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The Role of Intravenous and Topical Tranexamic Acid in Reducing Blood Loss in Total Hip and Knee Arthroplasty: A Review Article

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Review Article

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Abstract: Hip and knee arthritis can cause persistent pain and disability for patients and in this case, total hip arthroplasty (THA) and total knee arthroplasty (TKA) can be performed as it is an effective surgery for those patients. However, the main concern about the surgery is bleeding. Tranexamic acid (TXA) is an anti-fibrinolytic synthetic agent synthetically block plasminogen activation to plasmin and hence stabilization of blood clotting. TXA showed efficacy in reducing blood loss and it widely has several clinical usage including orthopedic field. To discuss the role of intravenous and topical TXA in THA and TKA. Scientific websites were used to search for articles related to this review; several keywords were focusing on the subject to get more researches. There were more than 20 articles included in the review. There was controversial to determine the best route to administrate TXA and which is superior as the high quality trials are lacking and there were differences between different study. However, using TXA either intravenously or topical showed efficacy and safety in both THA and TKA. Blood loss as well as blood transfusion was significantly reduced in both procedures with less adverse effects by using TXA.
Keywords: Tranexamic Acid, IV TXA, Topical TXA, Intra-articular TXA, THA, TKA.

INTRODUCTION

Management of hidden blood loss is considered challenging work for surgeons in THA and TKA, peri-operative blood loss in TKA varies between 800 ml -1800 ml [1]. In this case peri-operative anemia can be caused by blood loss and in turn it develops high morbidity and mortality [2].

Blood management strategies have been established to reduce blood loss and the need for blood transfusion and its products in TKA [3]. The Food and Drug Administration has approved the use of TXA as an anti-fibrinolytic agent to decrease bleeding in hemophiliacs' patients who performs tooth extraction [4]. TXA uses have been increased and extended to include uses in trauma and even in elective surgeries [5]. TXA was involved into multiple elective surgeries by orthopedic surgeons to reduce transfusion requirements and blood loss [6]. Efficacy and safety of TXA was demonstrated in both THA and TKA, but with debate regarding the suitable route of administration [7,8]. In this review it is aimed to study the role of intravenous, intra-articular, and topical TXA in THA and TKA.

MATERIALS AND METHODS

In this review, researches about the current subjects were obtained using scientific websites such as Google scholar and Pubmed. Several keywords were used to obtain the required researches, the keywords which were used: Tranexamic acid, Tranexamic acid for total knee arthroplasty, TKA, total hip arthroplasty, and THA. More than twenty articles were obtained, and they were published between the years 2001-2017.

DISCUSSION

TXA

TXA IUPAC name is 4-(aminomethyl) cyclohexane-1-carboxylic acid) (figure1,2) [9], it is an anti-fibrinolytic synthetic lysine-analogue agent [10]. TXA was first developed in 162 in Japan to synthetically block plasminogen-inhibiting capabilities [11, 12].

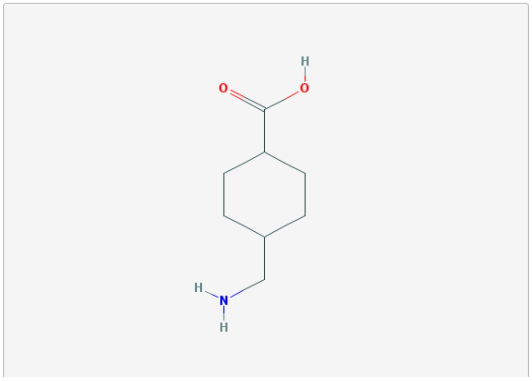

Fig-1: 2 Dimensional structure of TXA (source; PubChem[9])

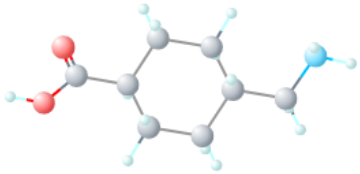

Fig-2: 3 Dimensional structure of TXA (source; PubChem[9])

TXA mechanism of action

TXA performs its effect by a competitive inhibition of the activation of plasminogen to plasmin by blocking the binding sites of lysine on plasmingen [13], (figure3) [14]. TXA inhibition of pasminogen causes fibrinolysis to delay as there is no plasmin formation, there is no binding to fibrinogen, so stabilization of the clot occurs [11]. In case of high concentration, it secondarily inhibits directly plasmin activity and formation [11]. 10mg/ml is the plasma concentration needed to achieve 80% inhibition of fibrinolysis, after 1 hour of intravenous dosing, the maximum concentration is achieved [12,15,16]. TXA effects last from 8 to 17 hours after administration [16-18]. TXA can be administrated orally, intravenously, intra-articularly and topically into the surgical field [19]. The optimal timing and dose is currently not standardized yet [5], however, the most common intravenous dose is 10-15mg/kg before inflation of the tourniquet/incision and before tourniquet deflation/ closure of the wound [16,20].

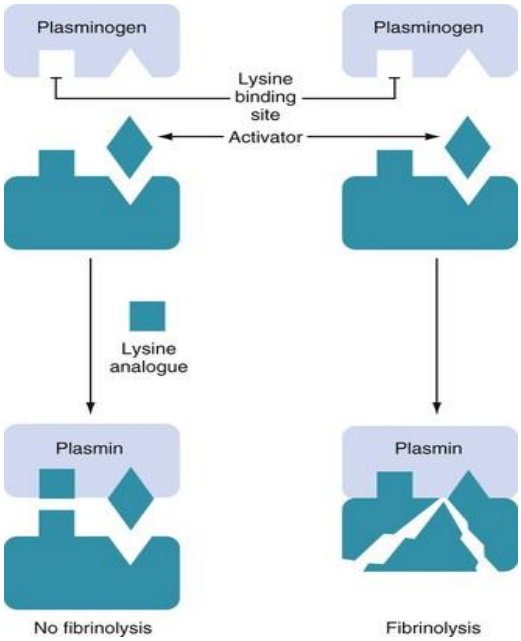

Fig-3: The mode of action of the synthetic lysine analogues TXA (source: Clinicalgate[14])

TXA clinical usage

TXA is mainly used for reducing peri-operative bleeding to avoid transfusion in cardiac and non-cardiac surgeries [21]. Both subsequent transfusions and blood loss are correlated with major mortality and morbidity [22,23]. Blood loss can be reduced by the use of anti-fibrinolytics in trauma, non-surgical disease and during major surgery [21]. Overwhelming evidence about the TXA probability to reduce transfusion by 38% was reported by a recent meta-analysis which compared TXA vs no TXA or a placebo in more than 10,000 patients undergoing surgery [24]. In Cochrane Review about the effect of anti-fibrinolytics on blood-loss and transfusion of allogeneic blood, it was reported that blood transfusion was significantly reduced by TXA by 39% which indicated absolute risk reduction of 18% [25]. In orthopedic surgery, the reduction of blood loss is critical, especially for spinal surgery, THA and TKA [21]. Using TXA in orthopedics was primary prescribed for THA and TKA as they are associated with significant complications and bleeding [18,19,26]. Kagoma *et al.* [27], supported that anti-fibrinolytic use in orthopedic surgery, where TXA dose of 10−15 mg kg-1 found to result in reduction in relative risk of transfusion (RR 0.52) and blood loss as well as no increased risk of thrombo-embolism. Regarding spinal surgery, the use of intravenous TXA showed reduction in the amount of blood transfused by 134.55 mL and postoperative blood loss by 389.21 mL as reported by a previous meta-analysis [28]. In cervical laminoplasty, intravenous use of TXA showed a reduction in blood loss (264 mL), but there was no reduction in intra-operative blood loss and no increase in complications [29].

Role, time and dose of TXA in THA and TKA

TKA is an elective operation which is performed for patients who suffer persistent pain and disability which caused by knee arthritis [30]. It was reported as a cost effective and effective operative treatment for end stage osteoarthritis (OA) [31-34]. It has been performed for more than 30 years [35]. The demand for this surgery is expected to increase by 673% to 3.48 million procedures in 2030 in US [36]. In TKA, the main concern is the perioperative bleeding, where the blood loss ranges between 800-1800 ml [1,37-39]. THA is a procedure for treating end stage hip diseases, it is an excellent surgical procedure [40,41]. It is estimated that this surgery will be grown by 174% by 2030 [36]. It is like TKA accompanied by blood loss which may result in series of several complications [42]. TXA safety and efficacy in THA and TKA have been shown, although argument about the route of administration still exist [7,8]. It was concluded that there was a significant benefit of using of TXA in reducing blood transfusion and blood loss in both TKA and THA, with better efficiency for TKA patients [43]. The first report on the efficacy of TXA to reduce the perioperative blood loss in total joint arthroplasty was published by Benoni et al [40], then the use of TXA in total joint arthroplasty was studied extensively [5]. TXA using in TKA effectively reduced need for transfusion, bleeding and post-operative drainage [44]. Because TXA is anti-fibrniolytic agent, the formation of harmful vascular thromboses was theoretically suggested [5]. However, according to meta-analysis and clinical trials, there was no clinical evidence on the increased risk of thrombo-embolic events such as stroke, deep vein thrombosis (DVT), myocardial infarction (MI), pulmonary embolism (PE) activated partial thromboplastin time, or prothrombin time [7,19,24,46-49]. Other studies suggested that increased risk of thrombotic events can be avoided by using postoperative prophylactic regimens against DVT such as low-molecular-weight heparin (LMWH), aspirin and warfarin as well as factor Xa inhibitor [11-13,50,51]. Regarding TXA uses in orthopedics, almost 900,000 elective joint replacement surgeries in which TXA was used peri-operatively, these cases were retrospectively reviewed by Poeran and colleagues [7] and they found no increased risk for acute renal failure, thromboembolic events, cardiac, cerebrovascular events, or in-hospital mortality. TXA showed its safety and efficacy as reported by two meta-analysis of using of TXA in THA [26] and TKA [52], where no evidence found for increased thromboembolic events as a result of using TXA. In TKA, reduction in blood loss was significant by 591 ml and reduction in transfusion requirements with homogeneity was found in subgroup analysis of high dose of TXA (> 4 g) [52]. The peri-operative use of TXA (versus non) in THA or TKA was studied [7] and it was found that blood transfusion was lower in patients who received TXA (7.7 vs 20.1%), also incidence of acute renal failure reduced (1.2 vs 1.6%), there were fewer thrombo-embolic events (0.6 vs 0.8%), as well as reduction in combined complications (1.9 vs 2.6%). By increasing the TXA dose (none, < 1 g, ~ 2 g and > 3 g), this resulted in decreasing odds (OR 0.31 to 0.38) of blood transfusion, and increased risk of complications was insignificant [7]. IV TXA is used as single dose or continuous infusion, the standard dose of IV TXA is 1 g dose (500 mg to 3g), several doses were reported in several studies and they ranged from 10-20mg/kg. In case of continuous infusion, dose range from 2 mg/kg/h for 20 hours to 10 mg/kg/h for 3 hours [53-55]. In a control randomized trial, it was found that the IV standard dose (1g) can be used with equal efficacy as weighted doses (20 mg/kg) [56]. Another randomized controlled trial demonstrated that three doses (adding a postoperative dose) may show more efficacies [57]. It was showed that doubling the IV dose of TXA resulted in a further reduction in blood loss in TKA postoperatively than single dose, especially in case of administrating dose preoperatively and intra-operatively and doubling the dose could also decrease the need for blood transfusion during the operation of arthroplasty [58]. Some authors reported that there was a potential increase in the thrombotic events as well as some cases of allergic

reaction [12]. Iwai et al [58] revealed that TXA wasn't associated with the risk of PE or DVT. Marra et al [59] confirmed efficacy and safety of TXA in reducing total loss of blood in TKA without increase in complication rate, but they couldn't identify a superior administrated protocol. Although there were several studies conducted to study the effect of TXA in reducing blood transfusion and bleeding in TKA, there was no consensus between them regarding time of TXA administration and its dose [43,57,60]. The positive influence of TXA usage was demonstrated at variable points before, during and after surgery and at multiple doses, however the optimum dosage and time weren't established yet [61,62]. It was found by reliable evidence that the use of topical TXA reduces blood transfusion and bleeding in surgical patients, however the risk of thromboembolism is unclear, where several studies didn't report this complication [46]. The topical administration of TXA results in reduction in plasma concentration of TXA by tenfold comparing to intravenous route [63,64], also with reduction in adverse outcomes [21]. High quality trials of topical TXA uses are lacking [21]. The topical administration of TXA involves 1 to 3 g of TXA mixed in normal saline for joint arthroplasty [46]. Using of topical TXA in TKA resulted in hemoglobin (Hb) drop (-0.94 g dL-1), total blood loss (-220 mL), transfusion risk (RR 0.47, 95% CI 0.26 to 0.84) and postoperative drain output (-268 mL) with no increase in thromboembolism [20], or disadvantage of systemic absorption [64]. Using a dose of > 2 g of topical TXA resulted in significant less transfusion requirement (RR 0.41, P = 0.05) [20]. It was reported that reduction of blood loss was (-396 mL) with relative transfusion risk of (RR 0.22) and drainage output and Hb drop, with no increased risk of thromboembolism in case of intra-articular injection of TXA in TKA [65]. There is a significant heterogeneity in the trails, two RCTs [66,67] showed that intra-articular injection of TXA in both THA and TKA resulted in reduction in blood loss, Hb drop and decrease the absolute risk of blood transfusion by 19.6% and 15.4%, respectively. Moreover, the length of stay in knee surgery was decreased by 1.2 days with no increase in thromboembolic events. The safety and efficacy of IV versus topical TXA in blood loss prevention in TKA is still debated [68]. It was reported that topical administration was superior to IV route [69], as topical TXA results in better local effect with less systemic absorption [70]. However, in another study it was found that IV route was more effective in reducing transfused units and Hb drop than topical administration [71]. Similarity in efficacy of topical and IV TXA in controlling blood loss was reported but with different doses [38]. It was demonstrated that there was no significant difference between topical and IV TXA in TKA regarding transfusion requirements, thromboembolic complications, blood loss and drain output [70]. Most of studies [26,73] showed that TXA reduced blood transfusion in THA operations. Also there was a significant reduction in intra-operative and post-operative blood loss bleeding [26,74]. It was reported that topical TXA in THA reduce the blood loss and transfusion as well as postoperative drainage, also it decreased the loss in Hb without increase in PE or DVT [75]. An additive effect was found by the combination of epinephrine and topical TXA, which was superior to using TXA alone [18]. It was concluded that the topical and IV route of TXA resulted in similar outcomes in THA patients, as both have similar effect on risk of complications (wound infection, PE, DVT) and decreasing blood loss [42]. The best regimen to decrease adverse outcomes and increase efficacy has yet to be established [7]. One study showed that administration of TXA as either preoperative single dose or 2 doses, one preoperative and one post-operative in patients underwent THA resulted in reduction in bleeding up to day 2 after surgery [7].

CONCLUSION

TXA has been proved to be safe and effective in reducing blood loss and blood transfusion in both THA and TKA. The optimum route of administration, dose and timing for administration of TXA is unclear as there were diversity in studies and populations as well as the doses used and their time.

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