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Efficacy and safety of tranexamic acid in the prevention of postpartum haemorrhage after vaginal delivery

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Abstract
Introduction: Postpartum haemorrhage is one of the leading causes of death in women who deliver after 20 weeks of gestation. The prevalence of PPH in India is 23%. Delayed diagnosis and poor management of PPH are associated with increased morbidity and mortality.
Material and Methods: This prospective randomised controlled study was conducted on one thousand women at period of gestation ≥37 weeks for vaginal delivery.
Aim and Objectives: To evaluate the role of tranexamic acid in decreasing blood loss after normal vaginal delivery.
Results: Majority of women belonged to 21-25 years age group in both the group. Blood loss at 3rd stage of labour in TXA group was 376.12±63.82 ml and in control group it was 654.08±86.61 ml. The mean haemoglobin reduction (pre-post) suggested that tranexamic acid group (0.44±4.3) had a significantly less haemoglobin drop as compared to control group (1.850±0.58). There was significant less fall in mean haemoglobin percentage (3.86% versus 16.15%) and mean haematocrit percentage (3.80% versus 12.72%) in TXA group as compared to control group. Forty four (8.8%) women in TXA group and seventy eight women (15.6%) in control group had postpartum haemorrhage. Twenty one (4.2%) women received blood transfusion in TXA group and forty four (8.8%) women in control group. Forty four women had PPH and out of which, 33 (6.6%) were managed medically and in 11 (2.2%) women, balloon tamponade was used along with additional uterotonics for control of PPH. In control group, a total of 78 (15.6%) women had PPH and 55 (11%) were managed by medically and 23(4.6%) by balloon tamponade along with additional uterotonics for control of PPH. The most common side effect was nausea/vomiting observed in both the groups.
Conclusion: Tranexamic acid was found to be safe and effective in reducing blood loss after normal vaginal delivery. There was less drop in haemoglobin and haematocrit in tranexamic acid group which reduced the risk of blood transfusion and additional uterotonics.

Keywords: Tranexamic acid, postpartum haemorrhage, vaginal delivery

Introduction

Postpartum hemorrhage (PPH) is one of the leading causes of death in women who deliver after 20 weeks of gestation [1]. It is defined by the World Health Organization (WHO) as postpartum blood loss in excess of 500 ml, it is a clinical diagnosis that encompasses excessive blood loss after delivery of the baby from a variety of sites: uterus, cervix, vagina and perineum. Blood loss during the first 24 hours after delivery is known as primary PPH, whereas blood loss from 24 hours up to 6 weeks after delivery is termed as late or secondary PPH. Primary PPH is also classified as either placental or extra-placental bleeding [2].

Postpartum haemorrhage (PPH) is a life threatening situation. It remains a major cause of maternal morbidity and mortality worldwide, especially in developing countries. There are 600,000 maternal deaths reported worldwide every year and 99% of these occur in developing countries. Postpartum haemorrhage accounts for 25% of the mortalities in developing world. The prevalence of PPH in India is 23%. In developing countries, where most births occur in homes or local clinics, the interventions needed to treat PPH like emergency referrals, obstetric care, blood transfusion, and surgery are simply out of reach for the majority of the women. Delayed diagnosis and poor management of PPH are associated with increased mortality and morbidity [3]. PPH has many potential causes, but uterine atony is the most common cause, responsible for 75-90% of cases of PPH followed by genital tract trauma, retained tissue and coagulopathy [4].

Although the presentation of PPH is most often dramatic, bleeding may be slower and seemingly less noteworthy but may still ultimately result in critical loss and shock. High-quality evidence suggests that active management of the third stage of labor reduces the incidence and severity of PPH [5]. Active management is the combination of (1) uterotonic administration (preferably oxytocin) immediately upon delivery of the baby, (2) delayed cord clamping and cutting and (3) controlled cord traction.

Rapid recognition and diagnosis of PPH is essential for successful management. Resuscitative measures, the diagnosis and treatment of the underlying cause must occur quickly before sequelae of severe hypovolemia develop. Medical management starts with uterotonics to control PPH. Oxytocin is the drug of choice. Ergot alkaloids are recommended in patients at high risk of PPH but contraindicated in patients with hypertension and heart disease. Prostaglandins are second line drugs. Misoprostol can be administered by sublingual, vaginal or rectal routes.

Tranexamic acid is a potent antifibrinolytic agent that exerts its effects by blocking lysine binding sites on plasminogen molecules and has potential to enhance the effectiveness of the patient own haemostatic mechanisms. Consequently, clot breakdown [fibrinolysis] is inhibited and bleeding is reduced [6].

Tranexamic acid can be given orally, intramuscularly and intravenously. There is good absorption after oral intake with a maximum plasma concentration after 2 to 3 hours. Generally tranexamic acid is well tolerated. Minor adverse effects such as gastrointestinal side effects such as nausea and vomiting are common. TXA in a planned surgery reduces the risk of blood transfusion, mean transfused volume and need for re-operation due to bleeding, without increasing thrombotic events [7]. Significant reduction in mean menstrual blood loss have been reported in women with menorrhagia treated with TXA, compared with placebo-treated women [8]. Tranexamic acid appears to be a promising drug for the prevention of PPH, but the results currently available are too limited to justify its widespread use.

Hence, the present study was planned to assess the efficacy of tranexamic acid in the prevention of postpartum haemorrhage after vaginal delivery. The primary outcome was measured by fall in haemoglobin, haematocrit values and amount of blood loss. The secondary outcome was assessed to study side effects of tranexamic acid and requirement of additional tranexamic acid and oxytocin.

Material and Methods

This prospective randomised controlled study was conducted during Ist March 2018 to 30th April, 2019. A total of one thousand women at period of gestation ≥ 37 weeks in labor room of Pt. B.D. Sharma, PGIMS, Rohtak for vaginal delivery were included. One thousand women who underwent vaginal delivery were randomized into two groups of 500 each by computer generated random numbers. In group 1 (TXA), women received 1 gram of tranexamic acid intravenously slowly within 2 minutes after delivery and in group 2 (control), women did not receive any drug.

Women having Eclampsia, HELLP syndrome, abruptio placenta and placenta previa, intrauterine death, disseminated intravascular coagulation, women having cardiac, renal and hepatic disorders, autoimmune disease, sickle cell disease, allergy to tranexamic acid, history of epilepsy or seizure, administration of low molecular weight heparin or antiplatelet agents during the week before delivery and history of thromboembolic episodes were excluded from the study.

Methodology

One thousand women who underwent vaginal delivery were randomized into two groups of 500 each by computer generated random numbers. A written and informed consent was taken from all women included in study. A detailed history included antenatal history and examination was carried out. Haemoglobin, bleeding time, clotting time, ABORh, glucose challenge test (GCT), venereal disease research laboratory (VDRL), thyroid stimulating hormone (TSH), viral markers and urine examination was done if not done earlier.

Active management of third stage of labour [AMTSL] was done by 10 IU oxytocin intramuscularly in both the groups. Just after delivery, a graduated collector bag was placed under buttocks to measure blood loss. In group 1, women received 1 gram of tranexamic acid intravenously slowly within 2 minutes after delivery and in group 2, women not received any drug. Placenta was removed by controlled cord traction. Pulse and BP charting was done every 15 minutes till 2 hours. Total post partum blood loss was measured at the end with graduated collector bag.

Women having postpartum haemorrhage were managed as per hospital protocol and 2nd dose of 1 gram intravenously tranexamic acid was repeated after 30 minutes, if required. Patient was asked about the side effects like nausea, vomiting, dizziness after the delivery. Blood sample for haemoglobin and haematocrit was taken after 24 hours postpartum and compared with antenatal levels.

Statistical analysis

At the end of the study, data was compiled and analyzed using SPSS version 21. Continuous variables were presented as mean±SD. The comparison of normally distributed continuous variables between the groups was performed by using Student's t test. For qualitative data, Chi-square test was used. A p-value of less than 0.05 was considered statistically significant.

Results

In the present study, maximum number of women belonged to 21-25 years age group i.e. 247 (49.4%) in group 1 and 244 (48.8%) in group 2 followed by 135 (27%) in group 1 and 126 (25.2%) in group 2 in 26-30 years age group. Mean age of women in group 1 was 24.25±4.02 years and in group 2 was 24.23±4.14 years (p=0.945, NS with 95% CI -0.4870 to 0.5270).

Majority of women were between 38-39 weeks period of gestation i.e. 242(48.4%) in group 1 and 251(50.2%) in group 2. A total of 138(27.6%) women in group 1 and 130(26%) in group 2 had ≥40 weeks period of gestation. Mean period of gestation of group 1 was 38.60±1.28 weeks and in group 2, it was 38.62±1.25 weeks with a range of 37-42 weeks (p >0.05, NS with 95% CI -0.1772 to 0.1372).

Parity distribution of the study population shows that in both the groups majority of women were primigravida i.e. 294(58.8%) in group 1 and 280 (56%) in group 2 (p=0.370, NS). Mean parity of group 1 women was 1.88±1.01 and in group 2, it was 1.46±0.71 (p< 0.001with 95% CI 0.3115 to 0.5285). In group 1, 388(77.6%) and in group 2, 376(75.2%) women found to have spontaneous onset of labour. A total of 112(22.4%) women were induced in group 1 and 124(24.8%) in group 2 (p=0.371, NS).

Cervigel was the most common inducing agent i.e. 75(66.96%) in group 1 and 86(69.35%) in group 2. Similarly, Mifepristone was used in 32 (28.57%) women of group 1 and 33(26.61%) women of group 2 (p=0.924, NS). Mean gestation age at the time of birth in group 1 was 38.56±1.28 weeks and in group 2, it was 38.58±1.28 weeks with a range of 36-42 weeks (p=0.945, NS with CI -0.1791 to 0.1391).

Table 1 shows high risk factors which found to be associated to postpartum haemorrhage.

Table 1: High risk factors of postpartum haemorrhage

Risk factors	TXA group (n=500) n (%)	Control group (n=500) n (%)	Statistical analysis
Induction of labour	84(16.8%)	90(18%)	0.616
Oxytocin augmentation	50(10%)	56(11.2%)	0.537
Previous history of PPH	12(2.4%)	15(3%)	0.558

Table 2: Mean comparison of blood loss at 3rd stage of labour

Blood loss (ml)	TXA group (n=500)	Control group (n=500)	Statistical analysis
Mean±SD	376.12±63.82 ml	654.08±86.61 ml	<0.001 Highly significant 95% CI -287.4128 to -268.5072
Range	300-500 ml	525-815 ml	

Table 2 shows comparison of blood loss at 3rd stage of labour in TXA group was 376.12±63.82 ml and 654.08±86.61 ml in control group (p< 0.001, HS with CI -287.4128 to 268.507). A total of 46(9.2%) women in TXA group and 88(17.6%) in control group needed uterotonics (p< 0.001, HS).

Comparison of mean haemoglobin before delivery and after 24 hours in TXA group shows that it decreased from 11.39±0.82 to 10.95±5.12 after 24 hours and found to be statistically insignificant (p >0.05 NS, 95% CI -0.0156 to 0.8956). Similarly, mean haematocrit comparison before delivery and after 24 hours in TXA group shows that it decreased from 37.89±9.95 to 36.45±13.10 after 24 hours and found to be statistically insignificant (p >0.05, 95% CI -0.0054 to 2.8854).

Comparison of mean haemoglobin before delivery and after 24 hours in control group also shows that it decreased from 11.45±0.83 to 9.60±1.41 after 24 hours and found to be statistically significant (p< 0.001 with 95% CI 1.7062 to 1.9938). Similarly, mean haematocrit comparison before delivery and after 24 hours in control group shows that it decreased from 37.25±19.36 to 32.51±2.78 after 24 hours and found to be statistically significant (p< 0.001 with 95% CI 3.0215 to 6.4585).

Table 3: Percentage of mean Hb and haematocrit fall among two groups

Mean Hb	TXA group (n=500)	Control group (n=500)	Mean difference	p value
Before delivery	11.39±0.82	11.45±0.83	0.06	p=0.250, 95% CI -0.1625 to 0.0425
After delivery	10.95±5.12	9.60±1.41	1.35	p=0.000 Sig., 95% CI 0.8834 to 1.8166
Difference	0.44±4.3	1.85±0.58		P=0.000 Sig., 95% CI 1.7912 to 1.0288
%	3.86	16.15		
Mean Haematocrit				
Before delivery	37.89±9.95 (%)	37.25±19.36 (%)	0.640	0.511 (>0.05 NS) 95% CI- 1.2726 to 2.5526
After 24 hours	36.45±13.10 (%)	32.51±2.78 (%)	3.94	p=0.000 Highly significant, 95% CI 2.7633 to 5.1167
Difference	1.44±3.15	4.74±16.58		
%	3.80	12.72		

Table 3 depicts percentage of mean Hb and haematocrit fall among two groups. In TXA group, mean haemoglobin fall was 3.86% as compared to 16.15% in control group. Similarly, mean haematocrit fall was 3.80% as compared to 12.72% in control group.

Mean duration of labour in TXA group was 15.12±6.83 hours and in control group, it was 15.31±6.67 & t 3rd stage of labour, it was 18.48±7.49 and 18.67±7.49, respectively (p >0.05 NS).

A total of 44(8.8%) women in TXA group and 78(15.6%) in control group had postpartum haemorrhage (p< 0.001). A total of 21 (4.2%) women received blood transfusion TXA group and 44 (8.8%) women in control group (p< 0.001).

Comparison of management of postpartum haemorrhage in TXA group women shows that 33 (6.6%) women having PPH were managed by additional uterotonics (misoprostol, oxytocin and carboprost) and 11 (2.2%)women were managed initially by additional uterotonics and bleeding was not controlled then by balloon tamponade. Similarly, in control group, a total of 78 (15.6%) women were managed in which 55 (11%) women were managed by additional uterotonics and 23 (4.6%) women by both additional uterotonics and balloon tamponade was done respectively. On statistical analysis, the difference among both the groups was found to be significant (p< 0.001 and <0.05). No patient required hysterectomy for management of PPH and not associated with any maternal morbidity and mortality.

Table 4: Complications

Complications	TXA group(n=500) n(%)	Control group (n=500) n(%)	Statistical analysis
Non severe side effects			
Nausea/vomiting	34(6.8%)	25(5%)	p=0.227 NS p=0.07 NS p=0.546 NS
Headache	29(5.8%)	17(3.4%)	
Dizziness	25(5%)	21(4.2%)	
Allergic reactions	0(0)	0(0)	
Severe side effects			
DVT	0(0)	0(0)	
Renal impairment	0(0)	0(0)	
Liver impairment	0(0)	0(0)	
Seizures	0(0)	0(0)	
Maternal death	0(0)	0(0)	

Table 4 shows various type of complications which occurred during the study period among both the groups.

General physical examination of the patients among two groups *viz*. Blood pressure, pulse rate and respiratory rate was found to be comparable and thus statistically insignificant (p >0.05 NS). Apgar score in TXA group at 1 minute was 8.68±1.14 and at 5 minute, 9.1±0.58. In control group, it was 8.58±1.23 and 9.04±0.99 at 1 minute and 5 minute respectively (p >0.05).

Discussion

Postpartum haemorrhage is one of the leading causes of death in women who deliver after 20 weeks of gestation. The prevalence of PPH in India is 23%. Delayed diagnosis and poor management of PPH are associated with increased morbidity and mortality. Hence rapid recognition and diagnosis of PPH is essential for successful management.

In the present study mean age was 24.25±4.02 years in TXA group and 24.23±4.14 years in control group (p=0.945, NS). Our study was found to be comparable with the studies reported by Elhamid *et al*. and Ifunanya *et al*. [9, 10].

Mean gestational age at labour was 38.60±1.28 weeks in TXA group and 38.62±1.25 weeks in control group (p>0.05, NS). The results of the present study was almost similar to studies reported by Elhamid *et al*. and Ifunanya *et al*. [9, 10].

In TXA group, 294 (58.8%) and in control group, 280 (56%) patients were nulliparous in the present study, similar to study reported by Ducloy-Bouthors *et al*. [11].

In TXA group, it was found in 84(16.8%) women and 90(18%) women in control group. Oxytocin augmentation was found in 50(10%) women of TXA group and 56(11.2%) women in control group. Previous history of postpartum haemorrhage was observed in 12(2.4%) and 15(3%) women of TXA and control group respectively (p >0.05). These findings found to be comparable with the study reported by Ifunanya *et al*. [10].

In the present study, there was no statistical significant differences between TXA and control group regarding maternal and obstetric characteristics including maternal age, gestational age, parity, onset and induction of labour (p>0.05).

Blood loss at 3rd stage of labour in TXA group was 376.12±63.82 ml and in control group, it was 654.08±86.61 ml ($p< 0.001$, HS) and tranexamic acid found to be effective in reducing blood loss in study group. In Ducloy-Bouthors *et al*. there was 173 ml blood loss in tranexamic acid group and 221 ml in control group and demonstrated that high dose TXA reduced blood loss in women with PPH[11] which was found to be similar to the present study.

In present study, forty six (9.2%) women were in TXA group and eighty eight (17.6%) in control group needed additional uterotonics ($p< 0.001$, HS). In Roy *et al*. study, there was a significant difference in requirement of additional uterotonics, only one (2%) women in study group as compared to eleven (22%) in control group needed uterotonics ($p< 0.001$, HS) [12].

In the present study, mean haemoglobin in TXA group was 11.39±0.82 gm/dl at labour and after 24 hours of delivery was 10.95±5.12 gm/dl. In control group, mean haemoglobin at labour was 11.45±0.83 gm/dl and 9.60±1.41 gm/dl after 24 hours of delivery. The mean haemoglobin reduction (pre-post) suggested that tranexamic acid group (0.44±4.3) had a significantly lower mean haemoglobin changes as compared to control group (1.850±0.58) suggesting that blood loss was decreased after the use of tranexamic acid.

The study conducted by Ageuden *et al*. showed that the mean reduction in terms of haemoglobin in control group (2.38 gm/dl) was higher than the TXA group (1.05 gm/dl) in normal deliveries among primiparas [13].

In the present study, there was significant less fall in mean haemoglobin percentage in TXA group as compared to control group (3.86% versus 16.15%) with highly significant difference. In Aguedan *et al*. there was baseline haemoglobin change of 8.70% in TXA group as compared to 19.45% in control group [13]. Mean haematocrit at labour in TXA group was 37.89±9.95% and 36.45±13.10% after 24 hours of delivery. In control group, mean haematocrit at labour was 37.25±19.36% and after 24 hours of delivery was 32.51±2.78% respectively. On statistical analysis, there was significant less fall of 3.80% in TXA group as compared to 12.72% in control group. In a study conducted by Roy *et al*, mean haematocrit pre-delivery in study group was 33.04% and post-delivery was 32.64% and in control group, pre-delivery was 32.60% and post-delivery was 31.40% showed that post-delivery haematocrit was significantly reduced in control group as compared to study group [12].

Forty four (8.8%) women in TXA group and seventy eight women (15.6%) in control group had postpartum haemorrhage ($p< 0.001$). The incidence of PPH was significantly reduced after use of tranexamic acid in the present study. In Elhamid *et al*. study, there was significant reduction in incidence of PPH in TXA group as compared to control group (5 (4.2%) versus 18 (15%), $p< 0.01$) [9].

In the present study, twenty one (4.2%) women received blood transfusion in TXA group and forty four (8.8%) women in control group ($p< 0.001$). In Sentilhes *et al*. study, the incidence of blood transfusion after the use of tranexamic acid was found statistically non significant [14].

Forty four women had PPH and out of which 33 (6.6%) were managed medically and in 11 (2.2%) women, balloon tamponade was used along with additional uterotonics for control of PPH. In control group, a total of 78 (15.6%) women had PPH and 55 (11%) were managed by medically and 23(4.6%) by balloon tamponade along with additional uterotonics for control of PPH ($p< 0.001$ and <0.05).

In the present study, the most common side effect was nausea/vomiting which was found in 34(6.8%) in TXA group and 25(5%) in control group. Similar results also reported by Elhamid *et al*. which found to be comparable with the present study [9].

Neonatal outcome observed in study population was same in both the groups. Study reported by Elhamid *et al*. also showed no significant differences in either apgar scores at 1 and 5 minutes or neonatal intensive care admission among both groups (p>0.05) [9].

Conclusion

Tranexamic acid was found to be safe and effective in reducing blood loss after normal vaginal delivery. In the present study, there was less drop in haemoglobin and haematocrit in tranexamic acid group which reduced the risk of blood transfusion and additional uterotonics. Tranexamic acid was not associated with any severe adverse drug reactions like thrombosis and hence it can be safely used for prevention of PPH.

References

1. Murray SS, McKinney ES. Foundation of maternal–newborn and women's health nursing. 5th ed. Missouri: Sounders Elsevier Publication, 2010, Pp. 731-8.
2. El-Refaey H, Rodick C. Postpartum Hemorrhage: Definition, Medical and Surgical Management. A Time for Change. Br Med Bull Oxford J 2010;96:205-17.

3. Armbruster D. Tackling the biggest maternal killer. How the prevention of postpartum haemorrhage initiative strengthened effort around the world. Washington DC, 2009. Available at: https://path.azureedge.net/media/documents/MCHN_popphi_tbmk_final_rpt.pdf.
4. Yousef F, Haider G. Postpartum Hemorrhage: An experience at tertiary hospital. J Surg Pak 2009;14:2-5.
5. Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. Cochrane Database Syst Rev, 2000. CD000007.
6. Novikova N, Hofmeyr GJ. Tranexamic acid for prevention postpartum haemorrhage. Cochrane Data System Review 2010;7:1-20.
7. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. Br Med J 2012;344:1-13.
8. Matteson KA, Rahn DD, Wheeler 2nd TL, Casiano E, Siddiqui NY, Harvie HS *et al*. Nonsurgical management of heavy menstrual bleeding: a systematic review. Obstet Gynecol 2013;121:632-43.
9. Elhamid AA, Hamdy A, Sileem SA. Single large dose of tranexamic acid before vaginal delivery: Is it beneficial? Egypt J Hosp Med 2017;69:2601-6.
10. Ifunanya NJ, Chukwu IC, Nobert OC, Blessing O, Darlington-Peter UC, Uchenna OV. Tranexamic acid versus placebo for prevention of primary postpartum haemorrhage among high risk women undergoing caesarean section in abakaliki: a randomized controlled trial. Open J Obstet Gynecol 2019;9: 914-22.
11. Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H *et al*. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care 2011;15:117.
12. Roy P, Sujatha MS, Bhandiwad A, Biswas B. Role of tranexamic acid in reducing blood loss in vaginal delivery. J Obstet Gynecol India 2016;66:246–50.
13. Jo-An Aguedan MG, Martin CPC. The prophylactic use of tranexamic acid for the reduction of blood loss after cesarean section and vaginal delivery in primiparas at a tertiary hospital in Manila: A single-blinded randomized controlled trial. Philippine Obstet Gynecol Soc (POGS) Res 2015;39:1.
14. Sentilhes L, Lasocki S, Ducloy-Bouthors AS, Deruelle P, Dreyfus M, Perrotin F *et al*. Tranexamic acid for the prevention and treatment of postpartum haemorrhage. Br J Anaesth 2015;114:576-87.