Original Research Paper

Volume - 13 | Issue - 08 | August - 2023 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

THE EFFECT OF PROPHYLACTIC INTRAVENOUS TRANEXAMIC ACID (TXA) ON BLOOD LOSS AFTER VAGINAL DELIVERY IN WOMEN AT LOW RISK OF POSTPARTUM HAEMORRHAGE: A RANDOMISED CONTROLLED TRIAL

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ABSTRACT **Objective:** To determine the effect of prophylactic Tranexamic acid (TXA) blood loss after vaginal delivery in women at low risk of postpartum haemorrhage. **Methods:** A double-blinded, randomized controlled trial was performed. It involved 120 women in labour for a vaginal singleton delivery, at term i.e > 37 weeks. Women were randomly allocated to receive either one gram intravenous TXA or placebo in addition to 10 IU oxytocin after delivery of the baby. Calculated blood loss was determined based on haematocrit before delivery and 12–24 h post-delivery. The quantity of blood loss was measured during two time periods: from delivery of the baby to placental expulsion and from placental expulsion to the end of the second hour after childbirth. **Results:** The mean (SD) calculated total blood loss was 180ml in cases vs 390 mL in controls, (P = 0.0001). Patients treated with TXA had a reduction in blood loss in the 3rd stage of labour (P=.0007) and reduced blood loss from the delivery of placenta to the end of 2hours after delivery (P=.000026). **Conclusion:** Prophylactic TXA reduces blood loss after vaginal delivery in women with a low risk of postpartum haemorrhage. The prophylactic use of TXA may reduce blood loss, complications occurring due to blood loss. **Abbreviations:** PPH = postpartum haemorrhage, RCT = randomized clinical trials, TXA = tranexamic acid.

KEYWORDS : Postpartum Haemorrhage, Tranexamic Acid, Vaginal Delivery

INTRODUCTION:

Postpartum haemorrhage (PPH), defined by the World Health Organization as "blood loss from the birth canal in excess of 500 mL during the first 24 hours after delivery" [1]. Blood loss during the first 24 h after delivery is known as primary PPH, whereas blood loss from 24 h up to 6 weeks after delivery is termed late or secondary PPH. The bleeding is also classified according to its site. Hence primary PPH is also classified as either placental or extra-placental bleeding.

In African and Asian countries, where most maternal deaths occur, PPH alone accounts for more than 30% of all maternal deaths. However, the figures of maternal death attributed to PPH differ when compared between low-income and developed countries [1]. In Sub-Saharan Africa, the probability of dying during child birth is significantly higher and uterine atony accounting for 60% to 80% of PPH cases.

In India, incidence of PPH is reported as 2% - 4% after vaginal delivery and 6% after caesarean section; with uterine atony being the cause in about 50% cases [2]. PPH accounts for more than two-thirds of maternal mortality, occurring due to obstetric haemorrhage [3].

A combination of quality antenatal care, skilled care at birth by active management of third stage of labour, the availability of high quality emergency obstetric care (with trained medical personnel and adequate infrastructure) and improved access to these services are essential to save many maternal lives.

TXA is a synthetic amino acid lysine analogue that forms a reversible complex with both plasminogen and plasmin by binding at lysine-binding sites. Since TXA was first reported by Okamoto [4] in 1962, it has been regarded as a potent inhibitor of fibrinolysis. This drug has been used successfully to reduce blood loss and blood transfusion requirements in the management of several clinical gynaecologic conditions, including menorrhagia, and interventional surgical procedures such as cervical conization and myomectomy [5]. Recently, the CRASH-2 [6] trial reported that early administration of TXA significantly reduces mortality in bleeding trauma patients. Based on these studies, TXA has been included in the World Health Organization (WHO) list of essential medicines [5]. The recently updated PPH treatment guidelines prepared by the WHO state that TXA may be used if other measures fail, but point out that the evidence base is poor and call for further clinical trials of TXA in PPH [5]. There are some randomized clinical trials assessing the effect of TXA on postpartum blood loss. Most of the studies have been performed during non-haemorrhagic elective caesarean deliveries.

Since PPH is the major cause of maternal mortality, more efforts should be put in to prevent it, identify early and reduce its severity. This study was directed towards one such clinical trial involving antifibrinolytic drug, TXA and its significance in the reduction of PPH.

MATERIAL AND METHODS:

This double-blind randomised controlled trial was conducted at DR. Rajendra Prasad Government Medical College, at Tanda, over a period of 1 year. The study was approved by the Ethics Committee of DR. Rajendra Prasad Government Medical College, at Tanda. Written consent was obtained from all the participants. Study inclusion criteria included singleton pregnancy, women with period of gestation >37weeks to <42weeks, live foetus. The following exclusion criteria were selected: women with past history of postpartum haemorrhage, history suggestive of bleeding disorders, underlying heart, liver, pulmonary, kidney diseases, multiple pregnancies, macrosomia, polyhydraminos, history of deep vein thrombosis, pre ecclampsia, ecclampsia, intra uterine death.

The sample size was calculated based on reference study by Mirghafourvand et al [7] (2015). The assumed mean blood loss of 396ml in the control group and a minimum reduction of 20% in the intervention group, with a significance level of 5% and 80% for

detecting a significant difference in total blood loss, the sample size was calculated to be 52 in each group. Assuming a likelihood of 10% attrition, 60 women were assigned to each group.

Sample size so calculated was verified by calculating with Open Epi, Version 3, Open source calculator-SSCC, sample size for cross sectional study.

Following informed consent from the recruited women they were assigned into control and intervention groups. Haemoglobin and haematocrit levels were measured before and 12–24 h after delivery. Blood loss was calculated according to haematocrit before and after delivery. This estimate was derived by multiplying the calculated maternal blood volume (0.75 x { [maternal height (inches) x 50] + maternal weight in pounds x 25]}) by the percentage of blood volume lost ({ predelivery HCT – post-delivery HCT}/ predelivery HCT).

In this study, a digital scale (with a 1-g error range) was used for measuring the weight of placenta, gauzes, gowns, sheets and tampons. After delivery of the anterior shoulder, women in the intervention group received one gram intravenous TXA and the control group received one gram placebo in 200 mL normal saline over 10 min. . Both groups received 10 IU oxytocin intramuscularly (I.M) after the delivery of the baby as a part of active management of third stage of labour. The dose of oxytocin received and other medications administered were recorded in both the groups.

Umbilical cord was clamped and cut immediately after delivery, and after ensuring separation of placenta, with a mild traction on the umbilical cord together with the maternal effort, the placenta was delivered using Brandt –Andrew's manoeuvre.

Duration of the third stage was measured and recorded in minutes. Immediately after delivery, a sterile, graduated, disposable under buttock drape was placed beneath the woman to collect blood loss, which was recorded. Blood loss was measured during two periods of time. The first period was from delivery of the baby to delivery of the placenta, and the second was from placental delivery to the end of the second hour after childbirth. Blood-soaked gauzes, gowns, sheets and tampons were all weighed before and after use (when they were blood-soaked), and blood loss was estimated using Gai et al [8] method:

Quantity of blood (mL) = (weight of used materials -weight of materials prior to use)/1.05.

Maternal vitals were recorded every 15 minutes in the first hour and every 30 minutes in the second hour after delivery, and the calculated data was recorded.

The data was entered in Microsoft Excel 2010 spread-sheet and analyzed. The normality of quantitative data was assessed using Kolmogorov –Smirnov test. Independent t-test was used for comparing mean of measured blood loss, calculated blood loss and duration of third stage of labour and mean differences of haemoglobin and haematocrit levels before and after delivery between the groups. The categorical data was then expressed as rates, ratios, proportions.

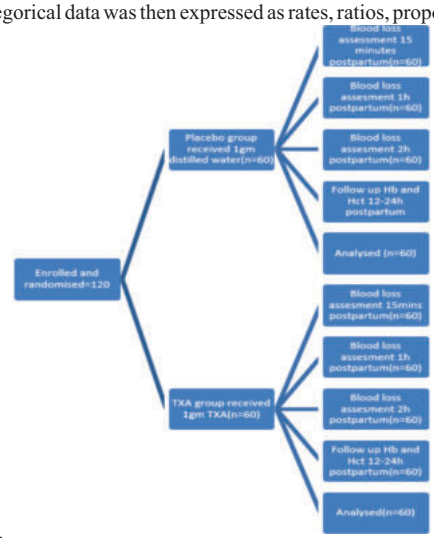

Figure 1

RESULTS:

There were no withdrawals from the study in either group, and all 120 pregnant women allocated into the groups were analysed (Fig 1). The two groups were similar in terms of socio-demographic, and also in terms of reproductive, delivery characteristics, newborn weight and placental weight.

Most (90%) deliveries were unassisted vaginal births with episiotomy. Eighty five percent of the participants had prenatal care during pregnancy. 40% had no previous experience of childbirth, and 79.16% of participants had received oxytocin in the first stage of delivery.

There was significant difference in the postpartum haemoglobin fall between the two groups (P = 0.0001). The haematocrit decline in the intervention group and in control group was statistically significant (P = 0.00001).

There was significant difference between the two groups in terms of the mean blood loss from delivery of the baby to placental delivery (P = 0.0007). The mean blood loss from placental delivery to 2 h postpartum in the intervention group was significantly less than in the control group (P = 0.000026). Additionally, the mean of calculated blood was significantly less in the intervention compared to the control group (182ml vs 309ml, P = 0.0001).

Table 1

Blood loss in cc	Cases no (%)	Controls no (%)	Total
10-50	45(75)	22(36.67)	67(55.83)
51-90	12(20)	24(40)	36(30)
91-130	3(5)	14(23.33)	17(14.16)
Total	60(100)	60(100)	120(100)

Table 2

Blood loss in cc	Cases no (%)	Controls no (%)	Total no (%)
10-50	5(8.33)	3(5)	8(6.67)
51-90	48(80)	25(41.67)	73(60.83)
91-130	4(6.66)	21(36)	25(20.83)
131-170	3(5)	7(11.66)	10(8.33)
>170	-	4(6.67)	4(3.34)
Total	60(100)	60(100)	120(100)

Table 3

Total blood loss in cc	Cases no (%)	Controls no (%)	Total no (%)
30-129	16(26.67)	3(5)	19(15.83)
130-229	42(70)	28(46.67)	70(58.33)
230-329	2(3.33)	28(46.67)	30(25)
330-379	-	1(1.66)	1(0.83)
>380	-	9(15)	9(7.5)
Total	60(100)	60(100)	60(100)

DISCUSSION:

The present study demonstrated that the total calculated blood loss was significantly lower in the TXA group than in the control group (Table3). Blood loss from delivery of the baby to the delivery of placenta (Table1) and blood loss from placental delivery to 2 h postpartum (Table2) in the intervention group was lesser than in the control group.

These results are consistent with the results of the following studies.

Yang et al [9] used TXA for preventing postpartum blood loss after normal vaginal delivery in 400 primiparous women in China. In this study the women were randomised into four groups: 1 g of TXA, 0.5 g of TXA, Aminomethyl benzoic acid or a placebo. TXA was given intravenously 2–3 min after the delivery and 10 units of oxytocin was injected immediately post-delivery. In the study by Yang et al., the difference between intervention and control groups was not significant in terms mean blood loss from delivery of the baby to placental delivery (P > 0.05), inconsistent with results of this study. They also reported that the mean total blood loss from foetal delivery to 2 h postpartum (243.3 vs 314.8 mL) and also the mean of blood loss from placental delivery to 2 h postpartum (129.7 vs 178.2 mL) were significantly less in the intervention group than in the placebo group (P < 0.05).

Gungorduk K et al [10] (2011) found that the mean estimated blood loss at the third and fourth stages of labour was significantly lower in the experimental group than that in the placebo group(261.5 ± 146.8 mL versus 349.98 ± 188.85 mL, respectively; p < 0.001). The frequency of

postpartum haemorrhage > 500 mL was also lower in the experimental group 4(1.8%) compared with that in the placebo controls (15, [6.8%]; relative risk, 3.76; 95% confidence interval, 1.27 to 11.15; p = .01).

Mirghafourvand et al [7] , in the study " prophylactic use of TXA in women with low risk of PPH" found that there was no significant difference between the two groups in terms of mean blood loss from delivery of baby to the delivery of the placenta(p=0.523). The mean blood loss from placental delivery to 2 h postpartum in the intervention group was significantly less than in the control group (P < 0.001). Additionally, the mean of calculated blood loss based on haematocrit was significantly less in the intervention compared to the control group (mean difference: 140, 95% CI: 9–272, P = 0.036). The frequency of calculated PPH more than 1000 mL was also lower in the TXA group (7% vs 18%, P = 0.048) than in the placebo group.

Movafegh et al [11] . and Senturk et al[12]. reported that the mean of blood loss during the intra partum period in the intervention group was also significantly less than that in the control group. The results were similar to our findings.

Limitation in this study was the relatively small sample size.

CONCLUSION:

In the TXA group, when compared with the placebo group, the mean calculated blood loss and measured blood loss from delivery of the baby to delivery of the placenta and delivery of placenta to 2 h postpartum in the intervention group were less than that in the control group that shows prophylactic effects of TXA on PPH. We speculate that TXA could be used as an effective complimentary medication, together with other ecbolic agents, to prevent postpartum blood loss in women with a low risk of postpartum haemorrhage and hence reduces complications due to PPH.

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