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Application of Tranexamic Acid in Total Hip Arthroplasty: Current Evidences

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Abstract

Huge amount of blood loss has been a big problem in the Total Hip Arthroplasty (THA). Several methods are being used to reduce intra operative or post-operative blood loss. Homologous blood transfusion is mostly preferred to compensate blood loss. But Tranexamic Acid (TXA) has been shown to be effective in reducing blood loss and lessen transfusion requirement in total hip replacement surgery. The main aim of the study is to find out the effectiveness and safety of TXA given pre and post-operatively to reduce the blood loss during a Hip replacement surgery. This article reviews the evidences provided by the different authors in their research papers. The review also discusses the appropriate dose and the form of application of TXA. The article states the need of protocol use of TXA in THA, in definite doses and the definite forms of administrations according to the safety concerns. The research articles were searched using the search engines such as PubMed, MEDLINE, Cochrane database, Ovid database, Embase database, Science Direct database, etc. The related articles which met our criteria were sorted and reviewed. The article related to use of TXA in THA in any form and any amount of doses, published after 2000 AD till date, in English were selected.

Keywords: Tranexamic Acid; Total Hip Arthroplasty; Blood loss; Method of administration; Venous thromboembolism

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Introduction

Major orthopedic surgeries are commonly associated with marked blood loss, and a subsequent need for blood transfusion is often encountered in absence of blood conservations strategies. The causes of bleeding are multi factorial, increased fibrinolytic activity being one of them. Surgery affects the coagulation systems and the fibrinolytic system shuts down due to increased release of plasminogen activator inhibitor [1]. Blood loss often leads to significant post-operative anemia predisposing to an increased risk for cardiopulmonary events, transfusion reactions, and increased health care costs [2]. Although bleeding from these surgical sites is usually controllable, there may be significant blood loss [3]. Fibrinolysis is stimulated by surgical trauma and further augmented by the use of a tourniquet, in cases where it is applicable [4].

Several approaches have been used to reduce intra operative blood loss, including autologous blood transfusion post-operative blood salvage use of a femoral intra medullary plug hypotensive anesthesia cryotherapy and Jones bandage use of fibrin tissue adhesive drain clamping [4], hypotensive anesthesia. The use of allogeneic blood products increases the rate of transmission of infectious diseases, modulates the immune response, and increases the risk of post-operative infection. Homologous blood transfusions are known to increase complications and morbidity [1]. The alternate approaches are administration of anti-fibrinolytic agents such as Tranexamic Acid (TXA) peri operative to stabilize the multiple micro-clots that form within the surgical wound [3]. TXA a has shown to be an effective agent to reduce the blood loss, but protocol use of drug in

Table 1: Use of tranexamic acid in total hip arthroplasty.

Authors	Year	Type of study	Intervention	Method of Adm.	Reduction of Blood loss/ Transfusions	Complications
Ekback et al. [6]	2000	RCT	10 mg/kg preoperatively and 1 mg/kg/h infusion for 10 h	IV	29% intraoperative 43% postoperative	5% cases of VTE
Benoni et al. [7]	2001	RCT	10 mg/kg preoperatively	IV	24% less blood loss postoperatively	1 case of VTE in TXA and Placebo group each
Husted et al. [8]	2003	RCT Double blind	10 mg/kg preoperatively and 1 mg/kg/h infusion for 10 h	IV	Total loss of 814 ml vs. 1231 ml	No cases of VTE
Hynes et al. [9]	2005	RCT Cohort study	20 mg/kg on induction	IV	Mean fall of Hb 3.8 g/dl vs. 2.8 g/dl	1 case of PE in TXA group
Johansson et al. [10]	2005	RCT Double blind	15 mg/kg before start of surgery	IV	Avg. 1.3 L blood loss in placebo vs. 0.97 in TXA group	No cases of complications
Claeys et al. [11]	2007	RCT	15 mg/kg preoperative	IV	237 ml less total blood loss	3 cases of DVT
Clave et al. [12]	2011	RCT	1 g stat at incision and 3 doses post operatively	IV	32% less post operative bleeding	0 cases
Imai et al. [13]	2012	RCT	1 g/stat once or twice	IV	Significant reduction in blood loss and transfusion	3 cases of VTE
Lee et al. [14]	2012	RCT	1 g TXA 2 h preoperatively, 6 h and 12 h postoperatively	Oral	Avg. 327 ml less blood loss than control group	0
Konig et al. [15]	2013	RCT	3 g/100 ml NS	Topical	25% less blood loss	0
Vijay et al. [3]	2013	RCT	10 mg/kg	IV	57% less blood loss postoperatively	No significant cases of VTE
Martin et al. [16]	2014	RCT Double Blind	2 g in 100 ml NS	Topical	38.8% less blood loss	2 cases of VTE
Hourlier et al. [17]	2014	RCT Double Blind	30 mg/kg stat or 10 mg/kg/h over 20 h.	IV	No patients required transfusion	0
Zeng Yi et al. [18]	2015	RCT	15 mg/kg 15 mg/kg+1 g/100 ml NS	IV IV+Topical	18% reduction 32% reduction	No difference among 3 groups in VTE cases
Wang et al. [19]	2016	RCT	15 mg/kg twice	IV	More than 30% reduction in blood loss	1 case of DVT
Ralley et al. [20]	2009	Retrospective	20 mg/kg	IV	Decrease in transfusion rate by 73%	No cases of VTE reported
Irrison et al. [21]	2012	Retrospective	15 mg/kg on incision, closure and QID 1st post op day	IV	34% Less blood loss	1 case of Angina Pectoris
Panchmatia et.al [22]	2012	Retrospective	1 g	IV	Significantly reduced	0
Poeran et al. [5]	2014	Retrospective cohort	<1000 mg, 2000 mg, >3000 mg	IV	69% reduction in transfusions	0.6% cases of DVT
Wind et al. [23]	2014	Retrospective	N/R	IV or Topical	14.5% reduction of transfusion	No cases of VTE
Gilbody et al. [24]	2014	Retrospective	3 g in 30 ml NS	Topical	96% less blood loss	1 case of DVT
Sukeik et al. [25]	2011	Meta-analysis	10 mg/kg 2-3 times or 1 g stat	IV	Significant reduction in blood loss and transfusion	No VTE complications
Gandhi et al. [2]	2013	Meta-analysis	10 mg/kg to 20 mg/kg 1 g 1.5 g to 3 g in NS	IV/IA Oral Topical	Significant reduction of blood loss through different criteria	No significant cases of VTE, PE etc.
Zhou et al. [26]	2013	Meta-analysis	10 mg/kg to 15 mg/kg in different ways	IV	Significant reduction of blood loss	19 (Non TXA group) vs. 15 (TXA group) cases of DVT
Wei et al. [27]	2015	Meta-analysis	N/R	IV or Topical	Significant reduction of blood loss	No increased risk

DVT: Deep Venous Thrombosis; PE: Pulmonary Embolism; TXA: Tranexamic Acid; IV: Intravenous; NS: Normal Saline; N/R: Not Reported; VTE: Venous Thrombo Embolism

TXA, with definite administration forms and doses still need to be determined.

TXA is a synthetic derivative of the amino acid lysine (4-aminoethyl cyclo hexane carboxylic acid), that exerts its anti-fibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules, thereby reducing the conversion of plasminogen to plasmin. Hence, it blocks the dissolution of hemostatic fibrin, which stabilizes fibrin structure and thus may decrease the blood loss secondary to increase fibrinolysis. TXA has been used in neuro, orthopaedic, cardiac, spine and maxillofacial surgeries and has reduced the amount of blood loss and subsequent need for blood transfusion [3]. The aim of this study is to evaluate the efficacy of intraoperative use of TXA on post-operative blood loss following surgeries for hip and femoral fractures. TXA has been reported to reduce blood loss and be cost efficient. One significant concern with TXA however, is the possibility that it, as well as other anti-fibrinolytics, could increase the risk of developing thromboembolic complications such as Deep Vein Thrombosis (DVT) [2]. Indeed, a recent study [5] found that the use of TXA may even make the use of blood salvage equipment unnecessary. Despite these promising results, valid data on safety are lacking, as large sample sizes are needed to determine this outcome. Thus concerns about the routine use of TXA remain. In this review we discuss the effectiveness of TXA in THA to the reduce blood loss and address the safety concerns regarding the adverse effects of the drug. We also review the questions of the method of administration of TXA and the appropriate dose.

Method

We specified and documented the methods of the analysis and inclusion criteria for this review. We searched for all Randomized Controlled Trials (RCT), retrospective studies and meta-analysis studies that studied the application of TXA in THA from 2000 to till date. The participants were adults who had undergone THA, regardless of the type or size of prosthesis used. Subgroup analyses were performed for patients with different characteristics. Potentially

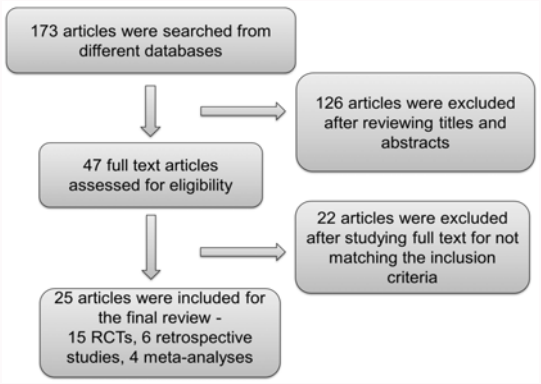

Figure 1: Summary of search results.

eligible trials were identified by searching the medical search engines like PubMed, MEDLINE, Cochrane database, Science Direct database, Ovid database, several orthopedic and transfusion journals. Search was done using a combination of keywords and the subject headings according to MEDLINE search strategy. "tranexamic acid", "total hip arthroplasty", "blood loss", "method of administration", "venous thromboembolism", were the keywords used. The search was focused on researches studying THA. Other joint transplants and radical orthopedic surgeries were rejected. Different variables like the type of study, doses, form of administration, amount of decreased blood loss, cases of post application complications were tabulated and studied (Table 1). Searches were restricted to English language. The review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Reference lists of all included studies and reviews related to the topic of the present meta-analysis were manually searched for other potentially eligible studies.

Results

Almost all the authors support the use of TXA for the reduction of blood loss. A brief summary of search results is presented in the (Figure 1). A total of 173 articles were found out during the search of different databases, and among them 126 articles were excluded after studying the titles and abstracts. Full texts of 47 articles were assessed for eligibility and 22 articles were excluded after studying for not matching the inclusion criteria. In the final study, 25 articles were included. We tabulated 15 RCTs [3,6-19], 6 retrospective studies [5,20-24] and 4 meta-analyses [2,25-27]. Review articles focusing on THA were also studied and were a clue in writing the conclusion. Comparison was made between the TXA and control groups. So, the comparison between the control and the TXA groups clearly states that the TXA is very useful in the reduction of blood loss. Few authors have found the intra operative reduction of blood loss. Most of the authors in their researches have found TXA more useful in reducing the post-operative blood loss than the intra-operative blood loss. All the authors have very carefully studied the safety concerns of the TXA, although drug is very useful for the reduction of post-operative blood loss, safety concerns for the VTE complications, including the DVT, PE, etc. have been a major concern for the researchers. The results have shown very good safety outcomes of the drug comparing the placebo and control groups. Results show that there were less VTE complications with TXA groups than the placebo or control groups.

Discussion

The most important finding of this present study was that TXA reduced total blood loss and post-operative blood loss, reduced the risk of transfusion significantly, reduced the average number of RBC transfusions per patient and did not appear to increase the risk of VTE [28,29].

There is a growing body of evidence that TXA, when used either as infusion or irrigation, has a substantial impact on blood loss and the need for post-operative transfusion following primary THA. Introduction of TXA into comprehensive blood management protocol in many hospitals for THA, a substantial drop in the frequency of transfusions has been noticed [23]. Other studies in the literature have reached similar conclusions. Sukeik et al. [25] reviewed 11 randomized, controlled clinical trials. In their review, they examined not only the rate of transfusion but also blood loss. They concluded that TXA reduced intra-operative blood loss by 104 mL and post-operative blood loss by 172 ml. Their review of the transfusion rate showed a statistically significant reduction. Furthermore, they also noted that there was no increased risk of complications, including deep vein thrombosis (DVT) and pulmonary embolism (PE), when TXA is utilized. Wang et al. [19] concluded that IV-TXA at 10 mg/kg significantly reduced blood loss and mitigated the decrease in hemoglobin and hematocrit after THA, but it did not significantly reduce the need for transfusions. In contrast, a dose of 15 mg/kg reduced both bleeding and transfusion requirements. Results argue for a dose of 15 mg/kg when using single-dose IV-TXA. Dahuja et al. [30] concluded that TXA decreased blood loss and significantly reduced transfusion requirements. The blood-sparing effect of TXA was most evident during the first 24 h after operation when blood loss was significantly reduced compared with the control group as shown by the drain output. Hourlier et al. [17] demonstrated, with a high level of evidence that a second dose of TXA did not lead to any clinical advantage over a single-injection regimen at doses considered effective in primary THA. Therefore, their team suggests single 30 mg/kg TXA dose as part of routine care in THA patients. As part of any comprehensive strategy to avoid transfusion and reduce post-operative bleeding, a prophylactic dose of 30 mg/kg TXA to be considered in primary THA with the potential for significant blood loss. Similarly, Johansson et al. [10] also argue for the single prophylactic dose of 15 mg/kg. In their RCT including 100 patients they found 25.4% less blood loss in average in compare to the placebo group, with no VTE complications. Hynes et al. [9] also argue for the prophylactic dose of 20 mg/kg stat IV during induction. They found 1 g/dl more of Hb levels in the patients using TXA than placebo. Claeys et al. [11] found a 15 mg/kg IV bolus preoperative dose would reduce 237 ml less blood loss in average. Ralley et al. [20] in their retrospective study including 234 patients conclude that 20 mg/kg stat does of TXA intra-operatively significantly increase the peri operative Hb levels and reduces the blood infusion requirements. Irisson et al. [21] suggested a dose of 10 mg/kg to 15 mg/kg. No additional benefits are obtained by increasing the bolus dose above 10 mg/kg to 15 mg/kg. Fibrinolysis activation persists for 12 h to 24 h after surgery, supporting the prolonged use of TXA during the post-operative period, which has been reported to increase efficacy. The study concludes that TXA therapy decreases blood loss and need of transfusion. A rational regimen of TXA therapy given intra-operatively and post-operatively seems effective and devoid of notable side effects. Poeran et al. [5] concluded that TXA was effective in reducing the need for blood transfusions while not increasing the risk of complications, including thromboembolic events and renal failure. The study provides the incremental evidence

of the potential effectiveness and safety of TXA in patients requiring orthopedic surgery. Panchmatia et al. [22] studied 273 patients in their clinical report, in which they conclude that the administration of 1 g of intravenous TXA is a safe and effective means of reducing operative blood loss and allogeneic blood transfusion rates in patients undergoing hip replacements. Their study did not demonstrate any increased risk of VTE in those receiving TXA. This is consistent with the findings of earlier studies and meta-analyses. Meta-analyses of 33 studies, done by Gandhi et al. [2] concluded that TXA leads to the statistically important reduction in total blood loss and fewer patients require allogeneic transfusions, with no apparent increased risk of thromboembolic complications.

Several authors have strongly supported the use of TXA in a topical form. Use of TXA is an effort to decrease the incidence of blood loss, blood transfusion with safety and overall decrease the cost of surgery. Researchers have found out that application can be either intravenous or as a topical agent applied to the intra-articular surfaces at the time of wound closure. So the use of TXA topically can be safer in patients with risk of VTE and also be more cost effective. Chimento et al. [31] also believes that the topical use of TXA is effective, does not lead to increased complications, and results in significant cost savings. Topical administration of TXA at the end of THA significantly reduced post-operative bleeding and risk for transfusion. The blood loss was 25% higher, in THA when TXA was not used. The drop in Hb was 27% higher, in THA when TXA was not used. In THA the TXA solution was at a concentration of 3 g TXA per 100 mL saline. The mean blood loss was significantly higher in the non-TXA patients in both THA group. Post-operative transfusions decreased dramatically with TXA, dropping from 15% to 1%. A study done by Konig et al. [15] also concluded the topical application of TXA significantly reduces post-operative blood loss and transfusion risk in THA. Wong et al. [32] concluded that topical application of TXA directly into the surgical wound reduced post-operative bleeding by 20% to 25% and resulted in 16% to 17% higher post-operative Hb levels compared with placebo, with no clinically important increase in complications. The topical application of 2 g of TXA in THA without drains results in a significant decline in blood loss, with no measurable side effects [16]. A 3 g dose of topical TXA for all THA as suggests Gilbody et al. [24]. The study shows the increased cost per case of THA due to the blood required for the allogeneic transfusion and the investigations. Indirect comparison of placebo-controlled trials of IV and topical TXA indicate that topical TXA application is superior to the IV administration. Topical TXA can be a viable alternative in patients with contraindications to IV TXA [33]. TXA of 2 g to 3 g in NS topically is suggested by many authors [15,16,31,32], who believe that topical TXA use is beneficial to patient health, is effective without compromising safety, and is economical.

While the potential thromboembolic risks of intravenous TXA administration have not been realized in clinical studies, the topical route may be attractive to surgeons caring for patients who are at increased risk of thromboembolic disease or in whom intravenous TXA is cautioned, e.g., renal impairment. Furthermore, the modes of delivery described for intravenous TXA vary from a single bolus given pre-operatively, to repeated boluses, to a continuous infusion, while topical instillation is a very simple way to deliver the drug. Administration of TXA in any form can be quite cost effective but topical method could be much more cost effective [34]. While there are differences in ideas between using TXA intravenously or topically, some authors have found a much effective results using both the methods at once [35].

While there is a conflict between the authors about the way to deliver the drug, we clearly can see a conflict in the dose of drug and frequency. Some authors have suggested a 10 mg/kg to 20 mg/kg IV preoperatively and then TID, QID or in infusion [6,8-11,17,19-21] while others have advocated for 1 g to 3 g of stat dose pre and post-operatively [5,12,22]. Similarly, for the topical use, 2 g to 3 g of TXA in NS has been suggested [15,16, 24]. There is no uniform opinion of the required dose, so an exact protocol of the required drug dose should be determined.

No statistically significant differences were noted in terms of VTE in a study concluded by most authors. So, with the evidences stated above with multiple authors TXA administered in any form can be considered safe. Anti fibrinolytic agents reduce the risk of transfusion by almost 50% and do not appear to increase the risk of VTE [36]. But, Zufferey et al. [37] have found the increase in hypercoagulable state while using TXA, there was a three-fold increased risk of vascular events with the use of TXA when compared with placebo. So, precaution must be taken in patients with risk factors such as VTE diseases or renal failure cases, topical or oral administration of drug may be preferred in such cases. Oral administration of TXA for the reduction of blood loss has been studied very less. We found only two studies advocating for the oral administration. McGrath et al. [38] which recommended oral administration of drug concludes that oral TXA is an effective and much cost effective way of reduction of blood loss. Lee et al. [14] recommended oral administration which considers it is safe and effective alternative to IV and topical administration.

Few authors have stated the importance of finding the exact amount of blood loss in all these studies. Although we calculate the amount of blood loss during the surgery and post-operatively by drains, the hidden blood loss is often missed. Use of appropriate amount of negative drain pressure also can help to determine exact amount of blood loss suggest [2]. Imai et al. [13] in their study, measured post-operative blood loss was only by drainage volume. So they suggest measurement of a fall in Hb level and calculation with preoperative and post-operative hematocrit values may be a more accurate method than directly measuring drainage volume because of hidden blood losses, such as post-operative hematomas. Such losses can be difficult to measure. So they conclude that TXA was not only effective but also safe in THA. But the criteria to measure the blood loss must be revised.

Conclusion

In conclusion, TXA has been shown in numerous reports to have a drastic impact on blood loss and transfusion rate. Almost all the studies support this. By the end of the review, our team concludes that TXA has a significant role in reduction of blood loss, which leads to need to decreased transfusion and decreased infection risks, also is very safe regarding the VTE complications. TXA should be considered for routine use in primary THA to decrease blood loss. Approving and extending the indications for the use of TXA in THA would be a useful measure to reduce costs and blood transfusions [33]. Intravenous infusion is the more predictable route of administration for maximum efficacy. However, for high risk patients with a potential increase in thromboembolic events following THA, there may still be benefits with a topical protocol. Oral administration needs further studies to prove the efficiency and

safety in such surgeries but is definitely one of the most cost effective methods. Different authors have suggested different doses in multiple ways can be administered. Most of the authors have supported the 15 mg/kg dose of TXA intravenously once preoperatively and then post-operatively in multiple doses. Some support TXA in infusions, while others support 1 g to 3 g of stat doses for better outcomes. So, a further studies needs to be performed to create standard protocol of the required dose.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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