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REVIEW ARTICLE

Comparison of topical and intravenous administration of tranexamic acid for blood loss control during total joint replacement: Review of literature

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Abstract *Purpose:* Many randomised controlled trials and meta-analysis studies have presented the efficacy of tranexamic acid (TXA) without an increase of complications. However, questions still remain about the type of administration, optimal dose and secondary outcomes of TXA in total hip arthroplasty and total knee arthroplasty. The aim of this review is to summarise the existing information in literature concerning the pharmacological characteristics of TXA, forms, doses, types of application and contraindications for its use.
Methods: A literature review containing 63 articles from the PubMed data starting from the first description of tranexamic acid until now was made in trying to present the existing information in a simple and effective way.
Results: TXA leads to statistically significant reduction of peri and postoperative bleeding and in that way decreases blood transfusion rates and the infection risk. Topical and intravenous (IV) use of TXA revealed similar results, with no increase of deep venous thrombosis. Therefore, topical TXA could be a reasonable alternative in patients with contraindications for IV application of TXA.
Conclusions: Blood loss control with TXA, a synthetic analogue of the amino acid lysine, may be an excellent and safe alternative to allogeneic blood transfusion after total hip arthroplasty and total knee arthroplasty. Further studies are needed to establish the efficacy of combined IV and topical administration of TXA with regard to diminishing blood loss and reducing hospital stay.

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The Translational Potential of this Article: This review briefly presents the pharmacological characteristics of TXA, forms, doses, types of application and contraindications for its use with regard to diminishing blood loss and reducing hospital stay for better therapeutic strategies in orthopaedics.

Introduction

Total hip arthroplasty (THA) is the most common operative procedure for osteoarthritis. It is associated with high perioperative blood loss between 700 mL and 2,000 mL, which leads to a longer hospital stay, impedes rehabilitation and may be poorly tolerated by patients with cardiovascular diseases. It is estimated that 65% of blood loss in THA occurs within the first 8 hours after surgery and often leads to significant postoperative anaemia [1]. For this reason, many patients need peri or postoperative blood transfusion. Commonly, 11—67% of the patients undergo blood transfusion [2,3], which increases the high economic costs of the procedure and could provoke an anaphylactic reaction, heart or renal failure and infectious disease [4—6].

Different blood-conserving techniques, such as autologous blood transfusion [7] or autologous fibrin tissue application [8], have been used in clinical practice to reduce the postoperative blood transfusion rates [9]. Autologous transfusion reduces the risks of infection, but is also expensive. To minimise blood loss, hypotensive anaesthesia is also used [10]. Another method for control of the perioperative blood loss is the application of antifibrinolitic agents including aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid. Among them, TXA has attracted the most attention [11—13].

Currently, in literature, there are numerous studies presenting the efficacy of TXA in reducing blood loss with no increase of complications. However, questions still remain about the type of administration, optimal dose and secondary outcomes of TXA in THA and total knee replacement (TKA). Herein, we reviewed the current literature on the pharmacological characteristics, forms, doses, types of application and contraindications for the use of TXA. The effects on blood coagulation of topically or intravenously administered tranexamic acid were evaluated.

TXA characteristics

TXA is a trans-stereoisomer of a synthetic amino acid with a molecular weight of 157 g/mol [14] which serves as an inhibitor of fibrinolysis and an activator of plasminogen. In 1962, for the first time, Okamoto et al [15] and Melander et al [16] independently described TXA. They discovered that the trans-form of 4-(aminomethyl)-cyclohexane-carbonic acid had antifibrinolytic properties. It is a white powder that forms crystals, which are soluble in water, acids and alkalis and slightly soluble in alcohol, but remain insoluble in organic solvents. Although described in 1962, the first study that examined its efficacy in reducing blood loss during THA was reported in 1997 [17]. In 2000, the first study that indicated its efficacy after THA was presented [18]. There are different studies, which revealed that the administration of TXA reduced the postoperative blood loss and the blood transfusion rates after THA [19,20]. *In vitro* studies reveal that TXA is 10 times more effective in reducing blood loss than aminocaproic acid. TXA is distributed throughout all body tissues, and its plasma half-life is 120 minutes [21]. After application, TXA levels are highest in the liver, kidneys and lungs. TXA is mainly eliminated through the renal system. Therefore, the doses of TXA in renal diseases should be corrected according to the levels of the creatinine in plasma. The recommended doses are according to the glomerular filtration rate (GFR): 50 mL/min, 50% of dose, GFR 10—50 mL/min, 25% of dose and GFR 10 mL/min, 10% of dose [22,23]. In contrast, in hepatic diseases, the dose does not need to be corrected due to the fact that the liver metabolises only a small amount of TXA [22].

Forms and doses of TXA

TXA is available in different forms: intravenous (IV), topical and oral. Each form needs different time to reach maximum plasma levels [5—15 min for IV injection, 30 min for intramuscular injection and 2 h for oral administration] [24]. Dahl et al [25] reported that the fibrinolytic response occurs in the early phases of operative procedures. TXA requires time for plasminogen to be activated.

Usually, doses used in hip and knee arthroplasty have been lower than doses for cardiac surgery, menstrual bleeding or in neurosurgery [26]. The dose of IV TXA in THA is 10—15 mg/kg or 1 g of TXA for IV use and 1—3 g for topical use, around 5 minutes before the skin incision. Benoni et al [27] reported that 3 hours after IV administration, the concentration of TXA in the plasma is above the minimum therapeutic level. Konig et al [28] and Yue et al [29] recommend that the dose of topically administered TXA be >2 g so it can play its role in reducing blood loss and transfusion rate.

It is estimated that only a small percentage of the IV injected TXA reaches the target location to inhibit tissue fibrinolysis and stabilise the clot, thus reducing bleeding [12]. It should be pointed out that the total blood loss and transfusion rate were not reduced with higher doses of TXA [12].

TXA in orthopaedics and trauma patients

Hiippala et al [30] presented one of the first randomised studies evaluating the efficacy of TXA in reducing blood loss

in TKA. In their study of 75 patients, the authors demonstrated that in a group of TKA, there was a significant reduction of blood loss. Poeran et al [31] also reported the efficacy of IV TXA in a retrospective cohort study based on 872,416 THA and TKA procedures. Reports from the Clinical Randomisation of Antifibrinolytics in Significant Haemorrhage trial have shown the results after IV application of TXA in 20,211 trauma patients. In the group of IV TXA, a significant reduction of thrombotic events and arterial thrombosis without an increased risk of venous thromboembolic events were observed [32].

Different authors report that the local application of TXA significantly reduces haemoglobin decrease and total blood loss [28,33–35]. Sukeik et al [12] reviewed a total of seven studies (comprising 350 patients) and established that TXA reduced intraoperative blood loss by 104 mL, postoperative blood loss by 172 mL and total blood loss by a mean of 289 mL. Na et al [33] reported that after THA, the fibrinolysis in the postoperative period could be reduced by TXA, which may lead to lower postoperative blood loss. However, the effect of TXA in reducing the need for blood transfusion is controversial. Some authors report a 14–20% reduction [28,34], whereas others report no difference [35,36].

IV application of TXA

IV application of TXA is the most common way of administration in TKA and THA. TXA is distributed in the extracellular and intracellular spaces and reaches a high plasma concentration. Andersson et al [37] stated that after IV injection of 10 mg/kg of TXA, the plasma levels were highest within 1 hour. Thirty percentage of TXA was excreted in the urine after 1 hour, 55% at 3 hours and 90% after 24 hours. The half-life of TXA was reported to be between 80 minutes and 120 minutes. Moreover, 15 minutes after IV application, TXA reaches similar levels in the synovial fluid as in plasma [37].

Different ways of IV TXA, such as prolonged infusion, repeated boluses and boluses at induction or closure, have been used in clinical practice [38]. The used doses of TXA are 10–30 mg/kg or 1–2 g. It should be pointed out that the time of application is also of importance. When used at the end of the procedure and 3 hours later, TXA did not reduce total blood loss [9].

Local administration of TXA

Local administration of TXA in the joint or periarticular tissue during closure has also been reported [38]. TXA stops fibrin clot dissolution and, in that way, allows better haemostasis. The plasma levels of topical TXA are around 70% lower than those after IV administration. The levels of TXA in plasma after low (1.5 g) and high (3.0 g) doses are 4.5 mg/L and 8.5 mg/L, respectively, whereas the plasma level 1 hour after 10 mg/kg of IV TXA was 18 mg/L [39].

Molloy et al [40] reported that TXA has a biological half-life of 2–3 hours within joint fluid. Sun et al [41] reported that the intraarticular use of TXA can minimise haemoglobin decrease, the need for blood transfusion and total blood loss. No significant difference in the occurrence of infection, deep venous thrombosis (DVT) or other adverse events has been reported. Locally applied, TXA has the advantage to directly affect the bleeding site, and thus reduces blood loss. The intraarticular injection of TXA is easy for application and also provides a high local concentration and diminished joint swelling and permits advanced wound healing and rapid rehabilitation [42,43]. Lin et al [44] reported that intraarticular TXA reduces the separation of drainage within the first 8 hours. In spite of this, no significant difference after 8 hours was reported. According to Martin et al [35] and Wind et al [36], local administration of TXA reduces blood loss and the transfusion rate but this is not statistically significant. In cases of higher amount of drainage fluid, a new application of TXA should be performed. Xu et al [1] reported that the preoperative use of TXA also has benefits.

Other routes of TXA administration also include oral and muscular forms. Via these routes, TXA reaches maximum plasma levels at 2–3 hours and 0.5 hour, respectively [45]. The doses are usually divided preoperatively and postoperatively. They have been established as low as 1.95 g by Fillingham et al [46] and as high as 6 g by Bradshaw et al [47]. Fillingham et al [46] after comparison of oral TXA and IV TXA in TKA found that oral TXA provided equivalent reductions in blood loss to IV at a cost of $14 compared with $47–$108 depending on the IV formulation selected. However, further studies need to reveal their efficiency and safety in THA and TKA, but it definitely seems that they are one of the most cost-effective methods.

Comparison between local and IV application

Present studies have demonstrated that there is no difference between wound irrigation and intraarticular injection at the time of surgery compared with IV administration of TXA [13,28,35,36]. Topical administration was also safer in patients with risk of venous thromboembolism (VTE) and also was more cost-effective; it also minimised the risk of systemic complications. [28,35,36,48]. The topical injection induced partial microvascular haemostasis by inhibiting the dissolution of fibrin clots in the affected area [49]. Machin et al [38] in their nonrandomised study did not observe any advantage to use topical TXA at wound closure together with IV TXA at the start of the operation. Martin et al [35] and Wind et al [36] considered that IV administration was better with more predictable results of maximal effect on diminishing blood loss. Ueno et al [13] reported that in THA, TXA reduced postoperative and total blood loss. The authors did not find significant differences between the type of administration connected to blood loss, haemoglobin levels, transfusion rates and systemic complications. However, they established that there was a difference in the amount of TXA between the topical (2 g) and IV (1 g) groups. Liu et al [50] in their meta-analysis study in patients after THA reported that the combined application of IV and topical TXA reduced the total blood loss compared with IV use alone. Moreover, they did not report an increased risk of complications. The relative disadvantage of combined TXA application is the prolonged operative time needed for joint injection. Meena et al [51] in their meta-analysis study examined eight randomised

clinical trials with 857 patients for the efficacy and safety of intraarticular TXA compared with IV route. These authors found that topical TXA has a similar efficacy to IV TXA in reducing total blood loss, drain output, transfusion rate and haemoglobin drop without any increase in thromboembolic complications. Li et al [52] evaluated 2056 patients after THA in their systematic review and meta-analysis study and established that topical TXA had a similar efficacy compared with IV TXA. No significant difference was found between topical and IV application of TXA regarding the blood loss, the transfusion rates, the haemoglobin drop and the thromboembolic complications. According to these authors, the advantages of topical use of TXA were as follows: easy application, reduced costs, lower systemic absorption and direct effect to the bleeding sites. Lin et al [53] in their meta-analysis study presented the results after using TXA in patients undergoing TKA. The authors found that after combined topical and intravenous administration, TXA decreased the total blood loss and the blood transfusion rates. However, they established that there is no significant difference between combined topical and intravenous TXA compared with topical or intravenous TXA. In addition, no increase in developing DVT was established. Chen et al [54] after reviewing 16 randomised controlled trials with 1,250 patients undergoing TKA and four randomised controlled trials involving 550 patients undergoing THA concluded that there was no significant difference between using topical and IV TXA in reducing blood loss or transfusion rate.

Contraindications for TXA application

There are no clear contraindications for TXA application apart from allergic reactions, history of venous or arterial thrombosis, acute renal failure, subarachnoid haemorrhage and seizure disorder [55]. The increased incidence of seizure disorders could be explained by the fact that TXA crosses the blood-brain barrier and interacts with glycine receptors [56]. Postoperative seizures have been reported in patients with renal dysfunction after high doses of TXA (50 mg/kg). In the current orthopaedic literature, there are no reports of seizures after usage of TXA. Colour vision impairment and visual disturbances could also be caused by the use of TXA. After literature review, we do not find studies indicating that different routes of application of TXA may provoke increased complications rates. According to Gilbody et al [34], the topical use of TXA could be safer than IV in patients with increased risk of thromboembolic events or with renal impairment. This is probably due to the fact that after local administration, the absorption rate from the joint is very low.

Reduction of hospital stay and risk of DVT and infection

TXA reduces the length of hospital stay by 0.6—1 day [28,34] with minimal or no increase in infection or venous thromboembolic events [28,35,36]. Different meta-analysis studies did not establish an increased risk of VTE, infection or adverse outcome after application of TXA [20,57—61]. However, Emara et al [62] reported a higher prevalence of DVT, pulmonary embolism and cerebrovascular events/strokes in patients after IV TXA in hemiarthroplasty. It should be mentioned that the IV administration of TXA decreases external blood loss but not hidden blood loss [63].

Conclusion

In conclusion, numerous prospective randomised controlled and meta-analysis studies have reported that TXA leads to statistically significant reduction of perioperative and postoperative bleeding and, in that way, decreases the blood transfusion rates and the infection risk during THA and TKA. Moreover, TXA is safe and does not increase the VTE rates. From the economical point of view, TXA is cost-effective and reduces the length of hospital stay. Topical and IV use of TXA revealed similar results, with no increase of DVT. Therefore, topical TXA could be a reasonable alternative in patients with contraindications for IV application of TXA. Further studies are needed to establish the efficacy of combined IV and topical administration of TXA with regard to diminishing blood loss and reducing hospital stay and to elucidate whether TXA reduces complication rates and improves postoperative recovery and whether different types of administration correspond with increased complications rates.

Author contributions

All authors conceptualised the study and participated in study screening, selection, data extraction and manuscript preparation. All authors provided intellectual content and approved the manuscript for publication.

Conflicts of interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jot.2017.12.006.

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