

Hemostatic Effect and Safety of TXA: An Umbrella Review

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Research article

Keywords: TXA, meta-analysis, TBL, transfusion rate, Hb drop, mortality, DVT, PE

Posted Date: October 19th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-81467/v1>

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Abstract

Aim

To evaluate the hemostatic effect and safety of tranexamic acid (TXA).

Methods

Meta-analyses were retrieved from databases. Risk ratios (RR), odds ratios (OR), weighted mean difference (WMD), standard mean difference (SMD) and 95% confidence intervals (CI) were extracted to compare the effectiveness of TXA in reducing TBL, transfusion rate, Hb drop, mortality, DVT, PE.

Results

In total, 136 trials (396 comparisons) including 17 kinds of surgeries were retrieved. The evidence for TXA using in total knee arthroplasty (TKA), total hip arthroplasty (THA), postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, cardiac surgery, menstrual bleeding, plastic surgery, myomectomy, nasal surgery was assessed as possible for the association of reducing TBL. The evidence for TXA using in TKA, THA, postpartum bleeding, orthopaedic surgery, shoulder arthroplasty was assessed as probable for the association of reducing transfusion rate. The evidence for TXA using in liver surgery, spinal surgery, hip fracture surgery, cancer, cardiac surgery was considered to be possible for the association of reducing transfusion rate. The evidence for TXA using in intertrochanteric fractures, orthopaedic surgery, hip fracture surgery was assessed as probable for the association of reducing Hb drop. The evidence for TXA using in TKA, THA, postpartum bleeding, shoulder arthroplasty was considered to be possible for the association of reducing Hb drop. The evidence for TXA using in trauma, gastrointestinal bleeding was assessed as probable for the association of reducing mortality.

Conclusion

This umbrella review indicated that TXA were regarded as effective to reduce TBL, transfusion rate, Hb drop, mortality, and did not increase the incidence of DVT and PE. However, more convincing evidence should be provided to further clarify the level of efficacy and safety of TXA.

Introduction

Antifibrinolytic drugs have been widely used in obstetrics and gynecology surgery, cardiac surgery, trauma, hip and knee replacement and other fields to reduce perioperative bleeding and blood transfusion [1]. Among them, tranexamic acid (TXA) is the most common type used in surgery, and its main mechanism has been deeply studied.

Fibrinolysis is related to the decomposition of fibrinolysis and the increase of vascular permeability under physiological or pathological conditions, as well as the occurrence, development and cure of fibrinolysis-induced reactions, bleeding symptoms and allergic reactions [2]. TXA can inhibit the effect of fibrinolytic enzyme and show hemostatic, anti-allergic and anti-inflammatory effects. (1) Anti-fibrinolytic enzyme effect. Aminocycline can strongly adsorb (LBS), which is the lysine binding site of fibrinolytic enzyme and plasminogen, and inhibit the binding of fibrinolytic enzyme and plasminogen to fibrin. Thus, the fibrinolysis induced by the fibrinolytic enzyme was strongly inhibited. Also, in the presence of anti-fibrinolytic enzymes such as macroglobulin 2 in serum, the anti-fibrinolytic effect of TXA was more obvious, and the hemostatic effect was more significant [3]. (2) Hemostatic effect. Abnormal hyperactivity of the fibrinolytic enzyme will cause platelet agglutination inhibition and coagulation factor decomposition. Mild hyperactivity first leads to the decomposition of fibrin. Therefore, it is considered that in general bleeding, TXA can inhibit fibrin decomposition and play a hemostatic role [4]. (3) Anti-allergic and anti-inflammatory effects. TXA can inhibit the production of kinin and other active peptides (guinea pigs and rats) which cause vascular permeability enhancement, allergy and inflammatory lesions [5]. Nowadays, there are many meta-analyses to study the efficacy and safety of TXA in clinical events, such as trauma or surgical bleeding in the brain, uterus and other organs rich in plasminogen activator. However, it is still inconsistent whether TXA is effective and safe enough and whether it can be used in all clinical applications. With the increase in the number of systematic reviews available, a logical next step to provide decision-makers in healthcare with the evidence they require has been the conduct of reviews of existing systematic reviews. Syntheses of existing systematic reviews are referred to by many different names, one of which is an umbrella review. An umbrella review allows the findings of reviews relevant to a review question to be compared and contrasted. An umbrella review's most characteristic feature is that this type of evidence synthesis only considers for inclusion the highest level of evidence, namely other systematic reviews and meta-analyses [6]. Therefore, we summarized the results of existing meta-analyses and comprehensively evaluated their quality. The purpose of this review is to explore the efficacy and safety of TXA and to provide more options for the clinical application of hemostatic drugs.

Methods

Search strategy

This is an umbrella review (Systematic collection and evaluation of multiple systematic reviews and meta-analysis of specific research topics). Two researchers systematically searched published systematic reviews and meta-analyses evaluating hemostatic effect and safety of TXA from inception to Aug 17th, 2019. Language was restricted to English. The databases we searched included Medline, Embase, PubMed, and The Cochrane Library. We used the following keywords: "TXA" and "meta-analysis". Full text of potentially qualified articles was screened by another two researchers respectively.

Inclusion and exclusion criteria

Inclusion criteria: (1) meta-analyses of RCTs assessing hemostatic effect and safety of TXA; (2) meta-analyses of observational studies evaluating hemostatic effect and safety of TXA.

Exclusion criteria: (1) no meta-analysis; (2) studies on genetic polymorphisms related to TXA; (3) studies with incomplete or erroneous data; (4) meta-analyses in which endpoints of TXA was only a little part of the outcome; (5) the studies included in the meta-analysis were completely overlapping; (6) the endpoints of meta-analysis were not of interest.

Data extraction

Two authors reviewed the contents of the retrieved meta-analyses independently. Total blood loss (TBL), Transfusion rate, Haemoglobin drop (Hb drop), deep venous thrombosis (DVT), pulmonary embolism (PE) and mortality were extracted and verified by a third author. The characteristics extracted was as follows: the first author, year of publication, number of studies, intervention measures in experimental group and control group, number of sample size, effect size (95%CI), meta-analyse metric, heterogeneity and p value. If a quantitative synthesis was done, we also extracted the study-specific relative risk estimates (risk ratio, odds ratio, mean difference, Std mean difference) together with the corresponding CI and the number of cases and controls in each study for each risk factor. In the event of a dispute, a third author would coordinate the settlement. In this umbrella review, all data were extracted from previously published studies, thus no patient consent and ethical approval were required.

Statistical analysis

For each meta-analysis, we estimated the effect size and its 95% CI with both fixed-effects and random-effects models. In order to compare hemostatic effect and safety of TXA more clearly, we unified the effect size as a forest plot. Between-study heterogeneity was assessed by the I^2 metric. I^2 ranges between 0% and 100% and is the ratio of between-study variance over the sum of the within-study and between-study variances. Values exceeding 50% or 75% are usually judged to represent large or very large heterogeneity, respectively. A p-value less than 0.05 was judged to be significant evidence. The criteria used for evidence categorization were showed in **Table 1**. Whenever more than one meta-analysis was conducted using the same endpoints, and the same study design and type of population, the most recent or most exhaustive study was considered. Stata (version 13.0) was used for statistical analysis and calculation.

Result

According to the retrieval strategy, 232 articles were initially obtained, of which 96 were excluded according to the type of articles by title evaluation. Through reviewing the abstract and full text, 136 studies (396 comparisons) [7-142] were finally included to compare the efficacy of TXA in reduction of TBL, transfusion rate, Hb drop, mortality, DVT and PE as shown in **Figure 1**. The effect sizes of each meta-analysis and baseline characteristics for 136 meta-analyses of TXA related to TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder

arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery, cardiac surgery, nasal surgery, gastrointestinal bleeding, trauma, liver surgery, cancer and myomectomy reported were shown in **Table 2**.

According to the largest studies, the meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery and nasal surgery reported significantly reduced TBL; the meta-analyses of TXA using for liver surgery and myomectomy reported that there was no significant difference in TBL; the meta-analyses of TXA using for cardiac surgery reported significantly increased TBL. The meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, shoulder arthroplasty, hip fracture surgery reported significantly reduced Hb drop; the meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, liver surgery, orthopaedic surgery, spinal surgery, hip fracture surgery, cancer and cardiac surgery reported significantly reduced transfusion rate; the meta-analyses of TXA using for trauma, shoulder arthroplasty, gastrointestinal bleeding, plastic surgery and myomectomy reported there was no significant difference in transfusion rate. The meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding and cardiac surgery reported there was no significant difference in DVT. The meta-analyses of TXA using for TKA, THA, trauma, intertrochanteric fractures and cardiac surgery reported there was no significant difference in PE. The meta-analyses of TXA using for trauma and gastrointestinal bleeding reported significantly reduced mortality; the meta-analyses of TXA using for liver surgery and cardiac surgery reported there was no significant difference in mortality as shown in **Table 3**.

However, considering all the effect sizes of the included studies, the results were controversial. Among them, 25 of 26 comparisons about TKA, 2 of 3 comparisons about TKA/THA, 8 of 10 comparisons about postpartum bleeding, 2 of 3 comparisons about cardiac surgery and all comparisons about THA, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery, myomectomy and nasal surgery still suggested a significant reduction of TBL. 1 of 26 comparisons about TKA, 1 of 3 comparisons about TKA/THA, 2 of 10 comparisons about postpartum bleeding and all comparisons about liver surgery suggested no significant difference on TBL. 1 of 3 comparisons about cardiac surgery suggested a significant increase on TBL compared with aprotinin. 6 comparisons evaluated the effect of intravenous combined topical application of TXA on TBL in TKA compared with intravenous or topical application of TXA alone. The results of 6 comparisons showed that the combined use of TXA significantly reduced TBL compared with TXA alone; 9 comparisons evaluated the effect of intravenous, topical or oral TXA on TBL in TKA. The results of 1 comparison showed that intravenous use of TXA significantly increased TBL compared with topical application of TXA; 8 comparisons showed that there was no significant difference among the three types of administration for TBL. 4 comparisons evaluated the effect of intravenous combined topical application of TXA on TBL in THA compared with intravenous or topical application of TXA alone. The results of 4 comparisons showed that the combined use of TXA significantly reduced TBL compared with TXA alone; 5 comparisons evaluated the effect of intravenous, topical or oral TXA on TBL in THA. The results of 5 comparison showed that there was no significant difference among the three types of

administration for TBL. 4 comparisons evaluated the effect of intravenous combined topical application of TXA on TBL in TKA/THA compared with intravenous or topical application of TXA alone. The results of 4 comparisons showed that the combined use of TXA significantly reduced TBL compared with TXA alone; 5 comparisons evaluated the effect of intravenous, topical or oral TXA on TBL in TKA/THA. The results of 5 comparison showed that there was no significant difference among the three types of administration for TBL.

15 of 16 comparisons about THA, 2 of 3 comparisons about TKA/THA, 8 of 9 comparisons about postpartum bleeding, 7 of 12 comparisons about spinal surgery, 3 of 4 comparisons about shoulder arthroplasty, 9 of 11 comparisons about cardiac surgery and all comparisons about TKA, intertrochanteric fractures, liver surgery, orthopaedic surgery, hip fracture surgery and cancer still suggested a significant reduction of transfusion rate; 1 of 16 comparisons about THA, 1 of 3 comparisons about TKA/THA, 1 of 9 comparisons about postpartum bleeding, 5 of 12 comparisons about spinal surgery, 1 of 4 comparisons about shoulder arthroplasty, 2 of 11 comparisons about cardiac surgery and all comparisons about trauma, gastrointestinal bleeding, plastic surgery and myomectomy suggested no significant difference on transfusion rate. 6 comparisons evaluated the effect of intravenous combined topical application of TXA on transfusion rate in TKA compared with intravenous or topical application of TXA alone. The results of 1 comparison showed that the combined use of TXA significantly reduced transfusion rate compared with TXA alone in TKA; 5 comparisons showed that there was no significant difference between the combined and separate administration in TKA. 8 comparisons evaluated the effect of intravenous, topical or oral TXA on transfusion rate in TKA. All comparisons showed that there was no significant difference among the three types of administration for transfusion rate. 2 comparisons evaluated the effect of intravenous combined topical application of TXA on transfusion rate in THA compared with intravenous or topical application of TXA alone. The results of 2 comparisons showed that the combined use of TXA significantly reduced transfusion rate compared with TXA alone. 3 comparisons evaluated the effect of intravenous, topical or oral TXA on transfusion rate in THA. The results of 3 comparison showed that there was no significant difference among the three types of administration for transfusion rate. 2 comparisons evaluated the effect of intravenous combined topical application of TXA on transfusion rate in TKA/THA compared with intravenous or topical application of TXA alone. The results of 2 comparisons showed that the combined use of TXA significantly reduced transfusion rate compared with TXA alone. 5 comparisons evaluated the effect of intravenous, topical or oral TXA on transfusion rate in TKA/THA. The results of 5 comparisons showed that there was no significant difference among the three types of administration for transfusion rate.

3 of 4 comparisons about shoulder arthroplasty and all comparisons about TKA, THA, TKA/THA, postpartum bleeding intertrochanteric fractures, orthopaedic surgery and hip fracture surgery still suggested a significant reduction of Hb drop; 1 of 4 comparisons about shoulder arthroplasty suggested no significant difference on Hb drop. 2 comparisons evaluated the effect of intravenous combined topical application of TXA on Hb drop in TKA compared with intravenous or topical application of TXA alone. The results of 2 comparisons showed that the combined use of TXA significantly reduced Hb drop compared with TXA alone in TKA. 7 comparisons evaluated the effect of intravenous and topical TXA on

Hb drop in TKA. The results of 1 comparison showed that the intravenous use of TXA significantly reduced Hb drop compared with topical application of TXA in TKA; 6 comparisons showed that there was no significant difference between the two types of administration for Hb drop. 4 comparisons evaluated the effect of intravenous combined topical application of TXA on Hb drop in THA compared with intravenous or topical application of TXA alone. The results of 3 comparisons showed that the combined use of TXA significantly reduced Hb drop compared with TXA alone in THA; 1 comparison showed that there was no significant difference. 3 comparisons evaluated the effect of intravenous and topical TXA on Hb drop in THA. The results of 1 comparison showed that the intravenous use of TXA significantly reduced Hb drop compared with topical application of TXA in THA; 2 comparisons showed that there was no significant difference between the two types of administration for Hb drop. 3 comparisons evaluated the effect of intravenous combined topical application of TXA on Hb drop in TKA/THA compared with intravenous or topical application of TXA alone. The results of 3 comparisons showed that the combined use of TXA significantly reduced Hb drop compared with TXA alone. 6 comparisons evaluated the effect of intravenous, topical or oral TXA on Hb drop in TKA/THA. The results of 2 comparisons showed that intravenous use of TXA significantly reduced Hb drop compared with oral or topical application of TXA; 4 comparison showed that there was no significant difference among the three types of administration for Hb drop.

2 of 3 comparisons about trauma, 2 of 7 comparisons about cardiac surgery and all comparisons about gastrointestinal bleeding still suggested a significant reduction of mortality; 1 of 3 comparisons about trauma, 5 of 7 comparisons about cardiac surgery and all comparisons about liver surgery suggested no significant difference on mortality.

All comparisons about TKA, THA, TKA/THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding, cardiac surgery showed that there was no significant difference on DVT.

All comparisons about TKA, THA, trauma, intertrochanteric fractures, cardiac surgery showed that there was no significant difference on PE.

A summary of evidence from the retrieved meta-analyses of TXA is shown in **Table 4**. The evidence for TXA using in TKA (combine administration vs single administration; TXA vs placebo), THA (combine administration vs single administration; TXA vs placebo), TKA/THA (combine administration vs single administration; TXA vs placebo), postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, cardiac surgery, menstrual bleeding, plastic surgery, myomectomy, nasal surgery was assessed as possible for the association of reducing TBL. There was probably no association between TXA and TBL in TKA (IV TXA vs topical/oral TXA), THA (IV TXA vs topical/oral TXA), TKA/THA (IV TXA vs topical/oral TXA) and liver surgery.

The evidence for TXA using in TKA (TXA vs placebo), THA (TXA vs placebo; combine administration vs single administration), TKA/THA (combine administration vs single administration), postpartum bleeding, orthopaedic surgery, shoulder arthroplasty was assessed as probable for the association of reducing

transfusion rate. The evidence for TXA using in TKA/THA (TXA vs placebo), liver surgery, spinal surgery, hip fracture surgery, cancer, cardiac surgery was considered to be possible for the association of reducing transfusion rate. There was probably no association between TXA and transfusion rate in TKA (combine administration vs single administration; IV TXA vs topical/oral TXA), THA (IV TXA vs topical/oral TXA), TKA/THA (IV TXA vs topical/oral TXA), trauma, intertrochanteric fractures, gastrointestinal bleeding, plastic surgery, myomectomy.

The evidence for TXA using in intertrochanteric fractures, orthopaedic surgery, hip fracture surgery was assessed as probable for the association of reducing Hb drop. The evidence for TXA using in TKA (TXA vs placebo; combine administration vs single administration), THA (TXA vs placebo; combine administration vs single administration), TKA/THA (TXA vs placebo; combine administration vs single administration), postpartum bleeding, shoulder arthroplasty was considered to be possible for the association of reducing Hb drop. There was probably no association between TXA and Hb drop in TKA (IV TXA vs topical TXA), THA (IV TXA vs topical TXA), TKA/THA (IV TXA vs topical TXA).

The evidence for TXA using in trauma, gastrointestinal bleeding was assessed as probable for the association of reducing mortality. There was probably no association between TXA and mortality in liver surgery, cardiac surgery.

There was probably no association between TXA and DVT in TKA, THA, TKA/THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding, cardiac surgery.

There was probably no association between TXA and PE in TKA, THA, trauma, intertrochanteric fractures, cardiac surgery.

Several other associations were found, but were often affected by heterogeneity or potential confounding factors.

Discussion

Hemostatic drugs can accelerate blood coagulation or reduce capillary permeability and stop bleeding [143]. The normal hemostatic mechanism depends on the integrity of the structure and function of vascular wall, platelet, coagulation system, anticoagulation system, fibrinolysis (fibrinolysis) system and hemorheology, as well as the physiological regulation and balance between them [144]. The hemostatic drugs used in clinic can either reduce the arteries and capillaries, or enhance the platelet function, or accelerate or strengthen the blood coagulation process, or inhibit the clot dissolution process to achieve the purpose of hemostasis [145].

The hemostatic drugs commonly used in clinic are mainly divided into 4 categories: 1. Antifibrinolytic drugs: (1) aminocaproic acid acts by inhibiting fibrinolytic system. It is mainly used for bleeding caused by the increase of fibrinolytic enzyme activity, such as obstetrics and gynecology, prostate, liver, pancreas,

lung and so on. Early or preoperative use of drugs during operation can reduce blood leakage during operation and reduce the amount of blood transfusion. Overdose can lead to thrombosis with a tendency to thrombosis or a history of thrombotic vascular disease. Renal insufficiency should be used with caution. Due to the side effects of this drug, it has been less used at present[146]. (2) the mechanism of aminomethylbenzoic acid (hemostatic aromatic acid) is the same as that of aminocaproic acid, and its effect is 4–5 times stronger than that of aminohexanoic acid. Suitable for lung, liver, pancreas, prostate, thyroid, adrenal gland surgery abnormal bleeding, obstetrics and gynecology and postpartum hemorrhage and pulmonary tuberculosis hemoptysis, sputum with blood, hematuria, prostate hypertrophy bleeding, upper gastrointestinal bleeding and so on. It has a significant effect on chronic blood oozing [147]. (3) the mechanism of aminocycline (hemostatic cyclic acid, thrombotic acid) is the same as TXA, and its effect is slightly stronger than that of aminomethylbenzoic acid. The indication is similar to hemostatic aromatic acid. It is used for all kinds of hemorrhagic diseases, abnormal bleeding during operation and so on. Side effects can be headache, dizziness, nausea, vomiting and other reactions[148].

2. Drugs to reduce capillary permeability: (1) phenolsulfonethylamine (hemostatic) works by promoting the process of coagulation. Can increase platelet aggregation and adhesion in the blood, promote the release of clotting substances, in order to accelerate blood coagulation [149]. Clinically, it is used to prevent and treat bleeding caused by surgical bleeding, thrombocytopenic purpura or Henoch-Schonlein purpura and other causes. This product can be used in combination with other types of hemostatic drugs. Less side effects. (2) carbacarbital (Anluo blood) is a semicarbazide of adrenaline oxidation product adrenaline, which is often used as sodium salicylate (carbacarbital) or sodium sulfonate (sodium caroesulfonate). This product can promote capillary contraction. Reduce the permeability of capillaries, increase the retraction of the broken end of broken capillaries, and play a hemostatic role. Indications: this product is often used in idiopathic purpura, retinal hemorrhage, chronic pulmonary hemorrhage, gastrointestinal hemorrhage, epistaxis, hemoptysis, hematuria, hemorrhoid bleeding, uterine bleeding, cerebral hemorrhage and so on. Side effects: this product is low toxicity, but not suitable for mass use, can induce epilepsy and mental disorders.

3. Thrombin drugs: (1) the common name of batroxine is snake venom hemagglutinin for injection, which is a kind of batroxobin extracted from Brazilian spear head. Clinically, it is used to treat bleeding caused by various causes, especially in patients with bleeding whose traditional hemostatic drugs are ineffective. Contraindication: bleeding caused by DIC and patients with a history of thrombosis or embolism are prohibited. In addition to emergency bleeding, the first 3 months of pregnancy should not be used. (2) Thrombin can directly act on the fibrinogen in the blood, promote the transformation into fibrin, accelerate the coagulation of the blood and stop the bleeding. Clinical use for trauma, surgery and oral hemostasis for gastrointestinal bleeding [150]. No injections.

4. Coagulation factors: (1) Vitamin K1 is a natural vitamin used for injection. The effect was stronger than that of K3 and K4. (2) Sodium bisulfite mono-naphthoquinone (vitamin K3) is a synthetic vitamin, which is used in the treatment of vitamin K deficiency. (3) methylnaphthalene hydroquinone (vitamin K4, acetylnaphthoquinone) is a synthetic vitamin, which is used for oral administration [151].

Fibrinolysis is related to the decomposition of fibrinolysis and the increase of vascular permeability under physiological or pathological conditions, as well as the occurrence, development and cure of fibrinolysis-induced reactions, bleeding symptoms and allergic reactions [152]. TXA can inhibit the effect of fibrinolytic enzyme and show hemostatic, anti-allergic and anti-inflammatory effects [153]. (1) Anti-fibrinolytic enzyme effect. Aminocycline can strongly adsorb (LBS), which is the lysine binding site of fibrinolytic enzyme and plasminogen, and inhibit the binding of fibrinolytic enzyme and plasminogen to fibrin. Thus, the fibrinolysis induced by fibrinolytic enzyme was strongly inhibited. In addition, in the presence of anti-fibrinolytic enzymes such as macroglobulin 2 in serum, the anti-fibrinolytic effect of TXA was more obvious, and the hemostatic effect was more significant [154]. (2) Hemostatic effect. Abnormal hyperactivity of fibrinolytic enzyme will cause platelet agglutination inhibition and coagulation factor decomposition. Mild hyperactivity first leads to the decomposition of fibrin. Therefore, it is considered that in general bleeding, TXA can inhibit fibrin decomposition and play a hemostatic role [155]. (3) Anti-allergic and anti-inflammatory effects. TXA can inhibit the production of kinin and other active peptides (guinea pigs and rats) which cause vascular permeability enhancement, allergy and inflammatory lesions [156].

In the current controversial situation, researchers are trying to use different methods to verify the safety of TXA. Because it is necessary to design a clinical trial with a large enough sample to illustrate the differences between these low probability events, the researchers turned to looking for answers to questions from some population-based databases in recent years. To answer our questions about the use of TXA in different clinical situations. There are limitations, such as the fact that these studies are retrospective, or that there is only limited clinical data and the risk of confusion. Although these randomized trials do not comply with strict inclusion or exclusion criteria, but are artificially defined, the benefits are considerable, such as the provision of large samples and the true clinical results of hundreds of hospital cases.

Poeran et al [157] have recently found that the use of TXA in most joint operations can benefit. Their study found that TXA is safe and effective in total hip or knee arthroplasty. In 872416 cases in 510 hospitals across the United States, the researchers found that the use of TXA reduced the rate of blood transfusions by 60 per cent or more. The application of TXA could reduce the incidence of allogeneic or autologous blood transfusion (7.7% vs. 20.1%, $P < 0.001$), thrombus-related complications (0.6% vs. 0.8%, $P < 0.0057$). The overall complications (1.9% vs. 2.6%, $P < 0.001$), the need for mechanical ventilation (0.1% vs. 0.2%, $P < 0.0003$), and the need to enter ICU (3.1% vs. 7.5%, $P < 0.001$). In addition, the median hospitalization cost of patients treated with TXA was relatively low ($P < 0.001$). Very importantly, while showing significant effectiveness, the use of TXA did not significantly increase the risk of complications, such as thrombus-related events (probability ratio 0.85: 1.02), acute renal failure (0.70: 1.11, This is a hidden danger to the use of antifibrinolytic drugs since protease inhibitors left the market), the overall complication (0.75: 0.98). The overall complications also include acute myocardial infarction, which is important because the pathogenesis of perioperative myocardial infarction is due to myocardial oxygen deficiency, coronary plaque rupture and platelet activation. If intraoperative bleeding is reduced as a result of the use of TXA, myocardial hypoxia caused by tachycardia and reduced hemoglobin in the blood can

be effectively reduced. In this regard, preliminary data using the same data set may indicate no increased risk in cases with a history of coronary artery disease, but there is a clear need for more research in this area. In providing the data, the authors point out that although the use of TXA is becoming more and more popular, only 11.2 per cent of patients were found to be using it in the 2012 year study. At the same time, they also stressed that although the use of TXA is safe in the population as a whole, the safety of using TXA in different subgroups needs to be further studied.

Another way to solve the safety problem of TXA is to reduce the amount of TXA in the whole body by local application of TXA in the surgical site. Gomez-Barrena et al[158] recently published an article in JBJS comparing the efficacy of local TXA and intravenous TXA in patients with primary total knee arthroplasty. A phase III single-center double-blind randomized controlled trial was conducted to demonstrate that local administration of TXA (3 g TXA dissolved in 100 mL saline) was no worse than twice intravenous administration of TXA (15 mg/kg TXA dissolved in 100 mL saline, once before the tourniquet was loosened. It was used 3 hours after operation). The main indicators were defined as the need for postoperative blood transfusions. The secondary indicators included blood loss through drainage at 3 hours 24 hours, hemoglobin levels 24 hours, 48 hours and 5 days after operation, and estimated total bleeding volume (calculated by the lowest hemoglobin level before and after operation). In addition, complications and serious adverse reactions, days of hospitalization and active motion range of knee joint after operation were also within the scope of their evaluation. The sample size was calculated by a maximum expected transfusion rate of 5%, based on a 0 transfusion rate in previous studies of total knee arthroplasty. In the preliminary results, the significance was set to unilateral 0.025, the test efficiency was 99%, and the sample size of each group was 39 cases. There was no statistically significant difference in the main results (the transfusion rate was 0 in both groups), and there was no significant difference in the secondary results (blood loss in 3–24 h drainage and the calculated amount of blood loss 48 h and 5 d after operation). The decline levels of hemoglobin at 24 h, 48 h and 5 d were similar between the two groups (local use of TXA group was 2.3 g/L, 2.1 g/L and 2.0 g/L). Intravenous use of TXA group was – 2.5, -3.4, -2.6 g/dL).

On the other hand, the use of TXA in orthopedic patients is more economically efficient. Its performance in reducing the hospitalization cost of patients with total hip and total knee arthroplasty makes its application prospect more bright. TXA itself is cheap (about \$6 per box on average), and studies by Poeran et al [157] have shown that it can significantly reduce the average hospitalization costs of patients. Given that the number of joint replacements is likely to continue to rise across the United States and elsewhere over the next decade, an economical and effective treatment is indispensable.

Overall, the evidence so far has irrefutably confirmed the role of TXA in joint replacement: it can effectively reduce bleeding and transfusion rates. At present, the data on its safety in perioperative period is considerable. However, for those at risk of thrombotic complications, the use of TXA still needs further research, as well as further research on the safe use of TXA and the minimum effective dose of TXA. Local use of TXA, is a better method than intravenous administration, especially in terms of reducing plasma concentrations. But strong enough evidence is still needed to prove its safety. At the same time,

because of its economy and clinical effectiveness, the overall dosage of TXA is increasing. However, with the expansion of the use of TXA, there will be more new problems, so it is necessary to continue to assess the risks and benefits of TXA, especially for those cases where there is a risk of adverse events. In order to provide evidence-based evidence to ensure the reasonable clinical use of TXA, an umbrella review that systematically assessing the hemostatic effect and safety of TXA is crucial.

In our study, the results of 136 meta-analyses (396 comparisons) [7–142] including TXA to reduce TBL, transfusion rate, Hb drop, mortality, DVT and PE were reviewed; these meta-analyses included 15 kinds of surgeries. Most of the evidence comes from meta-analysis of RCTs; only a few meta-analyses include observational studies. Based on these results, there may be evidence that TXA may be helpful in reducing TBL, transfusion rate, Hb drop and mortality in different kinds of surgeries. In terms of different ways of administration, intravenous combined topical application of TXA significantly reduced TBL in TKA and THA compared with intravenous or topical application of TXA alone; intravenous combined topical application of TXA significantly reduced transfusion rate in THA compared with intravenous or topical application of TXA alone; intravenous combined topical application of TXA significantly reduced Hb drop in TKA and THA compared with intravenous or topical application of TXA alone.

The potential clinical implications of this study are as follows: (1) This is the first umbrella review to assess the hemostatic effect and safety of TXA. The study summarized all meta-analyses of TXA used in different surgeries from the inception to now, and classified the endpoints according to the level of evidence. (2) 136 meta-analyses with 396 comparisons were retrieved which included a large sample size of participants compared to other studies. This was of great significance in the field of evidence-based medicine. (3) With the increase of RCT and meta-analysis, TXA is more and more widely used in reducing blood loss, but accompanied by great controversy. In this study, TXA used in surgeries reported by meta-analyses were systematically classified into three grade according to effect size, concordance of results, heterogeneity and potential confounding factors. Therefore, this study has a better reference value for clinical drug use than other meta-analysis and general review.

The limitations of this study are as follows: (1) Baseline characteristics were not considered and this may lead to mixed bias. (2) We used the effect sizes reported in the retrieved studies. Therefore, it is difficult to assess the effect of these baseline characteristics on the results. (3) The experimental group and the control group were not unified. The comparison of different meta-analyses of the same surgery may be of limited significance. (4) There is no internationally uniform standard for the level of evidence. Therefore, we can only make a summary of the existing meta-analyses as a reference, but cannot give the exact quantitative conclusion. (5) Intervention measures and medication doses were not uniform in different meta-analyses of the same surgery. Since the results of all meta-analyses cannot be directly combined, there is no accurate criterion for the effectiveness of different meta-analyses of the same medication. (6) Some different meta-analyses may include the same RCT, so there may be some duplications among the participants included in this review. (7) There are few studies on the use of TXA in some surgeries (such as Myomectomy, Cardiac surgery), so the classification of these studies may not be accurate. (8) There

may be no meta-analysis report on the use of TXA in some areas, but only sporadic RCT publication, we do not consider.

Summary points

This umbrella review indicated that TXA were regarded as effective to reduce TBL, transfusion rate, Hb drop and mortality in different kinds of surgeries, and did not increase the incidence of DVT and PE.

Future issues

(1) Future studies should include stratification by dose of TXA to definitively exclude mixed bias. (2) In the future meta-analyses, authors should pay attention to unifying the intervention measures in the experimental group or the control group to avoid the heterogeneity, and reduce the difficulty of the combined effect size of umbrella review. (3) Multicenter large sample size RCTs should be implemented to promote more representative meta-analyses creation, so as to provide more convincing evidence for assessing hemostatic effect and safety of TXA. (4) The international criteria of level of evidence for umbrella review should be identified as soon as possible, so as to provide reference for the development of umbrella review in the future.

Abbreviations

TXA = tranexamic acid, TBL = total blood loss, Hb drop = haemoglobin drop, DVT = deep venous thrombosis, PE = pulmonary embolism, RR = risk ratios, OR = odds ratios, WMD = weighted mean difference, SMD = standard mean difference, CI = confidence intervals, TKA = total knee arthroplasty, THA = total hip arthroplasty

Declarations

Acknowledgements

We are supposed by the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China

Availability of data and materials

All the data will be available upon motivated request to the corresponding author of the present paper

Consent for publication

Written informed consent was obtained from each patient to authorize the publication of their data.

Funding

2017GXNSFAA198352

Competing interests

All authors declared that there was no conflict of interest.

Authors' contributions

J.M. design the study; J.M. analyzed the data; J.M., D.H., L.S. and X.X. wrote the article; B.Z. reviewed the article.

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Tables

Due to technical limitations, table 1 to 4 are only available as a download in the Supplemental Files section.

Figures

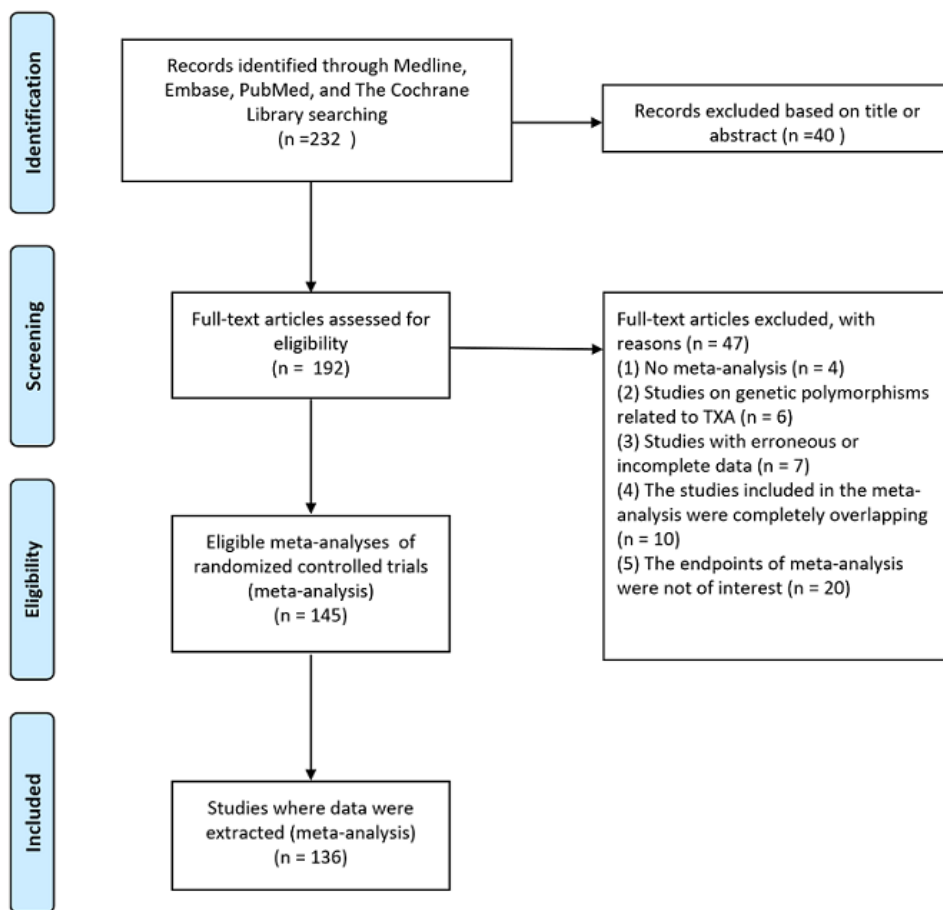


Figure 1

Flowchart

Supplementary Files

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