ORIGINAL RESEARCH PAPER

Orthopaedics

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STUDY THE EFFECT OF TRANEXAMIC ACID IN REDUCING POSTOPERATIVE BLOOD LOSS IN CEMENTLESS TOTAL HIP ARTHROPLASTY

Dr Sunil Kumar Rawat Assistant Professor Department Of Orthopaedics Sms Medical College & AGH, Jaipur

Dr Sanjeev Kansotiya* Assistant Professor, Department Of Orthopaedics, Mahatma Gandhi Medical College & AGH, Jaipur. *Corresponding Author

Dr Ashok Kumar Kuldeep Junior Specialist Department Of Orthopaedics District Hospital, Rajsamand, Rajasthan

ABSTRACT

Several techniques are available to minimize the likelihood of allogenic blood transfusion following the hip arthroplasty including intra-operative red cell salvage local anaesthesia, controlled hypotension and use of antifibrinolytics like tranexamic acid . The double blinded, placebo control hospital based interventional study was conducted on 60 patients by dividing them randomly in control and study group(TA), 30 patients in each group to study the effects of 1000 mg single dose of intravenous tranexamic acid in reducing postoperative blood loss in cementless total hip arthroplasty using American Society of Anaesthesiologists (ASA) grading system. We included in our study all patients less than 60 year of age except 2 patients. 30 patients were less than 40 year and 30 patients were greater than 40 years. The difference between the control group and the tranexamic acid group was significant (P value <.001) in all time intervals. In this study no significant difference was found in postoperative blood loss in age group <40 year and age group >40 years (P value >.05) in TA group.

1. INTRODUCTION

Several techniques are available to minimize the likelihood of allogenic blood transfusion following the hip arthroplasty. These techniques include autologous blood donation, Intra-operative red cell salvage local anaesthesia, controlled hypotension and use of antifibrinolytics (1-6).

Tranexamic acid and antifibrinolytic drugs are readily accessible substances promoting haemostasis and reduce bleeding and need for allogenic transfusion. Efficacy of these drugs has been investigated in Orthopaedics, cardiovascular, Hepatic and other surgeries (7).

Two of these drugs are aprotinin and tranexamic acid whose effects have been proved in various operations. Tranexamic acid (TXA) is a synthetic antifibrinolytic drug released in the 1970s. Although it is similar to the prototypical synthetic antifibrinolytic drug, Σ-amino-caproic acid (EACA), TXA is considered to have ten times the potency of EACA . The mechanism of action for synthetic antifibrinolytics is competitive blockade of the lysine-binding sites of plasminogen, plasmin, and tissue plasminogen activator. The reversible blockade impedes fibrinolysis and blood-clot degradation. Plasmin inhibition by TXA may also help prevent platelet degradation.

Relative to EACA, TXA has higher and more sustained antifibrinolytic activity in tissues, but both have a similar toxicity profile. Although TXA would appear to be the synthetic antifibrinolytic drug of choice, both drugs may be beneficial in states where there is an excess of fibrinolysis relative to the coagulation cascade.[8]

Tranexamic acid is inexpensive and carries a far less risk of anaphylaxis compared with aprotinin.

Elimination half life of intravenous TA is 2 hours, and volume of distribution is of 9 to 12 litres and main route of excretion is urinary (9).

TA has little effect when administered at the end of surgery and 3 hours later; reduction in blood loss after THA was not significant (10,11).

Significant reduction in postoperative (but not intra-operative) blood loss was associated with a single bolus of TA (10mg/kg) administered immediately before the operation(12).

The use of TA is not associated with increased thrombo em bolic events, because the effects of TA are more pronounced in operative wound than in peripheral venous blood. This is because generation of TPA ensues in wounds. Thus, TA acts as a clot stabilizer and not a clot promoter. (9,12,13)

The half life of TXA is approximately 80 min, provided there is normal renal function. Bolus and infusion dosing again vary, but pharmacokinetic evidence would suggest the use of 10–15 mg/kg loading dose, followed by an infusion dose of 1 mg/kg/hr or repeated bolus dosing [14]. Dosage adjustments are recommended in patients with renal insufficiency.

Nonsurgical uses of TXA include the management of bleeding associated with leukaemia, ocular bleeding, recurrent haemoptysis, menorrhagia, hereditary angioneurotic angio-oedema and numerous other medical problems.

The prophylactic administration of TXA reduces both blood transfusion requirements and the financial cost of cardiac surgery [15,16].

The use of TXA does not increase the risk of thromboembolic complications such as deep-vein thrombosis, pulmonary embolism, thrombotic cerebral vascular accident, or myocardial infarction [17,18].

A meta-analysis of studies using TXA for total knee arthro plasty supports the premise that it reduces total blood loss and reduces both the proportion of patients requiring allogenic blood transfusion and the total number of units of allogeneic blood transfused [19].

2. MATERIAL AND METHODS:

The double blinded, placebo control hospital based interventional study was conducted in the Orthopaedics emergency & outpatient department of SMS hospital, Jaipur during December 2011 to December 2013. The present study

was approved by the local hospital Ethics Committee. Informed consent was obtained from each patient. Sixty patients undergoing cementless THA were investigated in this study with inclusion criteria of 50±20 years of age with Body mass index (18.5 to 24.9-SI Unit) using American society of Anaesthesiologists (ASA) grading system. Patients with history of Severe Ischemic diseases, pulmonary embolism, deep vein thrombosis, hepatic/renal failure, allergy to tranexamic acid, bleeding disorders, patients receiving anticoagulant therapy were excluded from our study.

2.1 ASA GRADING-

American Society of Anaesthesiologists (ASA) grade is the most commonly used grading system [20]; accurately predicts morbidity and mortality.

In control group, 24 patients were in ASA grade 1 and 6 patients were in ASA grade 2. In tranexamic acid group, 21 patients were in ASA grade 1 and 9 patients were in ASA grade 2

ASA Grade	DEFINITION	MORTALITY %
I	Healthy individual with no systemic disease	0.05
II	Mild systemic disease not limiting activity	0.4
III	Severe systemic disease that limits activity but is not incapacitating	4.5
IV	Incapacitating systemic disease which is constantly life-threatening	25
V	Moribund, not expected to survive 24 with or without surgery	50

2.2 SURGICAL TECHNIQUE

After doing clinical examinations and all necessary laboratory work up surgeries were performed by postero lateral approach to hip joint with patient in lateral position. The prostheses used were an uncemented acetabular cup and a femoral stem. Lumbar anesthesia with isobaric bupivacaine hydrochloride (10–15 mg) was given to all patients.

2.2.1 Intra-operative management-

a) Tranexamic acid group(Study group)- At the time of arthroplasty, 1000 mg of tranexamic acid was admin istered intravenously five minutes before the skin incision.
b) Control group- At the time of arthroplasty in a patient, instead of tranexamic acid, normal saline was admi ni stered.

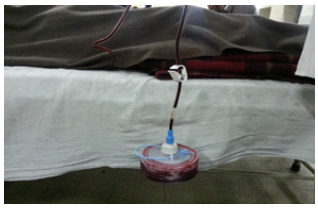
2.2.2 Post-operative management-

For deep vein thrombosis, the patients were assessed clinically for calf swelling, tenderness and oedema of the leg. When clinically indicated, duplex ultrasonography was performed and low molecular-weight heparin prescribed.

2.2.3 ASSESSMENT OF POSTOPERATIVE BLOOD LOSS--

Postoperative blood loss was measured by low vacuum suction drain (romovac drain; fig. a-c) at two hours intervals for the first twelve hours, at twenty-four hour postoperatively, and at the time of removal of drains. Time related changes in postoperative blood loss was measured every two hours for twelve hours and then again at twenty-four hours to determine the periods during which tranexamic acid had an effect and at the time of removal (48 hr). These patients were subsequently followed up for a period of 15 days.

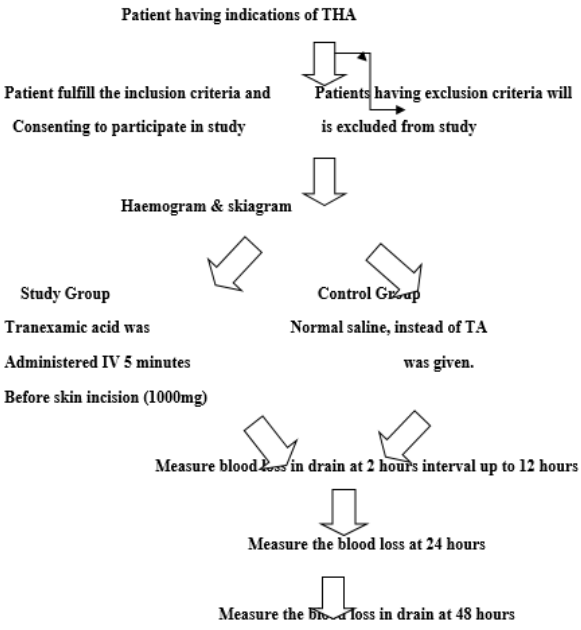
a.



b.

Fig.a-c: Postoperative blood loss in Romavac suction drain.

FLOW CHART



3. RESULTS

The mean age was 41.03 ± 8.79 years in control group and 44.33 ± 9.39 years in study group. Overall there were 30 cases were <40 year age and 30 cases were >40 year age in both groups. The male to female ratio in control group was 1:1 and in tranexamic acid group was 2:1.

In this study the data are presented as the mean and the standard deviation. The difference between the control group and the tranexamic acid group was significant (P value <.001) in all time interval as depicted in table1.

Table No.1: Mean ± SD of blood loss (in ml) according to Time interval (in hrs) of control & Tranexamic acid group

Time Interval (In hrs)	Blood loss in ml Mean + SD		P-value	Significance
	Control	TA group		

0-2	302.13 + 26.16	70.27 + 13.47	< .001	HS
0-4	465.23 + 42.40	120.63 + 16.56	< .001	HS
0-6	563.40 + 45.93	158.47 + 21.05	< .001	HS
0-8	629.70 + 52..31	185.70 + 23.53	< .001	HS
0-10	677.60 + 54.83	205.63 + 25.65	< .001	HS
0-12	712.07 + 54.15	220.57 + 26.66	< .001	HS
0-24	733.43 + 56.22	231.57 + 26.37	< .001	HS
0-48	744.67 + 57.17	239.77 + 28.33	< .001	HS

In this study no significant difference was found in postoperative blood loss in age group <40 year and age group >40 years (P value >.05) in control group as depicted in table 2.

Table No.2: Mean + Sd of blood loss (in ml) according to Time interval (in hrs) & age of control group

Time interval (in hrs)	Mean + Sd		P-value	Significance
	< 40 yrs (n=18)	> 40 yrs (n=12)		
0-2	307.17 + 26.81	294.58 + 23.18	> .05	NS
0-4	475.17 + 42.32	450.33 + 37.92	> .05	NS
0-6	573.78 + 45.00	547.83 + 42.80	> .05	NS
0-8	639.50 + 45.00	615.00 + 51.36	> .05	NS
0-10	685.90 + 52.86	665.20 + 55.38	> .05	NS
0-12	719.00 + 52.64	701.67 + 54.70	> .05	NS
0-24	739.72 + 52.87	724..00 + 59.67	> .05	NS
0-48	750.83 + 57.81	735.42 + 62.02	> .05	NS

In this study no significant difference was found in postoperative blood loss in age group <40 year and age group >40 years (P value >.05) in TA group as described in table 3.

Table No.3: Mean + SD of blood loss (in ml) according to Time interval (in hrs) & age of TA group

Time interval (hours)	Blood loss (ml) Mean + Sd		P-value	Significance
	< 40 yrs (n=12)	> 40 yrs (n=18)		
0-2	73.33 + 17.33	68.22 + 9.57	> .05	NS
0-4	124.58 + 20.60	118.00 + 12.53	> .05	NS
0-6	163.92 + 25.58	154.83 + 16.42	> .05	NS
0-8	191.58 + 29.56	181.78 + 17.38	> .05	NS
0-10	212.00 + 32.10	201.39 + 19.09	> .05	NS
0-12	227.00 + 33.22	216.30 + 20.08	> .05	NS
0-24	237.50 + 33.83	227.60 + 18.89	> .05	NS
0-48	247.75 + 37.31	234.40 + 18.42	> .05	NS

4. DISCUSSION

In an attempt to reduce bleeding and the need for allogenic blood transfusion, antifibrinolytic drugs such as tranexamic acid have been administered in association with a variety of surgical procedures.

Several studies have investigated the effect of tranexamic acid on intraoperative and postoperative blood loss in patients undergoing total hip arthroplasty with cement, but the efficacy of such treatment has not yet been clearly established. Postoperative blood loss tends to be higher in association without cement than it is in association with total hip arthroplasty with cement.

Several studies on peri- and postoperative bleeding using tranexamic acid have focused on cemented THA so far. Regarding cemented THA, the femoral canal and possibly the acetabular bony beds are closed off by cement, and the pressurization of cement has a ceasing effect on blood loss from intramedullary circulation. Therefore, postoperative bleeding tends to be higher in the cementless THA than in the cemented THA due to spontaneous bleeding from intrame dullary circulation.

According to Benoni G and Fredin H et al (11), significant reduction in postoperative (but not intra-operative) blood loss was associated with a single bolus of TA (10mg/kg) administered immediately before the operation and according to Yamasaki et al in uncemented THA patients, a bolus dose of TA 1000mg 5 minutes before the operation was associated with reduced postoperative (but not intraope rative) blood loss.

In our study, 60 patients were included only for cementless THA and a single bolus dose of TA 1000 mg 5 minutes before operation in postero-lateral approaches with the patient in lateral position and spinal anaesthesia with bupivacaine hydrochloride (10-15mg) was given to all patients and cementless hip endoprosthesis system was used for all arthroplasties. In all surgeries, average 90-120 minutes was taken for operation. And only postoperative blood loss was measured in our study.

We included all kind of pathologies of hip joint those have indication for cementless THA. 30 patients were having avascular necrosis of hip and 14 patients were having osteoarthritis of hip and 10 patients were of post-traumatic hip, 2 patients were of tubercular arthritis of hip, 3 patients were having bony ankylosis of hip and 1 patient was of perthe's disease.

With respect to the timing of administration of tranexamic acid, Benoni et al. initially administered it at the end of the operation and again 3 h later, and could not demonstrate significant reduction of peri- and postoperative blood loss. On the contrary, Ekb ck G et al. (21) reported that tranexamic acid initially given just before surgical incision and again 3 h later significantly reduced peroperative and postoperative drainage blood loss in cemented THA. Nakao et al. (22) reported that the concentration of plasminogen activator was increased by surgical intervention, especially between 30 min and 1 h after the start of operation. Similarly, plasminogen activator was reported to increase in this type of operation.

In view of this, it can be considered that tranexamic acid given

just before surgical incision could suppress the elevation of plasminogen activator, leading to the reduction of postoperative blood loss in cementless THA, as well as cemented THA. In addition, time related changes of blood loss in the first 4 h after the operation were significantly less in the tranexamic acid group than in the control group in the present study, which could be explained by the pharmacological action of the agent as described above. Accordingly, the second administration of tranexamic acid may have an additive effect on postoperative blood loss 3 h after the first administration. But in our study only single dose of tranexamic acid 1000 mg intravenous was given.

There is a concern that tranexamic acid may promote a hypercoagulable state, and several thromboses have been reported. Christie et al. showed that cardiopulmonary embolism occurs during cement injection of the femoral component in THA. However, some investigators have reported that tranexamic acid activates fibrinolysis but does not affect coagulation. Administration of tranexamic acid was not found to elicit DVT. Ekb ck G et al.(21) described that tranexamic acid reduced fibrinolysis by a decreased D-dimer and increased plasmin-antiplasmin complex . In the study, apparent symptomatic DVT was not found in any case of the tranexamic acid group.

The estimate of blood lost measurement of the volume lost in the drains do not account for the total amount of blood lost from the circulation (Flordal 1997). Some blood is extravasated as postoperative hematomas, which are difficult to detect and measure. Theoretical methods to estimate this hidden blood loss have been suggested (Lisander et al. 1996, Flordal 1997), but ultrasound is the method that most accurately measures the size of posttraumatic hematomas (Thorssonet al. 1993). But in our study we use subfascial drain for measurement of post operative blood loss.

In our study the number of clinical wound complications, such as discharge from the wounds or drain sites, infections or visible hematomas, did not differ between the groups.

According to our calculations, based on costs for the drug and for banked blood only, the use of tranexamic acid would save on expenditure. To our knowledge, with the possible exception of preoperative hemodilution and hypotensive anesthesia, this is the only blood saving method that would prove positive in similar calculations. The cost saving may be even greater if other aspects of blood transfusions, such as acute transfusion reactions, transmission of infections and effects on the immune system are considered. The risks for the patients, e.g. those associated with undetected hypovolemia and anemia, must be less and may (in some patients) result in a shorter hospital stay. We believe that the use of TA may be the easiest and cheapest method of reducing blood loss after THA.

The approach may not be sufficient to keep all patients transfusion-free, but it seems effective in reducing the number of patients receiving blood, as well as the total number of blood units used. We conclude that the use of a single-dose of tranexamic acid preoperatively is a simple, safe and cost-effective method for reducing blood loss and transfusions after THR. We recommend it for use in routine THR.

5. CONCLUSION

A single dose of intravenous tranexamic acid 1000mg given 5 minutes prior to cementless total hip arthroplasty done by postero-lateral approaches of hip is cost-effective and safe means of minimizing postoperative blood loss as well as the need for allogenic blood transfusion without increasing the risk of thromboembolic events with the greatest reduction in blood loss occurring during first four postoperative hours.

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