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Original Research Article

# The effect of tranexamic acid on blood loss after vaginal delivery and caesarian section

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ABSTRACT

**Background:** PPH is most common cause of maternal death, contributing to approximately 35% of maternal death all over the world. WHO (2017) recommended that tranexamic acid should be considered as a standard comprehensive PPH treatment package and must be used in all cases of PPH regardless of the cause of PPH.

**Objective:** To evaluate the effectiveness and safety of intravenous Tranexamic acid (TA) for reduction of postpartum blood loss after vaginal delivery and LSCS and to record any adverse effects following its administration.

**Materials and Methods:** This study was conducted as a randomized, double-blind, placebo controlled trial on females at high risk of PPH and delivered vaginally or via LSCS at our Institute. All the participants were randomly categorized into two groups study group (tranexamic acid) and control group. The two groups were compared with respect to efficacy (amount of blood loss and incidence of PPH) and safety (vitals and side effects).

**Results:** Mean blood loss from the delivery of placenta to the end of delivery and from end of delivery to 2 hours postpartum was significantly lower in study group as compared to control group ($p<0.05$). Incidence of PPH was significantly higher in control group ($p<0.05$). There was no statistically difference in the vital at the time of delivery between two groups ($p>0.05$). Most common side effect due to tranexamic acid in study group was nausea (16%) followed by vomiting and diarrhea in 9% and 1% respectively.

**Conclusion:** Tranexamic acid is an effective drug that can be used safely for prophylactic management of PPH regardless of its cause. This antifibrinolytic agent significantly reduce blood loss and incidence of PPH irrespective of type of delivery. Though, the drug is associated with minor side effects such as nausea, vomiting and diarrhea, it was not associated with major complications, thromboembolic phenomenon and maternal or perinatal morbidity and mortality.



## 1. Introduction

World Health Organization (WHO) define PPH as “Blood loss of 500 ml or more within 24 hours of delivery”. Severe PPH is defined as “Blood loss of 1000 ml or more within 24 hours of delivery”.[1] Though, in practice, it is not always possible to measure the amount of blood loss and it is not clear weather measuring the blood loss improves the care and outcome for the women. Even a small amount of blood loss that is sufficient to cause hemodynamic instability among female within 24 hours of delivery is termed PPH.[1] According to National Health Portal, Government of India, PPH is most common cause of maternal death, contributing to approximately 35% of maternal death all over the world. In India, the incidence of PPH is reported in 2 to 4% cases following vaginal delivery and 6% cases following cesarean section. Uterine atony is the most common cause of PPH

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(approximately 50%).[2] First one to two hours after the delivery (also called fourth stage) are critical, as uterine atony is most likely to occur during this period.[3,4] Majority of maternal deaths due to PPH can be effectively prevented by active management of third stage of labour and with prompt management of PPH with the help of uterotonics and fluid replacement.[2] In 2012, WHO recommended the use of uterotonic agent immediately following delivery to reduce the blood loss postpartum and to reduce the incidence of PPH.

Literature suggest that following vaginal delivery, approximately 1% women require transfusion but following instrumental or cesarean delivery, the requirement of blood transfusion may be as high as 5 to 6%.[5] Concern regarding shortage of blood and blood related products, cost of blood bank operations as well as transfusion related adverse effects have led to reduction of transfusion requirements during and after surgery.

Tranexamic acid has been identified as a promising agent for management of postpartum hemorrhage as it is efficacious in managing, controlling and reducing blood loss as well as associated mortalities during and after surgical procedures.[6] Tranexamic acid is an antifibrinolytic drug, which is a synthetic derivative of aminoacid lysine. It exerts its antifibrinolytic effect binding irreversibly to lysine binding sites on plasminogen molecules.[7,8]

Based upon the established efficacy of tranexamic acid for emergency surgery,[6] WHO recommended conditional use of tranexamic acid for treatment of PPH in 2012. The conditional use implies its use in cases where the bleeding is secondary to trauma or uterotonic failed to control the bleeding. Later, in 2017, a large double blind, randomized control trial called World Maternal Antifibrinolytic (WOMAN) trial, established the safety and efficacy of tranexamic acid in management of PPH. According to this trial, early use of tranexamic acid i.e. within 3 hour following delivery is effective in controlling bleeding and reducing maternal deaths in clinically diagnosed women with PPH.[9] Following this trial, WHO updated the recommendation on use of tranexamic acid in 2017. WHO (2017) recommended that tranexamic acid should be considered as a standard comprehensive PPH treatment package and must be used in all cases of PPH regardless of the cause of PPH.[10]

Previous studies have been done mainly to determine the efficacy of tranexamic acid in PPH following cesarean section.[11] However, literature is scarce regarding the use of tranexamic acid in controlling PPH following vaginal delivery. The present study was therefore aimed at evaluating the effectiveness and safety of intravenous Tranexamic acid (TA) for reduction of postpartum blood loss after vaginal delivery and LSCS and to record any adverse effects following its administration.

## 2. Materials and Methods

The present study was conducted as a randomized, double blind, placebo controlled trial on females at high risk of PPH and delivered vaginally or via LSCS at Department of Obstetrics and Gynecology, Lord Mahavir Civil Hospital, Ludhiana during the study period of two years i.e. from March 2019 to March 2021. Women with singleton pregnancy presenting in labor (cervical dilated more than 3 cm), with cephalic presentation, belonging to age above 18 years, with gestational age between 37 and 42 weeks, with high risk factors for PPH (such as polyhydramnios, fetal macrosomia, grand multiparity (five or more), chorioamnionitis and previous PPH) were included in our study. Exclusion criteria was patients allergic to tranexamic acid; patients with medical and surgical complications-renal insufficiency, previous history of thromboembolic disease, hypertension; Ante partum hemorrhage; Multiple pregnancies, Preeclampsia, Macrosomia, Polyhydramnios; bleeding diathesis, on Aspirin or Low molecular weight heparin and whose LSCS was done under general anesthesia.

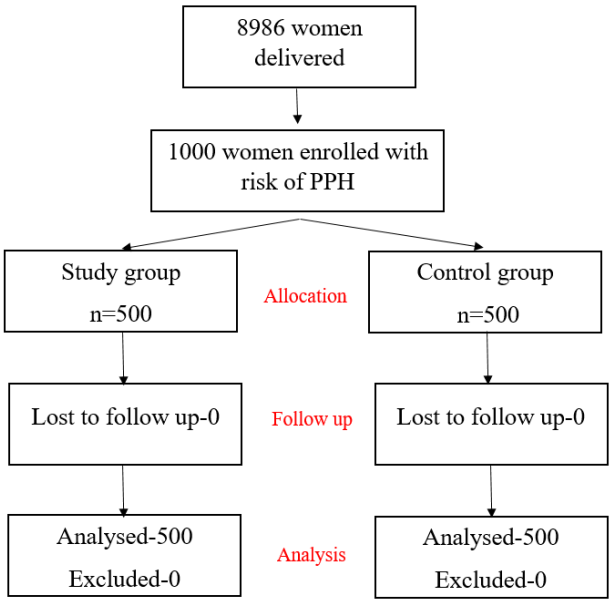


Chart 1: Consort flow chart

After obtaining ethical clearance from Institute's ethical committee, all the participants fulfilling inclusion criteria were enrolled. A total of 1000 pregnant subjects between 37 to 42 weeks gestation who presented in labour and delivered via Normal vaginal delivery or L.S.C.S. were selected. All the participants were randomly categorized into two groups

1. **Study Group:** (n=500) Patients who underwent Normal vaginal delivery or L.S.C.S and were given tranexamic acid, 1gm, i.v,30 minutes before incision.

2. **Control Group:** (n=500) patients who underwent Normal vaginal delivery or L.S.C.S and were not given tranexamic acid.

Detailed data regarding sociodemographic variables such as age, socioeconomic status etc. was obtained from all the study participants of both the groups and entered in questionnaire. All the participants were subjected to detailed obstetric and antenatal history. Previous history of abortion, PPH or any complication was also enquired and entered in questionnaire. All the females were subjected to detailed general and systemic examination at the time of admission. Further, the participants were subjected to Laboratory examinations which included CBC, LFT, RFT, Prothrombin time.

As per study protocol, 1gm/10ml tranexamic acid diluted with 20ml of 5% glucose was prepared and given in study group 30 minutes before incision. After delivery of the neonate, oxytocin 10 units IV drip and 20 units into the intra uterine wall were administered simultaneously. However, in control group, tranexamic acid was not given but Oxytocin was administered as in the study group.

Following this, Vitals such as heart rate (HR), Respiratory rate (RR), Blood pressure (BP) were checked immediately after placental delivery and 2 hours after birth.

Blood was collected via suction container, soaked gauge pads and operation table sheets. The blood loss was measured by weight and volume during two periods i.e. following placental delivery to the end of surgery and from the end of the operation to 2 hours after birth.

### 2.1. *Calculation of quantity of blood*

The quantity of blood = (weight of used materials+unused material –weight of all materials prior to surgery)/1.05, plus the volume included in the suction container after placental delivery.

Further, uterine contractility and placental separation, neonatal outcome and Side effects caused by tranexamic acid if any were documented.

The two groups were compared with respect to efficacy (amount of blood loss and incidence of PPH) and safety (vitals and side effects)

### 2.2. *Statistical analysis*

Data was compiled using MsExcel and analysed using IBM SPSS software version 20. (SPSS Inc., Chicago, IL). Categorical data was expressed as frequency and proportions whereas numerical data was expressed as mean and SD. Unpaired Student t-test was applied to compare the difference in quantitative variables between two groups whereas Chi-square test was used to compare the proportions between two groups. P values ≤0.05 qualify as significant results and those ≤0.001 as highly significant results.

## 3. Results

The study was conducted on a total of 1000 antenatal females with mean age of 23.39±2.99 and 23.18±2.81 years in study group and control group respectively. The two groups were comparable with respect to baseline variables as depicted in Table 1 (p>0.05).

Mean blood loss from the delivery of placenta to the end of delivery was significantly lower in study group (316.90±73.66 ml) as compared to control group (397±95.98 ml) (p<0.05). Similarly, mean blood loss from end of delivery to 2 hours postpartum was significantly higher in control group (p<0.05). Thus, total blood loss was significantly lower in study group (p<0.05) in which Tranexamic acid was given (Figure 1).

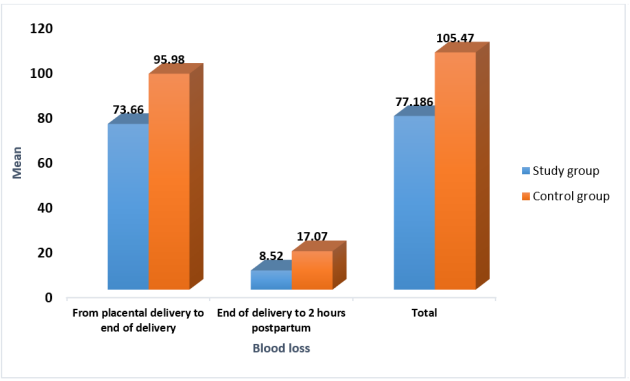


**Fig. 1:** Comparison of blood loss between two groups

Incidence of PPH was 7% in control group and 2% in study group. The observed difference in incidence of PPH was significantly higher in control group (p<0.05). Thus tranexamic acid was helpful in reducing blood loss and reducing the incidence of PPH (Figure 2).

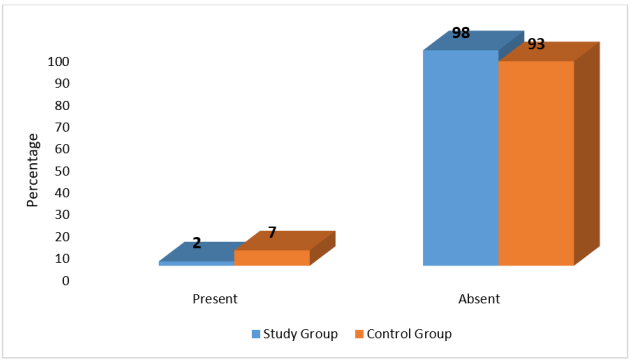


**Fig. 2:** Comparison of PPH between two groups

The hemoglobin level before delivery were comparable between study and control group (p>0.05), but hemoglobin level after delivery was significantly lower whereas fall in hemoglobin level was significantly higher in control group

**Table 1:** Comparison of baseline variables

| Baseline variables | | Study group (n=500) | | Control group (n=500) | | P value |
|---|---|---|---|---|---|---|
| | | n | % | n | % | |
| Age (Years) | 19-24 | 375 | 65 | 340 | 68 | 0.25 |
| | 25-29 | 100 | 20 | 155 | 31 | |
| | 30-34 | 20 | 4 | 0 | 0 | |
| | 35-39 | 5 | 1 | 5 | 1 | |
| | Mean | 23.39±2.99 | | 23.18±2.81 | | |
| Gravida | 1 | 360 | 72 | 368 | 73.6 | 0.09 |
| | 2 | 105 | 21 | 92 | 18.4 | |
| | 3 | 25 | 5 | 30 | 6 | |
| | ≥4 | 10 | 2 | 10 | 2 | |
| Abortion | 0 | 360 | 72 | 368 | 73.6 | 0.09 |
| | 1 | 105 | 21 | 92 | 18.4 | |
| | ≥2 | 35 | 7 | 40 | 8 | |
| Mode of delivery | NVD | 254 | 50.8 | 251 | 50.2 | 0.86 |
| | LSCS | 246 | 49.2 | 249 | 49.9 | |

**Table 2:** Comparison of two groups on the basis of hemoglobin

| Hemoglobin (mg/dl) | Study group (n=500) | | Control group (n=500) | | P value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Before delivery | 10.87 | 0.92 | 11.11 | 0.82 | 0.22 |
| After delivery | 9.83 | 0.91 | 9.03 | 1.66 | **0.001** |
| Fall in Hemoglobin | 1.10 | 0.37 | 1.93 | 1.28 | **0.001** |

as compared to study group (p<0.05) as shown in Table 2.

Table 3 shows that there was no statistically difference in the vital signs at the time of delivery between two groups (p>0.05). Mean systolic and diastolic blood pressure after 24 hours of delivery in both study group and control group was statistically similar (p>0.05).

Additional oxytocics were used in 2% cases in study group and 7% cases in control group and thus, use of oxytocic was significantly higher in control group as compared to study group (p<0.05). (Figure 3)

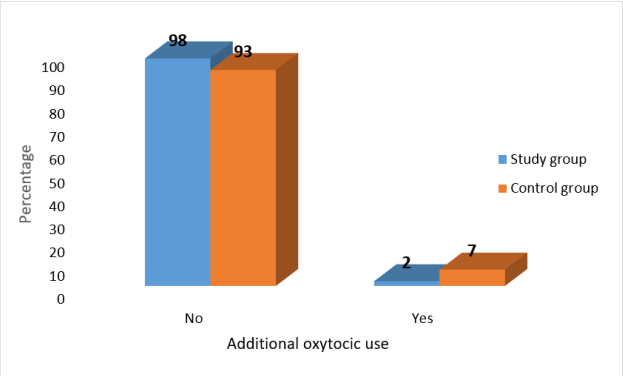


**Fig. 3:** Use of additional oxytocis in both the groups

Adverse effect due to tranexamic acid were observed in 26% cases in our study. Most common side effect due to tranexamic acid in study group was nausea (16%) followed by vomiting and diarrhea in 9% and 1% respectively.

## 4. Discussions

Tranexamic acid, an antifibrinolytic agent has been identified as a promising agent for management of postpartum after its efficacious role in various other procedures.[6] During the delivery of placenta, fibrinogen & fibrin are rapidly degraded, and there is activation of fibrinolytic system which leads to increase in plasminogen activators & fibrin degradation products (FDP) causing more bleeding. Tranexamic acid exerts competitively bind to blocking the lysine binding locus of the plasminogen and prevent the binding of plasminogen & plasmin to the fibrin substrate. Also, the agent inhibits the conversion of plasminogen to plasmin by plasminogen activators.[7,8] We aimed at evaluating the effectiveness and safety of intravenous TA for reduction of postpartum blood loss after vaginal delivery and LSCS and to record any adverse effects following its administration.

Overall, the incidence of PPH was 2% in study group and 7% in control group. The incidence of PPH was significantly higher in study group as compared to control group (p<0.0%). Also, the amount of blood loss from the delivery of placenta to the end of delivery as well as from end of delivery to 2 hours postpartum was significantly higher in control group (p<0.05). Total blood loss was 362.70±77.186 ml in study group which was significantly lower as compared to control group (476.70±105.47 ml) (p<0.05). Our study findings were supported by findings of Nargis et al., in which significantly higher blood losses from both placental deliveries to the end of cesarean section

**Table 3:** Comparison ofvitals between two groups

| Vitals | Study group (n=500) | | Control group (n=500) | | P value |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| Heart rate | 82.22 | 3.67 | 82.22 | 3.67 | 1.0 |
| Respiratory rate | 17.20 | 1.059 | 17.20 | 1.059 | 1.0 |
| SBP before delivery | 118.66 | 9.52 | 119.38 | 9.16 | 0.22 |
| DBP before delivery | 77.82 | 5.77 | 78.32 | 5.19 | 0.15 |
| SBP 24 hours after delivery | 122.12 | 10.05 | 122.86 | 10.22 | 0.25 |
| DBP 24 hours after delivery | 81.9 | 6.1 | 81.24 | 6.49 | 0.09 |

and from end of CS to 2 hours postpartum in control group as compared to study group was observed (p<0.05).[12] Sentilhes et al. also observed lower rate of clinically significant postpartum hemorrhage in tranexamic acid group as compared to placebo group (7.8% vs. 10.4%; P<0.05).[13] WOMAN trial also proved the efficacy of tranexamic acid in management of PPH. For management of PPH, tranexamic acid must be given as soon as possible preferably within 3 hours of onset of bleeding.[9]

As the use of tranexamic acid is efficacious in reducing the incidence of PPH and controlling blood loss, it has significant role in preventing fall in hemoglobin following delivery. Mean hemoglobin level before delivery were comparable between study and control group (p>0.05), but hemoglobin level after delivery was significantly lower in control group whereas fall in hemoglobin level was significantly higher in control group (p<0.05). This could be attributed to its antifibrinolytic effect which helps in reducing the blood loss.

Our study findings were supported by findings of Nargis et al., in which fall in hemoglobin was significantly higher in control group as compared to study group (p<0.05).[12] Similarly Bhavana et al. observed greater fall in the hemoglobin and haematocrit in placebo group as compared to tranexamic acid group.[14]

Vitals were stable throughout the observation period in females of both the groups before and after delivery in both the groups. No alterations in vitals were observed in both the groups (p>0.05). Similar findings were noted by previous studies by Nargis et al[12] and Bhavana et al.,[14] in which tranexamic acid was not associated with alteration of vitals during and after delivery.

WHO recommended the use of uterotonic agent preferably oxytocin immediately following delivery to reduce the blood loss postpartum and to reduce the incidence of PPH. Oxytocin administration enhances the myometrial contraction mechanism. In present study, tranexamic acid alone was effective in controlling the bleeding and the need for additional oxytocics was significantly lower in study group (2%) as compared to control group (7%). Our study findings were concordant with the findings of Sentilhes et al (2018) in which the need for additional uterotonic agents was significantly lower in TA group as compared to placebo group (7.2% vs. 9.7%; P<0.05).[13] Bhavana et al. also observed that tranexamic acid group had lesser requirement of uterotonic when compared to placebo.[14]

In general, tranexamic acid is associated with certain adverse effects which include nausea, vomiting, diarrhea, headache, backache, seizure, abdominal pain, fatigue, pulmonary embolism, deep vein thrombosis and in severe cases anaphylaxis.[15] We assessed the side effects in tranexamic acid group which were observed in 26% cases. Most common side effect due to tranexamic acid in study group was nausea (16%) followed by vomiting and diarrhea observed in 9% and 1% respectively. Nargis et al. documented that use of tranexamic acid was not associated with any side effects and or complications like thrombosis.[12] The observed difference in adverse effects between present study and reference study could be because the reference study only taken major adverse effect such as DVT etc. into account. Our study findings were concordant with the findings of WOMAN trial. Though adverse effect were observed in both the study and placebo group, but the difference in adverse effect between two groups was statistically insignificant (p>0.05).[9] Similarly, Bhavana et al. observed no major side effects in the tranexamic acid group.[14]

## 5. Conclusion

Tranexamic acid is an effective drug that can be used safely for prophylactic management of PPH regardless of its cause. This antifibrinolytic agent significantly reduce blood loss and incidence of PPH irrespective of type of delivery. Though, the drug is associated with minor side effects such as nausea, vomiting and diarrhea, it was not associated with major complications, thromboembolic phenomenon and maternal or perinatal morbidity and mortality. Thus, it must be given as a standard comprehensive package in all the cases of PPH as recommended by WHO.

## 6. Compliance with Ethical Standards and Conflict of interest

The authors declare no conflicts of interest to the contents of this manuscript. The study was conducted with the principles that have their origin in the declaration of Helsinki. The present study is randomized, double-blind, placebo controlled trial, in which consent was taken from the participants and it was approved by institutional ethics committee.

## 7. Source of Funding

None.

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