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Efficacy and Safety of Intravenous Tranexamic Acid in Control of Bleeding in Total Knee Replacement - A Randomised Clinical Trial

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Abstract
Background: *Major orthopedic procedures including total knee replacement, hip replacement, and spine surgeries are associated with severe bleeding because of extensive dissection through bony and fibrotic tissue, increased fibrinolysis due to tourniquet application, surgery and inability to cauterize bleeding bony surfaces. This study aims on the efficacy and safety of tranexamic acid which is an antifibrinolytic agent that decreases total blood loss in the prevention of bleeding in total knee replacement.*
Materials and Methods: *This Randomised Double Blind Controlled Clinical Trial was conducted after obtaining approval of Research methodology and institutional ethics committee and written informed consent from all patients. Adult patients of ASA I and II Class, of age 30-60yrs, satisfying the selection criteria, undergoing elective TKR surgery were selected and randomly allocated into two groups, Group 1 TU: Unilateral TKR patients received tranexamic acid 10 mg/kg intravenously before the tourniquet applications followed by 1 mg/kg/hour till the end of the surgery and Group 2, CU: Unilateral TKR patients not received tranexamic acid .Blood loss was measured in the post operative period after 4 hours and 24 hours.*
Results: *The two groups were comparable in terms of age, gender, preoperative Hb (gm/dl), PCV (%) and duration of surgery. A statistically significant reduction in blood loss by more than 65% was observed in patients who received tranexamic acid.*
Conclusion: *The observation of this study shows that tranexamic acid can significantly reduce perioperative blood loss without any side effects in patients undergoing total knee replacement.*
Keywords: *Total knee replacement, Tranexamic acid, Blood loss.*

INTRODUCTION

Total knee replacement is becoming a major orthopaedic procedure in the aging population, main indications being osteoarthritis and rheumatoid arthritis. Although general anesthesia can be safely provided for TKR, a prospective case control study found general anaesthesia and endotracheal intubation to be a major risk for non surgical complication after TKR[1]. Regional anaesthesia in the form of a neuraxial block can spinal or epidural or a combination of femoral and sciatic block can be provided for the surgery.

A pneumatic tourniquet is routinely inflated over the thigh during TKR to reduce intra operative blood loss and provide a ″blood less″ field for cement fixation of the femoral and tibial components. Tourniquet is usually inflated to a pressure 100 mm of Hg above the patients systolic

blood pressure for 1 to 3 hours. When the tourniquet is deflated, however, blood loss usually continues for the next 24 hours. After tourniquet release, mean arterial blood pressure decreases significantly, partly owing to the release of metabolites from the ischemic limb into the circulation and the decrease in peripheral vascular resistance. Bleeding can be hazardous as ultimately inadequate oxygen delivery can lead to multiple organ dysfunction and death. It can lead to increase in length of hospital stay, reoperations, prolonged operation time, necessitates transfusion to restore blood loss and increased cost. Transfusion of blood helps to restore circulatory volume and improves oxygen carrying capacity in the injured patients. However, transfusion have limitation and potentially negative consequences that should be considered[2] Inadequate hemostasis during surgery can lead to formation of hematoma post-operatively. Post-operative wound hematoma is the most important risk factor of wound infection after surgery; may require repeat operation for drainage and delay in wound healing. Management techniques include a wide range of interventions from improved surgical techniques, topical agents, improved anaesthetic techniques and conventional blood transfusion, the more advanced techniques of reducing blood loss like acute normo volumic hemodilution, intra-operative cell salvage and retransfusions. Antifibrinolytic agents too find a place in this armamentarium[2].Antifibrinolytic agents include synthetic lysine analogues like tranexamic acid and ε-amino caproic acid (EACA), which act by competitively inhibiting plasminogen. Tranexamic acid has little effect when it is given as a treatment after heavy blood loss. This lack of effect is probably because fibrinolytic activation is a cascade process that is most easily inhibited in its earlier phases. The early binding of plasmin receptors or platelets by tranexamic acid may also be important in reducing post-operative blood loss[3]

Tranexamic acid has been found to be 6-10 times more potent in vitro than EACA Tranexamic acid was discovered by OKAMOTO and OKAMOTO in 1962. They discovered the derivative of 4 amino methyl cyclohexane carboxylic acid which was later shown to consists of two isomers one of them being responsible for all the activity. OKAMOTO et al, (1964) identified it as the trans form of the molecule called as tranexamic acid [4,5]. Benoni et al,[8] conducted a randomized double-blind study of 86 patients to investigate the effect of tranexamic acid, on blood loss and blood transfusion in knee arthroplasty within 1hour and 4 hours postoperatively Tranexamic acid significantly reduced the number of patie-nts receiving blood transfusion and the number of blood units transfused to one-third in the treated group. Mean post-operative hemoglobin concentrations were significantly higher after prophylaxis. In this study our aim was to assess effect and safety of tranexamic acid in control of bleeding postoperatively after4 hours and 24 hours in patients undergoing unilateral TKR.

MATERIALS AND METHODS

After obtaining approval of Research method-logy and college ethics committee adult patients of ASA I and II Class of 30-60yrs age, satisfying the selection criteria, undergoing elective TKR surgery were selected. Patients were randomly allocated, into two groups as Group TU: Unilateral TKR patients received tranexamic acid and Group CU: Unilateral TKR patients not received tranexamic acid.

Exclusion Criteria were Patients with abnormal coagulation screening tests (platelet count, prothrombin time, activated partial thromboplastin time)history of drug allergy, patients with ingestion of aspirin or NSAIDS within seven days of surgery, renal or hepatic insufficiency, pregnant women**,** patients with ocular disease and ophthal-mological procedures other than corrective lensesand history of deep vein thrombosis or pulmonary embolism . Written informed consent obtained from all patients. All patients received oral ranitidine 150 mg, alprazolam 0.25mg and

metoclopramide 10 mg in the night and in morning of surgery as premedication.

After regional anaesthesia (combined spinal epidural anaesthesia) group TU patients were given Tranexamic acid immediately before inflation of the trouniquet. After a test dose of 1 ml, patients received a dose of 10mg per kg IV followed by an infusion of 1mg per kg per hour until skin closure. Patients were monitored postoperatively for 24 hours after the end of the surgery, blood loss was assessed in the drain 4 hours and 24 hours postoperatively Postoperative blood losses were assessed by measuring wound drainage until drains are removed (24hrs). During surgery and in postoperative period, measured blood losses were replaced with Ringer lactate in a 3:1 ratio or colloid 1:1 ratio. Factors known to influence intraoperative and postoperative blood losses were noted. These include tourniquet time, length of surgery, mean arterial blood pressure maintained during surgery and minimal core temperature achieved.

After surgery patients were shifted to post anaesthesia care unit for further management. Postoperative pain was managed with epidural infusion of 0.125% bupivacaine 4 - 6ml per hour. Hemoglobin, HR, BP, PCV and blood loss were measured in the postoperative period, after 4 hours and 24 hrs postoperatively. Drains were removed after 24 hours in the postoperative period.

All patients were monitored for side effects of tranexamic acid mainly nausea, vomiting, giddy-ness, hypotension and deep vein thrombosis.

The postoperative blood losses were assessed by measuring wound drainage until drains are removed (24 hours). Amount of Blood losses were measured in milli litres (ml) from the drains, 4 hours and 24 hours after the surgery.

Data were analyzed using computer software, Statistical Package for Social Sciences (SPSS) version 10. Data are expressed in its frequency and percentage as well as mean and standard deviation. To elucidate the associations and comparisons between different parameters, Chi square (χ^2) test was used as nonparametric test. Unpaired Student's t-test was used to compare mean values between two cases and controls. Paired 't' test analysis was employed to compare pre and post operative values of different parameters. For all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant.

RESULT

The two groups were comparable in terms of age, gender, preoperative Hb (gm/dl), PCV (%) and duration of surgery.{Table 1,2,3,4 fig 5,6}

The post operative blood loss, Hb and PCV were noted. The groups were comparable in the base line characteristics. The mean volume of drainage blood at 4 hrs and 24 hrs was 193.25 ml and 588 ml respectively in control groups whereas it was 97.75 ml and 286.2 ml respectively in patients who received tranexamic acid. P value <0.001 (table 5, fig7) This was considered statistically significant. None of the patients in any of the groups developed side effects of Tranexamic acid like nausea, vomiting, giddiness, hypotension and deep vein thrombosis. Tranexamic acid decreased total blood loss by more than 65%

Table 1. Age (years) distribution in two groups

Age (years)	Group	
	Cases	Control
30 - 39	3 7.50%	2 5.00%
40 - 49	7 17.50%	1 2.50%
50 - 59	25 75.00%	30 92.50%
Total	40	40

Chi square = 5.431; P > 0.05

The table shows the age distribution among the cases and control population.

No significant difference with respect to age.

Table 2. Sex distribution in two groups

Gender	Group	
	Cases	Control
Male	5	12
	12.50%	30.00%
Female	35	28
	87.50%	70.00%
Total	40	40

Chi square = 3.661; P > 0.05

The table shows the gender distribution among the cases and control.
No significant difference with respect to sex.

Table : 3 Comparison of pre and post operative Hb (gm/dl) between control and cases

Parameters	Group	Mean	± SD	t value	p value
Pre Operative Hb (gm/dl)	Cases	12.70	0.58	- 1.573	> 0.05
	Control	12.94	0.81		
Post Operative Hb (gm/dl)	Cases	12.69	0.59	0.869	> 0.05
	Control	12.57	0.68		

Comparison of pre and post operative Hb (gm/dl) between cases and control.
No significant difference between cases and control with respect to pre and post operative Hb (gm/dl)

Table:4 Comparison of pre and post operative PCV (%) between control and cases

Parameters	Group	Mean	± SD	t value	p value
Pre Operative PCV (%)	Cases	36.99	5.57	1.039	> 0.05
	Control	38.83	2.43		
Post Operative PCV (%)	Cases	37.94	1.78	- 1.913	> 0.05
	Control	37.52	1.81		

Comparison of pre and post operative PCV (%) between cases and control.
No significant difference between cases and control with respect to pre and post operative PCV (%)

Table 5. Comparison of post operative bleeding at 4 and 24 hrs. between control and cases

Parameters	Group	Mean	± SD	t value	p value
Post Operative Blood Drain @ 4 Hrs (ml)	Cases	97.75	98.72	- 10.857	< 0.001
	Control	286.20	48.02		
Post Operative Blood Drain @ 24 Hrs (ml)	Cases	193.25	20.18	- 39.871	< 0.001
	Control	588.00	59.28		

Comparison between cases and control with respect to post operative blood loss at 4 hrs. and 24 hrs.

FIG 5

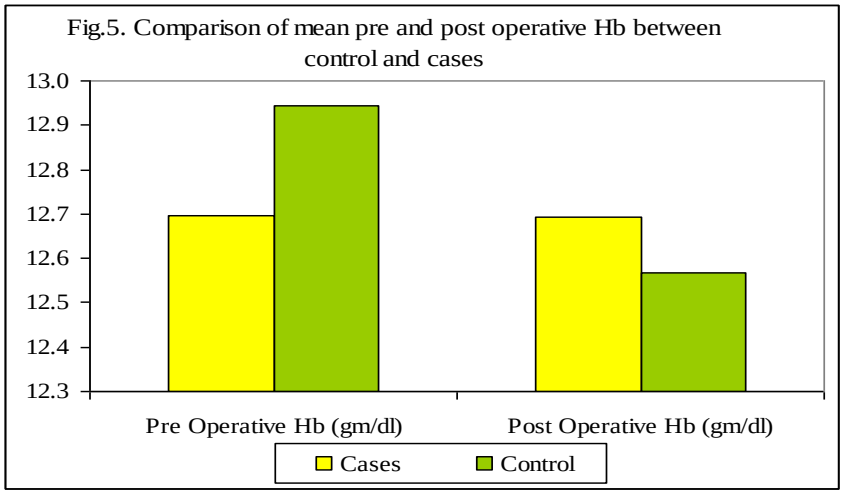


FIG 6

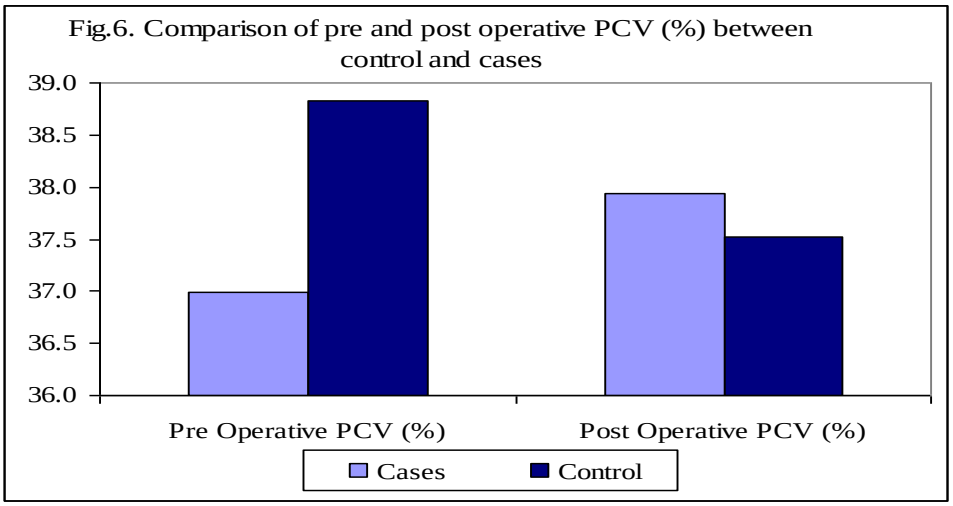
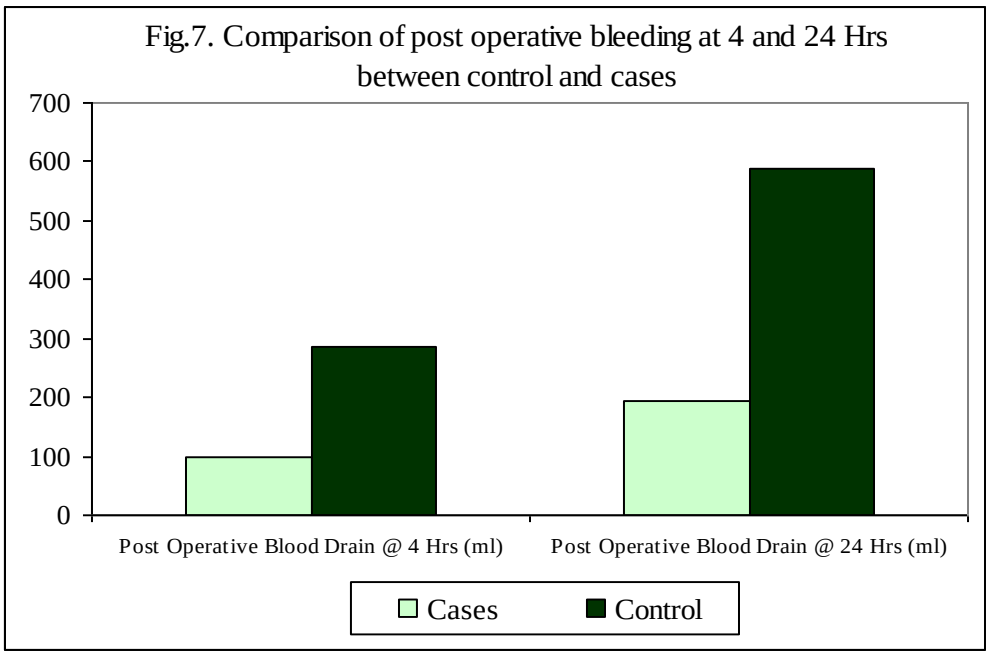


FIG 7



Graph shows decreased blood loss among cases compared to control both at 4 hrs. and 24 hrs.

DISCUSSION

In this study the effect of intraoperative tranexamic acid on blood loss after total knee replacement was assessed.

Tranexamic acid (trans-4–amino methyl cyclohexane carboxylic acid) is an antifibrinolytic agent which is seven to ten times as potent as epsilon aminocaproic acid (EACA)[11]. Tranexamic acid was discovered by OKAMOTO and OKAMOTO in 1962. They discovered the derivative of 4 amino methyl cyclohexane carboxylic acid which was later shown to consists of two isomers one of them being responsible for all the activity. OKAMOTO et al, (1964) identified it as the trans form of the molecule called as tranexamic acid [4,5]. The therapeutic effect of tranexamic acid is apparent when the haemostatic system has produced a fibrin clot which is prematurely dissolved by the proteolytic action of plasmin [8].

Previous research on tranexamic acid and thrombosis has failed to show any thrombogenic effect, even in patients who were treated for several days or even weeks [2,4,9] This may be due to the fact that fibrinolytic activity in vein walls is not affected by tranexamic acid [6,9].

As shown in numerous studies, the fibrinolytic response after trauma is biphasic with an increased activity during the first hours [9]. After knee replacement surgery the early post traumatic fibrinolysis is further augmented by that induced by the tourniquetThe dosage regimen adopted by us seems to be an adequate compromise between fibrinolytic inhibition and .the risk of inducing an augmented fibrinolytic response.[12,13]

Benoni et al,[10] evaluated whether fibrinolysis is associated with increased blood loss and whether fibrinolysis activation varies in the wound and peripheral circulation. Fibrinolysis in the wound is activated much more in the wound than in the peripheral venous blood. The higher activity in the wound is probably a consequence of blood coming into contact with potent activators of coagulation and fibrinolysis in wound tissue

.In our study the two groups were comparable in terms of age, gender, preoperative Hb (gm/dl), PCV (%) and duration of surgery. We had given tranexamic acid before inflation of tourniquet because fibrinolytic activation is a cascade pro-cess that is mostly inhibited in its earlier phases

The results were comparable to Cochrane review on fibrinolytic use for minimizing perioperative blood transfusion. It includes 21 trials of tranexamic acid vs control (Hip and knee replacement) and reviewed 993 patients in orthopaedic surgery. It showed that tranexamic acid, significantly reduced allogenic blood transfusion (56%) and total amount of blood lost during perioperative period (Average 440 ml) in orthopedic surgery.

In our study the total amount of blood loss during the perioperative period is average 286.2 ml in patients who received tranexamic acid.

Beoni et al showed 48% reduction in blood loss and 70% reduction in post operative blood transfusion with the use of tranexamic acid.

The total number of transfused units was 12 in the prophylactic group of 43 patients as against 40 in the placebo group of 43 ($p = 0.002$).

In our study there was a reduction in the blood loss by more than 65% in patients who received tranexamic acid. ($p = <0.001$). This reduction in blood loss was statistically significant.

P.N. Kakar, Nishkarsh Gupta [11], Pradeep Govil [12], Vikram Shah[4]done a randomized clinical trial in Bilateral total knee replacement and unilateral total knee replacement. Kakar et al shows that tranexamic acid decreased total blood loss by nearly 54% in Bilateral TKR and 40% in unilateral TKR and drastically reduced blood transfusion (> 80%).

None of the patients who received tranexamic acid had found any side effects like nausea, vomiting, giddiness, hypotension and deep vein thrombosis.

CONCLUSION

From this study it was observed that tranexamic acid in the dose of 10 mg/kg intravenously before the tourniquet applications

followed 1 mg/kg/hour till the end of the surgery can significantly reduce perioperative blood loss without any side effects in patients undergoing total knee replacement.

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