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Original Research Article

Tranexamic acid in prevention of postpartum hemorrhage in elective cesarean section

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ABSTRACT

Background: Postpartum hemorrhage is a common and occasionally life-threatening complication of labor. Cesarean section is associated with more blood loss in compared to vaginal delivery. Despite, there is a trend for increasing cesarean section rates in both developed and developing countries thereby increasing the risk of morbidity and mortality, especially among anemic women. The objective of this study was to evaluate the effect of preoperative administration of intravenous Tranexamic acid on blood loss during and after elective cesarean section.
Methods: This was a prospective, randomized controlled study with 160 eligible pregnant women of 37 or more period of gestation. They were all planned for elective cesarean section and were randomized into two groups either to receive 10ml (1gm) of Tranexamic acid intravenously or 10ml of normal saline. Blood loss was measured during and for 24 hours after operation.
Results: The mean estimated blood loss was significantly lower in women treated with Tranexamic acid compared with women in the placebo group (392.13 ml±10.06 vs 498.69 ml±15.87, respectively; $p<0.001$). The mean difference in pre-operative and post-operative hemoglobin levels was statistically significant in the Tranexamic acid group than in the control group (0.31±0.18 vs 0.79±0.23, respectively; $p<0.001$).
Conclusions: Pre-operative use of Tranexamic acid is associated with reduced blood loss during and after elective cesarean section. In a developing country like ours where postpartum hemorrhage is a major threat to the life of the mothers, it seems to be a promising option.

Keywords: Cesarean section, Postpartum hemorrhage, Tranexamic acid

INTRODUCTION

Maternal mortality remains a major challenge to health systems worldwide, despite of recent advances developed in modern era for its prevention. Postpartum hemorrhage (PPH) is a common and occasionally life-threatening complication of labor. PPH still accounts for nearly one-quarter of all maternal deaths globally.[1] Blood loss during Cesarean Section (CS) is more than vaginal delivery and hence authors can say that there is an increase in association between CS and PPH. There is an increasing trend for CS rates around the world.[2] Extensive tissue injury, as may occur during surgery, may lead to coagulopathy and bleeding.[3] Because blood transfusion is not always available, there is a need for strategies, in addition to standard uterotonics, to reduce blood loss during CS.

Anti-fibrinolytic drug, namely Tranexamic acid (TA) is one of them. TA is a synthetic derivate of the amino acid lysine. It reversibly inhibits the activation of plasminogen, thereby inhibits fibrinolysis and reduces

blood loss. TA has shown to decrease blood loss and need for transfusion in various surgeries thereby reducing the risk of death in bleeding trauma patients.[4-6] However, there are very few studies that have shown the benefits of using TA in CS to reduce the incidences of PPH. In addition, Cochrane systematic review, based on two RCT, has also concluded that TA decreases PPH. But it reported on only a few outcomes. Thus, further investigations are needed to confirm the efficacy and safety of this intervention in reducing the incidences of PPH.

Hence, this study was conducted to evaluate the effect of preoperative administration of TA on blood loss during and after elective CS delivery.

METHODS

The study was carried out in the Department of Obstetrics and Gynecology of BPKIHS; a tertiary care hospital in eastern Nepal, Dharan, during the period from September 2015 to August 2016. The study was conducted only after approval by Institutional Review Committee (IRC) of BPKIHS. Written informed consent was taken as per Helsinki guidelines prior to randomization into study and control group (Figure 1).

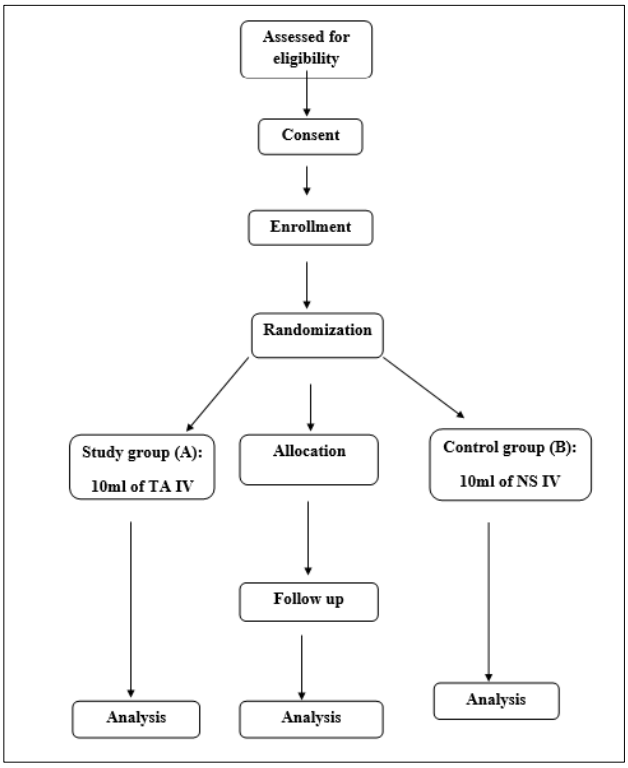

Figure 1: Flow chart of the study designed.

Inclusion criteria

- Pregnant women, with singleton pregnancy of 37 or more weeks of periods of gestation, who were planned for elective CS were approached to be included in the study.

Exclusion criteria

- Women with history of medical disorders (heart disease, liver, renal disorders, diabetes mellitus, hypertension or a known coagulopathy), with history of sensitivity to TA or contraindications to TA or patients taking anticoagulant therapy were considered ineligible for the study.

Among patients admitted for elective cesarean section, 160 patients fulfilling the inclusion and exclusion criteria were selected. Those 160 patients were randomly allocated to two groups using computer generated random table. Blood sample was taken to measure hemoglobin. Women in the study group were given 10ml (1g) of TA intravenously while women assigned to control group received 10ml of normal saline, about 10 minutes prior to surgery.

Skin incision was given, and rectus and peritoneum were opened up. Lower uterine transverse incision was given, and baby delivered. All the participants received usual dose of 20IU of oxytocin in 500ml of ringer lactate via infusion following delivery of the baby. Assessment of blood loss was started immediately after the uterine incision. Liquor and blood were collected by suction catheter separately.

The volume of blood loss in CS was assessed by the standard procedure. The dry weight of tetras used in the operation was taken before the operation. The wet weight of tetras weighed after operation. Then the difference was calculated. Blood volume was measured from the suction jar. The blood clots measured in grams were supposed to be equivalent to ml of blood. Clots equivalent to one closed fist considered equivalent of 500ml of blood. One gram of weight difference was taken equivalent to 1 ml. Total Blood loss was calculated. Additional oxytocics were used if required.

After delivery, APGAR score of the neonates was noted and they were further observed for next 24 hours to see if there was any need for additional intervention.

Patients were followed up to 24 hours for primary PPH. Blood loss was measured up to 24 hours postoperatively. The weight of all the pads used was weighed. Total blood loss up to 24 hours was calculated. In addition, hemoglobin level of the patient following 24 hours of surgery was compared to that prior to surgery.

In total, 160 patients (80 in each group) were enrolled in the study. With reference to the literature review,7 the estimated sample size came out to be 77 in each arm, taking into consideration the confidence level of 95% and power of study of 80% and adding 10% for various

errors. Hence, for easy calculation, 80 patients were considered in each arm in an average.

Statistical analysis

- Collected data were entered in Microsoft Excel 2007 and converted into SPSS 11.5 for statistical analysis.

The primary outcome was estimation of mean blood loss intra-operatively and post-operatively (up to 24 hours). Secondary outcomes included comparison between pre-operative and post-operative hemoglobin (24 hours apart), use of additional uterotonics additional surgical intervention to control PPH, neonatal outcome, and need for blood transfusion.

RESULTS

Patients were divided into case (TA recipient) and control (TA non-recipient) groups based on age, parity, period of gestations and history of previous section. The differences between the two groups based on these distributions were not significant statistically, and hence they were comparable (Table 1).

Table 1: Distribution of age group (in years), parity, period of gestation (in weeks) and history of previous section of participants into two study groups.

Character	Category	Group		P value	Remarks
		Tranexamic acid recipient n (%)	Tranexamic acid non-recipient n (%)		
Age group (In years)	≤20	4 (44.4)	5 (55.6)	0.520	Not Significant
	21-25	21 (52.5)	19 (47.5)		
	26-30	38 (55.9)	30 (44.1)		
	31-35	15 (38.5)	24 (61.5)		
	≥36	2 (50.0)	2 (50.0)		
Parity group	Nulliparity	18 (62.1)	11 (37.9)	0.125	Not Significant
	Primiparity	53 (50.5)	52 (49.5)		
	Multiparity	9 (34.6)	17 (65.4)		
Period of gestation group (in weeks)	37	8 (44.4)	10 (55.6)	0.705	Not Significant
	38	30 (54.5)	25 (45.5)		
	39	33 (49.3)	34 (50.7)		
	≥40	9 (45)	11 (55)		
History of previous section group	Yes	58 (47.5)	64 (52.5)	0.265	Not Significant
	No	22 (57.9)	16 (42.1)		

Table 2: Relationships between blood loss and participants in two study groups.

Character	Mean±SD		P value
	TA recipient	TA non-recipient	
Intra-operative blood loss	345.63±8.01	443.31±14.69	<0.001
Post-operative blood loss	46.50±6.29	55.38±6.30	<0.001
Total blood loss	392.13±10.06	498.69±15.87	<0.001

t-test was applied to various values in case and control groups and, thus, the results obtained. Mean intra-operative blood loss, mean post-operative blood loss and mean total amount of blood loss calculated among cases and controls is demonstrated in Table 2. All these interpretations were found to be significant statistically.

The mean pre-operative hemoglobin value recorded in case and control groups was not significant statistically. However, the mean post-operative hemoglobin recorded in cases (11.53 gm/dl with SD of 0.78) was statistically significant as compared to that of control group (11.09 gm/dl with SD of 0.74).

Similarly, mean difference in pre-operative and post-operative hemoglobin calculated among case group and control group (0.31 gm/dl±0.18 and 0.79 gm/dl±0.23 respectively) as shown in Table 3 was found to be significant statistically.

In this study, none of the individual either in case or control group needed additional oxytocics or any additional surgical intervention to control PPH. None of the candidate needed any blood transfusion. All of the newborns were alive and healthy at the time of delivery with APGAR score of 7, 8 and 9 at 1, 5 and 10 minutes respectively. Also, none of the newborns either of case or control groups were admitted in NICU.

Table 3: Relationships between investigations and participants in two study groups.

Character	Mean±SD		P value
	TA recipient	TA non-recipient	
Pre-operative hemoglobin	11.83±0.78	11.88±0.68	0.673
Post-operative hemoglobin	11.53±0.78	11.09±0.74	<0.001
Difference in pre-operative and post-operative hemoglobin	0.31±0.18	0.79±0.23	<0.001

DISCUSSION

Postpartum hemorrhage is notorious for being the leading cause of maternal morbidity and mortality worldwide.[8] Hence, effective and efficient interventions are being tried since ages for the prevention of PPH. TA has been used to treat bleeding for many years.[9] In recent years, TA has been used to prevent or decrease intra- and post-operative blood loss in various surgeries.[10-12] Its use in obstetric for prevention of postpartum hemorrhage through reduction of postpartum blood loss after CS or vaginal delivery is rather new. According to a recent systematic review of antifibrinolytic agents in PPH, a reduction in blood loss of 92 ml was found (CI 76 to 109 ml).[8]

Considering this potential scope of TA to aid in the reduction of the incident of PPH, the very study was conducted that investigated the efficacy of TA in reducing blood loss during and after an elective CS. In addition, this study also estimated the difference in pre-operative and post-operative hemoglobin levels to estimate blood loss, because the estimation of blood loss during CS is inaccurate and subjective due to the admixture with amniotic fluid.[13]

The result of present study showed significant reduction of intraoperative, postoperative and total blood loss in TA receiving group in comparison to NS receiving group. This finding is found to be consistent with the study conducted by Ali Movafegh et al, Ming-ying Gai et al, Kemal Gungorduk et al and Afshan Shahid et al who reported similar reduction in both intraoperative and postoperative blood loss, except for slight differences.[7,14-16] These differences can be attributed to the difference in the sample sizes, different methodologies for the measurement of blood loss and different duration of observation.

The mean pre-operative hemoglobin value of cases was comparable to that in control group. In contrast, mean post-operative hemoglobin drop in case and control group was significantly different. This finding is similar to the study of Amr H. Yehia et al and H. Abdel-Aleem et al strongly favoring the result of present study.[17,18]

According to the studies conducted by Gungorduk K et al and Ali Movafegh et al, it was seen that increased number of women in the placebo group than in the TA group required additional uterotonic agents.[7,14] However, in this study, neither the study nor the control group needed additional uterotonics or additional surgical interventions for the control of PPH.

Also, none of the participants needed blood transfusion. This could be an incidental finding. It might be because none of the participants included in this study had high risk factors like placenta previa, anemia, multiple pregnancy, etc.

In addition to this, the study showed no difference between the case and control groups in terms of neonatal morbidities. None of the newborns needed NICU admission. The APGAR scores observed at birth of neonates and at 5 minutes did not differ significantly between the control and case groups. Similar findings were also noted in study of Gungorduk K et al.[7]

In the present study, thromboembolic events or other side effects of the drug were not evaluated because the sample size was too low for adequate power. However, none of the women showed any signs or symptoms of thromboembolic events or other side effects. Moreover, this finding is favored by the study conducted by Lindoff et al that showed no evidence of thrombogenic effect of tranexamic acid in high risk group of women with complicated pregnancies undergoing CS.[19]

Limitations of the study: This study was randomized with adequate allocation concealment. The strength of this study includes its design as a randomized, double-blind, placebo-controlled trial. However, exclusion of high-risk cases for PPH during the enrollment can be considered as limitation of the study. As the study was mainly powered to evaluate the effect of preoperative administration of intravenous TA on blood loss during and after elective CS delivery, authors could not comment on the possible complications like thromboembolic events, use of additional uterotonic agents, and need for blood transfusion as the sample size needed to evaluate such parameters comes out to be much larger.

CONCLUSION

The present study provides evidence that pre-operative use of TA is associated with reduced blood loss during and after elective CS. The maternal and neonatal outcomes did not differ significantly, and no adverse outcome was reported. Thus, TA can be used effectively in women undergoing CS.

In a developing country like ours, where PPH is a major threat to the life of the mothers, it seems to be a promising option. However, the study was not powered to assess its safety especially the thromboembolic complications.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Review Committee (IRC) of BPKIHS, Nepal

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