COMPARISON BETWEEN INTRA-ARTICULAR AND INTRAVENOUS TRANEXAMIC ACID APPLICATION IN PRIMARY UNILATERAL KNEE JOINT REPLACEMENT

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ABSTRACT

Objective: To compare the efficacy of intra-articular and intravenous modes of administration of tranexamic acid in primary total knee arthroplasty in terms of blood loss and fall in haemoglobin level.

Study Design: Randomized controlled trial.

Place and Duration of Study: Study was conducted at the Department of Orthopaedics, Benazir Bhutto Hospital Rawalpindi, Pakistan for duration of six months, from May 2017 to Nov 2017.

Material and Methods: Seventy-eight patients were included in the study. Patients were randomly divided into group A and B. Group A patients undergoing unilateral primary total knee replacement (TKR) were given intra-venous tranexamic acid (TXA) while group B were infiltrated with intra-articular TXA. Volume of drain output, fall in haemoglobin (Hb) level and need for blood transfusion were measured immediately after surgery and at 12 and 24 hours post operatively in both groups.

Results: The study included 35 (44.87%) male and 43 (55.13%) female patients. Mean age of patients was 61 ± 6.59 years. The mean drain output calculated immediately after surgery in group A was 45.38 ± 20.75 ml compared with 47.95 ± 23.86 ml in group B (p=0.73). At 24 hours post operatively, mean drain output was 263.21 ± 38.50 ml in intravenous group versus 243.59 ± 70.73 ml in intra-articular group (p=0.46). Regarding fall in Hb level, both groups showed no significant difference (p>0.05). About 12.82% (n=5) patients in group A compared to 10.26% (n=4) patients required blood transfusion post operatively (p=0.72).

Conclusion: Intra-articular and intravenous TXA are equally effective in patients undergoing primary total knee arthroplasty in reducing post-operative blood loss.

Keywords: Drainage, Haemoglobin, Total knee replacement, Tranexamic acid.

INTRODUCTION

Increase in life expectancy over the past years has resulted in a dramatic rise in patients with osteoarthritis[1]. Primary osteoarthritis is the commonest type of knee joint disease where patients present with joint pain which increases with activity, stiffness of the joint and therefore functional compromise[2]. Total knee arthroplasty (TKA) is considered to be the best solution for such degenerative conditions of the knee which not only makes the patient pain free but also improves the functional outcome[3]. Patients who undergo TKA are at increased risk of per operative bleeding and can have a blood loss up to 1800 ml[4]. Such an amount of blood loss has a significant effect on the morbidity and mortality of the patient especially as majority of those undergoing TKA are elderly[5]. Blood transfusion has to be carried out in these patients to compensate for the loss of blood volume which is not without risk. This transfusion not only causes blood reactions, transmission of infections like human immunodeficiency virus (HIV) but can also can lead to heart failure[6]. Numerous studies have been carried out to find an effective way to reduce this blood loss and various intravenous and topical agents have been put to test[7,8].

Tranexamic acid (TXA) is an agent which has shown to reduce the peri-operative blood loss in TKA[9]. It inhibits the fibrinolysis by blocking plasminogen lysine binding sites competitively there by promoting clot formation[10]. Intravenous and topical application of TXA are the modes commonly employed for its administration.

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Intravenous TXA is often preferred and has been found to be a safe method with good efficacy. Many studies have confirmed that this route not only reduces the blood loss and therefore blood transfusion but also it is associated with less complications[11-13]. When compared with intravenous administration, intra-articular TXA has a greater concentration at the site of surgery and therefore its blood loss reducing effect lasts longer. Also the systemic absorption is less which decreases the incidence of thrombo-embolic phenomenon[14]. The contraindications to intravenous TXA which include thrombo-embolic events like myocardial infarction (MI), pulmonary embolism (PE), deep venous thrombosis (DVT) were not a contraindication to intra-articular TXA which further increased the safety of this route[14]. The effectiveness of TXA has been proved by various studies but despite that, controversy still remains regarding its optimal regimen and dose[11,15].

This study was conducted to determine the efficacy of intra-articular and intravenous modes of administration of TXA in terms of post operative volume of drain output, fall in haemoglobin level and the need for blood transfusion in patients undergoing primary unilateral knee joint replacement.

PATIENTS AND METHODS

This randomized controlled study was conducted at the Department of Orthopaedics, Benazir Bhutto Hospital, Rawalpindi, Pakistan from 12th May 2017 to 11th November 2017 after taking approval from the ethical committee of the hospital. All patients undergoing unilateral primary total knee replacement were included in the study. Exclusion criteria were patients with hepatitis B and C, history of previous knee replacement, bilateral total knee replacement, allergy to TXA, Hb less than 11g/dl in males and less than 10g/dl in females, renal dysfunction, cardiovascular disease (Like MI or atrial fibrillation), use of anticoagulants for 7 days prior to surgery and history of thromboembolic diseases like stroke, DVT or PE. Sample size of the study was calculated using open source calculator, Open Epi version 3.04, keeping confidence interval 95% and power of study 80%.

Seventy eight patients that met the inclusion criteria were randomly divided into two groups, A and B. An SPSS generated random number list was used for randomization where 78 study identity numbers were assigned randomly into either group A or B equally (39 each group). Each patient fulfilling the selection criteria was allocated study identity (ID) numbers in chronological order and then the study group corresponding to its ID number was allocated to that patient. All surgeries were performed by the same consultant orthopaedic surgeon employing mid vastas approach. Posterior cruciate ligament substituting total knee cemented prosthetics were used. All surgeries were done under spinal anaesthesia. The affected limb was elevated and exsanguinated using esmarch bandage after which tourniquet was applied. Inflation of the tourniquet was done up to a pressure of 350 mmHg. Group A patients were given two doses of TXA intravenously as 15mg per kg body weight. Each dose was diluted in 10ml normal saline. One dose was given 15 minutes before tourniquet inflation and the other 15 minutes after tourniquet deflation. Group B were infiltrated with 2g intra-articular TXA diluted in 100 ml normal saline after closure of wound. Tourniquet was removed after attaining hemostasis. A drain of 12G was placed in each wound after which the wound was closed in layers. The drain output was recorded 12 hourly and it was removed 48 hours after surgery. Blood transfusion was done only when the Hb levels were less than 8 mg/dl postoperatively. Both groups were observed immediately after the knee replacement and at 12 and 24 hours post-operatively for drain output, fall in Hb and need for blood transfusion.

A predefined post operative protocol was followed by all patients included in the study. Ankle pump exercises were started immediately after surgery. On 2nd post operative day, patients were made to stand and also continuous passive

motion exercises were started. They were discharged on the 7th post operative day.

Information was recorded on a pre-formed questionnaire and all the data were entered into Statistical Package of Social Sciences version 23. Categorical variables presented in the form of frequencies and percentages. Apart from descriptive statistics, both study groups were also tested for base line homogeneity based on variables gender, age and body mass index (BMI) through Chi-square test (for gender and side operated) and independent samples t test (for age and BMI). The variable duration of surgery was normally distributed so independent samples t-test at 5% level of significance was applied to compare both study groups. The variables "Immediate, 12- and 24-hour volume of drain output and fall in haemoglobin" were not observed to be normally distributed based on Shapiro-Wilk test so Mann Whitney-U test was applied to compare all these variables at 5% level of significance. A *p*-value less than 0.05 was considered statistically significant.

Table-IA: Demographic details.

	Intravenous TXA (Group–A) (n=39)	Intra-articular TXA (Group–B) (n=39)	*p*-value
Age of patients in years (mean ± Sd)	61.23 ± 7.13	60.77 ± 6.08	0.76
Body Mass Index (Kg/m^2)	25.60 ± 2.83	25.35 ± 2.75	0.68
Mean duration of surgery in minutes (mean ± Sd)	83.67 ± 3.60	83.18 ± 3.27	0.53

Independent samples t-test for numerical variables

Table-IB: Demographic details.

		Intravenous TXA (Group-A)	Intraarticular TXA (Group-B)	Total participants	*p*-value
Variables		**Frequency (%)**	**Frequency (%)**	**Frequency (%)**	
Distribution of Gender	Male	16 (45.7)	19 (54.3)	35 (100)	0.49
	Female	23 (53.5)	20 (46.5)	43 (100)	
Operated side	Right Knee	17 (47.2)	19 (52.8)	36(100)	0.65
	Left Knee	22 (52.4)	20 (947.6)	42 (100)	

Chi-square test for categorical variables

Table-II: Volume of post-op drain output group wise.

	Group A (mean ± Sd)	Group B (mean ± Sd)	*p*-value
Immediate volume of drain output (ml)	45.38 ± 20.75	47.95 ± 23.86	0.73
12 hour volume of drain output (ml)	237.69 ± 34.45	222.82 ± 60.39	0.76
24 hour volume of drain output (ml)	263.21 ± 38.50	243.59 ± 70.73	0.46

Table-III: Group distribution of fall in haemoglobin (Hb).

	Group A (mean ± Sd)	Group B (mean ± Sd)	*p*-value
Immediate fall in Hb	0.97 ± 0.47	0.82 ± 0.43	0.11
12 hour fall in Hb	1.16 ± 0.52	1.02 ± 0.45	0.20
24 hour fall in Hb	1.28 ± 0.63	1.16 ± 0.47	0.52

RESULTS

The 78 patients included in the study had a mean age of 61 ± 6.59 years. Mean age in group A was 61.23 ± 7.13 years while that in group B was 60.77 ± 6.08 years. Average BMI was 25.48 ± 2.78 Kg/m^2. BMI of patients in group A was 25.60 ± 2.83 while that of group B was 25.35 ± 2.75 Kg/m^2. The mean duration of surgery was 83.42 ± 3.42 minutes. Mean duration of surgery in

patients of group A was 83.67 ± 3.60 minutes while that of group B was 83.18 ± 3.27 minutes, as shown in table-IA.

Thirty-five (44.87%) patients were male and 43 (55.13%) female. Among the 78 patients under study, a predominance for the left knee was observed with 42 (53.85%) patients who had to undergo left knee arthroplasty as compared to 36 (46.15%) patients who required surgery on the right knee, as shown in table-IB.

Five (12.82%) patients in group A while 4 (10.26%) patients in group B were transfused 1 pint of blood post operatively (p=0.72).

DISCUSSION

The major issue that occurs with TKA is the per- and post operative blood loss associated with it[16,17]. Mostly it can vary between 800 to 1800 ml[4]. During TKA, resection of bone and muscle is done resulting in blood loss from the cut sections. Small amount of blood ooze can also occur which

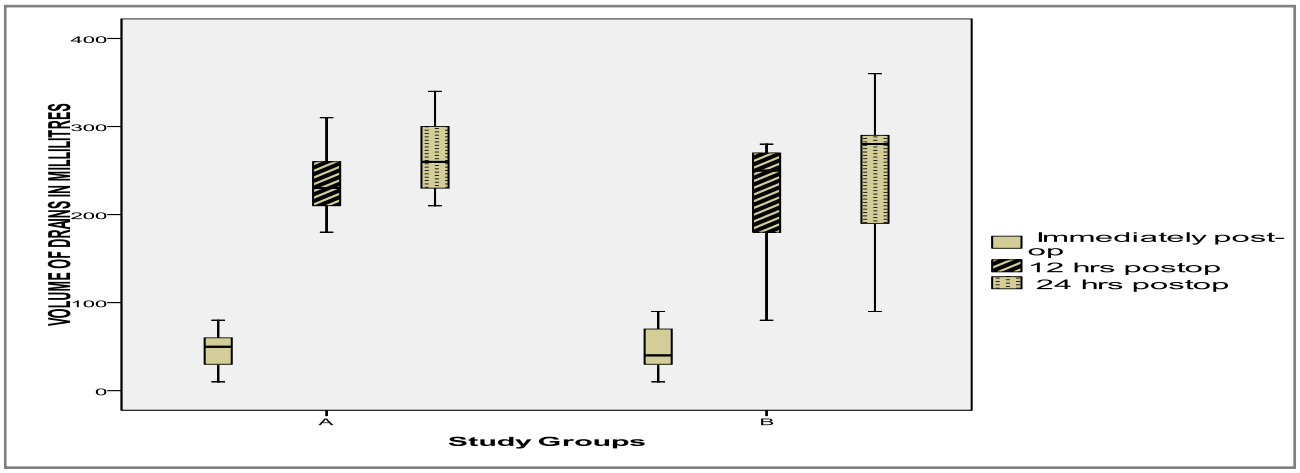

Figure-1: A box-plot exhibiting the differences of volumes of drainage in both study groups.

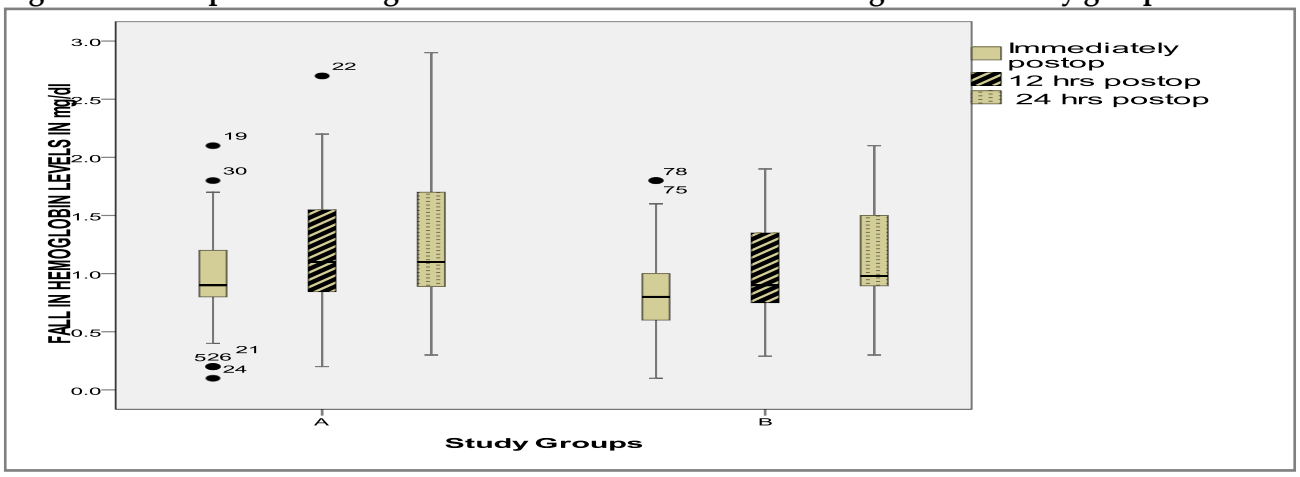

Figure-2: A box-plot exhibiting the differences of fall of haemoglobin level in both study groups.

The difference in means of immediate, 12- and 24-hour post-operative (post-op) volume of drain output in group A and B were not statistically significant (p>0.05) as shown in table-II, fig-1. The difference in means of immediate, 12- and 24-hour post-op fall in Hb level in group A and B were also not statistically significant (p>0.05) as shown in table-III, fig-2. is occult and therefore considered as negligible but it also contributes to the complications that may arise due to this blood loss[16]. TXA is an anti-fibrinolytic agent that works by promoting clot formation[10]. TXA has been used among various other agents to control the blood loss and is considered a preferred treatment modality which not only reduces the blood loss considerably but

also decreases the fatality rate. It has a significant role in reducing the cost of knee replacement[18]. Blood transfusion is an important factor that predicts the prolongation of hospital stay after TKA[9]. In a study carried out by Husted *et al*, the mean duration of stay after TKA was 3.8 days but 12% of the patients who had to undergo blood transfusion due to significant blood loss had a 3 times greater length of hospital stay[19]. Also ow rate of blood transfusion after TXA led to decreased transfusion associated complications and therefore the hospital costs were reduced to a great extent. From amongst the three proposed routes of administration of TXA i.e per oral, intravenous and intra-articular[20], intravenous and intra-articular modes were studied and compared in our study.

In our study the mean age of patients was 61 ± 6.59 years which was comparable to another study done by Steinhaus *et al* which was 65.8 years[21]. Ashraf *et al* carried out a similar study in which the mean age was 62 years[22]. In our study, 53.85% (n=42) patients were predominantly operated on left knee as compared to right knee in 46.15% (n=36). This was comparable to a study done by Memon *et al* in which 22 out of 39 (56.41%) undergoing TKA were left knees[23]. Average BMI was 25.48 ± 2.78 Kg/m^2. It was in accordance with a study by Memon *et al* in which it was calculated to be 29.21 ± 4.80 Kg/m^2 [23]. In another study published by McPherson *et al*, the average BMI of patients included in the study was 31.9 kg/m^2 [24]. This difference in BMI can be due to the regional differences among these study populations which could be attributed to dietary intake and levels of physical activity. Wang *et al* carried out a similar study in 2018 where no significant difference was found between the mean age of both groups and their BMIs when compared with our study[3].

Our study comprised of 44.87% (n=35) male and 55.13% (43) female patients. It was comparable to a study by Souza *et al* in which 79.1% patients undergoing TKA were females[25]. Mean operative time for TKA in our study was 83.42 ± 3.42 minutes. Ninty two minutes were taken by an experienced surgeon in a study done by Naranje *et al* whereas 97 minutes on average by a surgeon who had performed less than 300 knee arthroplasties[26]. The post operative drain output for group A immediately after surgery was 45.38 ± 20.75 ml. Group B patients had a mean drain output of 47.95 ± 23.86 ml (p=0.73). Whereas 12 and 24 hours post surgery, it was found to be 237.69 ± 34.45 and 263.21 ± 38.50 ml, respectively for group A patients while that of group B was 222.82 ± 60.39 and 243.59 ± 70.73 ml (p>0.05). The difference between these two groups was not statistically significant. Our results were supported by a study conducted by Gomez-Barrena *et al* where the group receiving intra-articular TXA had a drain output of 315.6 ml at 24 hours and the patients who were administered intravenous TXA had 308.1 ml drain output (p=0.948)[9]. When drain output of both groups was compared by Wang *et al*, no difference was found between them which favored our study[27]. While the study conducted by Arunkumar Vijay showed that amount of drain output in intra-articular group was 284.4 ml and that for intravenous group was 320.7 ml (p<0.05)[28]. Hence the above study proposed that intra-articular TXA was more effective in reducing blood loss after TKA which was in contrast to our study.

The next parameter we studied was the mean fall in the Hb level which when measured immediately post-op and at 12 and 24 hours after the surgery, the difference between two groups was not found to be significant with p-values of 0.11, 0.20 and 0.52, respectively. The results were similar to a study conducted by Fu *et al* who found that intra-articular and intravenous TXA administration were equally effective in terms of fall in Hb level[29]. The results of a study by Ameet Pispati were in contrast to our study where he showed that there was a significant fall in Hb level after intravenous administration of TXA which was calculated to be 1.6 g/dL as compared to patients who were given TXA intra-articularly and had a Hb fall of 0.9 g/dL (p<0.05)[30]. Many studies conducted in recent years have shown

intravenous and intra-articular TXA application to be equally effective, however a few demonstrated the superiority of intra-articular to intravenous TXA. One such study conducted by *Balasubramanian et al* showed intra-articular mode of administration to be superior to intravenous administration. He concluded that average fall of Hb was 0.72 ± 0.64 g/dL for intra-articular group and 1.36 ± 0.72 g/dL for intravenous group (p<0.05)[31]. Similar results were also shown by a study conducted by Khan *et al* at Ghurki Trust teaching hospital[32].

Regarding the need for blood transfusion, 5 (12.82%) patients in group A and 4 (10.26%) in group B were transfused one pint of blood in our study post operatively (p=0.72). Similar results were obtained by Chen *et al*, Fu *et al* and Ameet Pispati[33,29,30]. They showed that the amount of blood transfused post-operatively in both intra-articular and intravenous groups undergoing primary unilateral TKA did not have a significant difference. The results of Balasubramanian *et al* were different to our study where more patients with intravenous TXA had to be transfused blood as compared to the intra-articular group[31].

As according to the literature, there are concerns regarding thromboembolic complications after intravenous TXA administration where as intra-articular TXA has less systemic absorption, therefore it has greater safety profile. Intravenous TXA requires two doses for good efficacy while a single dose is infiltrated intra-articularly. Our study had certain limitations. Firstly, the study had a small sample size and secondly, the loss of blood and fall in Hb levels estimated 24 hours postoperatively could be unreliable due to hemodilution. Further studies need to be done with larger study groups; and for determination of accurate blood loss by taking into account the amount of fluid administered, per operative blood loss and drain output.

CONCLUSION

Intravenous and intra-articular TXA are equally effective in reducing blood loss in primary TKA. The aspect that makes intra-articular TXA superior is its ease of administration, local application and enhanced safety profile.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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