

# Frequency of Postpartum Haemorrhage with Intravenous Tranexamic Acid versus Placebo in Females Undergoing Caesarean Section at Term

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## ABSTRACT

**Background:** Obstetric haemorrhage is an important cause of maternal death and serious morbidity worldwide. Postpartum haemorrhage (PPH) can be prevented by a number of pharmacological agents and surgical procedures which can be used variedly. Among the pharmacological agents Tranexamic acid (TXA) is one of the most important drug that is used to prevent PPH. This study has been conducted to compare frequency of postpartum haemorrhage with intravenous Tranexamic acid versus placebo in females undergoing caesarean section at term.

**Objectives:** To compare the frequency of postpartum haemorrhage with intravenous Tranexamic acid versus placebo in females undergoing caesarean section at term.

**Methodology:** This trial was carried out at Department of Obstetrics and Gynaecology, unit 1, Lahore General Hospital, Lahore. The study was conducted after six months of approval of synopsis. Non-probability purposive technique of sampling was used for this study. Total 120 patients were recruited. Demographic details (name, age, gestational age) were obtained. Then, lottery method was used to divide patients randomly in two groups. The patients were given 1 gm. of intravenous Tranexamic acid in group T. Tranexamic acid was prepared in 20 ml of 5% dextrose by the addition of 1 gm (10 ml) of Tranexamic acid. In group P, placebo was given. Distilled water (10 ml) was added in 20 ml of 5% dextrose to prepare placebo. The injection was given 10 minutes before skin incision. Then females underwent caesarean section. After surgery, patients were shifted to ward and were followed-up there for 2 hours postpartum for assessment of blood loss. If blood loss was  $\geq 500$  ml, then PPH was labeled (as per operational definition). Both groups were compared by using chi-square test taking p-value  $\leq 0.05$  as significant. Frequency was calculated for parity. Data was stratified for age, parity and BMI to address the effect modifiers. Post-stratification Chi-square Test was used in order to check the significance. P-value  $< 0.05$  was taken as significant.

**Study Design:** Randomized Controlled Trial.

**Setting:** Department of Obstetrics and Gynaecology, unit 1, PGMI / Lahore General Hospital, Lahore.

**Duration:** Six months after approval of synopsis (18<sup>th</sup> June, 2015 to 18<sup>th</sup> December, 2015).

**Sample Size:** Total 120 cases were studied in two groups; Each group consist of 60 cases and it is calculated with 80% power of test, 5% level of significance and taking expected percentage of PPH i.e. 10% with TXA and 28% with placebo in females undergoing caesarean section at term.

**Results:** In this study 63 (52.5%) women who underwent C-Section have blood loss  $< 500$  ml, among these 40 patients were from TXA group and 23 patients were from placebo group. In 57 (47.5 %) women postoperative blood loss was  $> 500$  ml, among these 17 patients were from TXA group and 40 patients belong to placebo group. The study results show that postpartum hemorrhage was significantly less with TXA than placebo (14% versus 33%) respectively,  $P < 0.05$ . Statistically, two groups were significant different in terms of PPH (p-value=0.000). My hypothesis was clearly accepted according to results that there are less chances of postpartum haemorrhage with intravenous Tranexamic acid as compared to placebo in females undergoing caesarean section at term.

**Conclusion:** Our study results concluded that the postpartum hemorrhage was significantly reduced with Tranexamic acid in comparison with placebo (14% versus 33% respectively).

**Keywords:** PPH, C-Section at term, Tranexamic acid, postpartum blood loss

**INTRODUCTION**

Caesarean section is a frequently encountered surgical procedure in women of child bearing age. The incidence of caesarean section in many parts of the world is much high (25-30%). Complications by caesarean section delivery are much higher as compared to normal vaginal delivery. One of the common complication documented is postpartum haemorrhage (PPH).(1)

As, rate of caesarean section is also continuously on the rise (7.3% in Pakistan), so reduction of blood loss at caesarean delivery is important to minimize the morbidity and mortality because of this procedure.(2) Tranexamic acid (TXA) being fibrinolysis inhibitor is used to decrease the blood loss during surgical procedures.(3)

TXA has also shown the decrease in blood loss in pregnancy and postpartum. Past studies proposes that the probability of blood transfusion significantly decreases (up to 34%) by the use of TXA in elective procedures.(4, 5) Another systemic review of anti fibrinolytic agents in PPH provides some evidence that blood loss is reduced during two hours of delivery by the use of TXA.(6)

Effect of TXA on caesarean delivery has also been studied and shows that TXA reduces the chances of blood transfusion due to reduction in blood loss.(7) A randomized trial found that the frequency of PPH was quite lower with TXA than placebo (31.1% versus 63.2%; respectively,  $P < 0.05$ ). (8) Mayur et al., also found that TXA had significantly low occurrence of PPH than placebo i.e. 10% versus 28%, respectively ( $P < 0.05$ ). (9) But XU et al., has found that within two hours, PPH was observed in 1.1% patients of TXA group while 1.2% in placebo group. The difference was found to be insignificant ( $P > 0.05$ ). (10)

Rationale of the present study is to compare the frequency of postpartum haemorrhage with intravenous Tranexamic acid versus placebo in females undergoing caesarean section at term. Tranexamic acid has been a cost saving intervention. In a low resource country like Pakistan, where blood is neither freely available nor properly screened and owing to rising costs of blood bank services, Tranexamic acid can be used to save lives. Although effect of this drug has been studied worldwide, this study will help strengthen our local documentary evidence regarding efficacy of tranexamic acid in this regard. Moreover, in literature contradiction has also been observed. Through this study we want to confirm that whether

TXA is effective in preventing PPH after caesarean section and can help to reduce the burden of hospital and physicians. Results of this study will help us to implement prophylactic usage of TXA to prevent PPH.

**OBJECTIVES:** To compare the frequency of postpartum haemorrhage with intravenous Tranexamic acid versus placebo in females undergoing caesarean section at term.

**Operational Definitions**

**Postpartum haemorrhage:** It was labeled if there was  $\geq 500$ ml blood loss within 2 hours of lower segment caesarean section. Blood loss was calculated by subtracting the weight of dry pads from the weight of soaked pads on a weighing machine, where 1 gram was equivalent to 1 ml.

**Hypothesis:**

There are less chances of postpartum haemorrhage with intravenous Tranexamic acid as compared to placebo in females undergoing caesarean section at term.

**MATERIALS AND METHODS**

**Study Design:** Randomized Controlled Trial.

**Setting:** Department of Obstetrics and Gynaecology, unit 1, PGMI / Lahore General Hospital, Lahore.

**Duration:** Six months after approval of synopsis (18<sup>th</sup> June, 2015 to 18<sup>th</sup> December, 2015).

**Sample Size:** Total 120 cases were studied in two groups; Each group consist of 60 cases and it is calculated with 80% power of test, 5% level of significance and taking expected percentage of PPH i.e. 10% with TXA and 28% with placebo in females undergoing caesarean section at term.

**Sampling Technique:** Non probability consecutive sampling

**Sample Selection:**

**Inclusion Criteria:** Females of age 18-40 years , and of parity  $< 6$  with singleton pregnancy at gestational age  $> 37$  weeks (on USG and antenatal record) planned to undergo caesarean section.

**Exclusion Criteria:**

➤ Severe medical illness including heart (abnormal ECG), liver (AST  $> 40$  IU, ALT  $> 40$  IU), kidney (creatinine  $> 1.2$  mg/dl),

- brain disease (medical record) and blood disorders (PT>20sec, APTT>15sec).
- Patient allergic to Tranexamic acid (screen through history).
- Thrombo-embolic event in the past
- Placental pathology such as previa, abruption (seen on USG)
- PIH (BP≥140/09mmHg), preeclampsia (PIH with +1 proteinuria on dipstick method) or eclampsia (convulsions with PIH with or without preeclampsia)
- Patients requiring blood transfusion due to anemia (Hb<10gm/dl)

**Data Collection Procedure:** After taking approval from hospital ethical committee, 120 patient fulfilling selection criteria was included in the study from labour room of Department of Obstetrics and Gynecology, PGMI / Lahore general hospital. Demographic details (name, age, gestational age) and informed consent were obtained. Then, lottery method was used to divide patients randomly in two groups. In group T, patients were given 1 gm of intravenous Tranexamic acid. Tranexamic acid was prepared in 20 ml of 5% dextrose by the addition of 1 gm (10 ml) of Tranexamic acid. Distilled water (10 ml) was also diluted in 20 ml of 5% dextrose to prepare placebo. The injection was given 10 minutes before skin incision. Then females underwent caesarean section by a single surgical team. After surgery, patients were shifted to ward and were followed-up there for 2 hours postpartum for assessment of blood loss. If blood loss was ≥500ml, then PPH was labeled (as per operational definition). The outcome of the patient will be measured by the amount of blood loss with each drug. The drug which will reduce the amount of blood loss will be defined. Data was collected by means of proforma.

**Data Analysis:** Data analysis was done by using SPSS version 17.0. Quantitative variables like age and gestational age were measured as mean ± SD. Qualitative variables such as parity and PPH were measured in terms of frequency and percentage. Chi-square test was used for the comparison of both groups taking p-value ≤0.05 as significant. Frequency was calculated for parity. Data was stratified for age, parity and BMI to address the effect modifiers. Post-stratification. Chi-square Test was used in order to check the significance. P-value <0.05 was taken as significant.

**RESULTS**

In this study total 120 women undergoing C-Section were enrolled which were divided into two groups (60 in each), one which was treated with Tranexamic acid and others was treated with placebo. The average age of patients in the study population was 27.89±3.62 years with minimum and maximum ages of 19&33 years respectively. In this study the mean duration of pregnancy was found to be 39.53±1.71 weeks with minimum and maximum durations of 37& 42 weeks respectively. In our study the mean value of postoperative blood loss in women was 469.23±238.61 ml with minimum and maximum postoperative blood loss of 200 & 850 ml respectively. **Table#1**

The study results show that the frequency of women with parity 1, 2, 3, 4 and 5 was 28, 25, 47, 16 and 4 respectively. It was found that women with parity 3 show the highest frequency.

In this study, Postpartum Hemorrhage was found in 57(47.5%) women while in 63 (52.5%) postpartum hemorrhage was not found. **Table#2**

The study results show that 43(35.81%) women enrolled in the study were having Body Mass Index equal to and less than 20, 55 (45.8%) women were having BMI 21-26 and 22 (18.3%) women were having BMI equal to and greater than 27.

In our study 114 (95%) women were from Age group 21-35, while only 6 (5%) women were having age equal to and less than 20.

In this study 63 (52.5%) women underwent C-Section have blood loss <500 ml, while 57 (47.5%) women postoperative blood loss was >500ml. **Table#3**

The study results showed that postpartum hemorrhage was significantly less with TXA than placebo (14% versus 33%) respectively, P<0.05. Thus, the two groups were significantly different from each other in terms of preventing PPH i.e p-value=0.000. Thus, there are less chances of postpartum haemorrhage with intravenous Tranexamic acid as compared to placebo in females undergoing caesarean section at term. **Table#4**

**Table 1:** Descriptive statistics of Postoperative Blood Loss (ml)

	<b>N</b>	120
	<b>Mean</b>	469.23
	<b>SD</b>	238.61
<b>Postoperative Blood Loss (ml)</b>	<b>Minimum</b>	200
	<b>Maximum</b>	850

**Table 2:** Frequencies of PPH (Postpartum Hemorrhage) among the subjects

n=120		Frequency	Percentage
PPH	Yes	57	47.5 %
	No	63	52.5 %

**Table 3:** Frequencies of postoperative blood loss among the subjects

n=120		Frequency	Percentage
Postoperative Blood Loss (ml)	< 500 ml	63	52.5%
	>500 ml	57	47.5 %
	Total	120	100 %

**Table 4:** Comparison of presence of PPH according to TXA (cases) and Placebo (control) group.

Groups n=120	PPH		
	Yes	No	Total
TXA (cases)	17 (14%)	43 (36%)	60 (50%)
Placebo (controls)	40 (33%)	20 (17%)	60 (50%)
Total	57 (47.5%)	63 (52.5%)	120 (100%)

Chi Square value = 17.678 p-value=0.000 (Significant)

## DISCUSSION

Postpartum hemorrhage (PPH) is an important cause of maternal death and accounts for about 25 % of total maternal mortality figures worldwide. Incidence of PPH is approximately 3-15% in the literature. Pharmacological agents Uterotonics are found to be the only effective means for the prevention of PPH.

Antifibrinolytic drug like tranexamic acid (TXA) is potentially useful agent that compliments the effect of uterotonics in the prevention of PPH. Studies have shown its role in reduction of blood loss in elective surgery, hemorrhage in heavily bleeding trauma and blood loss during menstruation.(68) Tranexamic acid exerts its antifibrinolytic action by occupying the lysine-binding site of plasmin and plasminogen molecules, it therefore prevents these molecules from binding to fibrin. In addition to the above effect, TXA prevents the plasminogen from converting in to plasmin. These actions of TXA were noticed for the first time by Okamoto in 1962. Since then, TXA has been widely used for the treatment of menorrhagia and for the reduction of blood loss during elective surgery. It has been

observed to reduce blood transfusion requirement by one-third in elective surgery. In our study 120 women undergoing C-Section were enrolled which were divided into two groups, cases and controls (60 in each), one of which was treated with Tranexamic acid and others was treated with placebo. The mean of patients' age in present study was found to be 27.89±3.62 years with minimum and maximum ages of 19 & 33 years respectively. JF Deux et al, 2001 shows the mean age of 32 ± 6.1 years in women with PPH.(69) In this study, Postpartum Hemorrhage was found in 57 (47.5%) women while in 63 (52.5%) postpartum hemorrhage was not found. My Study shows that(20) PPH occurs in two third of women who underwent C-Section. The study results show that postpartum hemorrhage was significantly less with TXA than placebo (14% versus 33%) respectively. P<0.05.

Thus both groups were significantly different i.e p-value=0.000. My hypothesis was clearly accepted according to results that there are less chances of postpartum haemorrhage with intravenous Tranexamic acid as compared to placebo in females undergoing caesarean section at term.

Another study conducted by Gai M-y and coworkers (40) in china showed that TXA causes significant reduction in blood loss from the time of delivery of placenta till 2 hours post-delivery .This study showed reduction in blood loss by 30% as compared to control group. TXA also reduced the incidence of postpartum hemorrhage by 25.7% in the study group (2 cases in study group versus 35 cases in control group; P value was 0.029).These results correlated well with our study.

Yang H. et al (70) showed similar results. TXA significantly reduced postpartum blood loss after vaginal delivery. The occurrence of postpartum hemorrhage was 6.4 % in study group as compared to 25.3% in control group, which is statistically significant .There was no significant adverse effects. Thus, TXA is efficient and safe in reducing PPH.

Sentilhes L. et al (71) evaluated TXA in postpartum hemorrhage and showed that TXA significantly decreased the amount of blood loss and the incidence of postpartum hemorrhage in subjects with vaginal delivery to the tune of about 20% as compared to control group. The results were found similar to that in our study. Gohel M. et al (72) evaluated TXA in cesarean section .They showed that TXA reduces significant blood loss

from the completion cesarean section to 2 hours postpartum, 75.71 ml versus 133.03 ml in the study and control group respectively ( $P= 0.001$ ). It also significantly reduces the quantity of blood loss from placental delivery to 2 hours postpartum. 372.71 ml in the study group versus 469.70 ml in the control group ( $P= 0.003$ ). These results were comparable to our study. Sekhvat L. and coworkers (8) conducted a prospective randomized study recruiting 90 primigravid as who were planned to undergo cesarean section after division into two groups. Their results showed that TXA significantly reduced the blood loss from the completion of cesarean section for further two hours;  $28.02 \pm 5.53$  ml versus  $37.12 \pm 8.97$  ml in tranexamic acid and control group respectively ( $P 0.000$ ). The outcome was similar to our study. Another study also shows inconsistency with our results, Molloy et al, 2007 shows that 52.9% reduction in amount of blood loss post-operatively by using TXA.(73) Gungorduk et al (9) studied the effectiveness and safety profile of Tranexamic acid (TA) in reduction of intra operative haemorrhage during C-section. A placebo controlled randomized study was conducted using double-blinding technique on 660 females who were planned to undergo C-Section. There was a significant reduction in the average blood loss in the patients who were administered TXA as compared to those who were given placebo ( $499.9 \pm 206.4$  ml in the TXA group and  $600.7 \pm 215.7$  ml in the placebo group;  $p<0.001$ ). Less number of women (2.1%) had a blood loss more than 1000 ml in TXA group as compared to placebo group (5.8%). Thus TXA is safe and effective to be used for blood loss reduction in C-Section. In another study by Movafegh, et al,(56) 100 pregnant females were randomly divided into two groups one of which received TXA and placebo was given to the other group. Blood loss was measured and oxytocin usage was recorded for two hours postoperatively. The study showed similar results with significant reduction in blood loss in the TXA group both intra and postoperatively ( $P< 0.001$ ). A randomized, case control study carried out on 174 females who underwent C-Section. 88 females received TXA injection just before the start of Caesarean section in comparison to 86 in the control group. The measured the amount of blood loss from the placental removal till the completion of procedure and for the first two hours postoperatively. Physical examination findings like blood pressure, heart rate, respiratory rate and certain hematological

investigations including Hb, platelets and clotting profile were observed in both groups.

The results show that significantly less blood was lost ( $p = 0.01$ ) in the 2 hours postoperative period in TXA group ( $46.6 \pm 42.7$ ) as compared to control group ( $84.7 \pm 80.2$ ). Similarly, the amount of total blood loss from delivery of placenta to 2 hours postpartum was also less ( $p = 0.02$ ) in the TXA group ( $379.2 \pm 160.1$ ) as compared to the control group ( $441.7 \pm 189.5$ ). No significant difference was found in the blood loss between the two groups from delivery of placenta till the completion of cesarean. ( $p = 0.17$ ). PPH was efficiently controlled in the TXA group as compared to the control group (81 versus 65 which is 92.0% and 75.6% respectively). TXA did not cause significant change in vital signs.(61). However, certain short term side effects occurred more frequently in TXA group.

This study confirmed the role and efficacy of TXA in reduction of blood loss in females who had undergone Caesarean section. All of these studies show similar results to the present study.

## CONCLUSION

This study results concludes that the postpartum hemorrhage was significantly reduced with TXA as compared to placebo (14% versus 33%) respectively.

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