POST PARTUM HEMORRHAGE PREVENTION WITH TRANEXAMIC ACID IS EFFECTIVE AND SAFE IN COMPARISON TO PLACEBO

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ABSTRACT

Objective: To compare the tranexamic acid effectiveness and safety with placebo for prevention of post partum hemorrhage (PPH) on general population of Lahore.

Study Design: Randomized double blind placebo control trial.

Place and Duration of Study: This study was conducted over a period of two years and six month (Jan 2015 to Jun 2017) in Ranger Hospital and Cavalry Hospital Lahore.

Material and Methods: A total 600 cases were randomly selected from obstetric outpatient departments of both hospitals for delivery. Patients were divided in two groups, 300 patients received tranexamic acid and 300 patients received placebo. In tranxamic acid group, in cases of vaginal deliveries a loading dose of 01 gram tranexamic acid was injected intravenously at delivery of anterior shoulder. In cases of lower segment caesarean section it was administered intravenously prior to abdominal incision. Those patients who failed to response, a second dose of 01 gram tranxamic acid were repeated at 30 minutes - 01 hour interval. In similar manner placebo was injected in second group.

Results: In tranexamic acid group, 289 (96%) patients responded successfully. Second dose was needed in 8 patients. Out of these 8 cases, 4 patients responded successfully. Those 4 women who failed to respond to tranxamic acid, 2 patients had venous thrombosis, 1 case was of placenta increate and 1 case was of uterine atony. Life saving total abdominal hysterectomy was performed in case of placenta increate. The patient of uterine atony required surgical intervention.

In this study tranexamic acid administration was associated with reduction in blood loss after vaginal delivery 88.2 ± 15.5 mlversus 300 ± 35 ml in placebo group, and was significantly effective (p<0.001). In case of caesarean sections, blood loss was reduced 153.2 ± 21 ml in tranexamic acid group versus 745 ± 72.5 ml in placebo. The reduction was significant (p<0.001). Minor gastrointestinal side effects were common after tranexamic acid use. Thromboembolic events were same in both groups.

Conclusion: Tranexamic acid effectively reduced post-partum blood loss along utro-tonics. Tranexamic acid is a safe drug which can reduce the primary PPH along with utrotonics.

Keywords: Caesarean section, Primary postpartum hemorrhage, Tranexamic acid, Vaginal delivery.

INTRODUCTION

Post partum hemorrhage (PPH) is potential life threatening complication of both vaginal delivery and caesarean section, and globally the primary cause of nearly one quarter of all maternal deaths[1]. Traditionally it is defined as blood loss more than 500 ml at vaginal delivery and 1000 ml at caesarean section. Antenatal hemoglobin level affects patient's response to postpartum bleeding. Depending the amount of blood loss together with pre-existing anemia, an untreated PPH, can lead to hypovolemic shock, multiorgan failure and loss of life within 2-6 hours. Mild self- limiting instances hold penalties for patient's puerperium in the form of fatigue, tiredness, failure of breast feeding, need for haematinics or possible want of blood transfusion. Haemodynamic disturbance may not appear post delivery even after 1000ml of blood loss, if patient have normal pre-delivery heamoglobin level. On the other hand patient with anemia, can develop tachycardia, air hunger and faintness with loss of 200ml of blood. Current definition of primary PPH includes, a

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hemorrhage resulting in a heamatocrit drop of >10% or a hemorrhage that need immediate blood transfusion[2]. Morbidity and mortality of patients can be reduced with active management of third stage of labor, and with early use of tranxamic acid intravenously[3].

The target of WHO is to meet the fifth millennium development goal aimed to reduce maternal deaths by three-quarters between 1991 and 2015. In UK the most recent Confidential Enquiry into Maternal Deaths reported significant progress in twentieth century by achieving the rate 0.56 per 100,000 births[4]. Few countries in world were able to achieve it[5]. In many areas of Sub-Saharan Africa, maternal death rates from PPH bleeding remain at least as high as that of 19th century Britain (6 deaths per 1000 births)[6]. It is reported that 12% survivors after post-partum hemorrhage suffer from post-natal anemia. Recently cesarean rate has increased in both developed and developing countries which would increase risk of PPH. According to Pakistan National Forum on Women Health (PNFWH), more than 8,000 women die and about 150,000 women suffer from PPH and its complications every year in Pakistan[7]. The rationale for study is to lower the occurrence rate of maternal mortality and morbidity, it is vital to reduce blood loss in cesarean section and vaginal delivery. Management of such cases requires diagnosis, resources, organizational support, skilled labor and ward staff, with updated World Health Organizatin (WHO) recommendation on tranexamic acid use for the prevention of PPH.

MATERIAL AND METHODS

This study was carried out from January 2015 to June 2017 into Ranger Hospital Lahore, and Cavalry Hospital Lahore. It is randomized double blind placebo control trial for prevention of primary PPH among women age range of 16 to 42 years, for vaginal delivery or lower segment caesarean section. Sample size was calculated by WHO calculator by taking 80% power of test and α=5% Mean values of two groups are 347.17 ± 108.6 and 517.72 ± 150. Total 600 patients were selected by non-probabalility consecutive sampling. Patients were randomly divided into two groups by lottery method. Inclusion crieteria are, the woman's age range 16 to 42 years and above 28 weeks of gestation. The patients have given consent for study according to standard procedure, and blood hemoglobin level was measured before delivery. Exclusion crieteria are women with age <16 years or >42 years, gestation less than 28 weeks and refused for study procedure consent. Women with medical diseases such as, renal disease, asthmatic problems, cardiac diseases, pregnancy induced hypertension, chronic hypertension, and pregnancy with diabetes were also excluded. Cases of acquired color vision defect, subarachnoid hemorrhage, active thromboembolic disease and reactive air way diseases were disqualified for study. It was not administered in case of hypersensitivity to tranexamic acid or any of its components.

In cases of vaginal deliveries active management of 3rd stage of labour with standard uterotonic (syntocinon) was done. One gram injection of tranexamic acid was given intravenously over 10 minutes at delivery of anterior shoulder, or prior to abdominal incision in cases of lower segment caesarean section. Since results were based on the total volume of blood loss, it was collected in a suction bottle immediately after the delivery of baby. To capture spatter drops of blood a large perineal pad was placed below buttock. All the blood soaked gauze pieces and pads were weighed in a plastic bag. In cases of persistent bleeding second dose of 01 gram was injected after half to one hour. The primary end point was to measure blood loss. Secondary end point was to measure the change in hemoglobin level. Both the drugs were compared for side effects. Training and monitoring of ward staff continued throughout the duration of trial.

Data analysis were done by using SPSS version 16. Descriptive statistics were used like mean, standard deviation, frequency and percentage. Both the treatments were compared using independent samples t-test and chi-square/

fisher's exact test. A *p*-value <0.05 was considered as statistically significant.

RESULTS

Six hundred women were selected, and randomly divided in two equal groups. In tranexamic acid group mean age of women was 26.8 ± 6.4 years with range (16 to 42 years). Placebo group has women's age 28.5 ± 5.39 years with range (16 to 42 years).In tranxamic acid group, primigravida were 52 (17.3%) and 50 (16.7%) in placebo group. Number of multipara were more in this region as appeared in group one 248 (82.7%) and 250 (83.3%) in group two, (*p*=0.82). Patients with singleton pregnancy who received tranexamic acid were 286 (95.3%), and 287 (95.7%) received placebo injection. Women with twin gestation, 14 (4.7%) cases received tranexamic acid and 13 (4.3%) placebo injection. Spontaneous vaginal delivery and caesarean section number, was equal in both groups. In group one lower genital tract trauma occurred in 68 (22.7%) cases and in group two 72 (24%) patients with a *p*-value 0.70. In tranexamic acid group, 289 (96%) patients responded successfully. Second dose was needed in eight patients. Four patients (1.3%) of group one and 3 cases (3%) of group two have uterine atony who received second dose. Second dose was repeated to patient with placenta increate. Out of these 8 cases, 4 patients responded successfully. Those 4 women who failed to respond to tranxamic acid, 2 patients had venous thrombosis, 1 case was of placenta increate and one case was of uterine atony. Life saving total abdominal hysterectomy was performed in case of placenta increate and the patient of uterine atony required surgical intervention. Pre delivery hemoglobin was 10.4 ± 2.5g/dl in tranexamic acid

Table-I: Pre treatment variable between groups.

Pre Treatment Variables	Tranexamicacid group (n=300) N(%)	Placebo group (n=300) N(%)	*p*-value
Age (Mean ± Sd)	26.8 ± 6.4	28.5 ± 5.3	<0.001
Parity Primigravida Mutipara	 52 (17.3) 248 (82.7)	 50 (16.7%) 250 (83.3%)	0.82
Singleton Twin	286 (95.3) 14 (4.7)	287 (95.7%) 13 (4.3%)	0.84
Total vaginal deliveries	180 (60)	180 (60%)	1
Total lower segment caesarean sections	120 (40)	120 (40%)	
Lower genital tract trauma	68 (22.7)	72 (24%)	0.70
Uterine atony	4 (1.3) 296 (98.7)	3 (1) 297 (99)	0.99
Pre delivery heamoglobin level (Mean ± Sd)	10.4 ± 2.5	9.8 ± 2.1	0.0015
Reduction in blood loss after vaginal delivery (Mean ± Sd)	88.2 ± 15.5	300 ± 35	<0.001
Reduction inblood loss after LSCS (Mean ± Sd)	153.2 ±21	745 ±72.5	<0.001
Drop in heamoglobin level (Mean ± Sd)	1.04 ± 0.9	1.5 ±1.1	<0.001
Treatment failure	1 (0.3)	3 (1)	0.62
Blood transfusion	12 (4)	49 (16.3)	<0.001

group and 9.8 ± 2.1g/dl in placebo group (p<0.05). Reduction in blood loss in cases of vaginal deliveries was compared; 88.2 ± 15.5 ml in tranexamic acid group and 300 ± 35 ml in placebo group (p<0.001) (table-I) was observed.

Blood loss was reduced, in cases of lower segment caesarean section.In tranexamic acid group, 153.2 ± 21 ml and in placebo, it was 745 ± 72.5 ml. Drop in heamoglobin level was 1.04 ± 0.9 in cases of injection tranexamic acid and 1.5 ± 1.1 in cases of injection placebo with a p-value<0.001. Treatment failure in group 1 was 1(0.3%) and in group 2 was 3 (1%) with a p-value is 0.62. Blood transfusion was done in 12 cases of tranexamic acid group and in 49 patients of placebo group with a p-value of <0.001.

Table-II: Side effects of both treatment.

Variables	Injection Tranexamic Acid N(%)	Placebo Injection N(%)	p-value
Dose	1gm	1gm	
Nousea	10 (3.33)	2 (0.7)	0.02
Vomiting	10 (3.33)	1 (0.3)	0.01
Diarrhea	8 (2.7)	1 (0.3)	0.038
Headach/seizure	7 (2.33)	2 (0.7)	0.18
Skin irritation	9 (3)	1 (0.3)	0.01
Venous thrombosis	1 (0.3)	1 (0.3)	1

Side effects of tranexamic acid such as, nausea, vomiting, diarrhea, and skin irritation was significant as compared to placebo. Only one patient has venous thrombosis in each group. Detail are in table-II.

DISCUSSION

Japan in 1965 made a synthetic derivative of amino-acid lysine. Its weight is 157 Da and is anti-ifibrinolytic drug. It functions by competitively inhibiting, the plasminogen activator enzyme in tissues and activation of plasminogen to plasmin. This lead to formation of plaminogen-tranexamix acid complex. The complex prevents fibrin binding and fibrinolysis. The second mechanism of action is, it directly inhibit plasmin activity and in higher doses reduce its formation. These properties made it way as a prophylactic drug to reduce intra-operative and post-operative blood loss in cardiac, orthopedic, gynecological, urological surgeries and trauma center emergencies. Later on, its efficacy was found in abnormal uterine bleeding and orodental surgeries[9]. Its anti-fibrinolytic properties can be used in vaginal deliveries and lower segment caesarean section for reducing postpartum blood loss and prevention of PPH. In third stage of labour fibrinogen is degraded to fibrin. The fibrinolytic activity last for 6-10 hours. Adding tranexamic acid along uter-tonics can reduce this process.

During third stage of labour, strong myometrial contractions with oxytocin administration enhances the placental separation from uterine wall. At this time physiologic and haemostatic changes occur, which comprises increase platelet activity with massive release of coagulation factors and a parallel increase in fibrinolytic activity. Adding tranexamic might be able to decrease fibrinlytic activity and facilitate the haemostatic process. It supports theoretical rationale for the use of anti-fibrinolytic agents to reduce postpartum blood loss[10]. It is found in recent studies that plasma concentrations of 5 to 10 mg/L has no effect on platelets, prothrobin time, activated partial thromboplastin time and clotting factors. At this concentration 3% of it is bound to plasma protein. If plasma concentration is outside the therapeutic level than thrombin time will prolonged[11]. Tranexamic acid is minimally metabolized and excreted by kidney in unchanged form. Therefore in renal disease patient dose adjustment is required. It is

contraindicated in hypersensitivity to drug, thrombo-embolic disease, subarachnoid hemorrhage, acquired defective vision and hormonal contraception's[12]. It is available in form of capsule, injection and for topical use as well. It crosses placental and blood - brain barrier. In lactating mothers it is excreted through breast milk, but only 1% of serum concentration.

This study examined the efficacy of tranxamic acid in preventing PPH for vaginal delivery and cesarean section In it decrease in volume of blood loss, hemoglobin levels, maternal mortality and complication regarding tranexamic acid had been reviewed. Blood loss in our study was reduced in vaginal deliveries by mean volume of 88.2 ± 15.5ml as compared to placebo 300 ± 35 ml by mean volume. In lower segment cesarean section blood loss reduced by mean volume of 153.2 ± 21 compared to placebo 745 ± 72.5 ml by mean volume and $p<0.001$. Same results are found in systemic review and meta analysis in Shanghai China, tranexamic acid use in lower segment cesarean section results in reduced blood loss by mean volume of 141.25 ml and in normal vaginal delivery by mean volume of 22.88 ml as compared to control group[13]. Gundorkuk and colleagues carried a double blind randomized control trial in which they had sample of 439 women who received single dose of 1 gram of tranexamic acid at the delivery of anterior shoulder. The result was significant reduction of blood loss in tranexamic acid group 261.5 ± 146.8 ml than placebo group 349.98 ± 188.85 ml[14]. The systemic review by Tito D. Tubog, reportedthat uterotonics and tranexamic acid in combination reduces amount of postpartum blood loss and hemoglobin level compared to control, and 77% reduction for postpartum blood transfusion[15].

In a review article by BJ Hunt, tranexamic acid and utrotonics in combination reduces postpartum blood loss and requirement of blood transfusion compared to control. It was found that blood loss was reduced significantly ($p=0.041$) in tranexamic acid group (173 (59-377) ml) than in controls (221 (105–564) ml)s[16].

In our study complication such as venous thromboembolic events, seizures and renal complication were not observed at higher rates than placebo. Tranexamic acid has well documented safety profile and no increase in thromboembolic events has been observed by women trial[17]. Same results were found in california maternal quality care collaborates[18].

This research decorated the clinical importance of quantitative assessment of postpartum bleeding and valuable insight into the prevention, diagnosis and treatment of affected patients. We use bedpan as a valuable tool for uncomplicated collection of blood by ward staff but it cannot be used as a routine out side the clinical trial. In this clinical assignment two patients had venous thrombosis one in each group and were dealt amicably. This proved it safety to use at this dose. Fortunately we had no maternal death. It was the outcome of the woman international randomized controlled trial which revealed 31% decrease in death due to obstetric PPH[17]. One of our subject end up in uterine atony and surgical treatment was opted. Other patient diagnosed with placenta inreata and life saving hysterectomy was done.

We did not encountered any serious complication of injection tranexamic acid. It was repeated after 30 minuts to one hour same as CMQCC California Maternal Quality Care Collaborates hemorrhage protocol. Minor complications such as nousea, vomiting, headaches were treated symptomatically.

CONCLUSION

Tranexamic acid effectively reduced postpartum blood loss along utro-tonics. Tranexamic acid is a safe drug which can reduce the primary PPH alongwith utrotonics.

CONFLICT OF INTEREST

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

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