ORIGINAL RESEARCH

Intraarticular vs Intravenous Tranexamic Acid in Reduction of Blood Loss in Primary Total Knee Replacement

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ABSTRACT

Aim: To study the efficacy of topical intraarticular vs intravenous tranexamic acid (TXA) in reducing blood loss following primary total knee replacement (TKR).

Materials and methods: A phase 3, single center, double blind and randomized controlled study was conducted in the Department of Orthopedics, Sri Ramachandra University, Chennai, Tamil Nadu. A prospective study of 100 patients lasted from July 2013 to July 2015.

Results: Postoperative transfusion rates were zero in both the groups (intraarticular and intravenous). The mean 48-hour drain collected is 285.6 ml in group A (intraarticular), while it is 325.8 ml in group B (intravenous); the mean drop in hemoglobin is 1.7 gm/dl in group A (intraarticular) while it is 2.4 gm/dl in group B (intravenous).

Conclusion: This study shows that topical intraarticular administration of TXA has better efficacy than intravenous TXA in controlling postoperative blood loss following primary uncomplicated TKR with no significant complications.

Keywords: Intraarticular, Intravenous, Total knee replacement, Tranexamic acid.

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Conflict of interest: None

INTRODUCTION

Total knee arthroplasty (TKA) is a major orthopedic operation that involves significant blood loss because of extensive soft tissue release and bone cuts. The intravenous administration of tranexamic acid (TXA) has shown good results in controlling perioperative blood loss following primary total knee replacement total knee replacement (TKR) TXA, but the complications associated with the intravenous administration of the TXA

limit the use in most of the patients. Thus, intraarticular administration of TXA may serve as an effective alternative for intravenous administration. The advantages of intraarticular administration are reduced systemic absorption, maximum concentration at the bleeding site, can be used in patients with renal impairment, cardiovascular diseases, cerebrovascular conditions, ease of administration, and furthermore, the use of tourniquet in TKR results in negligible intraoperative blood loss but notable postoperative blood loss, which is the ideal scenario for using intraarticular hemostatic agents. The aim of this study is to study the efficacy of topical intraarticular vs intravenous TKR in reducing blood loss following primary TKR.

MATERIALS AND METHODS

A phase 3, single center, double blind and randomized controlled study was conducted in the Department of Orthopedics, Sri Ramachandra University, Chennai, Tamil Nadu, India. This is a prospective study of 100 patients from July 2013 to July 2015. The inclusion criteria for the study were patients undergoing unilateral primary TKR, patients of all age groups, patients of both sexes, both osteoarthritis and rheumatoid arthritis patients and patients who received brand name cyklokapron (tranexamic acid) only were included. The exclusion criteria for the study were patients undergoing bilateral simultaneous TKR, revision TKR, patient needing extensive lateral or posterior release/extensive synovectomy, patients with bleeding diathesis, patients with any contraindication for TXA and patients with severe cardiopulmonary and renal diseases. Totally 100 patients were included in which 50 patients were randomly given intravenous tranexamic and 50 patients were given intraarticular TXA. After obtaining written informed consent from the patients and after obtaining our Institutes Ethical Committee clearance (CCP-MED/13/OCT/09//80), this study was conducted. The collected data were analyzed with Statistical Package for the Social Sciences (SPSS) 16.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and standard deviation were used for continuous variables. To find the significant difference between the bivariate samples in paired groups (pre- and

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postoperative) paired sample t-test was used and for independent groups (IA and IV) unpaired sample t-test was used. To find the significance in categorical data chi-square test was used. In all the above statistical tools the probability value 0.05 is considered as significant level. The biochemical schematic formula of TXA is given in Figure 1. The mechanism of action of TXA is given in Figure 2.

TECHNIQUE

All patients were operated by a single surgeon using standard technique with mid vastus approach with tourniquet inflated 100 mm Hg above systolic blood pressure without exsanguinations. Both cruciate retaining and cruciate substituting were done. The wound following the surgery was closed in layers with intraarticular drain and compression dressing. Tourniquet was used in all cases. Patients who underwent primary TKR were randomized into two groups. One group received 2 gm of TXA through the drain (Fig. 3) after skin closure that was clamped for 1 hour following surgery and another group received 10 mg/kg TXA in 100 ml of normal saline intravenously, one dose before tourniquet release and second dose 3 hours after the surgery.¹ The postoperative assessments

were blood transfusion rates, drop in hemoglobin levels between the two groups, postoperative blood loss measured in drain 48 hours following the surgery and wound healing. The complications, such as deep vein thrombosis, pulmonary embolism, hematoma and hypersensitivity were assessed clinically.

RESULTS

This study involved 100 patients (n = 100); 26 male patients and 74 female patients who underwent primary TKA. They were divided into two groups 50 in each with 38 female patients in intravenous group, 36 female patients in intraarticular group, 12 male patients in intravenous group and 14 male patients in intraarticular group (Fig. 4) with $p > 0.05$ (Table 1). Group IV represents intravenous hereafter and group IA represents intraarticular in the tables below. A total of 38 patients underwent left primary TKR and 62 patients underwent right TKR (Fig. 5). The difference in hemoglobin is done as independent sample t test (Table 2). The mean age group of the patients in the study group were 69 years (Table 3) (Fig. 6) and the mean body mass index (BMI) was 28 (Table 3). Among the 100 patients, the indication for primary TKR was osteoarthritis in 93 patients and rheumatoid arthritis in 7 patients. Group IV stands for intravenous and IA stands for intraarticular. The mean preoperative hemoglobin of the 50 patients (n = 50) in the intravenous group was 10.90 gm/dl and in the intraarticular group was 10.88 gm/dl. The mean postoperative hemoglobin of the 50 patients (n = 50) in the intravenous group was 9.04 gm/dl and in

Fig. 1: Tranexamic acid

Fig. 2: Mechanism of action

Fig. 3: Intraarticular injection of tranexamic acid through drain

Fig. 4: Sex distribution

Fig. 5: Side distribution

Fig. 6: Age distribution

Table 1: Statistical analysis methods and significance- Chi-square test

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson chi-square	0.208	1	0.648	—	—
Continuity correction	0.052	1	0.820	—	—
Likelihood ratio	0.208	1	0.648	—	—
Fisher's exact test	—	—	—	0.820	0.410
No. of valid cases	100	—	—	—	—

the intraarticular group was 9.56 gm/dl $p < 0.05$ (Table 3). The mean preoperative hematocrit value of the 50 patients in the intravenous group was 32.02 and in the intra-articular group was 32.18. The mean postoperative hematocrit value of the 50 patients in the intravenous group was 27.26 and in the intraarticular group was 28.60 $p < 0.05$ (Table 3). The mean drop in hemoglobin of the 50 patients in the intravenous group was 1.86 gm/dl and in the intraarticular group was 1.32 gm/dl $p < 0.05$ (Table 3 and Fig. 7). The mean drop in hematocrit in the intravenous group was 4.76 and in the intraarticular group was 3.58 $p < 0.05$ (Table 3). The postoperative blood transfu-

Fig. 7: Hemoglobin difference between pre- and postoperative

sion rates were zero in both the intravenous and the intra-articular group. The mean 48 hours blood loss in drain in the 50 patients of the intravenous group was 320.7 ml and in the intraarticular group was 284.4 ml $p < 0.059$ (Table 3). The wound healing was found to be normal in both the groups. One patient in the intraarticular group developed

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Table 2: Independent samples t-test

		Levene's test for equality of variances		t-test for equality of means						
		F	Sig.	T	Df	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
HB DIFF	Equal variances assumed	2.487	0.118	4.808	98	0.000	0.540	0.112	0.317	0.763
	Equal variances not assumed	—	—	4.808	97.168	0.000	0.540	0.112	0.317	0.763
PCV DIFF	Equal variances assumed	0.491	0.485	3.162	98	0.002	1.180	0.373	0.439	1.921
	Equal variances not assumed	—	—	3.162	94.357	0.002	1.180	0.373	0.439	1.921

HB DIFF: Hemoglobin difference; PCV DIFF: Packed cell volume difference

Table 3: Mean drop in hemoglobin and mean blood loss in both groups

		Levene's test for equality of variances		t-test for equality of means						
		F	Sig.	T	Df	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
Equal variances assumed	Equal variances assumed	2.073	0.153	-1.026	98	0.307	-1.160	1.131	-3.404	1.084
	Equal variances not assumed			-1.026	96.794	0.307	-1.160	1.131	-3.404	1.084
Equal variances not assumed	Equal variances assumed	0.493	0.484	0.777	98	0.439	0.280	0.360	-0.435	0.995
	Equal variances not assumed			0.777	89.655	0.439	0.280	0.360	-0.436	0.996
Equal variances assumed	Equal variances assumed	0.018	0.895	0.107	98	0.915	0.020	0.187	-0.351	0.391
	Equal variances not assumed			0.107	97.862	0.915	0.020	0.187	-0.351	0.391
Equal variances not assumed	Equal variances assumed	0.622	0.432	-2.804	98	0.006	-0.520	0.185	-0.888	-0.152
	Equal variances not assumed			-2.804	97.998	0.006	-0.520	0.185	-0.888	-0.152
Equal variances assumed	Equal variances assumed	1.601	0.209	-0.350	98	0.727	-0.160	0.457	-1.068	0.748
	Equal variances not assumed			-0.350	96.939	0.727	-0.160	0.457	-1.068	0.748
Equal variances not assumed	Equal variances assumed	0.025	0.874	-2.511	98	0.014	-1.340	0.534	-2.399	-0.281
	Equal variances not assumed			-2.511	97.860	0.014	-1.340	0.534	-2.399	-0.281
Equal variances assumed	Equal variances assumed	0.777	0.380	3.242	98	0.002	36.300	11.196	14.081	58.519
	Equal variances not assumed			3.242	96.440	0.002	36.300	11.196	14.077	58.523

HB: Hemoglobin; PCV: Packed cell value

hematoma which was diagnosed clinically on the 4th post-operative day which needed surgical hematoma evacuation. No other patients had any complications clinically, such as deep vein thrombosis, pulmonary embolism and hypersensitivity.

DISCUSSION

Tranexamic acid is a synthetic analog of the amino acid lysine. It exerts an antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen, thereby reducing the conversion of plasminogen to

plasmin (fibrinolysin), an enzyme that degrades fibrin clots and fibrinogen. Its biological half life–2 hours, elimination is renal, via glomerular filtration; 90% of the dose is excreted within 24 hours after administration of 10 mg/kg. A study² showed that the total measured perioperative blood loss in primary uncomplicated TKA is around 1000–1500 ml and postoperative blood loss is estimated around 700–800 ml. Tranexamic acid administration has decreased postoperative blood transfusion.³ Various methods of compensating blood loss are allogenic blood transfusion, autologous transfusion, Normovolemic hemodilution and cell salvage. The common side effects of intravenous administration of TXA are nausea, vomiting, diarrhea, dizziness, vision changes, and slurred speech. The absolute contraindication of the drug include severe renal impairment, pregnancy, hypersensitivity, subarachnoids hemorrhage and active intravascular clotting. The complication associated with the drug include venous and arterial thrombosis and thromboembolism, ureteral obstruction and pulmonary embolism, increased incidence of leukemia, hyperplasia of the biliary tract, cholangioma, and adenocarcinoma of the intrahepatic biliary tract. The study⁴ conducted in wed that it reduced absolute risk of blood transfusion by 15.4% and reduced blood loss by 368 ml compared to placebo. Topically applied TXA was effective in reducing the need for blood transfusion following TKR without important additional adverse effects. A prospective randomized study⁵ involving 89 patients comparing topical administration of 2.0 gm TXA, *vs* IV group administration of 10 mg/kg. The perioperative change in hemoglobin level, showed a decrease of 3.06 in the IV group and 3.42 in the topical group. Based on this study, to 254 patients underwent unilateral primary cemented TKR received intraarticular TXA topical TXA has similar efficacy to IV TXA for TKA patients with no major complication.

In our study, efficacy of intravenous TXA was compared with the efficacy of intraarticular TXA in controlling blood loss following primary TKA. The study group consisted of patients of statistically similar age, sex and BMI. The postoperative transfusion rates were zero in both the intravenous and intraarticular group. In the study group, the mean drop in hemoglobin in the intravenous group was 1.86 and the mean drop in hemoglobin in the intraarticular group was 1.32 ($p = 0.0005$). This shows that the intraarticular administration of TXA has better efficacy in reducing drop in hemoglobin between the pre- and postoperative period than the intravenous group. In the study group, the mean drop in hematocrit in the intravenous group was 4.76 and the mean drop in hematocrit in the intraarticular group was 3.58 ($p = 0.002$). This shows that the intraarticular administration of TXA has better efficacy in reducing drop in hemato-

crit between the pre- and postoperative period than the intravenous group. In the study group, the mean 48 hours blood loss in drain in the intravenous group was 320.7 ml and the mean 48 hours blood loss in the intraarticular group was 284.4 ml ($p = 0.002$). This shows that the intraarticular administration of TXA has better efficacy in reducing blood loss through drain in the postoperative period than the intravenous group. One patient who received intraarticular TXA developed hematoma formation which was surgically evacuated. None of the patient in the intravenous group had hematoma formation. None of the patients developed any other complication, such as DVT, pulmonary embolism and hypersensitivity. Wound healing was normal in all the patients involved in the study group.

CONCLUSION

Total knee replacement is a major orthopedic surgery with a large amount of blood loss in the perioperative period because of the extensive soft tissue release. Intravenous administration of TXA served as an effective tool in controlling blood loss following primary TKR. But the complication associated with the intravenous administration of TXA makes its use limited. This study has shown that the intraarticular administration of the TXA has better efficacy in reducing the drop in hemoglobin and hematocrit and blood loss through drain with negligible complication. This study supports the use of intraarticular TXA in controlling blood loss following primary TKA.

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