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Role of Prophylactic Tranexamic Acid in Reducing Blood Loss during and After Lower Segment Caesarean Section

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Abstract

This is a prospective randomized control which studies intravenous tranexamic acid administration and its role in minimizing blood loss in caesarean delivery. The study was carried out in the department of obstetrics and gynecology (inpatient only) of Central Hospital, South Eastern Railways, Kolkata from August 2018 to August 2020. The patients were selected randomly and assigned into two groups to receive either tranexamic acid or placebo i.e. Normal Saline. The study concluded that prophylactic use of tranexamic acid significantly reduces the amount of blood loss during and after lower segment caesarean section.

Keywords: Tranexamic acid; Prophylactic; Blood loss; Lower Segment Caesarean Section

Introduction

Annually, more than 500,000 women expire worldwide due to pregnancy and delivery related reasons. The majority of mortality and morbidity due to Postpartum Hemorrhage (PPH) mainly enlists severe anemia, blood transfusion, prolonged hospital stays and wide range of infection. PPH can reach disastrous proportions during caesarean section. While caesarean delivery accounts for an average of 1000 mL blood loss, on the other hand VD has a loss of around 500 mL [1]. Consequently, it is requisite to halt blood loss successfully, explaining the requirement of this study. Pharmacologic management has a salient role in this respect. Although multiple alternatives for averting PPH are at one's disposal (modalities include intravenous ergometrine, intra-muscular carboprost and misoprostol), additional breakthroughs in this field are required, chiefly the discerning of safe, convenient and cost-effective regimens. Pro-hemostatic drugs such as Tranexamic acid deliver supportive hemostasis to uterotonics, principally oxytocin and merits evaluation to assess whether it meets these criteria. Tranexamic Acid (TXA) is derived from lysine that affects the reversible blockade of the lysine binding sites on plasminogen molecules. As a consequence, TXA prevents plasminogen conversion to plasmin, a molecule responsible for the degradation of fibrin [2]. It is having been seen that TXA potency is ten times that of Aminocaproic acid [3,4]. A systematic review of RCTs of anti-fibrinolytic agents in planned surgical patients spotted 211 randomized controlled trials [5]. The outcomes revealed that aprotinin and TXA diminished the risk of blood transfusion by 34% and 39% respectively. An RCT assessed TXA for the treatment of PPH and it showed that a high dose of TXA reduces blood loss in women with PPH [6]. TXA could remarkably decrease maternal mortality and morbidity, as it was seen that TXA might lessen the want for hysterectomy, risk of severe anemia and elude blood transfusion. Although there are many studies showing effectiveness of tranexamic acid in reducing blood loss in different surgeries, but such studies are lesser in number in the field of caesarean section. So, the aim of this present study is to evaluate the ramifications of IV tranexamic acid on blood loss during and after Caesarean Section. The main side effects are nausea and diarrhea. Other adverse effects include headache, giddiness and thrombophlebitis of injected vein. Rarely, cases of vascular thrombosis or thromboembolism, and occasionally retinal artery and retinal vein occlusions have been revealed with TXA. Some cases with acquired hemophilia presented with pulmonary thrombosis when tranexamic acid was used [7]. Tranexamic acid <10 mg/mL in blood has no repercussions on the platelets, the clotting or bleeding time or various coagulation factors. Tranexamic acid, nevertheless, at blood concentrations >10 mg/mL prolongs the prothrombin time [8].

Materials and Methods

Study was carried out in the department of obstetrics and gynecology (inpatient only) of Central

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Hospital, South Eastern Railways, Kolkata from August 2018 to August 2020.

Study Design

It was a hospital based, prospective randomized, placebo controlled, clinical study in which the patients were selected randomly and assigned into two groups to receive either 1 g (in 10 ml) of intravenous tranexamic acid dissolved in 100 ml of Normal Saline (study group; n=36) or placebo i.e. 100 ml of Normal Saline (control group; n=36).

Study Population

All primigravida/multigravida getting admitted in obstetrics and gynecology department of South Eastern Railway Central Hospital, Kolkata.

Inclusion criteria:

1. Singleton pregnancy

2. Term pregnancy (37 completed weeks to 41+6 weeks) without any medical complication.

3. Maternal age 18 to 34 years.

4. Received regular Antenatal care.

5. Patient giving written informed consent.

Exclusion criteria:

1. Pregnancy related complications for instance pre-eclampsia, polyhydramnios, macrosomia.

2. Placenta previa or placental abruption.

3. Previous two or more Caesarean section.

4. Grievous medical or surgical issues of the kidney, heart, liver and brain, blood dyscrasias, coagulation disorders, severe anemia and any psychiatric disorder.

5. Thromboembolism

6. Allergy to tranexamic acid

Sample Size

Sample of 72 volunteer pregnant women were selected, who fulfilled the inclusion and exclusion criteria. The following formula was used for the sample size n:

$$n = (Y_{\alpha/2}+Y_{\beta})^2 \times (p_1(1-p_1) + p_2(1-p_2))/(p_1-p_2)^2,$$

where $Y_{\alpha/2}$ is the critical value of the Normal distribution at α/2 (for instance confidence level of 95%, α is 0.05 and the critical value is 1.96), Y_{β} is the critical value of the Normal distribution at β (e.g. for power of 80%, β is 0.2 and critical value is 0.84) and p_1 and p_2 are the expected sample proportions of the two groups. Thus, there was a need of 36 patients for each group with 87% power at 95% confidence level. The number of patients in each group was in the ratio 1:1. Thus the required sample size was 72.

Sample technique

The patients were selected randomly and assigned into two groups. The random numbers were used from Kevin Conroy: 5120 Random Numbers (<5k, 2002) [Called the JavaScript pseudo-random number generator.] Website: RandomNumber.org, 2004.

Methodology

The Institutional Ethics Committee had approved the study protocol. Written, informed consent was sought from the patients. The patients' family members were counseled accordingly. A consecutive sample of 72 volunteer pregnant female patients were recruited for the study and randomly distributed amongst study and control groups. Pre-operative vitals and investigation reports were recorded for all 72 patients. The average weight of antenatal women was considered as 70 kg, and accordingly 1-gram dose was decided upon for the patients. TXA injection 1-gram TXA in 10 ml i.e. 100 mg/ml was dissolved in 100 ml normal saline and administered intravenously to the study population @ 10 ml/min (over 10 min), 20 min before skin incision. Tranexamic acid used was as per hospital supply and no brand was given preference over the other. 100 ml of Normal Saline was given to the control group. Spinal anesthesia was given to all patients. After delivery, routine care was given to control and study groups i.e. 10 units of oxytocin added to ringer lactate to run intravenously over 20 min to 30 min. Blood loss was measured during CS, after draining the amniotic fluid completely from placental delivery till two hours post-partum by gravimetric method. Gravimetric method is capable of only a rough estimation; nevertheless, it is the most practical [9]. Blood in the suction container was measured. Soaked mops used in surgery and intraoperative perineal sheet were weighed by electronic weighing machine prior to and following surgery. The cumulative blood loss in ml was ascertained as the summation of: Blood in mops {wet weight - dry weight} + Blood in perineal sheet {wet weight - dry weight} + Blood in suction container. Amniotic fluid and the volume of blood lost prior to placental delivery was excluded from the study. Average blood loss from mops and sheets was computed employing the formula derived by Gai et al. [10].

(Weight of soaked material – Weight of dry material)

Blood from mops and sheets = 1.05

(1.05 is the specific gravity of blood at 37°C.)

[Weight of wet and dry material in gram (gm) and blood from mops and sheets in milliliter (ml)]

The blood estimated in the suction container after placental delivery was added to the above to calculate the total intra-operative blood loss. Following 2 h of operation, the total pads used and their weight were estimated. The total weight of dry pads was deducted from the total weight of wet pads, and changed into ml from the formula used by Gai et al. [10] to get the 2-h post-op blood loss.

Weight of soaked pads – Weight of same number of dry pads

Blood in pads = 1.05

Postoperatively patients (in both groups) were monitored and vitals (heart rate, blood pressure, respiratory rate, pallor and urine output) recorded. Hemoglobin, platelet, PCV, BT and CT testing was done 24 h following surgery for all patients and compared with the preoperative values. Routine care was administered to all patients, input-output chart was monitored and patients observed for bleeding from the vagina till day they were discharged.

Statistical analysis

Statistical software: The statistical software SPSS version 20 has been used for the analysis.

Statistical analysis: Categorical variables are expressed as number of patients and percentage of patients and compared across the groups using Pearson's chi square test for Independence of Attributes/Fisher's Exact Test as appropriate.

Continuous variables have been expressed as Mean, median and standard deviation and compared across the groups using Mann-Whitney U test. Alpha level has been taken as 5%, i.e. if any p value is less than 0.05 it has been considered as significant.

Results and Analysis

Mean amount of blood collected in suction, in study (case) group is 100.23 ml with SD 16.74 ml, where as in control group the volume is 229.93 ml with SD 39.75. P value is <0.001 which indicates difference in suction collected blood in both groups is significant. Mean blood in mops and sheets in case group 416.89 ± 63.02 and in control group 505.25 ± 79.62. P value is <0.001 indicating significantly more blood in mops and sheets in control group. Total intra-op blood loss in case group is 517.12 ± 72.07 and control group 735.18 ± 109.95. p value <0.001 indicate significantly more blood loss in control group. Both post-op blood loss and total blood loss (intra + post-operative blood loss) difference in case and control group is significant as p value is <0.001. This indicates significantly more blood loss in control groups.

Table shows there is a significant difference between case and control group regarding post-op pallor as the p value is 0.031. Pallor is more in control group.

P value <0.001 signifies significant difference in post op pulse between case and control group. In control group mean post op pulse is more than mean of study group. Difference in post-op systolic blood pressure, diastolic blood pressure and respiratory rate is not significant as p value is >0.05. Difference in post-op hemoglobin between two group is significant as p value <0.001. Difference in post-op PCV between two groups is significant as p value is <0.001. Differences of pre and post-op hemoglobin and PCV between two groups are significantly more in control group as p value is <0.001. No sign of thrombosis was noted in any mother either in study group or

Table 1: Distribution of patients based on intra-operative blood loss, post-operative blood loss and total blood loss (ml).

	Group							
	Case			Control				
	Mean	Median	SD	Mean	Median	SD	p Value	Significance
Blood in Suction	100.23	99.35	16.74	229.93	229.65	39.75	<0.001	Significant
Blood in mop + sheet	416.89	408.19	63.02	505.25	497.81	79.62	<0.001	Significant
Total Intra Op Blood loss	517.12	505.69	72.07	735.18	719.45	109.95	<0.001	Significant
Post Op Blood loss	65.84	65.35	7.68	115.56	114.35	15.81	<0.001	Significant
Total Blood loss Intra + Post Op	582.97	575.71	73.25	850.74	836.29	119.49	<0.001	Significant

Table 2: Post-operative distribution of pallor in the study and control groups.

		Group		Total		
		CASE	CONTROL		p Value	Significance
Post OP Pallor	**Absent**	19	10	29	0.031	Significant
	Present	17	26	43		
Total		36	36	72		

Table 3: Distribution of patient based on post-op vitals.

	Group							
	Case			Control				
	Mean	Median	SD	Mean	Median	SD	p Value	Significance
Post OP Pulse	85	85	7.61	91.92	92	4.61	<0.001	Significant
Post OP Systolic BP	111.81	110	7.11	111.28	110	7.61	0.995	Not Significant
Post OP Diastolic BP	70.22	70	3.96	69.97	70	4	0.775	Not Significant
Post OP Respiratory Rate	14.03	14	1.66	13.89	14	1.79	0.78	Not Significant

Table 4: Distribution of patient based on post-op hematological parameters (24 hours after closure of skin incision).

	Group							
	Case			Control				
	Mean	Median	SD	Mean	Median	SD	p Value	Significance
Post OP Hb	10.78	10.5	0.93	9.55	9.4	0.84	<0.001	Significant
Hb Difference Pre & Post OP	0.18	0.2	0.14	1.31	1.2	0.44	<0.001	Significant
Post OP PCV	33.81	33	2.75	31.58	31	2.78	0.001	Significant
PCV difference Pre & Post OP	1.03	1	0.56	3.39	3	1.34	<0.001	Significant
Post OP Platelet Count	1.99	2	0.48	1.98	2.05	0.4	0.607	Not Significant
Post OP BT	3.09	3	0.66	3.16	3.2	0.76	0.693	Not Significant
Post OP CT	9.81	9.6	0.96	10.08	9.85	1.09	0.318	Not Significant

Table 5: Distribution of patients based on side effect profile.

		Group		Total		
		Case	Control		p Value	Significance
Nausea	**Absent**	27	30	57	0.384	Not Significant
	Present	9	6	15		
Total		36	36	72		
Vomiting	**Absent**	28	31	59	0.358	Not Significant
	Present	8	5	13		
Total		36	36	72		
Diarrhea	**Absent**	34	34	68	1	Not Significant
	Present	2	2	4		
Total		36	36	72		
Signs of Thrombosis	**Absent**	36	36	72	NA	NA
Total		36	36	72		

Table 6: Distribution of patients based on need of excess oxytocin (above 20 unit).

		Group		Total		
		Case	Control		p Value	Significance
Need of Excess Oxytocin	No	36	32	68	0.115	Not Significant
	Yes	0	4	4		
Total		36	36	72		

in control group. Post-operatively nausea was present in 9 patients in study group and in 6 patients in control group. As p value is 0.384, the difference is not significant. Post-op vomiting present in 8 patients in study group and 5 patients in control. P value = 0.358 indicating that the difference is not significant.

Above table shows there is need of excess oxytocin (more than scheduled total 20 units after delivery of the baby) in control group than in study group by approximately 11.11%.

Discussion

In the course of placental delivery, fibrinolytic system activation leads to brisk fibrinogen and fibrin degradation, and consequently plasminogen activators and Fibrin Degradation Products (FDP) increase. Such activation might last up to 6 h to 10 h postpartum, resulting in incessant bleeding. Tranexamic acid occludes the lysine binding locus of the plasminogen and plasmin molecules, thus preventing the binding of plasminogen and plasmin to the fibrin substrate. TXA additionally inhibits activation of plasminogen to plasmin by inhibiting plasminogen activators. The result analysis showed that, in lower segment caesarean section, tranexamic acid notably minimizes bleeding after delivery of placenta till 2 h postpartum. Reduction in blood loss in intra and postpartum periods was noted, i.e. from time of delivery of placenta to skin closure and from skin closure to 2 h postpartum. The study group had average total blood loss (intra-operative + post-operative blood loss) of 582.97 ± 73.25 ml, while control group had an average blood loss of 850.74 ± 119.49 ml. Four patients with post-partum hemorrhage in the control group required 10 units of additional oxytocin infusion, while none in test group had post-partum hemorrhage. Leila Sekhavat et.al [11] conducted a prospective randomized study on 90 primigravida patients divided amongst two groups who subsequently had caesarean section. Their results showed that tranexamic acid remarkably decreased the blood loss from the conclusion of caesarean section to 2 h postpartum. Their study results and our conclusions were comparable. The difference being they included exclusively primipara patients but our study had no such inclusion criteria based on parity. The study by Movafegh et al. [12] revealed that iv administration of 10 mg/kg of tranexamic acid 20 min before skin incision significantly reduced intra and postoperative blood loss, as well as the amount of intraoperative oxytocin used. The dose of tranexamic acid administered in this study was different compared to our study. The tranexamic acid group showed significantly reduced mean blood loss on comparison with the control group for both intra op bleeding (262.5 ± 39.6 *vs.* 404.7 ± 94.4 ml) and postoperative bleeding (67.1 ± 6.5 *vs.* 141.0 ± 33.9 ml; p<0.001), respectively, considering similar patient's mean age, weight and duration of surgery in the two groups. These results were consistent and comparable to our study. A similar study was done by Ming-ying Gai, et al. [10] in China to study the efficacy of tranexamic acid in reducing bleeding from the time of delivery of placenta to 2 h postpartum. The intervention reduced bleeding 2 h postoperatively, 42.75 ± 40.45 ml in the study group compared to 73.98 ± 77.09 ml in the control group (p=0.001) but did not reveal any reduction in blood loss in post-placental delivery. This can be attributed to the fact that; tranexamic acid was given only 10 min prior to the skin incision. So, we preferred to give tranexamic acid 20 min prior to spinal anesthesia. The study by Gungorduk et al. [13] showed similar results. The dose of TXA administered (1 gm., regardless of patient's weight) was similar to our study. A blood loss of 499.9 ± 206.4 ml in tranexamic acid group versus 600.7 ± 215.7 ml in control group (p<0.001) was documented. Additionally, women in the placebo group required additional uterotonic drugs (14.5%) as compared to the patients receiving TXA (8.5%). The results were comparable to our study. The study by Gohel et al. [14] in the Indian Journal of Obstetrics and Gynecology showed that tranexamic acid significantly decreased blood loss from the end of LSCS to 2 h postpartum: 75.71 ml in the study group *vs.* 133.03 ml in the control group (p=0.001). It also significantly decreased the post placental

delivery blood loss to 2 h post-partum: 372.71 ml in the study group, *vs.* 469.70 ml in the control group (p=0.003). Two studies on effect of tranexamic acid in reducing blood loss after vaginal delivery by Zheng S, Yang H et al. [15] showed significant decrease in occurrence of postpartum hemorrhage.

Abdel-Aleem H et al. [16] conducted a randomized controlled trial on all pregnant women with singleton fetus planned to have elective caesarean section at ≥ 37 weeks gestation and showed similar results. Blood loss was estimated during and for two hours postpartum. Results showed that Mean total blood loss was 241.6 (SE 6.77) ml in the test group *vs.* 510 (SE 7.72) ml in the control group. A systematic review and meta-analysis to assess the efficacy and safety of Tranexamic Acid (TA) in decreasing blood loss and reducing transfusion needs for patients going through a Cesarean Section (CS) or Vaginal Delivery (VD) was done by Li C, et al. This showed that TXA reduces Postpartum Hemorrhage (PPH) and severe PPH, and brings down blood transfusions [17]. A meta-analysis of Randomized Controlled Trials (RCTs) was conducted by H-Y Wang et al. in which 11 RCTs were included with a total of 1276 women in TXA group and 1255 in without TXA (control) group. Total blood loss during and after CS was significantly less in TXA group than in control group. A significant decrease was noted in intraoperative and postpartum blood loss in TXA group on comparing with control group. Reduction in hemoglobin and hematocrit values after Caesarean Section were both significantly low in TXA group as compared to control group. The difference of PPH was seen to be statistically significant between these groups (Risk Ratio (RR) 0.57, 95% CI 0.37 to 0.89, P=0.01). Requirement for blood transfusion was significantly lower in TXA group than control group (RR=0.23, 95% CI 0.10 to 0.57, P<0.01) [18]. In our study, post operatively, there was significant increase in pallor in the control group. Twenty-six patients had pallor in control group versus 17 in study group (p=0.031, highly significant). Other parameters like systolic and diastolic blood pressure, pulse and respiratory rate did not have any significant difference amongst the two groups (p value >0.5 for both the parameters). Both the studies by Movafegh et al. [12] and Gai et al. [10] showed no significant derangement in post-op vitals. Difference in post-operative hemoglobin levels noted between the two groups was significant. The study group showed significantly lower pre and post-operative hemoglobin values compared with the control group. The post-operative PCV mean values were 33.81 in the study group and 31.58 in the control group with a p value =0.001 which is significant. Other parameters *viz.* Platelet count, BT CT were not significantly different amongst the two groups (p value >0.5 for both the parameters). The results were consistent with the studies by Movafegh et al. [12] and Gai et al. [10]. Bhavana, Abhishek; Mittal, Suneeta et al. conducted a study for evaluation of tranexamic acid prophylactically in blood loss reduction during and following caesarean section. Hemoglobin and hematocrit decreased significantly in placebo group compared to test (tranexamic acid) group. The post-operative vitals or side effects showed no changes in the tranexamic acid group [19]. Hemoglobin and hematocrit reduction were not significant in TXA group as compared to control group in a meta-analysis of Randomized Controlled Trials (RCTs) conducted by H-Y Wang et al. [18]. Side effects of tranexamic acid like nausea, vomiting and diarrhea were not significantly more in the study group. These results are consistent with previous studies. Thrombosis during pregnancy and puerperium is 5 to 6 times higher than the general population. Increased risk of thrombosis should be contemplated, especially in the postpartum LSCS period, when tranexamic acid is administered. In our study, no patients developed thrombosis. A systematic review and meta-analysis for assessment of the efficacy and safety of Tranexamic Acid (TXA) in reducing blood loss and lowering transfusion needs for patients undergoing Cesarean Section (CS) or Vaginal Delivery (VD) showed no evidence of increased risk of Deep Vein Thrombosis (DVT), while the minor side effects were more common [17].

Conclusion

Prophylactic use of tranexamic acid significantly reduces the amount of blood loss during and after lower segment caesarean section.

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Limitation

1. It is an interventional study. So, more the number of patients, more is the accuracy even though a significant number of patients (n=72) were included in this study.

2. Data was collected from a tertiary health care center which is a referral hospital for the entire South-Eastern Railway employee population and their families as well. So, the results cannot be extrapolated to total population.

3. To study the long-term adverse effects on neonates, longer follow up and more studies are required.

4. Gravimetric method is not the ideal method of blood loss estimation. However, it was the best suited and most practical method in the present set up at SERCH and with the resources provided.

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