Section: Obstetrics and Gynaecology

Original Research Article

EFFECT OF TRANEXAMIC ACID ON BLOSS AS AN ADJUVANT TO UTEROTONICS AT ELECTIVE CAESAREAN SECTION: A DOUBLE-BLIND RANDOMISED CONTROLLED TRIAL

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Abstract

Background: Obstetric haemorrhage is a threat to antenatal women and is a major cause of maternal morbidity and mortality. India is in the phase of achieving the sustainable development goal of reducing the maternal mortality rate to 70 per 100000 live births. This study has shown the effect of tranexamic acid, an antifibrinolytic, in preventing postpartum haemorrhage during caesarean section. **Aim:** This study aimed to investigate the effect of tranexamic acid as an adjuvant in elective caesarean section. **Materials and Methods:** The participants were randomised into a tranexamic acid group (n=50) and a placebo group (n=49). They were administered either tranexamic acid or a placebo (sterile water) at 10 mg/kg body weight. As per the department's protocol, all women were administered oxytocin as an intravenous infusion during caesarean section. Blood loss was calculated during the caesarean section. Among the 100 antenatal women recruited in this study, the results were analysed in 99 women. **Results:** The mean blood loss in tranexamic acid and placebo groups were 557.30±187.16 ml and 673.22±324.54 ml, respectively. The difference in mean blood loss was 115.92 ml between the groups, which was statistically significant (p=0.03). No notable maternal or perinatal side effects were observed in this study. **Conclusion:** The use of tranexamic acid as an adjunct to routine uterotonics in caesarean sections significantly reduced blood loss.

INTRODUCTION

Pregnancy and childbirth are considered second births for women. Since age, maternal death during parturition due to haemorrhage has been one of the biggest threats to women's lives, especially in developing countries. There has been a consistent march towards reducing maternal mortality during the last two decades by implementing the Millennium Development Goals 2015. Although Southern Asia has shown a 64% reduction in maternal mortality (1990-2013), we are achieving a 75% reduction in maternal mortality with the set goal of Sustainable Development Goals 2030.[1]

Haemorrhage is the most common cause of maternal mortality and morbidity, and various preventable methods and strategies have emerged in the field of research. Recently, tranexamic acid has been considered a promising drug for reducing blood loss in elective surgeries and caesarean sections. Therefore, it can perfectly complement uterotonics in preventing postpartum haemorrhage.

This study aimed to investigate the effect of tranexamic acid on blood loss and to observe tranexamic acid's maternal and foetal side effects.

MATERIALS AND METHODS

This double-blind, randomised controlled trial was conducted on 100 women in the Department of Obstetrics and Gynecology, JIPMER, Puducherry, between 2015 and 2016, after the postgraduate research monitoring committee and Institute Ethics Clearance. (PGRMC NO: PGMRC/OG/02/2014; Institute Ethics: JIP/IEC/SC/2014/1/480).

Inclusion Criteria

All primi gravidae/multigravidae with a singleton pregnancy aged between 18 and 45 years were scheduled for elective caesarean section at term gestation under spinal anaesthesia.

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Exclusion Criteria

Women with obstetric/co-morbid medical risk factors for PPH, such as grand multipara, antepartum haemorrhage (abnormal placentation), polyhydramnios, macrosomia, severe anaemia, and co existing obstetric conditions such as pre-eclampsia, HELLP syndrome, and acute fatty liver of pregnancy (AFLP) were excluded.

One hundred antenatal women were divided into 50 groups (tranexamic acid and placebo groups). After recruitment and obtaining written consent, participants were allowed to participate in the trial. They were assigned random numbers according to a block randomisation chart. Demographic parameters were noted, and the pre-operative Hb and haematocrit levels were measured a day before surgery. Vital parameters such as pulse rate and blood pressure were also recorded. The opaque sealed envelopes containing the agent (tranexamic acid or placebo), assigned as per the randomisation chart, were given to the anaesthetist.

The agent in the envelope (either tranexamic acid or placebo) was diluted in 100 ml of normal saline at a dose of 10 mg/kg body weight and administered to the participants as a slow intravenous infusion approximately 20 minutes before the skin incision. Cadre senior registrars and surgeons performed all caesarean sections to eliminate bias of expertise. The electronic weighing machine was used to weigh the dry mops, pads, and gauze. After placental delivery, the suction bottle was changed to minimise bias in calculating blood loss due to mixing amniotic fluid.

All the participants were given 1.5 IU of oxytocin in 500 ml of Ringer lactate as slow IV infusion as a part of a prophylactic measure for the prevention of postpartum haemorrhage and 1.5 IU in another 500 ml of Ringer lactate if necessary (as per department protocol). All mops, gauze, and pads used in the surgery were weighed using an electronic weighing machine. After delivery of the placenta, blood in the suction bottle was measured and noted.

Blood loss was calculated using the following formula: The sum of blood collected in the suction bottle and the loss calculated from the soaked mops, gauzes, and pads gave the total blood loss during the caesarean section. In addition to oxytocin and tranexamic acid, other uterotonic drugs, such as methergine, carboprost (PGF2 α), and misoprostol (PGE1), were administered whenever necessary. Blood pressure and pulse rate were recorded in the 2nd hour after surgery. Postoperative haemoglobin and haematocrit levels were measured using an auto analyser 48 hours after surgery. The participants were frequently interrogated for the side effects of the drug tranexamic acid until discharge.

Statistical Analysis

Continuous variables, such as mean blood loss, pre-operative and postoperative haemoglobin, haematocrit, and blood pressure, were analysed in terms of mean ± SD using an unpaired t-test. The difference in haemoglobin and haematocrit between the pre-operative and postoperative periods of the groups was analysed using the Mann-Whitney U test. All statistical analyses were performed at a 5% significance level ($p<0.05$) using SPSS 19.

RESULTS

This study recruited 100 antenatal women with singleton pregnancies planned for elective caesarean section at term who fulfilled the inclusion criteria. Of the 100 women, 99 were analysed, and one was excluded because of anaesthesia-related complications.

Variables such as age and parity between the tranexamic acid and placebo groups were not statistically significant. The mean age of women in the tranexamic acid group was 28.6 (± 4.96), and in the placebo group was 26.4 (± 4.12). There was no significant difference in age between the groups($p=0.20$). [Table 1]

The distribution of women using parity was homogeneous; most were multigravidas in both groups. There were only seven primigravidas in the tranexamic acid group and nine in the placebo group. There was no significant difference in parity between groups ($p =0.89$).

The mean pre-operative haemoglobin was 10.53 (± 1.09) g/dl in the tranexamic acid group and 10.48 (± 1.04) g/dl in the placebo group. The mean haematocrit in the tranexamic acid group was 30.66 (± 2.89) %, and that in the placebo group was 30.67 (± 4.27) %, which was not statistically significant ($p=0.99$). The two groups showed no significant differences in pre-operative systolic and diastolic blood pressure and pulse rate.

The common indications for caesarean section in the groups were doubtful scars, two previous LSCS, malpresentation, cephalopelvic disproportion, and IVF conception. The distribution of women in both groups based on the indications for caesarean section was similar. [Figure 2]

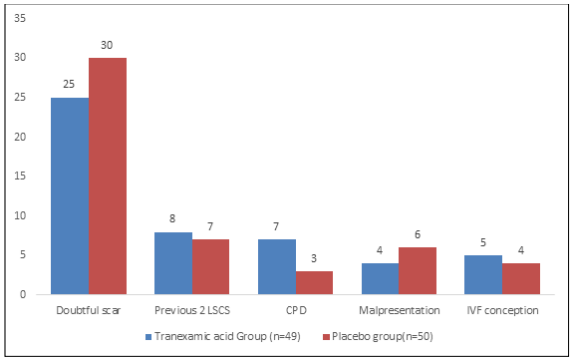

Figure 1: Distribution of women based on the indications for caesarean sections

The mean blood loss in the tranexamic group was 557.30 ± 187.16 ml and 673.22±324.54 ml in the placebo group. The mean blood loss in the two groups was statistically significant ($p=0.03$). [Table 1]

The groups' postoperative blood pressure and pulse rate did not show a statistical difference from the pre-

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operative blood pressure. The mean postoperative haemoglobin and haematocrit levels in the tranexamic acid group were 10.27 (±1.06) g/dl and 30.27 (±1.94) %, respectively. Similarly, the placebo group showed postoperative haemoglobin and haematocrit as 10.44 (±0.98) g/dl and 30.76 (±2.28), respectively. [Table 2]

The difference in the mean haemoglobin, haematocrit, blood pressure, and pulse rate between the postoperative and pre-operative periods of the groups was calculated using the paired sample "t" test. No statistically significant difference in haemoglobin levels between the groups during the pre-operative and postoperative periods (p=0.08). Similarly, the difference in the haematocrit between the pre-operative and postoperative periods between the groups was not statistically significant (p=0.48). [Table 3]

Of the total women (99) who underwent caesarean section, seven women had blood loss of more than 1000 ml. Of the seven women who had PPH, only one was from the tranexamic acid group, in contrast to the six women in the placebo group. [Figure 2]

The number of women who required additional uterotonic agents was one in the tranexamic acid group and six in the placebo group. In the placebo group, two women required methergine (0.2 mg) and four women required carboprost (250 µg) + methergine (0.2 mg) to control bleeding. In the tranexamic acid group, one woman required methergine (0.2 mg) to reduce bleeding during the caesarean section. There was no need for the further use of additional uterotonic drugs during the postoperative period. None of the patients in the groups required a blood transfusion.

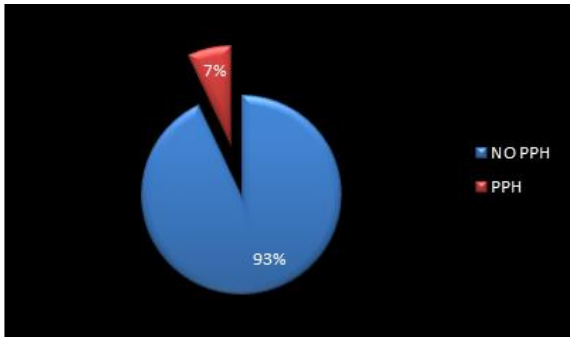

Figure 3: Distribution of PPH between the groups

All neonates were born with good APGAR scores. Minor transient side effects of tranexamic acid, such as nausea, vomiting, and headache, were observed in the participants during the hospital stay (until postoperative day 4). No minor side effects were observed among the women in the groups. This study did not evaluate thromboembolic events because the sample size was too small for adequate power. However, the participants in this study did not develop signs or symptoms of thromboembolic events.

Table 1: Characteristics of variables between the study and control groups

Variable	Tranexamic Acid Group	Placebo Group	P-value
Age (years)	28.59 ± 4.96	26.39 ± 4.12	0.2
Parity	1.08 ± 0.70	1.10 ± 0.61	0.89
Pre-operative Haemoglobin (gm%)	10.53 ± 1.09	10.48 ± 1.04	0.83
Pre-operative Haematocrit (%)	30.66 ± 2.89	30.67 ± 4.27	0.99
Pre-operative SBP (mm of Hg)	113.88 ± 9.76	114.66 ± 11.24	0.71
Pre-operative DBP (mm of Hg)	74.33 ± 6.76	75.54 ± 6.91	0.38
Mean blood loss (in ml)	557.30±187.16	673.22±324.54	**0.03**

Table 2: Postoperative outcome variables between the study and control group

Postoperative	Tranexamic acid Group	Placebo group	P-value
Systolic blood pressure (mm Hg)	117.43±8.92	119.00±8.10	0.36
Diastolic blood pressure (mm Hg)	76.43±6.58	76.72±6.33	0.82
Pulse rate (beats per minute)	85.82±8.77	84.66±9.8	0.53

Table 3: The difference in haemoglobin between the pre-operative and postoperative periods in the groups

		Tranexamic acid Group	Placebo group	P-value
Haemoglobin (g/dl)	Mean pre-operative	10.53 ± 1.09	10.48 ± 1.04	0.08
	Mean postoperative	10.27 ± 1.06	10.44 ± 0.98	
	Mean difference	0.25 ± 0.68	0.04 ± 0.49	
Haematocrit (%)	Mean pre-operative	30.66 ± 2.89	30.67 ± 4.27	0.48
	Mean postoperative	30.27 ± 1.94	30.76 ± 2.28	
	Mean difference	0.39±2.01	0. 08±4.36	

DISCUSSION

Tranexamic acid is a synthetic derivative of lysine that binds to lysine binding sites in the plasminogen molecule via non-competitive inhibition. The fibrin polymers generated from the coagulation pathway are prevented from binding to plasminogen molecules, thereby inhibiting the fibrinolytic pathway. Surgical fields, including general surgery, orthopaedic surgery, neurosurgery, cardiopulmonary bypass, spinal transplantation surgeries, and abnormal uterine bleeding, have used tranexamic acid as an essential drug for the management of bleeding.[2,3]

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One of the largest trials to study the effect of tranexamic acid in bleeding, the CRASH-2 trial (Clinical Randomization of An Antifibrinolytic in Significant Haemorrhage -2), studied the effect of tranexamic acid in 20,000 randomised adult trauma patients. The tranexamic acid group showed a decrease in 4.9% mortality due to haemorrhage, which was significantly lower than that in the placebo group (5.7%).[4] Blood is a scarce source in developing countries, and the risks associated with transfusions, such as HIV and Hepatitis B, are high. Hence, antifibrinolytic drugs such as tranexamic acid and aprotonin are important in preventing surgical bleeding.

Caesarean section is associated with a higher risk of postpartum haemorrhage. A blood loss of more than 1000 ml is considered a postpartum haemorrhage. The incidence of blood transfusions was also higher in these patients. Hence, newer agents, such as tranexamic acid, an antifibrinolytic, have been used to reduce the incidence of PPH and blood transfusion. This study aimed to investigate the effect of tranexamic acid on blood loss during caesarean sections. The average age of the individuals in the tranexamic acid group was 28 years, and the average age in the placebo group was 27 years. This shows that the age groups of the participants were similar in this study. Most women in both groups were multigravidas, and parity was not statistically different. Bhatia and Deshpande recruited 100 primigravidas who were planned for caesarean section at term. There were no differences between the groups in the demographic variables of age, parity, and indication for caesarean sections. Women with medical disorders such as renal and liver disease and obstetrical conditions such as placenta previa, abruption placentae, polyhydramnios, severe anaemia, or a history of thromboembolic disorder were excluded from the study. Hence, individuals in both groups had homogenous demographic characteristics.[5]

The present study showed a significant reduction in blood loss by using tranexamic acid as an additional prophylactic drug during caesarean sections. The mean blood loss calculated during the tranexamic acid and placebo groups in the caesarean section was 557.30±187.16 ml and 673.22±324.54 ml, respectively. The difference in mean blood loss between the tranexamic acid and placebo groups was 115.9 ml, which was statistically significant. A similar randomised case-controlled study was conducted by Gobbur et al. on 100 antenatal women who underwent caesarean section (both emergency and elective), and showed a mean blood loss of 71.4 ml in the tranexamic acid group. They concluded that tranexamic acid significantly reduced blood loss during caesarean section ($p = 0.004$) with no major side effects.[6]

Babita et al. conducted a case-control study on blood loss using tranexamic acid during caesarean section. They administered one gram of tranexamic acid as an intravenous infusion to the study group, while the control group did not receive any treatment. All patients in the intravenous and intramuscular groups were administered 10 IU oxytocin. They were also administered 400 µg sublingual misoprostol. The mean blood loss in the study group was 222.07 (± 97 ml) and 274.5 ml in the control group, and this was statistically significant ($p < 0.05$).[7] The reduction in blood loss in the tranexamic acid group was statistically significant in subsequent studies.[8,9]

The tranexamic acid dose used in the present study was 10 mg/kg body weight, which is more appropriate for its therapeutic action. The present study used only oxytocin as a routine oxytocin unless indicated, unlike other studies that used other uterotonics, such as misoprostol and carboprost. Hence, the effect of tranexamic acid on blood loss was analysed more effectively. Moreover, the present study was designed as a placebo-controlled, double-blind trial to minimise observer bias in calculating blood loss during caesarean section.

Xu et al. conducted a study on the role of tranexamic acid in preventing postpartum haemorrhage during caesarean sections on 174 primigravida. It was found that 19 women in the tranexamic acid group and 28 in the control group had postpartum haemorrhage. However, they did not mention the characteristics of the women in the groups with postpartum haemorrhage. The sample size of this study was not sufficiently powered to comment on the role of tranexamic acid in the prevention of postpartum haemorrhage.[10]

In the placebo group, six women had a blood loss of more than 1000 ml and required additional uterotonic drugs other than oxytocin-like methergine and carboprost. In the tranexamic acid group, one woman had a blood loss of more than 1000 ml and required an additional uterotonic drug, methergine. There was no need for blood transfusions in either group.

The effect of tranexamic acid on the incidence of postpartum haemorrhage and the need for additional uterotonic drugs in the groups cannot be ascertained clearly, as the sample size was small. Hence, further trials with larger populations are needed to establish the effect of tranexamic acid in preventing postpartum haemorrhage.

Senturk et al. found that the decline in haemoglobin was comparatively less in the tranexamic acid group than in the placebo group ($p=0.034$). The difference in haematocrit between the pre-operative and postoperative periods in the groups was also significant, with a p-value of 0.002.[11] A study by Chandrakala and Venketeswaralu on the effect of tranexamic acid on blood loss in caesarean section showed that the decline in haemoglobin level in the postoperative period between the groups was not statistically significant.[12]

Tranexamic acid, an antifibrinolytic drug, belongs to category 'B' of drug classification. The expected minor side effects are nausea, vomiting, headache, hypotension, and major side effects such as deep vein thrombosis and foetal thrombosis. Pregnancy and postpartum period are considered hypercoagulable

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states because of the change in the proportion of coagulant and anticoagulant factors that occur during pregnancy. Tranexamic acid increases the risk of thromboembolism five to six times in women undergoing caesarean section.[13] Tranexamic acid has been used as a prophylactic agent to reduce blood loss in caesarean sections in many trials with no reported major side effects.

In their study, Goswami et al. used various doses of tranexamic acid, such as 10 mg/kg and 15 mg/kg body weight, and did not report any major side effects. Only two patients in the study group who received 15 mg/kg body weight tranexamic acid experienced nausea and vomiting.[14] Gastrointestinal side effects such as nausea and vomiting occurred in 10% and 4% of the cases in the study group, respectively, in a study conducted by Chandrakala and Venkateswaralu. They did not report any major side effects.[12] The present study did not report any maternal or neonatal side effects; the patients were discharged in good physical condition.

CONCLUSION

Tranexamic acid can be suggested as a biochemical adjunct to oxytocin during caesarean section because it reduces blood loss. This is expected to be highly beneficial in women who are at risk of postpartum haemorrhage (women with anaemia, abruptio placentae, placenta previa, multiple pregnancies, and polyhydramnios) because even a small amount of blood loss will affect maternal health. It may be concluded that tranexamic acid, as an adjunct to routine uterotonics during caesarean section, has significantly reduced blood loss. No notable maternal or neonatal health side effects were observed during the study.

Recommendations

However, the safety concerns of tranexamic acid on maternal and foetal health cannot be established with a small sample size. Safety concerns regarding the use of tranexamic acid in caesarean sections, especially for its thromboembolic potential, need further evaluation in larger trials. Hence, large-scale multicentre trials targeting the safety profile of tranexamic acid are required before its routine use in clinical practice.

Conflict of interest: The authors (s) declare no conflicts of interest regarding the publication of this paper.

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