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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