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Prospective study to compare efficacy of systemic, local and combined administration of tranexamic acid in reducing blood loss in total knee arthroplasty

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Abstract
Perioperative blood loss is a major challenge to surgeon in TKA. There are different methods to reduce blood loss in total knee arthroplasty (TKA). The efficacy of both systemic and local tranexamic acid (TXA) administration is demonstrated in the literature. The aim of the present study was to compare the efficacy of systemic, local and combined (systemic + local) administration of TXA in reducing blood loss after TKA. 47 patients undergoing TKA were divided into three groups (IV 18 cases; IA 20 cases, and combined (IV + IA) 9 cases) corresponding to the method of TXA administration. Demographic data, preoperative hemoglobin and platelet levels were collected. The primary outcome was the maximum hemoglobin loss, while the secondary outcomes were the amount of blood in the drain (cc/hour) and the rate of transfusions. Student's t-test or a $\chi 2$ test was used to evaluate between-group differences, using $p<0.05$ as the cut-off for statistically significant differences. The average age of the patients was 66.2 years and there was no significant difference in demographic and preoperative haemoglobin levels. No significant differences in the outcome measures were found between intravenous and intraarticular groups, but there was a significant difference between intraarticular vs intravenous and intraarticular vs combined groups with respect to maximum hemoglobin loss, blood in drain and transfusion rates, which were more in intraarticular group. TXA administration is safe and effective in reducing total blood loss in TKA. Intravenous and combined methods seems to be better in reducing blood loss in TKA, however intraarticular has still a role to play in patients with contraindications to systemic TXA in reducing blood loss in TKA.

Keywords: Tranexamic acid, TXA, TKA, Total knee, arthroplasty, bleeding, blood loss

1. Introduction
Perioperative bleeding in total knee arthroplasty (TKA) is of a major concern to orthropaedic surgeon [1-4]. The blood loss during TKA ranges from 800ml to 1800ml [1-4]. The use of tourniquet reduces the blood loss and gives a bloodless field during surgery, it actually increases fibrinolytic induced blood loss post operatively and reduces the risk of venous thromboembolism [1, 5, 6]. There are different methods to reduce blood loss in TKA which include perioperative blood donation, perioperative red cell salvage and maintenance of hypotension during surgery [1, 7, 8]. Perioperative blood transfusion further complicates matter in terms of transmissible infections, allergic reactions and increased costs to the patient [1, 7, 8]. Pharmacological approaches using anti fibrinolytic drugs like tranexamic acid have been used to reduce this as the cause of post operative bleeding is considered due to hyperfibrinolysis [9]. Tranexamic acid (TXA) is a fibrinolytic inhibitor which prevents clot lysis by blocking proteolytic activity of plasminogen activators [9]. There are various studies which show the efficacy of TXA in reducing perioperative blood loss in total knee arthroplasty [10-18]. However, administration of TXA through intravenous route increases the risk of thrombotic events which can also pose difficulty in patients who are prone for deep vein thrombosis (DVT) [11]. The need for DVT prophylaxis with low molecular heparin complicates this even further, while it reduces the chances of DVT due to surgical procedure, postoperative immobilization and the drug TXA itself, but can increase the bleeding postoperatively [12-15]. TXA is also contraindicated in patients with allergy, arterial or venous thrombosis, acute renal failure, intra cranial haemorrhage and epilepsy [11].

In order to avoid complications related to thrombotic events by intravenous TXA there have been studies to reduce such complications by topical intraarticular administration on TXA before wound closure or through a the drain with or without drain clamping [1, 4, 14, 17, 18]. This study is aimed to compare the efficacy of systemic, local and combined administration of tranexamic acid in reducing blood loss in total knee arthroplasty, a study similar to that of Marra *et al*.

2. Materials and Methods

The study is a prospective study conducted at Sree Balaji medical college and hospital, BIHER, chromepet, Chennai, India between July 2016 and June 2018. All patients, irrespective of age and gender, who underwent primary TKA in dept of Orthopaedics were enrolled. They were evaluated for surgery. Demographic data, co-morbidities, Pre-operative Hb and platelet levels were collected.

2.1 Patient distribution and allocation

The patients were divided into three groups, corresponding to tranexamic acid administration used:
Group 1 – intravenous (IV),
Group 2 – intraarticular (IA),
Group 3 - combination of IV and IA.

Patients with contraindications to TXA like history of deep vein thrombosis, myocardial infarction, heart failure, valvular stenosis, ischemic stroke, coagulopathy, severe liver or kidney disease were allocated to group 2 that is IA group. The other patients were randomly allocated to all the groups.

2.2 Method of drug administration

Group 1 - TXA was administered at 10mg/kg in 50ml of saline solution over 10 minutes during induction and 3 hours later.
Group 2 - washing with 1 gm of TXA in 10 ml of sterile saline solution for 2 minutes after placement of final components and injecting 1gm of TXA in 10ml of sterile saline solution after closure through the drain and clamped for 2 hours.
Group 3 - combination of above two methods.

2.3 Surgery Protocol

All the surgeries were performed using standard medial para patellar approach with cemented components and using tourniquet during cementation phase alone.

2.4 Postoperative protocol

All the patients received LMWH 12hrs after surgery and continued for 7 days. In all group 2 patients i.e IA group, drain was placed without suction and drain kept clamped for at least 2 hours after the surgery. Repeat haemoglobin testing was done on postoperative day 1 and day 2.
Knee mobilization and weight bearing were allowed between day 1 and day 2 post operatively. Continuous passive mobilisation was started from postoperative day 1. Drain was removed on postoperative day 2.

2.5 Follow-up

Patients were followed up for a period of minimum of 3 months to check for incidence of any Complications like DVT, thrombotic events and infections were recorded.

2.6 Outcome measurements and statistics

The primary outcome measured is maximum Haemoglobin loss, which is a measure of difference In preoperative and lowest postoperative Hb levels. The secondary outcomes measured were amount of blood in drain (cc/hr) and rate of transfusion. The Hb cut-off for transfusion was 8gm/dl. Follow-up was done to look for any cases of DVT as a complication.
The groups were compared using Student's t-test/chi square test. $P< 0.05$ was taken as statistically significant.

3. Results

We had 47 patients in our study there were 24(51%) male and 23(49%) female patients in the study with mean age of 66.2 years. There were 18(38.3%) patients in Group 1(intravenous group), 20(42.5%) patients in Group 2 and 9(19.2%) patients in Group 3. The distribution of patients is shown in Table 1. There was not much difference between the age and sex distribution between the three groups. However, the three groups were not homogenous in that all those patients with contraindications to systemic TXA and comorbidities towards thrombotic events were allocated to group 2, while other patients were randomly allocated to all the groups. The mean preoperative Hb of Group 1, 2 and 3 were 13.53gm%, 13.25gm% and 12.30gm% respectively. The lowest preoperative Hb of Groups 1, 2 and 3 were 11.27gm%, 9.6gm% and 10.57gm% respectively. The preoperative Hb was not significantly different between the three groups, however, the postoperative Hb was significantly lower in group 2 as compared to group 1 and group 3. The mean surgical time in groups 1, 2 and 3 were 65, 68 and 67 minutes respectively which was not significantly different. (Table 1)

Table 1: Basic data of Groups

	Group 1 Intravenous (n=18)	Group 2 Intraarticular (n=20)	Group 3 Combined (n=9)
Mean AGE	66.38	65.35	67.44
Gender [M/F]	11/7	8/12	5/4
Haemoglobin (gm%) (Mean)			
Preoperative	13.53	13.25	12.30
Lowest Post Operative	11.27	9.675	10.57
Mean surgical time in minutes	65 minutes	68 minutes	67 minutes

The primary outcome of the study was maximum haemoglobin loss. The mean±SD maximum haemoglobin loss in Group 1 is 2.272±0.507), group 2 is 2.690±0.595 and group 3 is 2.033±0.838. There was no significant difference between group 1 and group 3($p=0.36$) but there was significant difference between group 1 and group 2($p=0.026$), and group 2 and group 3($p=0.023$). The secondary outcomes were blood in drain and transfusion rates. The blood in drain. The mean±SD of blood in drain in group 1 is 7.88±1.28cc/hr, group 2 is 9.75±1.585cc/hr and group 3 is 7.77±2.108cc/hr. There was no significant difference between Group 1 and Group 3($p=0.886$) but, there was significant difference between group 1 and Group 2($p<0.001$), and group 2 and group 3($p=0.009$). The transfusion rate in group 1 was 11.1%,

group 2 was 30% and group 3 was 11.1%. There appears to be a necessity of more blood transfusion in group 2 as compared to group 1 and group 3, however statistically there was no significant difference in transfusion rates as tested by chi-square test for the 3 groups(p=0.226). There were no complications of DVT, thrombotic events and infection during the follow-up in any of the patients in all the groups. (Table. 2)

Table 2: Outcomes of the study

	Maximum Hb Loss	Blood in drain	Transfusion rate
Group 1(IV)	2.272±0.507	7.88±1.278	11.1%
Group 2(IA)	2.690±0.595	9.75±1.585	30%
P	0.026	<0.001	
Group 2(IA)	2.690±0.595	9.75 ± 1.584	30%
Group 3(IV+IA)	2.033±0.838	7.77±2.108	11.1%
P	0.023	0.009	
Group 1(IV)	2.272±0.507	7.88±1.278	11.1%
Group 3(IV+IA)	2.033±0.838	7.77±2.108	11.1%
P	0.36	0.886	

4. Discussion

Perioperative blood loss is a major concern to the operating surgeon especially during joint replacement surgeries due to cutting of the bone. There are various methods to reduce the perioperative blood loss. The options that are available, are preoperative blood donation, acute normovolemic hemodilution, perioperative red cell salvage, and certain anesthetic techniques (deliberate hypotension, normothermia). Certain pharmacological interventions that have been used with success are recombinant human erythropoietin, TA, and aprotinin [4, 6]. Blood loss due to surgery puts patients at risk due to cardiovascular complications. Allogenic blood transfusion given for blood loss post operatively carries the risk of immunological and non-immunological adverse effects, such as transfusion reactions and transmission of infectious agents (AIDS and hepatitis viruses) and adds to medical cost [1, 7, 8, 19-21]. Antifibrinolytics are a class of drugs that have been in use since the 1960s. TA is an analog of the amino acid lysine. It competitively inhibits plasminogen activation and plasmin binding to fibrin, thus inhibiting fibrin degradation. Since it works by reducing breakdown of fibrin once formed, it is not procoagulant per se, but rather supportive of coagulation already in progress [22-24]. This makes it potentially well-suited for use in reducing post-operative bleeding, where surgical hemostasis has been achieved and fibrinolytic activity needs to be suppressed to help maintain hemostasis without promoting venous thrombus formation [10, 25, 26].

There are various studies which show the efficacy and safety of TXA through IV route when given as a single dose at induction or even when a second or third dose is added postoperatively [27-29]. A randomized controlled trial by Levine *et al*., in a demonstrated that a standard dose of 1g IV was as efficient as weighted doses (20 mg/kg) [30]. There are studies which have shown further reduction of postoperative blood loss with additional doses of TXA postoperatively as compared to single dose of TXA at induction. A double iv dose of TXA when given preoperatively and intraoperatively showed further reduction in blood loss as compared to single dose of TXA in a study by Iwai *et al*. [31]. similarly, Maniar *et al*., also in a randomized controlled trial, added one more dose postoperatively to demonstrate that a three-dose regimen is more effective [32]. Most of the studies confirmed the efficacy of different doses of IV TXA in reducing transfusion rates and total blood loss [27, 33-38]. However, there are studies which have reported a potential increased risk of thrombotic events and some cases of allergic reaction [11]. For these reasons, the IA route of TXA administration was proposed. Different Authors have confirmed the efficacy of IA administration, albeit proposing different doses and different methods of topical administration (washing or through the drain) [24, 38-42], in particular, Georgiadis *et al*. randomized patients to two groups receiving either 2 g of TXA in 75 ml of saline or a placebo solution intraoperatively, the Authors demonstrated a significant reduction of total blood loss in the TXA group, without the potential complications related to IV administration [39]. Patel *et al*., in a study of 89 patients who underwent a primary TKA, demonstrated that IV administration of 10 mg/kg of IXA and IA administration of 2 g TXA were equally effective in reducing blood loss [17]. similarly, various recent studies have demonstrated the efficacy of IA TXA administration in reducing blood loss after TKA [24, 29, 40-47]. Furthermore, recent meta-analyses showed no difference between topical and IV TXA administration [44, 48-55], even though some Authors reported conflicting results [43, 46, 47, 56]. There are only few studies in the literature that have examined the association of an IV protocol with a local one in patients undergoing TKA. Jain *et al*. showed better results in terms of mean total blood loss, transfusion rate and haemoglobin drop, using a combined protocol compared to only IV administration [57]. similarly, Lin *et al*., in a study of 120 patients, demonstrated greater reductions in blood loss, haemoglobin drop, total drain amount and transfusion rate using a combined protocol compared to IA administration alone [28]. Karaaslan *et al*. evaluated the efficacy of an association of three different methods of TXA administration in bilateral TKA: A bolus dose of 15 mg/kg 10 min before the inflation of the tourniquet, followed by IA administration of 3g 10 min before the deflation of the tourniquet, associated with an IV infusion of 10 mg/kg/h for 3h following the surgery, the Authors concluded that this method of TXA administration was effective in reducing total blood loss in bilateral TKA [34]. Huang *et al*. compared the results of IV TXA administration (3 g) with those of a combined approach (1.5 g IA and 1.5 g IV). the Authors concluded that the two approaches were similarly effective in reducing transfusion rate and total blood loss, but the combined protocol gave better results in terms of maximum decline of haemoglobin, drainage volume, postoperative knee pain, knee swelling, length of hospital stays and short-term satisfaction [29]. Marra F in their study divided the patients into 3 groups IV, IA and combined groups and found that no differences in haemoglobin loss, amount of blood in the drain, and rate of transfusions between the combined protocol and topical administration alone. on the contrary, less haemoglobin loss was found in the

combined group compared with the IV only administration group (p=0.02). However, it must be emphasized that patients in the IV group had significantly higher preoperative haemoglobin values than those of the combined (IV + IA group), With regard to the secondary outcomes (blood in drain and transfusion rate), no differences were detected between the three groups. in conclusion, although the combined protocol was found to be superior to the IV protocol, both are comparable to the IA protocol in terms of efficacy.

no significant differences in maximum loss of haemoglobin were observed between the different treatment groups, with the exception of the finding of a greater value in the combined than in the IV one.

In view of the established efficacy of TXA in TKA irrespective of the method of administration, we conducted a study in 47 patients, divided into IV administration, IA administration, and a combination of the two. The aim of this study was to evaluate whether one method of administration was more effective than the others. The results of the study showed There was not much difference between the age and sex distribution between the three groups. However, the three groups were not homogenous in that all those patients with contraindications to systemic TXA and comorbidities towards thrombotic events were allocated to group 2, while other patients were randomly allocated to all the groups. The mean preoperative Hb the three groups were similar. The lowest preoperative Hb was lease in IA group. The preoperative Hb was not significantly different between the three groups, however, the postoperative Hb was significantly lower in group 2 as compared to group 1 and group 3. The mean surgical time was not significantly different in the three groups. The primary outcome of the study was maximum haemoglobin loss which showed that there was no significant difference between IV and combined group but there was significant difference between IV versus IA and IA versus combined groups with intraarticular group having more haemoglobin loss. The secondary outcomes were blood in drain and transfusion rates. The blood in drain. There was no significant difference with respect to blood in drain between IV and combined groups, but, there was significant difference between IV and IA ($p<0.001$), and IA and Combined group($p=0.009$) with IA groups having more blood in drain. The transfusion rate in group 1 was 11.1%, group 2 was 30% and group 3 was 11.1%. There appears to be a necessity of more blood transfusion in group 2 as compared to group 1 and group 3, however statistically there was no significant difference in transfusion rates as tested by chi-square test for the 3 groups($p=0.226$). There were no complications of DVT, thrombotic events and infection during the follow-up in any of the patients in all the groups. A further limitation is the absence of a control group. That said, the efficacy of TXA, whether administered topically or systemically, has previously been extensively described and is widely accepted. Though it appears that intravenous and combined TXA is better than intraarticular alone, but still it is better than not using TXA. Finally, the power of the study was certainly reduced by the small size of the sample. TXA in TKA is safe and efficient in reducing total blood loss, hemoglobin loss, blood in drain and transfusion rate. intravenous TXA administration is reported to be related to an increased thrombotic risk, but this assumption is not completely confirmed by the literature. instead, there is agreement regarding the comparable efficacy of IA TXA administration, which is not associated with a potential increased thrombotic risk. Intraarticular TXA can be used even in patients with contraindications to systemic TXA and reducing the blood loss.

5. Conclusion

TXA is a safe modality to reduce the perioperative blood loss in TKA administered either intravenous or intraarticular or combined methods. Though the intravenous and combined modes of administration shows better results in terms of maximum haemoglobin loss, blood in drain and postoperative transfusion, intraarticular TXA still can have a good role in patients with contraindications to TXA.

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