Original Research Paper

**Orthopedics**

**WHETHER COMBINEDLY ADMINISTERED TRANEXAMIC ACID IN TKR IS MORE EFFECTIVE THAN ONLY INTRAVENOUS ADMINISTRATION?**

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**ABSTRACT**

**Introduction:** The aim of our study is to compare efficacy of 3 doses of intravenous (IV) Tranexamic acid (TXA) versus combined IV and intraarticular TXA in reducing blood loss and transfusion requirement in patients who underwent primary total knee arthroplasty.

**Material and Methods:** Group A patients were administered 3 IV doses of TXA. Group B patients were administered 1 gram of IV and 2 grams of IA dose.

**Results:** The mean 48 hrs drain collection was 238.33 ml in group A and 149 ml in group B. Mean hemoglobin drop is 2.39 gm% in group A and 1.74 gm% in group B. Post operative blood transfusion was required in 12 patients (40%) of group A and 5 patients (16.67%) of group B.

**Conclusion:** IA with IV TXA is more beneficial than IV TXA in reducing blood loss in primary total knee arthroplasty.

**KEYWORDS:** Total knee arthroplasty, Tranexamic acid, Route of administration

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**Introduction**

Total knee arthroplasty (TKA) is well established treatment modality for severe Osteoarthritis knee. Patients requiring TKA is likely to increase in the near future due to increase in life expectancy. Substantial perioperative blood loss with systemic complications remains a concern [1, 2]. Many methods are used to manage blood loss such as tourniquet application, blood transfusion, administration of haemostatic agents and autologous transfusion [3]. Allogeneic blood transfusion increases the risk of adverse events, and adds to the financial burden on the patients [4].

The use of Tranexamic acid (TXA) is proven as an effective method to minimize the blood loss and transfusion rates in total knee arthroplasty (TKA) without increasing the risk of thromboembolic events (TEE) [5]. Many studies have been done using TXA intravenously as well as topically to prove its efficacy [6, 7]. In these studies, different dosing regimens have been used for both IV and topical TXA. Some studies have demonstrated better results with two IV doses over single dose [8, 9] while some have compared single topical dose to one or two IV doses [10, 11, 12]. However, the available studies have shown mixed results, hence the aim of this study is to compare the effectiveness and safety of combined and isolated IV route of TXA administration in TKA.

**Material and Methods**

Institutional ethical committee approval was taken and the study was conducted in a Tertiary Medical Institute. This study includes patients who got operated between May 2014 and August 2017 for Total knee Arthroplasty. The inclusion criteria was patients operated for Total knee Arthroplasty who had normal preoperative platelet count, prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio. The exclusion criteria were a known allergy to TXA, known cardiac or respiratory disease; congenital or acquired coagulopathy; prothrombin time, partial thromboplastin time and international normalized ratio.

The use of TKA without increasing the risk of TEE remains a concern [1, 2]. Many methods are used to manage blood loss such as tourniquet application, blood transfusion, administration of haemostatic agents and autologous transfusion [3]. Allogeneic blood transfusion increases the risk of adverse events, and adds to the financial burden on the patients [4].

The study was a retrospective study to investigate the effects of IV TXA vs IV plus topical TXA. Sixty patients were assigned to two groups with thirty patients in each group.

(I) Group A- Patients were administered:
- 1st dose- 1 gram TXA IV 20 minutes prior to tourniquet deflation
- 2nd dose- 1 gram TXA IV 3 hrs after 1st dose and
- 3rd dose- 1 gram TXA IV 6 hrs after 1st dose.

(II) Group B- Patients were administered:
- 1st dose- 1 gram TXA IV 20 minutes prior to tourniquet deflation
- 2nd dose- 2 grams TXA in 100 milliliters (mL) normal saline topically after arthrotomy closure.

We observed a significant decrease in Hgb drop (Table no. 1) and total drain amount with the Group B compared to Group A. Group B also had a significant decrease in total intraoperative blood loss and transfusion rate. A transfusion was provided for any Hgb less than 9.0 grams/deciliter (g/dl).

The established practice of transfusion in our unit is that patients are transfused if:
1. Postoperative Hgb is < 9 mg/dl
2. Physiological signs of inadequate oxygenation such as hemodynamic instability or symptoms of myocardial ischemia occur
3. Drainage of more than 1 liter of blood in the first 24 hours.

**Results**

Mean age of study population was 64 years [Figure 1]. 70% were females and 30% were male patients. Indication for surgery in all the patients was osteoarthritis knee.

In Group A patients, the intra-operative bleeding ranged from 150ml to 400ml (Mean 262.33ml), drain ranged from 100ml to 400ml (Mean 238.33ml) (Figure no. 1), Hgb drop ranged from 0.7 to 4.6 g/dl (Mean 2.39) (Figure no. 2). 2.39) (Figure no. 2). 12 of the 30 patients (40%) required blood transfusion post-operatively. 3. Drainage of more than 1 liter of blood in the first 24 hours.

In Group B patients, the intra-operative bleeding ranged from 200ml to 350ml (Mean 248.00 ml), drain ranged from 100ml to 250ml (Mean 149.00ml) (Figure no. 1), Hgb drop ranged from 0.7 to 3.3 g/dl (Mean 1.74) (Figure no. 2). 5 of the 30 patients (16.67%) required blood transfusion post-operatively.

We observed a significant decrease in Hgb drop (Table no. 1) and total drain amount with the Group B compared to Group A. Group B also
had a significant decrease in total blood loss and transfusion rates (Table no. 2) compared to Group A (Table no. 3).

Discussion-
TXA is a synthetic anti-fibrinolitic agent that competitively inhibits the activation of plasminogen to plasmin, an enzyme that degrades fibrin clots, fibrinogen, procoagulant factors V and VIII. At higher concentration, TXA also acts directly to inhibit plasmin activity. Consequently, there is a decrease in proteolytic action on the fibrin monomers and fibrinogen, which results in clot stabilization. The trauma of surgery activates fibrinolysis by promoting the release of tissue plasminogen activator. Although the body naturally inhibits fibrinolysis by 24 hours after surgery, anti-fibrinolytic agents such as TXA can block the activation of plasminogen to plasmin earlier and thereby decreasing the perioperative blood loss.

TXA can be given as preoperative, intraoperative or postoperative dose, or various permutations combining these three doses. TXA, when given intravenously, has a wide distribution throughout the extracellular and intracellular compartments. It diffuses rapidly into the synovial fluid. Dose of 10-20 mg per kg body weight intravenously is used. Its biological half-life is 3 hours in the joint fluid and 90% of it is eliminated within 24 hours by glomerular filtration. Meta-analyses have shown that intravenous TXA effectively reduces the perioperative blood loss and incidence of blood transfusion after TKR, without increasing the risk of thromboembolic events (TEE)[12-16].

TXA can be given as a topical wash or infused into the knee joint after arthroscopy closure. Topical administration of TXA induces microvascular hemostasis via preventing dissolving the fibrin clot. Compared to intravenous administration, its benefits include ease of administration, ability to achieve maximum concentration at the bleeding site and minimal systemic absorption. Wind et al. compared the two forms of TXA and reported decreased transfusion requirements with both forms of TXA compared to placebo [17]. However, many common medical conditions including renal impairment, cardiovascular diseases, cerebrovascular conditions and the concurrent presence of hormonal treatment may preclude the use of intravenous TXA at the time of surgery [18].

Most intravenous regime of TXA advocates use of minimum two doses. Maniar et al. noted that a single regimen of IV TXA cannot be recommended as the most effective regimen. The three-dose IV regimen of Pre operative, Intra operative and Post operative doses produced maximum effective reduction of drain loss and total blood loss [8]. Seo et al. [19] and Sarzaeeen et al. [11] in their study noted decreased postoperative Hb drop with intravenous administration as compared to intra-articular administration.

Soni et al. concurred with Maniar et al. and concluded that intra-articular regimen of TXA is as effective as three doses IV regimen in preventing blood loss without any difference in thromboembolic complications[20].

A recent study by Gomez-Barrema et al [21] compared topical IA TXA (3 g) with 2 IV doses (15 mg/kg each) of TXA in preserving blood loss in patients undergoing primary unilateral TKA. They analyzed 39 patients in each group (78 total) and reported no inferiority of topical TXA to IV TXA when analyzed for transfusion rate, blood loss, and Hb drop. Another study which compared 3 g of IA TXA with 3 doses of IV TXA (10 mg/kg each) involved 40 patients in each group and concluded that IA TXA is equally effective as a 3-dose IV regimen in reducing blood loss during TKA [19]. In another recent study by Patel et al., Hb level drop was 3.06 in the IV group and 3.42 mg/dL in the topical group. They showed that two groups were statistically the same with regard to Hb drop, drain output, and rate of transfusion [10]. In a recent meta-analysis, Wang et al. showed that topical TXA is similar to IV TXA in reducing blood loss and rate of transfusion without compromising patient safety [22].

In contrary, some studies have found that intra-articular administration of TXA leads to better results. Recently, Hamlin et al. showed that topical TXA diminished the rate of transfusion compared to IV TXA in patients who underwent primary TKA (0% versus 2.4%) [23]. In a systematic review and meta-analysis, Alshryda et al. showed that the indirect comparison of topical and IV TXA indicated that topical administration is a more appropriate route [12]. Similarly, Ishida et al. reported intra-articular administration of TXA not only decreased blood loss but also decreased joint swelling after TKA [24].

Despite several studies proving the efficacy of both intra-articular and intravenous TXA in reducing blood loss after TKR, the ideal route of administering TXA will remain a topic for ongoing debate and controversy in the upcoming years.

The conflicting findings across these studies are possibly contributed by: (I) the variation in surgical techniques using conventional intra- and extramedullary jigs or computer-assisted surgery; (II) the variation in dosing regimen for intravenous TXA, with some studies giving one dose while others giving three doses; (III) the variation in indications for blood transfusion across hospitals.

Conclusion
IA with IV TXA is more beneficial than IV TXA in reducing blood loss in primary total knee arthroplasty. Topical administration of TXA had better efficacy than intravenous administration in reducing total blood loss, drain output, blood transfusion and haemoglobin drop, without any increase in thromboembolic complications.

Declaration of conflicting interests
Nil

Table no. 1-

<table>
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<th>Parameter</th>
<th>Group A (n=30)</th>
<th>Group B (n=30)</th>
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<tr>
<td>Age (Mean±SD)</td>
<td>63.97±7.65</td>
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<td>Sex (M/F)</td>
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<td>Intra-op Bl. loss (Mean±SD)</td>
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