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Efficacy of tranexemic acid in controlling perioperative blood loss in TKR patients using intravenous V/s intraarticular route

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Abstract
Preoperative blood loss is common in total knee replacement. Tranexamic acid can reduce active bleeding. It is the most effective antifibrinolytic agent available. Our objective was to compare the efficacy of tranexamic acid in controlling perioperative blood loss in adult patients undergoing total knee replacement using intravenous versus intraarticular route. An analytical cross-sectional study was conducted on 95 patients who underwent total knee replacement surgery in our institution. Patients were selected for intravenous (group A) and intra articular (group B) by simple randomization. During the postoperative period, the amount of blood in the drain and post-operative hemoglobin at 48 hours were collected and total blood loss was calculated. Mean pre-operative hemoglobin in group A was 11.73 and in group, B was 11.86. Average blood loss in the drain was 305 ml and 293 ml in group A and group B respectively. Average total blood loss was 464ml and 438 ml in group A and B respectively. Average fall in Hb was 0.69 and 0.80 in group A and group B respectively at 48hours. One patient in each group was transfused with allogeneic blood. There were no clinically evident DVT cases in either group. In conclusion, both intraarticular and intravenous tranexamic acid were found to be equally effective in controlling perioperative blood loss in total knee arthroplasty patients with no significant increase in thromboembolic complications.

Keywords: Tranexamic acid, total knee arthroplasty, peri operative blood loss, intra articular, intra venous

Introduction
Total knee arthroplasty (TKA) is associated with a risk of bleeding sometimes requiring blood transfusion. Intra and post-operative bleeding in TKA carries the risk of developing an intra articular hematoma which could subsequently get infected. This carries the risk of a longer hospital stay, increased cost and morbidity. Allogenic transfusion of blood is also associated with complications.

There are various ways of reducing post-operative blood loss and the need for transfusion like autologous blood transfusion (haemodilution), keeping the knee in 90 degrees flexion for 6 hours post operatively, use of fibrin sealants, use of tranexamic acid etc. Tranexamic acid (TXA), being inexpensive, effective and safe has become a popular choice for controlling blood loss in TKA.

Though the effectiveness of TXA in controlling blood loss is widely demonstrated in various studies [1, 2, 3], it's efficacy when given intra venous and intra articular in TKA is still debated[3]. There are only a few studies in the literature comparing the results of tranexamic acid given through different routes in our population [4, 5, 6]. Our objective was to assess the efficacy of tranexamic acid in controlling peri operative blood loss in adult patients undergoing total knee arthroplasty using intravenous versus intra articular route.

Materials and Methods
After obtaining institutional research committee approval, we have conducted an analytical cross-sectional study. We included adult patients with primary osteoarthritis of the knee between 50 to 85 years. Patients with bilateral simultaneous TKA, rheumatoid arthritis, post-traumatic arthritis, revision TKA, thromboembolic disorders, bleeding diathesis, and a history of allergy to medications were excluded from the study.

We conducted this study between January 2017 and October 2019. There were 110 patients with primary osteoarthritis of the knee who underwent TKA during the study period. Three patients didn't give consent. Nine patients were excluded because they were taking aspirin or/and clopidogrel for cardiac disease. Three patients with varicose veins were also excluded. Finally, 95 patients who underwent total knee arthroplasty at our institution were included in the study.

We divided them into two groups by simple randomization. In group (A), tranexamic acid 1gram was given before the skin incision in 100 ml saline for 10 minutes and 1gram after the release of tourniquet. In group (B), 2 grams of tranexamic acid was given intra articular diluted in 50 ml normal saline after the closure of the joint capsule.

Informed consent was obtained from all participants. We routinely do a complete hemogram, blood sugar, serum electrolytes, ECG, and chest X-ray for all of our patients. A liver function test, clotting time, and bleeding time were done in all the persons included in our study.

All patients were given 1.5gms of cefuroxime as a prophylactic antibiotic 30 minutes before surgery. Antibiotic was continued for 48 hrs post-operatively on a twice-daily basis. All surgeries were done under combined spinal-epidural anaesthesia. The procedure was done by experienced surgeons. Tourniquet was used for all cases. A midline incision with a medial parapatellar approach was used. Cemented total knee arthroplasty was done in all cases. Tourniquet was removed before wound closure. The wound was closed in layers after obtaining hemostasis. All cases were finished within an average of 90 minutes. A negative suction drain was put in all cases before closing the wound. The drain was left clamped for 4 hours. After 4 hours the drain tube was unclamped. It was removed on the second postoperative day.

A knee brace was given and non-weight-bearing mobilization was started on the day of surgery. Walking with the help of a walker was started from the second day onwards

During post-operative period, amount of blood in the drain and post-op Hb at 48 hours was noted.

Total blood loss was calculated using below formula

$Hb(loss) = BV \times [Hb(i) – Hb(e)] \times 0.001 + Hb(t)$

$Blood\ loss = 1000 \times Hb\ (loss) / Hb(i)$

Hb(i) - Hb value before surgery (g/L)

Hb(e) - Hb value after surgery (g/L), Hb (t) total Hb transfused (g)

Hb (loss) = loss of Hb (g)

BV – estimated blood volume

Blood volume was estimated by the following formula

Average blood volume= Patient weight (kg) * (Average blood volume in mL/kg), where the average blood volume per demographic (mL / kg) was taken as 75 for adult male and 65 for adult female

The haemoglobin balance formula was conceived on the basis that blood loss can be estimated using three parameters: patient's estimated blood volume, pre- and postoperative haemoglobin concentrations, and also considering a euvolaemic state between the pre- and postoperative time points at which the patient's haemoglobin concentration is measured.

Results

Mean pre-operative haemoglobin in group A was11.86 and in group B was 11.73. Average blood loss in drain was 293 ml and 305 ml in group A and group B respectively. Average total blood loss was 438ml and 464ml in A and B groups respectively. Average fall in hemoglobin was 0.80 and 0.69 in group A and group B respectively at 48hours. One patient in each group was transfused with allogenic blood. There were no clinically evident DVT cases in either group.

Table 1: Age and Gender distribution among study patients

Age and Gender Distribution among study Patients			
Variable		**Mean**	**SD**
Age	Mean & SD	66.8	7.5
	Range	46 - 81	
	Category	N	%
	45-55 years	7	7.4%
	56-65 years	31	32.6%
	66-75 years	45	47.4%
	> 75 years	12	12.6%
Sex	Males	41	43.2%
	Females	54	56.8%

Table 2: Comparison of Blood transfusion performed between 2 two groups.

Comparison of Blood transfusion performed b/w 2 different types of administration of Tranexamic Acid using Chi Square Test						
Blood Transfusion	**Group A**		**Group B**		**χ^2 Value**	**P-Value**
	n	**%**	**n**	**%**		
Yes	1	1.5%	1.00	3.3%	0.321	0.57
No	64	98.5%	29.00	96.7%		

Table 3: Distribution of study patients in two groups.

Distribution of study patients based on the route of administration of Tranexamic Acid			
Variable	**Category**	**n**	**%**
Route of Administration	Group A	65	68.4%
	Group B	30	31.6%

Table 4: Comparison of mean Weight, Blood Loss & Drain (in ml) observed during post op interval period between two groups

Comparison of mean Weight, Blood Loss & Drain (in ml) observed during post op interval period between 2 different types of administration of Tranexamic Acid using Mann Whitney Test							
Variable	**Route of Administration**	**N**	**Mean**	**SD**	**Mean Diff**	**Z**	**P-Value**
Weight	Group A	65	68.11	6.33	0.28	-0.665	0.51
	Group B	30	67.83	6.15			
Total blood loss (ml)	Group A	65	464.65	219.81	25.68	-0.538	0.59
	Group B	30	438.97	220.40			

Drain (in ml)	Group A	65	305.54	157.60	12.21	-0.563	0.57
	Group B	30	293.33	185.11			

Table 5: Comparison of mean Haemoglobin levels (gm %) observed during Pre and Post op interval period between two groups.

Comparison of mean Haemoglobin levels (gm%) observed between Pre and Post op interval period in 2 different types of administration of Tranexamic Acid using Student Paired t Test							
Route of Administration	**Time**	**N**	**Mean**	**SD**	**Mean Diff**	**t**	**P-Value**
Group A	Pre op	65	11.73	1.15	0.69	1.304	0.12
	Post op	65	11.03	1.18			
Group B	Pre op	30	11.86	1.20	0.80	1.189	0.09
	Post op	30	11.06	1.23			

Discussion

Total knee arthroplasty (TKA) is associated with a risk of bleeding and need for blood transfusion. There are various ways of reducing post-operative blood loss and the need for transfusion.

Haemodilution, which may be used to reduce blood loss, involves removing some of a patient's blood immediately before surgery, supporting the blood pressure with the infusion of fluids, and then returning the blood once blood loss is complete. This can be effective, but requires personnel to collect the blood and storage facilities [7].

Post-operative blood loss can also be controlled by keeping the knee in 90 degree flexion for 6 hours immediately after surgery [8]. Newer modalities like use of fibrin sealants has been shown to be effective, but the cost is prohibitive for their routine use in TKA [9].

Allogenic transfusion of blood is also associated with complications apart from the cost involved [10]. So, a method to reduce the chances of blood loss and thus the need for an allogenic transfusion will benefit patients undergoing total knee arthroplasty

Tranexamic acid (TXA), being inexpensive, effective and safe has become a popular choice for controlling blood loss in TKA [1].TXA is a synthetic derivative of the amino acid lysine and binds the 5 lysine binding sites on plasminogen. This inhibits plasmin formation and displaces plasminogen from the fibrin surface. It may also directly inhibit plasmin and partially inhibit fibrinogenolysis at higher concentrations [11].

Total of 95 patients who had undergone total knee replacement in our institution were selected randomly for this study.60 patients were given tranexamic acid through intravenous route and 35 patients were given through intra articular route.

Average total blood loss was 464 ml and 438 ml in the intra venous and intra articular group respectively and the difference was not statistically significant (p=0.59). Average fall in hemoglobin was 0.69 and 0.80 in the intra venous and intra articular group respectively and the difference was not significant statistically. Average drain output at 48 hours was 305 ml and 293 ml in the intra venous and intra articular group respectively and again the difference was not statistically significant. There were no thrombo embolic events or other serious adverse reactions

In a randomised control trial, comparing the efficacy of intravenous and intraarticular TXA Enrique Gomez-Barrena etal demonstrated noninferiority of intraarticular TXA when compared with the intravenous route with no safety concerns [3]. A meta-analysis noted no significant differences in the transfusion requirement, postoperative complications, blood loss, and change in hemoglobin levels between intravenous and topical TXA [12]. There are reports of the efficacy and safety of combined administration of intravenous and topical tranexamic acid in primary knee replacements with lower blood loss and drainage volume [13].

The topical (intra-articular) use of tranexamic acid reduces blood loss and transfusion rates following total knee replacement [14]. In total knee arthroplasty when TXA was given intra venous, intraarticular, and by combined route, no significant difference was found in maximum hemoglobin loss, drain volume, and rate of transfusions [15]. In a meta-analysis of RCTs, Cid *et al* found that tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty [16]. The transfusion rates were significantly lower in the topical application when compared to the intravenous administration [17].

A single intra-articular dose and two intravenous doses of TXA give equivalent efficacy and safety in the management of blood loss at TKA [6]. An RCT demonstrated that intra-articular tranexamic acid is equally effective as three doses of intravenous regimen in reducing blood loss in TKA [4]. Intraarticular TXA is as effective and safe as compared to intravenous TXA. Intraarticular administration is a preferred method because of ease of administration and lack of systemic absorption [5].

Use of TXA has helped in reducing the blood loss and thus the need of blood transfusions in primary knee replacements. Different studies including ours have demonstrated equal efficacy of topical/intra articular TXA in controlling blood loss without significant thromboembolic events or other adverse effects.

We have a small sample size. Although our study has demonstrated comparable efficacy of intravenous and intraarticular tranexamic acid in controlling perioperative blood loss in adult patients undergoing total knee replacement, we would suggest future studies with a larger number of patients to solve this controversy better.

Conclusion

There is no difference in the perioperative blood loss and significant adverse effects in primary total knee arthroplasty for osteoarthritis in adult patients when tranexamic acid is given by intravenous or intraarticular routes.

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