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ORIGINAL ARTICLE

DOES TRANEXEMIC ACID REDUCE BLOOD TRANSFUSION REQUIREMENTS PERIOPERATIVELY IN PATIENTS UNDERGOING SPINE STABILIZATION SURGERIES? A PROSPECTIVE RANDOMIZED DOUBLE BLINDED CONTROLLED STUDY

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ABSTRACT: BACKGROUND: Spine surgeries may involve uncontrolled bleeding, resulting primarily from large vein and persists even after the wound is closed. Proper patient positioning, use of hypotensive anaesthesia regimen and normothermia reduces blood loss, additional measures to reduce bleeding & transfusion requirement must be considered in spine surgery. **MATERIALS AND METHODS:** Forty patients of both sexes between the age group 21 to 60 years belonging to ASA I to III who were scheduled for spine stabilization surgeries was enrolled for the study were randomized into two groups with 20 in each. Anaesthetic technique was standardized. Group T received Tranexamic acid bolus of 10 mg/kg i.v. over 15 min. after patient positioning followed maintenance infusion of 1mg/kg/hr. And Group N Equivalent volume of Normal saline. Intra-operative blood losses was measured by weighing sponges, measuring suction drainage and estimates of blood loss on the surgical drapes and gowns by the attending anesthesiologist. Post-operative blood losses were assessed by measuring wound drainage until drains withdrawal. Investigations like Hb, Platelet, PT and APTT were done pre and post-operatively. Patients were assessed postoperatively daily for any clinical evidence of deep venous thrombosis. **RESULTS:** Pre-operative haemoglobin in group T and N were 13.56±1.171 and 12.98±1.488 gm% respectively. Post-operative haemoglobin in group T and N were 11.97±1.351 and 11.07±1.044 gm% respectively. There was a statistically significant drop in haemoglobin in control group post operatively. (p=0.024)Mean intra-operative blood loss in group T was 1042.65 ± 147.535 ml and in group N 1149.25 ± 157.85 ml. Control group had higher intra-operative blood loss compared to Tranexamic acid group, which was statistically significant. (p=0.033).There was no difference in mean drop in haemoglobin, mean number of units of blood transfusion among study groups. **CONCLUSION:** Tranexamic acid in bolusdosage of 10 mg/kg i.v. over 15 min. after patient positioning followed maintenance infusion of 1mg/kg/hr significantly decreases intra-operative blood loss, thereby decreasing the requirement of intraoperative blood transfusion. However it does not have any major impact on post-operative blood loss. No thrombotic complications or other adverse events were noted in this study.

KEYWORDS: Spine surgery, Blood loss, Tranexamic acid, Blood transfusion.

INTRODUCTION: Spine surgeries may involve uncontrolled bleed. This might be related to incorrect positioning of the patient. Pressure on the abdominal contents would be transmitted to the inferior vena cava and then to the epidural venous system causing increased bleeding. Any pressure on the anterior abdominal wall causes vertebral venous pressure to increase.[1] Bleeding in spine surgeries has some specificities.

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It results primarily from large vein bleeding & persists after the wound is closed. Therefore additional measures to reduce bleeding & transfusion requirement must be considered in spine surgery.[2]

Position of the patient during surgery and the provision of a hypotensive anaesthetic regimen were once considered the most important contributions of the anesthetist to decreasing blood loss.[3] Intra-operative blood loss varies according to the anaesthetic agent used[4] and with the type of anesthesia.[5,6] Simple elevation of the surgical site may reduce blood loss but may risk embolism in regions with non-collapsing veins.[7] Maintaining normothermia reduces blood loss, because of the deleterious effects of hypothermia on platelet function.[8] Blood coagulation can also be compromised by fluid replacement & profound haemodilution. Moderate crystalloid substitution accelerates rather than inhibits blood coagulation; however with advanced crystalloid haemodilution blood coagulation may become compromised.[9]

The use of colloids may also compromise coagulation, hydroxyethyl starch more than gelatin and serum albumin.[10] A combination of generous amounts of crystalloids with some colloids may be optimal to maintain blood coagulation and avoid blood loss as resulting from coagulopathy.[11] Now, several pharmacological haemostatic agents are being used by anaesthetists as blood saving agents.

Tranexamic acid, a synthetic antifibrinolytic agent binds to the lysine binding site of plasminogen and blocks the binding of plasminogen to the fibrin surface.[12] Thus plasminogen activation is prevented and fibrinogen is delayed. Tranexamic acid reduces intra-operative bleeding & transfusion requirements in cardiac surgeries,[13] Total knee replacement surgeries,[14,15] scoliosis surgeries.[16,17]

MATERIALS AND METHODS: This study was conducted at a tertiary level hospital at Bangalore, between May 2006 to May 2007. Forty patients of both sexes between the age group 21 to 60 years belonging to ASA I to III who were scheduled for spine stabilization surgeries was enrolled for the study. Approval of institutional ethical committee was taken. A written, informed consent was obtained from all patients.

Patients with history of a bleeding disorder, abnormal coagulation screening tests (Platelet count, prothrombin time, activated partial thromboplastin time), known or suspected allergy to medications used (Tranexamic acid, Midazolam, Fentanyl), BMI > 30kg/m2, history of deep vein thrombosis (DVT) or pulmonary embolism, renal or hepatic insufficiency were excluded from the study.

RANDOMIZATION: Based on a computer generated random number table using Microsoft Excel, all the patients were randomized into 2 groups, with 20 patients in each group. Group T received Tranexamic acid bolus of 10mg/kg i.v. over 15 min. after patient positioning. A maintenance infusion of 1mg/kg/hr. And Group N Equivalent volume of Normal saline.

Patients were assessed and evaluated as per the routine preoperative protocol. All the patients were kept nil by mouth 6 hours before the surgery. Patients were taken in operating room. Monitoring included ECG, pulse oxymetry, noninvasive blood pressure, ET CO2 and temperature.

All patients had general anesthesia with standard premedication with Glycopyrolate 0.005mg/kg, Midazolam 0.04mg/kg and Fentanyl 1-2mg/kg. Induction with Thiopentone 3-5mg/kg and Vecuronium 0.1mg/kg. Anesthesia maintained with 66% N2O in O2, muscle relaxant & Isoflurane. Minute ventilation titrated to maintain normocarbia.

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Anaesthetist who gives study drug was blinded, using a infusion pump, patients of group T received Tranexamic acid 10 mg/kg i.v bolus over 15min. after induction of anaesthesia and before skin incision followed by maintenance infusion of 1mg/kg/hr continued until skin closure. Patient of group N received equalent volume of Normal saline as bolus infusion followed by maintenance.

Before the surgery, a Hb transfusion trigger point was determined for each patient according to the following criteria, for men over 60 years, women over 65 years and patients with a history of atherosclerotic disease, Left ventricular dysfunction (Ejection Fraction<35%), severe pulmonary obstructive disease (Forced Expiratory Volume1 <1.5L/min), the transfusion trigger was 11gm/dl. For all other patients the transfusion trigger was 10gm/dl. But they could be reclassified to the higher trigger by the attending physician or anesthesiologist if they had signs of hemodynamic instability. Patient received a unit of blood if the attending anesthesiologist or surgeon deemed it clinically unsafe to withhold transfusion.

During surgery, measured blood losses was replaced with crystalloid in 3:1 ratio and / or with hestarch 6% in 1:1 ratio, until Hb concentration fell below the transfusion trigger point. Thereafter patients received whole blood transfusion. Intra-operative blood losses was measured by weighing sponges, measuring suction drainage and estimates of blood loss on the surgical drapes and gowns by the attending anesthesiologist. Post-operative blood losses were assessed by measuring wound drainage until drains withdrawal. Investigations like Hb, Platelet, PT and APTT were done pre and post-operatively. Patients were assessed postoperatively daily for any clinical evidence of deep venous thrombosis

STATISTICAL ANALYSIS: Continuous data were expressed as mean ± SD. Categorical data were expressed as number (%). Analysis of variance (ANOVA) was used to compare study parameters among the three groups. Post-hoc Tukey test was used to find pair wise significance. Chi-square/ Fisher Exact test was used to compare categorical data among the three groups. $P < 0.05$ was considered statistically significant.

RESULTS:

Demography		**Group T (n=20)**	**Group N (n=20)**	**p-Value**
Age (yrs)		35.6±12.39	38.65±11.97	0.4337
Sex	Male: Female (%)	12:8 (60:40)	12:8 (60:40)	0.4123
BMI		24.47±1.45	24.09±1.52	0.4243
ASA Grades	ASA I: ASA II (%)	15:4(75:25)	14:6(70:30)	0.7232
Duration of surgery		3.65 ± 0.63	3.925±0.67	0.0953

Table 1: Demographics

We enrolled 40 patients with 20 in group T who received Tranexamic acid and 20 patients in group N who received Normal saline. Patients were demographically well matched with respect to age, sex, BMI, ASA grade and duration of surgery. (Table-1)

Pre-operative haemoglobin in group T and N were 13.56±1.171 gm% 12.98±1.488 gm% respectively. Post-operative haemoglobin in group T and N were 11.97±1.351 gm% and 11.07±1.044 gm% respectively. There was a statistically significant drop in haemoglobin in control group post

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operatively. (p=0.024)There was no change in mean platelet count, mean prothrombin time post-operatively in both study groups. However there was of statistically significant increase (p=0.0098) in APTT post-operatively in control group with no clinical implications. (Table-2)

	PRE OPERATIVE		p-Value	POST OPERATIVE		p-Value
Groups	**Group T**	**Group N**		**Group T**	**Group N**	
Hb (Gm%±SD)	13.56±1.171	12.98±1.488	0.178	11.97±1.351	11.07±1.044	0.024
Mean Platelet count in x 106/cc3	2.43±0.554	2.40 ±0.432	0.872	2.00±0.432	1.9±0.405	0.569
Mean PT in seconds (Control = 13 secs)	13.6±0.502	13.75±0.638	0.414	13.7±0.571	13.75±0.550	0.779
Mean APTT in seconds (Control = 28 secs)	29.9±1.372	29.75±1.118	0.706	29.45±1.571	30.65±1.182	0.0098

Table 2: Showing changes in laboratory parameters in study groups. T- Tranexamic acid, N-Normal saline, PT-Prothrombin time, APTT-Activate partial thromboplastin time

Mean intra-operative blood loss in group T was 1042.65 ± 147.535 ml and in group N 1149.25 ± 157.85 ml. Control group had higher intra-operative blood loss compared to Tranexamic acid group. This difference was statistically significant. (p=0.033). While post-operative blood loss in group T and N was 1.59 ± 0.55998 and1.91 ± 0.88965 ml, which was not significant statistically.(p=0.181). There was no difference in mean drop in haemoglobin, mean number of units of blood transfusion among study groups. (Table-3, Fig-1)

Groups	Group T(n=20)	Group N (n=20)	P value
Intra-operative blood loss			
Mean blood loss in ml ± SD	1042.65 ± 147.535	1149.25 ± 157.85	0.033
Post-operative blood loss			
Mean blood loss in ml ± SD	318.75 ± 93.4975	354.25 ± 116.43	0.294
Post-operative Drop in Hemoglobin			
Mean drop in Haemoglobin in gm/dl ±SD	1.59 ± 0.55998	1.91 ± 0.88965	0.181
Intra-operative blood transfusion			
Mean number of units of blood transfusion ±SD	1.0 ± 0.64889	1.3 ± 0.57124	0.128

Table 3: Showing changes in bloodloss, drop in Haemoglobin, blood transfusion in different settings among study groups. T- Tranexamic acid, N-Normal saline

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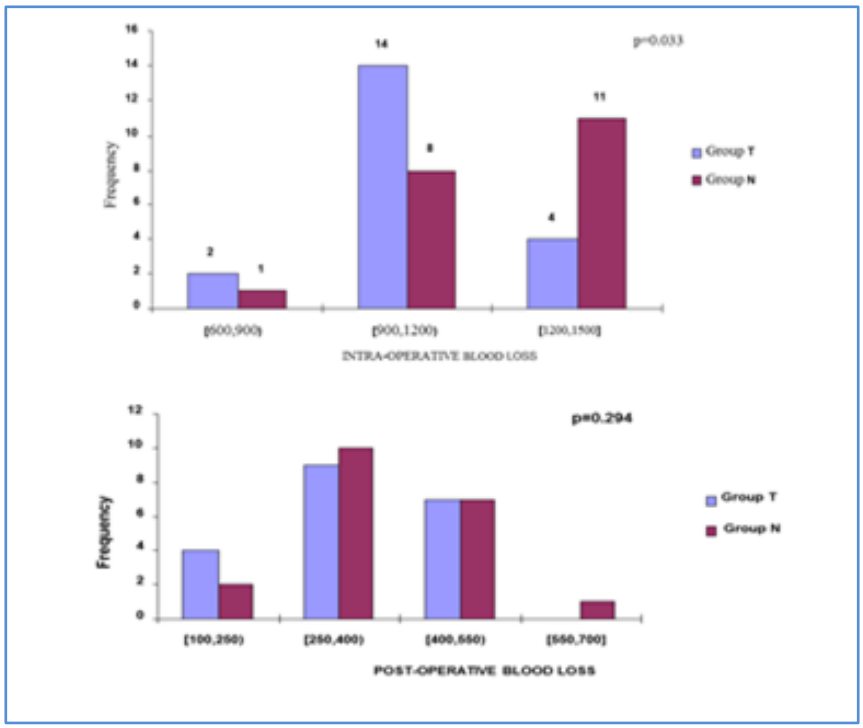

Fig. 1: Graph showing intra-operative and post-operative blood loss

DISCUSSION: Spine surgeries carry the risk of significant blood loss, which often complicates the surgical approach and increase the transfusion requirements.[18] The bleeding is primarily from direct internal vertebral venous plexus which cover the spinal canal floor,[19] and persists after the wound is closed.[18] The most important factor influencing the intra operative bleeding in spine surgeries is the incorrect positioning of the patient.[1] Pressure on the abdominal contents would be transmitted to the inferior vena cava, and then, to the epidural venous system, thus causing increased bleeding.[20]

Maintaining normothermia reduces blood loss. Hypothermia has deleterious effects on platelet function.[8] A combination of generous amounts of crystalloids with some colloids may be optimal to maintain blood coagulation and avoid blood loss as resulting from coagulopathy. Controlled hypotension has been used to decrease surgical blood loss.[11]

Some surgical procedures are associated with excessive blood loss and/or deranged haemostasis in patients without pre-existing haemostatic abnormalities (Cardiopulmonary bypass, liver transplantation, prostatic surgery and some orthopedic procedures).

Several pharmacological haemostatic agents are currently being used as blood-saving agents in such conditions.[4]

There are also many studies done with using other pharmacological agents.

Sagripanti et al[21] reported that Desmopressin acetate, 1-desamino-8-D-argenine vasopressin (DDAVP), a synthetic vasopressin analogue in patients with prolonged bleeding time secondary to antiplatelet drugs (aspirin) may also benefit from the effect of the drug as it promptly normalizes primary haemostasis and shortens the bleeding time in most of these patients.

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Antonia Dalman et al[22] compared efficiency of Tranexamic acid and ε- Aminocaproic acid in patients undergoing liver transplantation and concluded that Tranexamic acid reduces red cell transfusion better than ε-Aminocaproic acid.

David et al[17] conducted a randomized trial of Tranexamic acid to reduce blood transfusion for scoliosis surgery in 40 patients. 22 of them received Tranexamic acid and 18 were in control group. The results review that the Tranexamic acid reduces the peri-operative transfusion requirements.

Ek back et al[23] studied the efficacy of Tranexamic acid in 40 patients undergoing total hip replacement. 20 of them were injected with tranexamic acid prophylactically i,e pre incisional of 10mg/kg i.v. and infusion of 1mg/kg till end of the surgery, other 20 in the control group. He reported that the Tranexamic acid decreased the peri-operative bleeding, probably by reducing induced fibrinolysis.

In our randomized prospective study, 40 patients were enrolled. 20 in the study group received Tranexamic acid and other 20 in the control group received equivalent volume of isotonic saline. The Tranexamic acid was given a bolus of 10mg/kg i.v. over 15 min. after induction of anesthesia and before skin closure.

Horrow et al[24] and Briget et al[25] independently demonstrated that, the therapeutic plasma concentration of Tranexamic acid (5-10mg/l) can be achieved with a bolus of 10mg/kg i.v. followed by an infusion of 1mg /kg/hr.

Our findings are in line with previous studies conducted under similar surgical conditions demonstrating a significant reduction in intra-operative blood loss. And also less post-operative blood loss with a subsequent decrease in transfusion requirement with Tranexamic acid.[26,27,28] Benoni et al[29] and Ekback et al[23] independently reported a reduction in intra-operative blood loss when Tranexamic acid was given prophylactically i.e., pre incisional of dose of 10mg/kg and maintenance dose of 1mg/kg i.v. till end of the surgery.

We controlled some factors shown to influence blood loss and transfusion requirements in posterior spine stabilization surgeries like operating time, BMI, duration of postoperative suction drainage.[30,31] Attention was focused to adequately protect pressure points to minimize central venous pressure.[32] Any fluid added in the operative field for surgical need was carefully quantified. Pre and post-operative hematocrit levels did not differ significantly between control and case groups, which suggest a similar trigger for transfusion in each group.

In study group there was a significant decrease in peri-operative blood loss. The statistical significance is shown by p-value of 0.033. The mean blood loss in case group was 1042 ml compared to that of control group of 1149 ml.

This significant in blood loss is because of the antifibrinoylitic characteristic of Tranexamic acid. It blocks the lysine binding site on plasminogen, which is essential for binding to fibrin, and there by fibrin. This binding to plasminogen prevents the breakdown of fibrin.[3]

There was no significant post-operative blood loss in the case group (318 ml) and the control group (354 ml). Because of the half-life of tranexamic acid is 80 to 120 min.[25]

No patients in our study experienced any complication from the use of tranexamic acid. Except in one case where hypotension was noted after injecting slow bolus dose of tranexamic acid. This event can also be attributed to the other reasons like prone position and increased intra-abdominal pressure.[1]

No investigations beyond physical examination and history taking were done to rule out other complications. The primary concern when administering an antifibrinolytic drug is the potential

increased incidence of thromboembolic events. The use of tranexamic acid in patients undergoing total knee arthroplasty did not increase the incidence of deep venous thrombosis.[17,28,33]

A common misconception is that synthetic antifibrinolytic drugs increases blood clotting. David et al[17] showed that the drug do not alter blood clotting, but rather slow dissolution of blood clots. Benoni et al.[29] Reported that Tranexamic acid is not associated with thromboembolic events because the effects of tranexamic acid is more pronounced in operative wounds than in the peripheral venous blood.

CONCLUSION: Tranexamic acid in bolus dosage of 10 mg/kg i.v. over 15 min. after patient positioning followed maintenance infusion of 1mg/kg/hr significantly decreases intra-operative blood loss, thereby decreasing the requirement of intraoperative blood transfusion. However it does not have any major impact on post-operative blood loss. No thrombotic complications or other adverse events were noted in this study.

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