COMPARISON OF PERIOPERATIVE USE OF TRANEXAMIC ACID WITH PLACEBO IN PATIENTS WITH HIP FRACTURES IN TERMS OF FREQUENCY OF DEEP VENOUS THROMBOSIS

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ABSTRACT

Objective: To compare perioperative use of tranexamic acid with placebo in patients with hip fractures in terms of frequency of deep venous thrombosis.
Study Design: Quasi experimental study.
Place and Duration of Study: CMH Orthopedics department Rawalpindi, from Apr 2017 to Oct 2017.
Methodology: A total of 306 patients presenting with hip fracture, 50 to 90 years of age were included. Patients with Hip fractures presenting with sepsis, hypercoagulable state, pregnancy and breast feeding and contra-indication to tranexamic acid were excluded. The sample size was divided into two equal groups by lottery method, Tranexamic Acid (TXA) and Placebo. The patient was followed till 15th post op day for the purpose of study and at 15th post op day a Doppler ultrasound was performed on both lower limbs and presence or absence of deep venous thrombosis was recorded.
Results: The mean age of patients in group A (tranexamic acid group) was 70.80 ± 11.13 years and in group B (placebo group) was 71.50 ± 11.30 years. Out of these 306 patients, 215 (70.26%) were male and 91 (29.74%) were females. Deep venous thrombosis was seen in 31 patients in group A (tranexamic acid group) and 14 patients in group B (placebo group) with *p*-value of 0.006.
Conclusion: Frequency of deep venous thrombosis was observed more in patients receiving perioperative intravenous tranexamic acid as compared to control.

Keywords: Deep vein thrombosis, Hip fractures, Tranexamic acid.

INTRODUCTION

A hip fracture is a femoral fracture that occurs in the proximal end of the femur (the long bone running through the thigh), near the hip. Hip fractures are classified as intracapsular, which includes femoral head and neck fractures, or extracapsular, which includes trochanteric, intertrochanteric, and subtrochanteric fractures. The location of the fracture and the amount of angulation and comminution play integral roles in the overall morbidity of the patient, as does the preexisting physical condition of the individual. Fractures of the proximal femur are extremely rare in young athletes and are usually caused by high-energy motor vehicle accidents or significant trauma during athletic activity. Other causes may be an underlying disease process such as Gaucher disease, fibrous dysplasia, or bone cysts.

Hip fractures are seen globally and are a serious concern at the individual and population level. By 2050 it is estimated that there will be 6 million cases of hip fractures worldwide[1]. One study published in 2001 found that in the US alone, 310,000 individuals were hospitalized due to hip fractures, which can account for 30% of Americans who were hospitalized that year[2]. Another study found that in 2011, femur neck fractures were among the most expensive conditions seen in US hospitals, with an aggregated cost of nearly $4.9 billion for 316,000 inpatient hospitalizations[3]. Falling, poor vision, weight and height are all seen as risk factors. Falling is one of

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Received: 10 Mar 2018; revised received: 10 Jul 2018; accepted: 13 Jul 2018

the most common risk factors for hip fractures. Approximately 90% of hip fractures are attributed to falls from standing height[4].

Hip fractures are among the most common fractures encountered in geriatric population. Theassociated mortality rate is about 50% in first six months and 30% at 1 year[5]. Hip fracture surgery is associated with significant amount of blood loss, frequently requiring blood transfusion. Patients with hip fractures are usually frail and elderly and are particularly vulnerable to anemia and hypovolemia. Transfusions in these patients can cause complications including anaphylactic reaction, allergic reactions to blood products, infections and even death. Current standards of medical care recommend limited use of blood products.

Tranexamic acid use has been shown to decrease perioperative blood loss in various studies[6]. However its use has not been void of complications. Numerous complications have been reported including nausea, vomiting, diarrhea, headache, orthostatic reactions, blurred vision, and vertigo. Of peculiar concern is its antifibrinolytic action which stabilizes formed clots which can theoretically lead to increased risk of asymptomatic and symptomatic deep venous thrombosis (DVT) and embolism. Many studies have suggested postoperative DVT to be a potential and devastating complication with the use of tranexamic acid but as yet no concrete evidence is available[7].

A study published in 2010 shows that the probability of vascular thrombotic events like DVT, pulmonary embolism and stroke at 6 weeks was 16% in the tranexamic acid group and 6% in the placebo group. Their trial supports our hypothesis that tranexamic acid may promote a hypercoagulable state and predispose to increased risk of DVT[8]. However, patients in our country might behave differently as incidence of DVT in Asian countries is different than the western population[9].

Therefore, we planned this study to investigate the effect of intravenous tranexamic acid on DVT outcomes in our population, so that effective treatment can be recommended.

METHODOLOGY

This Randomized controlled trial was conducted at CMH Orthopedics department Rawalpindi from 30th April 2017 to 29th October 2017. Sample size was calculated by using WHO sample size calculator, keeping power of test 80%, level of significance 5%, anticipated population proportion P1 = 16%[5], anticipated population proportion P2 = 6%[8], sample size is 153 in each group. Consecutive sampling technique was used to collect the sample for the study. Patients of both genders presenting with hip fracture in Emergency and outpatient department of CMH Rawalpindi, aging from 50 to 90 years were included in the study. Exclusion criteria was diagnosed cases of hypercoagulable state like malignancy and blood dyscrasias or patients with Hip fractures presenting with sepsis. Pregnancy or breast feeding was also part of exclusion criteria. Patients with contraindication for tranexamic acid (previous arterial or venous thrombosis, creatinine clearance <30 ml min−1, previous seizure or estroprogestative therapy) were also excluded from the beginning.

The study was conducted at the Combined Military Hospital (CMH) Orthopedics department, Rawalpindi after the ethical approval from the Institutional Review Board. Patients presenting with hip fracture either in Out Patient Department or Emergency Room were enrolled in study after fulfilling the inclusion and exclusion criteria and informed consent was attained.

The study population was divided into two equal groups by lottery method, Tranaxemic Acid (TXA) and Placebo. Five ml Injection of normal saline was given intravenously as placebo. Injection TXA was given intravenously as 15 mg/kg body weight at the time of anesthesia. Both groups were blinded by the person doing randomization and denoted as either group A and B. After allotting groups all units were sealed in envelops and handed over to research team.

When patient was enrolled in study a random envelop was opened by the anesthetist and the drug prescribed were administered to the patient. The patient was followed till 15th post op day for the purpose of study and at 15th post op day a Doppler ultrasound was performed on both lower limbs and presence or absence of DVT was recorded. At the end of study both groups were un-blinded and data collected was analyzed.

Routine mechanical methods of thrombo prophylaxis like ankle pumps and TED stockings were advised to every patient as per department protocol, however no chemoprophylaxis was administered. If any patient develops symptomatic DVT within the period of 15 days, he/she was treated accordingly. All patients gave consent and strict confidentiality was maintained. This study had no negative or compromising effect on the quality of the treatment.

The collected information was entered and analyzed by SPSS version 22.0. Age of the patients was presented as mean and standard deviation. The qualitative variables (gender and DVT) were evaluated and presented as frequency with percentage. The frequency of DVT of two groups was compared with chi-square test. post-stratification chi square was applied to see their effect on DVT. The *p*-value ≤0.05 was considered as significant.

RESULTS

Age range in this study was from 50 to 90 years with mean age of 71.23 ± 11.22 years. The mean age of patients in group A (tranexamic acid group) was 70.80 ± 11.13 years and in group B (placebo group) was 71.50 ± 11.30 years. Majority of the patients 155 (53.92%) were between 71 to 90 years of age (table-I).

Out of these 306 patients, 215 (70.26%) were male and 91 (29.74%) were females with ratio of 2.4:1. DVT was seen in 31 patients in group A (tranexamic acid group) and 14 patients in group B (placebo group) with p-value of 0.006 (table-II). Stratification of DVT with respect to age of

Table-I: Age distribution for both groups (n=306).

Age (years)	Group A (n=153)		Group B (n=153)	
	No. of patients	% age	No. of patients	% age
50-70	73	47.71	68	44.44
71-90	80	52.29	75	55.56
Mean ± SD	70.80 ± 11.13		71.50 ± 11.30	

Table-II: Frequency of deep venous thrombosis in both groups.

		Group A (n=153)		Group B (n=153)		*p*-value
		No. of Patients	% age	No. of Patients	% age	
Deep Venous Thrombosis	Yes	31	20.26	14	9.15	0.006
	No	122	79.74	139	90.85	

p-value is 0.006 which is statistically significant.

Table-III: Stratification of deep venous thrombosis with respect to age groups.

Age of patients (years)	Group A (n=153)		Group B (n=153)		*p*-value
	Deep Venous Thrombosis		Deep Venous Thrombosis		
	Yes	No	Yes	No	
50-70 years	23 (31.51%)	50 (68.49%)	7 (8.75%)	73 (91.25%)	<0.0001
71-90 years	8 (11.76%)	60 (88.24%)	7 (9.33%)	68 (90.67%)	0.636

Table-IV: Stratification of deep venous thrombosis with respect to gender.

Gender	Group A (n=153)		Group B (n=153)		*p*-value
	Deep Venous Thrombosis		Deep Venous Thrombosis		
	Yes	No	Yes	No	
Male	21 (17.50%)	89 (82.50%)	12 (11.43%)	93 (88.57%)	0.119
Female	10 (23.26%)	33 (76.74%)	2 (4.17%)	46 (95.83%)	0.007

patients in both groups has shown in table-III. Gender stratification in both groups has been shown in table-IV.

DISCUSSION

Hip fractures are associated with numerous adverse events and increased mortality up to 1 year after the event[10]. Hidden blood loss in hip fractures, in addition to intraoperative blood loss, may be as high as 1500cc[11]. The rate of blood transfusion in the perioperative period for hip fracture patients is reported between 20% and 60%[12]. Total blood loss, and thus rate of transfusion, is greater for extracapsular hip fractures compared to intracapsular hip fractures. A meta-analysis of 20 studies found a significantly increased risk of postoperative bacterial infection in patients who receive an allogenic blood transfusion in the perioperative period[13]. In addition to the increased risk of infection, patients who require blood transfusion following hip fracture have an increased hospital length of stay.

Numerous antifibrinolytics have been used to limit bleeding in orthopaedic surgery and prevent the need for blood transfusion[14]. One of these antifibrinolytics, tranexamic acid (TXA), is a synthetic derivative of the amino acid lysine and acts as a competitive inhibitor in the activation of plasminogen to plasmin, therefore preventing the degradation of fibrin. As a result of the CRASH-2 trial[15], which demonstrated reduced mortality in trauma patients who received TXA, the WHO added TXA to the essential drugs list. Currently TXA is not routinely used in patients with hip fractures in the USA, despite its common use worldwide and proven efficacy in reducing blood loss in other populations.

Numerous studies have investigated the safety and efficacy of TXA in patients undergoing elective orthopedic surgery, including total joint replacement and spine surgery[16]. The consensus from this literature is overwhelmingly in favor of administration of TXA given the decrease in blood loss, transfusion rates and cost[17]. Although several individual studies have found increased risk of thromboembolic events in groups receiving TXA[18], larger studies and meta-analyses have uniformly found no increased risk of thrombosis[19]. Present study was conducted to compare perioperative use of tranexamic acid with placebo in patients with hip fractures in terms of frequency of DVT.

Several investigators have expressed concern that TA causes a hypercoagulable state and there is a trend in increased risk of vascular events[20]. Two large meta-analyses have not found any increased risk of thromboembolic episodes with systemic TA[21]. The effects of TA are more pronounced in operative wounds than in peripheral venous blood because generation of tissue plasminogen activator occurs in wounds, and this may be the reason why systemic TA may be safe.

In a recent meta-analysis, Ker *et al*[20] analyzed the effect of topical TXA on bleeding and DVT incidence. In studies by Wong *et al*[21] and Sa-Ngasoonsong *et al*[22] that were reviewed in the meta-analysis, duplex ultrasound scanning was used in all patients on the second and third postoperative days and on the fourth postoperative day, respectively, and no significant increase in DVT incidence was observed. It is important to observe, however, that the ultrasound examinations were performed during the period in which patients were still on anticoagulant therapy, and before the known peak incidence of DVT on the sixth day. In study by Ishida *et al*[23] duplex ultrasound scanning was performed only for patients exhibiting symptoms[24].

CONCLUSION

Frequency of deep venous thrombosis was observed in patients receiving perioperative intravenous tranexamic acid as compared to control.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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