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COMPARATIVE EVALUATION OF INTRAVENOUS TRANEXAMIC ACID AND HEMOCOAGULASE TO PREVENT BLOOD LOSS IN MAJOR ORTHOPAEDIC LOWER LIMB SURGERY

Anaesthesiology

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ABSTRACT

Introduction: Lower limb orthopaedic surgeries can lead to significant intra-operative blood loss. Numerous techniques have been tried to reduce this blood loss. One of the two most common pharmacological agents used for this purpose in tranexamic acid and haemcoagulase. Both are known to decrease blood loss in lower limb orthopaedic surgeries. We conducted this study to compare their effectiveness which will further help clinicians to make more informed decisions.

Material and methods: All the patients undergoing lower limb orthopaedic surgery between 01, June 2018 and 01, May 2019 were made part of this study. They were randomly allocated into tranexamic acid (T) group and haemcoagulase (H) group. Many parameters including blood loss were noted among both the groups and compared against each other.

Results: The two groups did not had any statistical difference in terms of haemodynamic parameters but there was significantly lower blood loss in H group compared to T group. There was no significant difference in terms of fall in haemoglobin and haematocrit in both groups.

Conclusion: Our statistical analysis of the data showed that there was significant difference in terms of blood loss among both the groups with Hemocoagulase group having significantly lower blood loss compared to tranexamic acid group.

KEYWORDS

Tranexamic acid, Haemocoagulase, Lower limb orthopaedic surgery, Blood loss

INTRODUCTION

Blood conservation strategies have a very important role in the care of a patient with orthopedic long bone fractures and lower limb joint replacements. The procedure is considered as a major orthopedic surgery, where a significant amount of blood loss is expected both during and after surgery. Tranexamic acid (TXA) and Hemocoagulase, are utilized to diminish perioperative blood loss, has been touted as a profitable adjunct to numerous perioperative blood conservation methods.

A haemostatic agent reduces blood loss and need for blood transfusion [1]. Antifibrinolytic agents in current use are the naturally occurring serine protease inhibitor aprotinin, the synthetic protease inhibitor nafamostat and the synthetic lysine analogues epsilon aminocaproic acid and tranexamic acid [2].

Tranexamic acid is a competitive inhibitor of plasminogen activation. The intravenous tranexamic acid has been shown to be very useful in reducing blood loss in major hip surgeries [3-7]. The antifibrinolytic agent Tranexamic acid potentiates the blood clotting system to prevent bleeding. Hemocoagulase is a mixture of purified enzymes isolated from the venom of South American viper, called bothropsatrox, which is free from neurotoxin and other toxic substances. By combination of thrombin like activity and thromboplastin like activity, Hemocoagulase accelerates initiation, formation and stabilisation of clotting process. Hemocoagulase is generally used perioperatively in orthopaedic major surgeries. Hemocoagulase decreases bleeding time and clotting time by promoting coagulation cascade at bleeding site and hence diminishes blood loss.It does not cause intravascular coagulation in therapeutic doses, and only augments the physiological process of coagulation.

As we found from different studies that tranexamic acid and Hemocoagulase, when used perioperatively reduces blood loss in various surgeries and decreases the chances of allogenic blood transfusion. In this study we aim to compare the efficacy of two drugs over each other regarding the prevention of blood loss during surgery and their effect on hemodynamic parameters and coagulation profile.

METHODS

Research design

The study was a prospective, time bound, hospital based, double blind randomized control trial and the study was conducted from 01, June 2018 to 01, May 2019 (11months). Patients undergoing lower limb orthopaedic surgeries were enrolled for this study and they were divided into 2 groups Group T and Group H (30 patients per group). The study was conducted at the tertiary care hospital, following the approval gained from the scientific and ethical committee. This randomized, double-blinded study comprised 60 patients who were scheduled for elective orthopaedic lower limb surgeries. Randomization was done by using a simple computer programme for randomly allocating treatment. The observer who assessed the blood loss and persons who conducted anaesthesia were unaware of the study drug. Patients were also unaware of the given study drugs. Continuous data was summarized as Mean ± SD (standard deviation) while discrete (categorical) data in number and percentage.Quantitative data was analysed by, mean, SD, Unpaired "t" test and qualitative data was analysed by percentage, Chi square test, fisher exact test. P value of <0.05 was taken as significant and P value of <0.001 was taken as highly significant. P value of >0.05 was deemed as non-significant.Statistics software used was SPSS 16.0 and Randomization was done by computer generated random numbers.

Study subjects

Inclusion criteria for study subjects was age between 18 to 65 years, patients of ASA grade I and II and patients scheduled for elective femoral fractures & hip surgeries. Exclusion criteria included patient's refusal, patients having respiratory, cardiac or systemic dysfunction, renal insufficiency, liver impairment, patients having DVT or bleeding disorders, patients on anticoagulant therapy, pregnant or lactating females and patients with known allergy to study medications.

Based on computer generated randomization patients were randomly allocated to the groups as group T (tranexamic acid group; n=30) and group H (haemcoagulase group; n=30)

Data collection

Informed consent of the patient was obtained during preoperative anaesthetic check-up one day prior to surgery after explaining the patient with the patient information sheet. After arrival in Operation theatre, Electrocardiography, pulse oximeter and non-invasive blood pressure cuff measurements were attached and the base line heart rate, blood pressure (SBP,DBP, MAP) and SpO_2 were noted. Prefilled unlabelled syringes containing study drugs, tranexamic acid 500mg and haemcoagulase 2 IU diluted up to 20ml with normal saline were administered to group T and group H patients respectively prior to spinal anaesthesia. The patients were monitored intraoperatively for hemodynamic parameters and blood loss.

Intraoperative quantity of blood loss was measured by weighing swabs, sponges, operative drapes and by measuring the volumes in the suction bottles after surgery and postoperatively by measuring the amount of blood collected in drain in post anaesthesia care unit.

After the surgery was over, patients were shifted from operating room to PACU. Patients were followed up to 24 hours post operatively. For the study, hypotension was defined as fall of systolic blood pressure more than 20% from the baseline value or systolic blood pressure less than 80 mmHg. Bradycardia was defined as heart rate below 50 beats per minute.

RESULTS

The mean age of the patients in the group T was 55.47±6.79years while it was 54.6±10.83years in group H. There was no significant difference in age distribution in both groups (P>0.05). Out of 60 patients, group T have 15(50%) male and 15 (50%) female as compared to group H, in which there were 18 (60%), male and 12(40%) female patients, which was statistically comparable. (P>0.05). The number of ASA I patients in Group T and group H were 14 and 15 respectively. The number of ASA II patients in group T and group H were 16 and 15 respectively. ASA distribution in both the groups were comparable as per chi-square test and statistically not significant (p>0.05). The duration of surgery was 96.50+18.76 minutes for Group T & 100.00+20.47 for Group H. There was no statistically difference in the duration of surgery between group T& H (P>0.05). The type of surgery distribution in both the groups were comparable as per chi-square test and statistically not significant (p>0.05). Both the groups i.e. group T & group H were comparable with respect to pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and oxygen saturation at all point of observations. There was no statistically difference between two groups with respect to the above hemodynamic parameters (P>0.05).

Mean total blood loss was significantly more in group T (Tranexamic acid) patients as compare to group H (Hemocoagulase) patients. It was 642.67±121.54 ml in group T patients and 519±79.84 ml in group patients, which was statistically significant (p=0.001). There was no statistically significant difference between both the groups with respect to the percentage fall in haemoglobin& hematocrit (P>0.05). Both the groups were comparable with respect to the baseline as well as 24-hour postoperative platelet count (P>0.05). There was no statistically significant difference in the preoperative mean PT, APTT & INR between the two groups. After 24 hours also, there was statistically no significant difference in PT, APTT & INR between the two groups**.**

The incidence of intraoperative side effects in the form of Hypotension was reported in 3(5%) patients in group T& in 3(5%) patients in group H. Bradycardia was reported 1(1.7%) patient in group I. However, shivering was reported in 3(5%) patients in group T& 2(3.3%) patients in group H. 48(80%) patients does not recorded any side effect. There was no statistical significance in the two groups(P>0.05).

From our results, we concluded that administration of haemcoagulase 2IU significantly reduced the total blood loss perioperatively in comparison to tranexamic acid given in a dose of 500 mg bolus dose in orthopaedic hip & femoral surgeries without affecting haemodynamic parameters and coagulation profiles. No untoward complications were noted in both the groups.

Table1: Comparative parameters of tranexamic acis And haemocoagulase group

Age Group		GROUP : TRANEXAMIC ACID	GROUP:HAEMCOAGULASE	P value
	≤30 years	0(0%)	2(6.67%)	0.42
	31-40 years	1(3.33%)	1(3.33%)	
	41-50 years	5(16.67%)	4(13.33%)	
	51-60 years	17(56.67%)	12(40%)	
	>60 years	7(23.33%)	11(36.67%)	
	TOTAL	30(100%)	30(100%)	
Sex Distribution	Male	15(50%)	18(60%)	0.43
	Female	15(50%)	12(40%)	
	TOTAL	30(100%)	30(100%)	
ASA grade				
	ASA grade 1	14(46.67%)	15(50%)	0.79
	ASA grade 2	16(53.33%)	15(50%)	
	TOTAL	30(100%)	30(100%)	
Duration of surgery				
		96.5 minutes (mean)	100 minutes (mean)	0.49 NS
Blood loss				
		642.67 ml (mean)	519 ml (mean)	0.001
Mean percentage fall in haemoglobin				
		10.25% (mean)	9.75% (mean)	
Mean pulse rate/min				
	Pre op	80.1±7.82	78.4±7.06	0.38
	After giving Drug	77.7±6.82	77.1±6.74	0.73
	After 5 min	75.9±8.18	75.2±6.05	0.71
	After 15 min	74.3±8.4	74.1±6.74	0.92
	After 30 min	75.1±9.52	74.7±6.85	0.85
	After 45 min	72.83±8.1	71.6±5.95	0.5
	After 60 min	72.9±6.41	72.3±6.07	0.71
	After 75 min	71.8±7.13	72.7±6.19	0.6
	After 90 min	73.57±7.58	73.3±6.84	0.89
	After 105 min	71.97±6.85	72.2±8.03	0.9
	After 120 min	73.27±6.36	72.8±7.74	0.8
Mean arterial blood pressure				
	Pre op	97±4.9	96.7±5.97	0.83
	After giving Drug	91.1±4.95	90.1±6.42	0.5
	After 5 min	84±4.75	84.3±5.81	0.83
	After 15 min	82.43±5.04	80.4±6.47	0.18
	After 30 min	79.37±7.6	81.6±5.99	0.21
	After 45 min	76.87±5.64	78.3±4.46	0.28
	After 60 min	79.5±4.3	79.4±3.67	0.92
	After 75 min	79.5±4.84	80.17±4.73	0.59
	After 90 min	78.67±3.15	80.1±3.26	0.09
	After 105 min	77.8±2.76	78.7±2.95	0.23
	After 120 min	78.33±1.65	79.5±3.19	0.08
Incidence of side-effects				
	Bradycardia	1(3.33%)	0	0.41
	Hypotension	5(16.67%)	3(10%)	
	Shivering	2(6.66%)	3(10%)	
	None	22(73.33%)	24(80%)	
	TOTAL	30(100%)	30(100%)	

DISCUSSION:

One of the most common complications of orthopaedic surgery is excessive bleeding which frequently leads to transfusion of allogenic blood products, which exposes patients to the risk of transfusion-related adverse effects, including allergic reactions, transfusion errors and blood-borne infections (particularly HIV and hepatitis).Therefore, various antifibrinolytic and procoagulant agents are used during orthopaedic surgery to prevent excessive blood loss during and after surgery and to minimize transfusion requirements.

Jansen et al[8] and Gupta P et al[9] had observed the effect of TXA with 10mg/kg and 500mg respectively. Similarly, Li ping et al [10] and Wei JM et al [11] had observed the results with 2IU of haemcoagulase .All these studies have found significant reduction in blood loss without any untoward complications So we have planned to observe the effect of TXA and haemcoagulase with a fixed dose of 500mg and 2IU respectively.

Similar to our study,Jansen et al. [8] in their study of TXA conducted on 42 patients found significant reduction in Intraoperative and post-operative blood loss. Gupta P et al [9], also found that the

intraoperative blood loss was found to be 1065 ± 123.7 mL in control group C and 567.5 ± 83.15 mL in TXA group T. Hence, there was a significant reduction in the amount of blood loss.**Li Ping et al [10]** in their study on 40 patients also concluded that Haemcoagulase reduces the total blood loss in orthopedic surgeries after 24hrs.Similarly, Wang Dan et al [12], also concluded that the effects of haemcoagulase on perioperative blood loss and coagulation in patients with low molecular heparin anticoagulation, undergoing total hip replacement was lesser than the control group. It was found that Intraoperative and postoperative 24 h bleeding volume were 629 ± 97 mL and 273 ± 87 mL in control group, and they were 312 ± 79 mL and 213 ± 74 mL with 2 IU of intravenous haemcoagulase (P<0.05). Similarly,Hui-Min Hu et al [13]in their study showed the total perioperative blood loss was approximately 31% lower in patients given Hemocoagulase versus placebo (700.5 ± 45.81 vs 485.7 ± 30.01 mL, P=0.001), The Hemocoagulase group had significantly less intraoperative blood loss (326.1 ± 24.16 mL) compared to the placebo group (556.0 ± 43.58 ml). Our finding was consistent with that of Roopa MN et al [14] who also found that Intraoperative blood loss is less in haemcoagulase group 268.32±62.92ml than in TXA group 340.72±182.75ml.

S. Hiippala et al[15] and Yamasaki et al [16] in their study also found that there was no change in Hb &Hct values TA group on the first postoperative day.Roopa MN et al [14]in his study on batroxobinTXA and Hui-Min Hu et al [13] in their study on botropase also did not found any statistically significant difference between parameters like Hb and Hct.

Similar to our studyJansen et al. [8] also found that TXA did not induce platelet activation. Indeed, platelet count, a marker of platelet activation, was same in both TXA and placebo group. Similar to our study Li Ping et al [10] in their study on 40 patients also found that Haemcoagulase didn't affect the platelet counts, there was no significant difference in platelet count between the haemcoagulase and placebo groups

Similar to our study Jansen et al. [8] in their study on TXA conducted on 42 patients found that after 24 hrs. PT and aPTT were unaffected, indicating that the observed blood loss was not caused by any major deficit in coagulation factors.**Li Ping et al [10]** in their study on haemcoagulase used perioperatively in orthopaedic surgeries on 40 patients also concluded that after 24hrs there was no significant change in coagulation state. Bhavani S. Vijay et al [17] in their study on 45 patients undergoing hip & femoral surgeries with TXA found no significant differences in coagulation parameters.Shenoy et al [18] in their study on 15 human volunteers also found the intramuscular and intravenous administration of haemcoagulase didn't affect the PT, APTT values.Haemcoagulase is involved only in the conversion of fibrinogen and does not affect other coagulation factors or cells. Therefore, its haemostatic effect occurs only at the point of injury avoiding large-scale intravascular coagulation.

In our study, Hypotension was reported in 5(16.67%) patients in group T and in 3(10%) patients in group H. Bradycardia was reported 1(3.33%) patient in group T. shivering was reported in 2(6.6%) patients in group T & 3(10%) patients in group H. However, 22(73.33%) and 24(80%) patients in group T and H do not recorded any side effect. However side effect such as hypotension, shivering, bradycardia may occur due to effect of sub arachnoid block. The incidence of side effects were statistically comparable (P=0.733) between the groups. Our findings are consistent with Roopa MN et al [14], Bhavani S. Vijay et al [17] and **LiPing et al [10]** as they also did not observe any significant side effects with either TXA or haemcoagulase.

Limitations:

Due to the basic nature of research sample size was limited. Further research with larger sample will further help in better validation of our results. Our study was limited to orthopaedic procedures.

CONCLUSION:

From our results, we concluded that administration of haemcoagulase 2IU significantly reduced the total blood loss perioperatively in comparison to tranexamic acid given in a dose of 500 mg bolus dose in orthopaedic hip & femoral surgeries without affecting haemodynamic parameters and coagulation profiles. No untoward complications were noted in both the groups.

However, studies should be conducted to find out the possibilities of using haemcoagulase and tranexamic acid in patients with IHD, valvular heart disease and hypertension. A multicentric trial with large study group should be carried out for further validation of the study. Also, further studies should be carried out to evaluate efficacy of multiple doses of haemcoagulase and tranexamic acid on perioperative blood loss.

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