug-related severe adverse events were, however, also recorded.

Statistical evaluation and meta-analysis

In each study, the risk of VTE was evaluated as risk difference (RD) and risk ratio (RR) between a group of TXA-treated patients and a group of control patients. The meta-analysis was done, as usual, by pooling these effect indexes. A fixed effect, inverse variance pooling of the RD was performed. This index enables the calculation of an important pharmaco-economic index, the number needed to treat in order to avoid an event. The heterogeneity χ^2 was also calculated, as the I^2 for the

variation of RD due to heterogeneity. The same approach was used for the RR.

Since many of the studies provide zero-events, the estimate of the pooled RD is less biased than that of the pooled RR, although it is not very accurate. Indeed, even the RD method cannot avoid recourse to correction for lack of continuity, to adjust for zero. Moreover, some authors view the use of the RD unfavourably, since this method yields wide confidence intervals when events are rare, with poor statistical power^{89,90}. A method recently developed by Tian and colleagues⁹¹ for the RD, suitable for rare-event meta-analysis, appears appealing. It performs exact fixed effect meta-analysis for rare-events data without the need for an artificial continuity correction. This procedure combines the confidence intervals for the RD obtained from all studies. For the classical RD and RR we used Stata v15.0 (StataCorp LLC, College Station, TX, USA), whereas for Tian's RD we used the R package "exactmeta" (<https://cran.r-project.org/web/packages/exactmeta/index.html>).

Results

Literature search and study characteristics

In total, 824 articles were identified from the initial electronic and manual search, which was concluded on 7 September 2017 (Figure 1). Of these, 572 were excluded because they focused on other topics. Thus, 244 potentially relevant articles were selected; the next screening led to the exclusion of 171 additional studies (case-reports, reviews, protocols of randomised clinical trials, duplicates, studies containing no informative data). The remaining 73 randomised studies¹⁶⁻⁸⁸

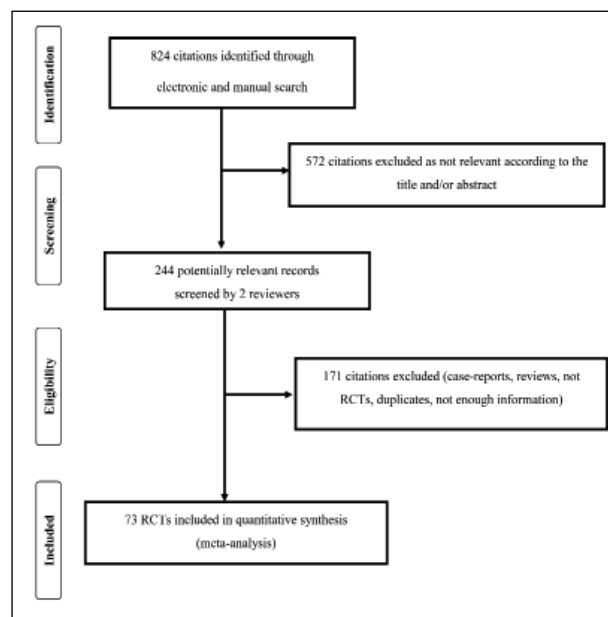


Figure 1 - Flow chart of the inclusion of the studies. RCTs: randomised controlled trials.

were included in the systematic review (see Online Supplementary Table SI for the main characteristics and results of the included studies), while six further studies^{57,73,76,78,80,86} were excluded from meta-analytical pooling because they were uncontrolled. Overall, 4,174 patients who received intravenous TXA and 2,779 controls who received no treatment were enrolled in the 73 studies evaluated. With regards to the type of major surgery, 46 studies^{16-18, 20-22,24,25,27,33-35,38,39,42,43,45-49,51-53,56-62,66-70,73-78,84-87} (2,960 cases and 1,924 controls) were focused on total hip arthroplasty, 20 studies^{19,23,26,28-32,37,41,44,50,55,63,64,71,79,80,82,83} (924 cases and 564 controls) on total knee arthroplasty, six studies^{36,40,54,65,72,81} (237 cases and 242 controls) on hip fracture surgery and one study⁸⁸ (53 cases and 49 controls) on shoulder arthroplasty. The dosing and timing of intravenous TXA varied from study to study. However, in the majority of cases (45/73 studies, 61.6%) it was given before or during and after surgery at a bolus dose ranging between 10 and 20 mg/kg. In 12 of the 73 studies (16.4%) TXA was also administered as a continuous intravenous infusion during surgery and/or postoperatively at a dose ranging between 1 and 10 mg/kg/hour. Sixty-four of the 73 (87.7%) selected trials also reported informative data on the administration of thromboprophylaxis. In the majority of the studies (50/64, 78.1%), thromboprophylaxis consisted of low molecular weight heparin given at various dosages (see Online Supplementary Table SI) and for a period ranging between 5 days and 6 weeks postoperatively. In six studies, low molecular weight heparin was followed by the direct oral anticoagulant rivaroxaban administered at a dose of 10 mg/day. In seven other studies rivaroxaban was given alone at the same daily dose for 7-14 days post-operatively. Only one study used unfractionated heparin, while thromboprophylaxis with warfarin or aspirin alone was performed in one and three studies, respectively. In two other studies only mechanical antithrombotic prophylaxis was provided.

Outcome analysis

The primary outcome analysed was the incidence of VTE. The VTE screening method performed was reported in 67/73 (91.8%) studies. In the majority of the cases (40/67 studies, 59.7%) VTE screening was based only on clinical examination (presence of symptoms and signs of thromboembolism), while in 24 additional studies (35.8%) an investigation with ultrasound or venography was also routinely associated. An additional laboratory screening for VTE (measurement of D-dimer levels) was also performed in four studies. The post-operative follow-up period ranged between three days and three months.

The overall incidence of VTE was 86 in 4,174 (2.1%) patients who received intravenous TXA and 55

in 2,779 (2.0%) control patients. A raw RD of 0.0008 and a raw RR of 1.0411 could thus be calculated. Excluding the six uncontrolled studies, the incidence of VTE was 77 in 3,417 TXA patients (2.2%), and the related raw indexes were RD=0.0027 and RR=1.1386.

With regards to the type of VTE, six (6/86, 7.0%) patients in the TXA group and five (5/55, 9.1%) patients in the control group had a pulmonary embolism, while the remaining patients (80/86 [93.0%] in the TXA group and 50/55 [91.9%] in the control group) experienced deep vein thrombosis.

The pooled meta-analytical RD was 0.001 (95% CI: -0.005 to 0.007). No heterogeneity was found, with an $I^2=0.0\%$. The statistical significance of the test of RD=0 was $p=0.745$, so the evidence against the null hypothesis of no difference between the two groups was very modest (Figure 2A). The number needed to treat was 1,000. The calculation of the RR was disturbed by many zero-event studies, which could not be evaluated. The pooled meta-analytical RR was 1.067 (95% CI: 0.760 to 1.496). No heterogeneity was found, with an $I^2=0.0\%$. The statistical significance of RR=1 was $p=0.708$ (Figure 2B). Tian's RD was 0 (95% CI: -0.007, 0.009), with a $p=1$.

Other severe adverse events possibly related to the administration of TXA occurred so rarely (5/3, 396, 0.1%) that a statistical analysis could not be performed.

Discussion

Major orthopaedic surgical procedures, in particular total hip and knee arthroplasties, are continuously increasing worldwide due to population aging. For instance, in the USA alone, nearly 1,000,000 total knee and hip arthroplasties are performed each year⁹². Despite advances in surgical techniques, intra- and post-operative blood loss remains one of the most common and important complications associated with such operations, exposing patients to increased impairment of functional ability, longer stays in hospital and, ultimately, increased morbidity and mortality⁹³. Allogeneic blood transfusion, a life-saving procedure used to correct post-operative anaemia, can, albeit rarely, be associated with serious adverse events⁹⁴. In this context, a restrictive red blood cell transfusion strategy^{95,96} and the implementation of a patient blood management programme (PBM)⁹⁷⁻¹⁰¹ in order to correct pre-operative anaemia have become the mainstay of management of patients undergoing major orthopaedic surgery. With regards to the latter issue, one of the most interesting methods of decreasing peri-operative blood loss and reducing the need for post-operative transfusion is based on the use of TXA and several hundreds of trials have assessed the potential beneficial effect of this pharmacological agent given topically and

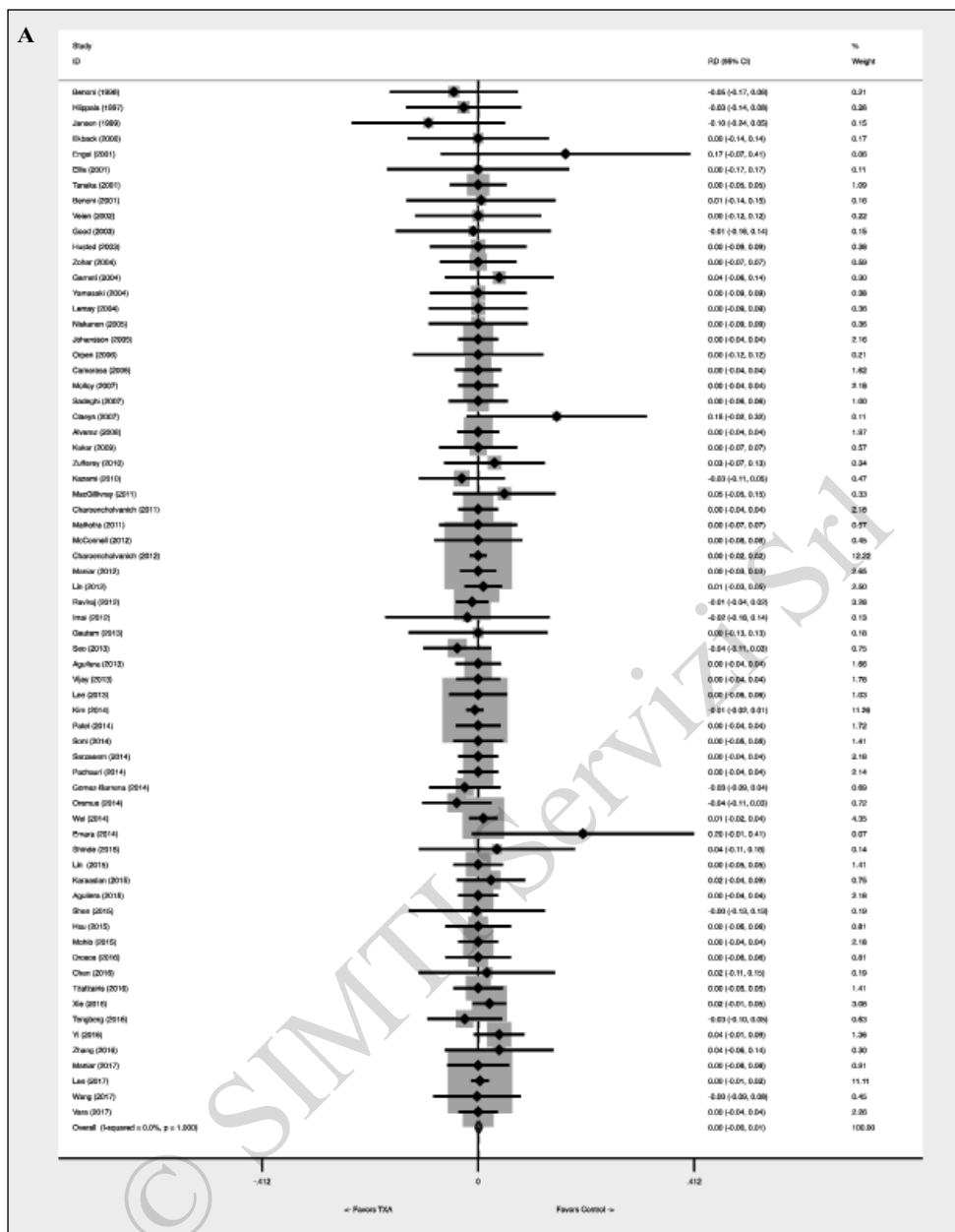


Figure 2A - Effect of tranexamic acid on VTE risk: meta-analytical pooling. *Continued on next page.*
 The effect was comparatively measured as risk difference (Figure 2A) and risk ratio (Figure 2B). Squares denote the risk difference and risk ratio, with their size being proportional to the weight assigned to the study. Horizontal bars indicate the 95% CI for each study. The diamonds represent the aggregate effect, with their width representing the 95% CI of the total effect. CI: confidence interval; RD: risk difference; TXA: tranexamic acid; VTE: venous thromboembolism.

or intravenously^{102,103}. While the benefit of intravenous TXA in significantly reducing the risk of post-operative blood loss and the need for allogeneic blood transfusion has been demonstrated consistently by several systematic reviews and meta-analyses^{11,14,104,105}, some concerns remain still among orthopaedic surgeons regarding its safety, in particular the risk of VTE. Thus, in order to contribute to a definitive response to these important concerns, we performed a systematic review and meta-

analysis focused on the safety of intravenous TXA in major orthopaedic surgery, particularly regarding its association with VTE risk.

After a systematic electronic and manual search, we identified 73 randomised clinical trials including almost 7,000 patients. Such a large number of studies and patients enrolled, much larger than any other systematic review or meta-analysis previously published, is due to the pooling of all the randomised clinical trials

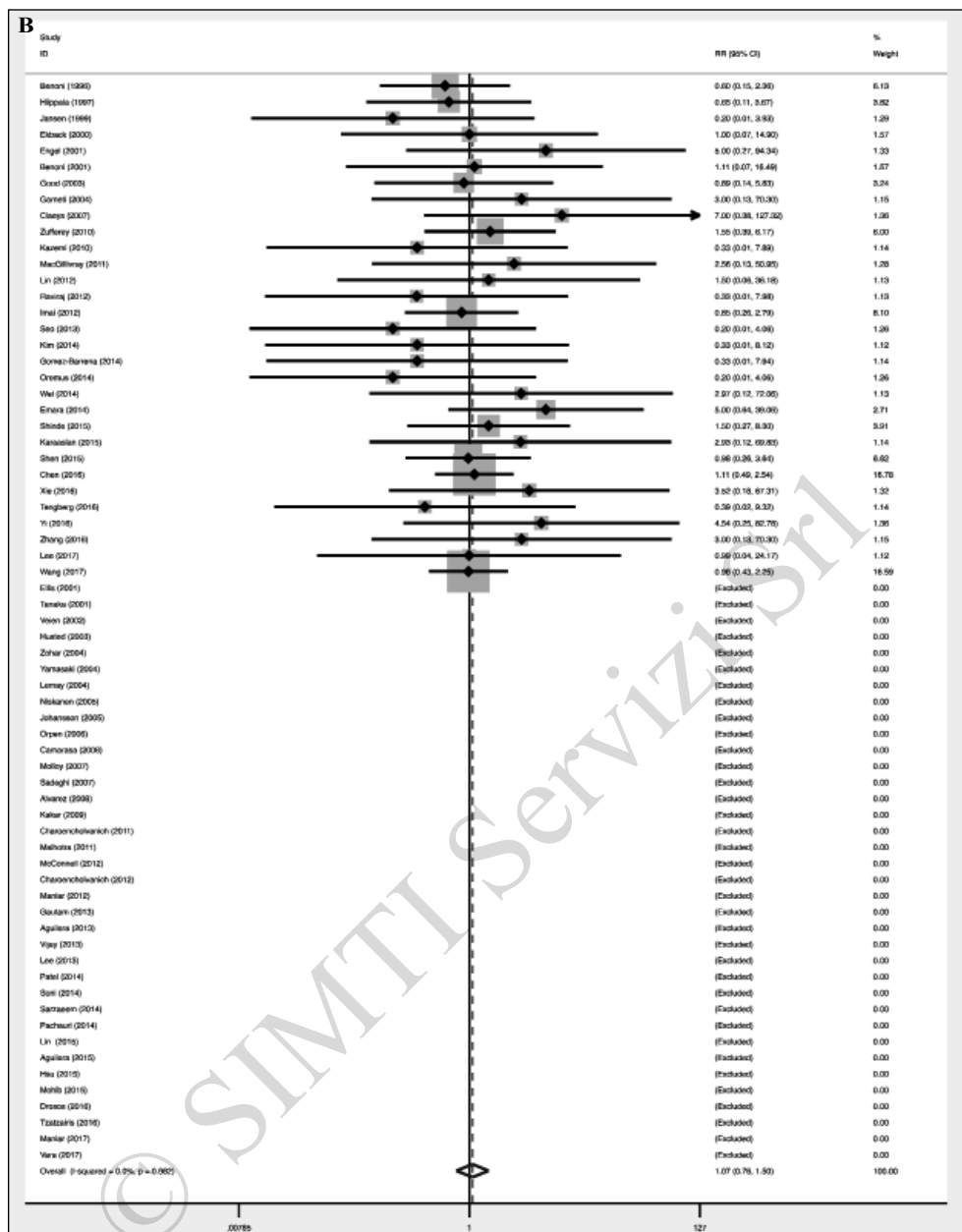


Figure 2B - Effect of tranexamic acid on VTE risk: meta-analytical pooling. *Continued from previous page.*
 The effect was comparatively measured as risk difference (Figure 2A) and risk ratio (Figure 2B). Squares denote the risk difference and risk ratio, with their size being proportional to the weight assigned to the study. Horizontal bars indicate the 95% CI for each study. The diamonds represent the aggregate effect, with their width representing the 95% CI of the total effect. CI: confidence interval; RR: risk ratio; TXA: tranexamic acid; VTE: venous thromboembolism.

evaluating the intravenous administration of TXA in the setting of any type of major orthopaedic surgery (i.e., total hip, knee and shoulder arthroplasties and hip fracture surgery).

After meta-analysis, we found that the risk of VTE, measured as RD and RR, in patients who received intravenous TXA was not significantly different from that in untreated controls. The negligible effect size of TXA on thromboembolic adverse events was also

confirmed using the Tian's RD (which was zero), a statistical method developed to overcome the limitations due to rare events (such as the thrombotic events recorded in this meta-analysis). In addition, no significant difference in the distribution of the different types of VTE (i.e., pulmonary embolism and deep vein thrombosis) was recorded in both cases and controls.

While the large number of studies evaluated represents the main strength of our systematic review, it

must be pointed out that a significant proportion of these randomised clinical trials differed from each other with regards to study design and, in particular, TXA dosing and timing of administration. In addition, different antithrombotic prophylaxis regimens and VTE screening methods were applied in the various studies. Moreover, the baseline risk of thromboembolic events varies considerably depending on whether major orthopaedic surgery is performed on the upper or lower limbs.

All these variables could have influenced the occurrence and detection of VTE. Nevertheless, in spite of such limitations, no heterogeneity in the randomised clinical trials was detected by the I^2 index (0%), which further validates the results of our study.

In conclusion, this systematic review and meta-analysis demonstrates the safety of the intravenous administration of TXA in patients undergoing major orthopaedic surgery. Our results, together with those from other previously published meta-analyses which document the efficacy of TXA and support the beneficial effect of this agent, TXA should, therefore, be used in orthopaedic surgery in the frame of PBM programmes.

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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