

Role of Prophylactic Tranexamic Acid in Reducing Blood Loss during Elective Caesarean Section: A Randomized Controlled Study

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ABSTRACT

Introduction: Obstetric haemorrhage accounts for 20-25% of maternal mortality and morbidity. Anti-fibrinolytics are being widely used in field of surgery. It is also used to reduce heavy menstrual blood loss.

Aim: To analyse the effectiveness of Tranexamic Acid (TXA) in reducing blood loss during elective caesarean section.

Materials and Methods: This interventional, randomized, parallel group study was done in the Department of Obstetrics and Gynaecolgy, PSG IMSR, Coimbatore, from June 2014 to May 2015.

It was conducted on 120 women undergoing caesarean section. They were allocated to either Study or Control group by computer generated random number tables. TXA was given prior to surgery in study group in addition to the routine care {10 units of oxytocin added to the intravenous drip soon after baby delivery} whereas, the control group had routine care alone. Blood loss was measured in both groups by gravimetric method. Haemoglobin before and after surgery was estimated and the percentage of difference was compared.

Statistical Analysis: Primary outcome variables were volume of blood loss and percentage fall in haemoglobin before and after surgery. Secondary outcomes were duration of surgery, proportion of subjects with >500ml of blood loss, need for additional uterotonics and side effects. Unpaired t-test and Chi-square test were used to compare the outcome variables.

Results: There was significant reduction in blood loss calculated from placental delivery till end of surgery: 347.17ml in study group versus 517.72ml in control group (p<0.001). Another parameter studied was the percentage of fall in haemoglobin before and after surgery and the number of subjects who had more than 10% fall in haemoglobin. 9.3% of subjects in study group and 39% of subjects in control group had more than 10% fall in haemoglobin (p<0.01). There were no immediate post-operative complications to the mother and neonate.

Conclusion: TXA significantly reduced the amount of blood loss during Lower Segment Caesarean Section (LSCS). Use of TXA was not associated with adverse effects. Thus, TXA can be used safely and effectively in subjects undergoing LSCS.

Keywords: Fibrinolysis, Haemoglobin, Haemorrhage, Morbidity, Prevention

INTRODUCTION

Every year over five lac women die worldwide due to causes related to pregnancy and delivery. Postpartum Haemorrhage (PPH) accounts for the major part of the mortality as well as morbidity like severe anaemia, need for blood transfusion, hospital stay and infection. Millennium Development Goal 5 targets for reduction of maternal mortality rate by 75% by 2015, which means 5.5% reduction per year is required. People at high risk of PPH account for only small percent of all maternal deaths. Majority of morbidity and mortality happen in those with no risk factors and cannot be predicted. In an analysis of 1620 women in rural India, it was found that 9.2% experienced PPH. No maternal or socio-demographic factors differed between women with PPH and those without [1]. Though the incidence of early PPH (occurring within 24 hours of delivery) is lower in caesarean section than vaginal delivery, the former is a major surgery and causes greater blood loss. Hence, it is essential to prevent the blood loss effectively in a feasible way, thus, explaining the need for this study.

Apart from obstetric, surgical and radiological interventions, pharmacologic management also plays an important role in this aspect. Uterine atony is the most common cause for PPH. First line of therapeutic management for PPH is oxytocin [2] Other modalities include intravenous ergometrine, intra-muscular carboprost and misoprostol. Prohaemostatic drugs such as TXA provide a complementary biochemical haemostatic effect to the well proven uterotonics, especially oxytocin. Systemic anti-fibrinolytic agents are widely used in surgery. A systematic review of randomised controlled trials of anti-fibrinolytic agents in elective surgical patients identified 211 randomised controlled trials [3]. The results showed that aprotinin reduced the risk of blood transfusion by 34% and TXA by 39%. TXA is an analogue of lysine that inhibits fibrinolysis by competitively binding to plasminogen. It prevents the lysis of formed clot by inhibiting activation of plasminogen and plasmin. It is ten times more potent than Amino- caproic acid [4,5]. TXA has been shown to reduce uterine blood loss in non-surgical aspect. A study done on women with menorrhagia has showed significant reduction in mean menstrual blood loss in those treated with TXA [6]. A randomized controlled trial assessed TXA for the treatment of PPH and it showed that a high dose of TXA reduces blood loss in women with PPH [7]. Several RCTs have analysed the prophylactic role of TXA (described in discussion) and have shown significant results in reducing blood loss [8-16]. TXA might reduce the need for hysterectomy, reduce the risk of severe anaemia and avoid the need for blood transfusion; hence, this could contribute significantly to the goal of reducing maternal mortality.

MATERIALS AND METHODS

This study was approved by the Institutional Human Ethics Committee (IHEC), PSG Institute of Medical Sciences and Research, which has been recognised by the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). The study was conducted among subjects in PSG hospital who were to undergo elective caesarean section, over one year from June 2014 till May 2015. Sample size was calculated using the formula as $\{2 \times SD^2 \times (Z\alpha^2 + Z\beta^2)^2\} \div \{M_2 - M1\}^2$. Reference for incidence of PPH in study and control arms was taken from a RCT conducted in Karachi [17]. In this study, incidence of PPH was 30% in placebo group versus 13% in TXA group. Power of study was set at 80% and two sided confidence interval at 95%. Taking these into account, the minimum number of women needed to produce statistically significant figure was 58 in each group; hence totally 120 subjects were chosen for the study- 60 in each group.

One hundred and twenty term, primiparous / multiparous (parity not more than two) with singleton pregnancy, who were planned to be delivered by elective LSCS were enrolled. They were divided into 2 groups as control and study by random number table method (computer generated). Each group comprised of 60 subjects. It was an open study (not blinded). Subjects of age between 19 and 34 years and gestational age of 37 to 42 weeks of pregnancy were included. Subjects having medical problems like gestational hypertension, chronic hypertension and severe pre-eclampsia, renal disease, heart disease complicating pregnancy and having coagulation disorders were excluded from the study. Subjects allergic to TXA, those with history of thromboembolic disorders, those having tendency for increased bleeding like abnormal placentation, multiple pregnancy, polyhydramnios, previous two or more caesarean sections and those who had blood transfusion due to anaemia were also excluded from the study.

After obtaining informed consent from the subjects, they were allotted to either of the two groups by simple randomization procedure. Preoperative haemoglobin was estimated in both the groups. In past studies involving LSCS, the doses used were either a bolus of 1gm [9,10,16] or 10mg/kg [8] intravenously. It was mentioned in a study [11] that 15mg/kg dose was more effective without increase in adverse effects. Taking the average weight of antenatal women as 70kg, 1 gram dose was chosen for this study. TXA injection was prepared by diluting 1 gram (10ml) TXA in 100ml of normal saline. TXA was administered as intravenous infusion (over 15 minutes), at least 20 minutes prior to skin incision, to those in study group. No drug was given to the control group. Spinal anaesthesia was given for all the participants. Surgery was done by assistant professors with MD degree, with experience of minimum of 3 years. After delivery of the neonate, routine care was given to both the groups i.e., 10 units of oxytocin was added to ringer lactate and allowed to flow at rate of 75 to 100ml/hour for 3 hours after surgery. No subjects were eliminated from study.

The blood loss was measured following placental delivery till the end of the surgery by gravimetric method. Blood collected in the suction container was noted. Soaked mops and operation table perineal sheet were weighed by electronic scale before and after the surgery. The total amount of blood loss (ml) was determined as the sum of: 1) Blood absorbed by soaked mops {wet weight of used mop - dry weight} +; 2) Blood absorbed by perineal sheet during vaginal toileting {wet weight - dry weight} +; 3) Blood collected in suction container. Amniotic fluid and the volume of blood lost before placental delivery were not included in the study. One mg weight was taken as equivalent to 1ml of blood [18]. Only the intraoperative blood loss was calculated; postoperative period was not included. Gravimetric method gives only approximate estimation, however it is considered to be the most practical [19]. Duration of surgery was calculated as the time between skin incision and skin closure. Postoperatively patients (in both arms) were monitored for 4 hours. Vitals (heart rate, blood pressure, oxygen saturation) were monitored which were stable. Haemoglobin estimation was done at 24 hours after the surgery for all the patients to compare with the preoperative value. Routine care was given- bladder catheter was removed after 12 hours, input- output chart was maintained and patients were observed for any increased bleeding per vaginum. Participants were observed till day of discharge. There were no immediate postpartum and neonatal complications.

STATISTICAL ANALYSIS

Statistical analysis was done by SPSS 16.0 software. Mean and standard deviation were calculated for age, weight, amount of blood loss, duration of surgery. Unpaired t-test was used to find the significance between the two groups with regards to the continuous variables: amount of blood loss and duration of surgery. Chi-square test was to find significance in the incidence of increased blood loss (>500ml) and the incidence of >10% fall in haemoglobin between the two groups. Probability value $p \le 0.05$ was taken as the level of significance.

Incidence of >10% fall in haemoglobin in each of the groups and their comparison was taken as the main variable. Alpha error was taken as 0.01 to reduce sampling and manual errors since sample size was low. Formula used for calculating power was:

Power = $\phi \{ [\Delta / \sqrt{(p_1q_1/n_1 + p_2q_2/n_2)}] - z_1 - \alpha/2 * \{ (\sqrt{p_3q_3} [1/n_1 + 1/n_2) / (\sqrt{p_1q_1/n_1} + p_2q_2/n_2) \}$

 $p_1, p_2 = incidence of groups$

$$\begin{aligned} & q_1 = 1 - p_1; \quad q_2 = 1 - p_2 \\ & p_3 = (p_1 + k p_2) \ / \ (1 + k); \quad q_3 = 1 - p_3 \\ & \Delta = [p_2 - p_1] \end{aligned}$$

 n_{1} , n_{2} = sample size of groups

 $\alpha = probability of type 1 error$

z = critical z value for a given α or β

 ϕ = function converting critical z value to power

Power obtained using above formula was 90.2%. Explanation for higher power: there is a visibly heavy difference between control and study group with regards to the primary variable. Hence error incidence will be insignificant and power will be high.

RESULTS

There was no statistically significant difference between the two groups with respect to the baseline characteristics as age, weight, height, parity and gestational age [Table/Fig-1,2]. Baseline haemoglobin was checked for all participants, hence, post-operative value and the difference in haemoglobin were calculated [Table/Fig-3]. There was no significant difference with regards to indications for LSCS: previous caesarean, malpresentation, gestational diabetes, hypothyroid, asthma, fetal complications like IUGR between the two groups [Table/Fig-4].

There was significant difference between two groups in the following primary outcomes: blood loss from placental delivery till end of surgery, percentage of difference in haemoglobin and secondary outcomes: duration of surgery and proportion of patients with > 500ml of blood loss [Table/Fig-5,6].

Parameter	Study (n= 60)			ontrol (n= 60)	p-value	
Age (years)*	26.77±2.807			.82±2.801	0.99	
Weight (kg)*	71.41±6.04	4	72.	.46±5.71	0.84	
Height (m)*	1.563±0.0	5	1.582±0.066		0.49	
BMI (kg/m²)*	29.38±1.2		29.12±2.3		0.63	
Parity	Primiparous: 7/60 (11.66%) Multiparous: 53/60(88.33%)		Primiparous: 7/60(11.66%) Multiparous: 53/60(88.33%)			
	[Table/Fig-1]: Demographic features. *values are in mean±SD					
Gestational Age		Study * N (%)		Control ** N	(%)	
37w- 37w+6d		17 (28%)		24 (40%)		
38w-38w+6d	38w-38w+6d			26 (43%)	1	
39w-39w+6d		8 (13%)		9 (15%)		
40w-40w+6d		1 (2%)		1 (2%)		
[Table/Fig-2]: Gestational age in weeks (w) + days (d). *57% of study population belong to 38w – 38w+6d of gestation **43% of control population belong to 38w – 38w+6d of gestation						

S.no	Control (C)/ Study (S)	Pre op Hb (g/ dl)	Post op Hb (g/ dl)	% differ- ence in Hb(%)	Additional uterotonics
1.	С	10.4	8.9	14.42	20 units synto added to drip
2.	С	11.8	9	23.72	
3.	S	11.2	10.6	5.35	
4.	С	13	12.9	0.76	20 units synto in drip
5.	S	11.9	12.2	2.52 *	
6.	S	13	12.9	0.7	
7.	С	12.1	11.7	3.31	
8.	S	12.3	11.4	7.32	
9.	S	10.9	10.9	_	
10.	C	11.5	10.6	7.82	
11.	S	10	8.8	12	20 units synto in drip
12.	S	13.2	14.1	6.81 *	
13.	S	12.3	11.6	5.7	
14.	C	11.7	10.6	9.4	
15.	С	12	10.4	13.33	
16.	S	12	12.3	2.5 *	
17.	С	11.4	10.9	4.4	
18.	S	10.6	10.2	3.8	
19.	S	13.4	12.9	3.7	
20.	С	11.4	11.1	2.6	
21.	S	11.3	10.8	4.42	
22.	С	11.4	8.9	21.92	20 units synto + inj methergin
23.	S	11.7	10.6	9.4	
24.	С	11.1	9.2	17.12	
25.	S	13.6	14	2.94 *	
26.	S	11.9	11.5	3.36	
27.	S	12.4	12.8	3.23 *	
28.	S	11.4	10.8	5.26	
29.	С	11.6	9.8	15.52	
30.	С	13.1	13	0.76	
31.	С	13.9	12.9	7.2	
32.	S	14.9	14.8	0.67	
33.	C	11.8	11.3	4.2	
34.	C	12.1	12	0.83	
	c	13.1	11.6	11.5	
35.	S	11.3	11.0	0.88 *	
36.					
37.	S	11.9	12.2	2.5 *	
38.	S	10.4	9.4	9.6	
39.	С	11.1	10.5	5.4	
40.	С	11.1	10.6	4.5	
41.	S	11.5	12	4.3 *	
42.	S	11.7	12.4	6 *	
43.	С	10.4	10.4	-	
44.	S	11.9	12.8	7.6 *	
45.	С	11.6	10.7	7.7 *	20 units synto in drip
46.	С	12.5	11.5	8	
47.	S	12.4	13.4	8.1	
48.	С	11.8	10.3	12.7	
49.	С	12.6	11.7	7.1	
50.	S	12.1	12.5	3.3 *	
51.	S	12.5	13.8	10 *	
52.	S	11.4	12.2	7*	
53.	C	10.6	9.5	10.4	
54.	c	12.4	11.1	10.4	

55.	S	11.5	11.3	1.7	
56.	С	12.9	12.3	4.7	
57.	S	12.1	11.8	2.5	
58.	S	10.4	9.4	9.6	
59.	С	11.2	9.7	13.4	
60.	S	12.3	11.9	3.3	
61.	С	13.3	12.3	7.5	
62.	S	13.6	13.5	0.7	
63.	С	12.1	11.9	1.65	
64.	S	10.8	10.7	0.92	
65.	C	11.1	11	0.9	
66.	S	11.5	10.9	5.26	
67.	C	13.1	11.9	9.2	
68.	S	11.3	8.9	21.2	20 units synto in drip
69.	C	13	12.6	3.07	
					0 E ma matharain is
70.	С	10	8.5	15	0.5 mg methergin iv
71.	S	11.9	10.9	8.4	
72.	S	12.3	12.1	1.6	
73.	С	11.8	9.9	16.1	
74.	S	11.4	10.8	5.26	
75.	С	12.1	11.4	5.8	
76.	S	11.6	10.8	6.9	
77.	S	10	9.8	2	
78.	S	12.1	11.4	5.78	
79.	С	10.6	10.1	4.7	Inj methergin, prostadin
80.	С	12.6	11.7	7.1	
81.	С	13	12.7	2.4	
82.	С	12.4	11	11.29	
83.	С	12.3	11.5	6.5	
84.	S	11.8	11.3	4.4	
85.	С	13.8	12.5	9.4	
86.	С	10.8	8.7	19.4	
87.	S	12.5	12.3	1.6	
88.	S	13.1	12.5	4.6	
89.	С	12.7	10	21.2	20 units synto + inj methergin
90.	S	12.1	12.1	-	
91.	S	13.1	11.6	11.5	
92.	С	11.9	11.1	6.7	
93.	С	11.8	10	15.3	Inj prostadin im
94.	S	12.5	12.2	2.4	
95.	С	12	10	16.7	
96.	C	12.4	10.3	16.9	
97.	C	13.2	11.5	12.8	
98.	S	11	10.6	3.6	
99.	S	12.8	12.9	0.7 *	
100.	S	12.0	10.4	18.1	
101.	C	10.1	10.4	5.94 *	
101.	s	12.7	10.7	5.5	
102.	S	12.7	12	5.9	
	S				
104.		10.2	10.1	0.9	
105.	С	10	9.1	9	
106.	S	11.7	11.3	3.42	
107.	S	11.9	12.5	5 *	
108.	С	12.7	11.2	11.8	
	С	12.6	11.9	5.5	
109.	S	12.0		0.9 *	

111.	S	12	11.5	4.2	
112.	С	11.5	9.3	19.1	10 units synto added in drip
113.	С	11.3	10.1	10.6	
114.	С	13.6	12.6	7.4	
115.	S	10.4	10.2	1.9	
116.	S	11.4	10.4	8.7	20 units synto added
117.	С	12.6	11.1	11.9	
118.	С	11.1	10.9	1.8	
119.	С	10	8.1	19	
120.	С	13.8	13.4	2.9	
[Table/Fig-3]: Baseline laboratory value.					

Control
49 (CS {27- previous LSCS 22- previous LSCS with medical disorders}
1
9
17
5
-
-
1
6

** most common indication in Control: Previous LSCS-81.6% (49/60)

Group	Amount of Blood Loss		Duration of Surgery	
	Mean(ml)	Standard deviation	Mean(min)	Standard deviation
STUDY	347.17	108.6	56	10.36
CONTROL	517.72	150	70.33	11.93
p-value	<0.001		<0.001	
[Table/Fig-5]: Comparison of blood loss and duration of surgery.				
Unpaired t-test applied				

GROUP	>500ml blood loss	>10% fall in haemoglobin *		
STUDY	2/60 (3.3%)	4/43(9.3%)		
CONTROL	36/60(60%)	23/59(38.9%)		
p-value	<0.001	<0.01 (0.0083)		
[Table/Fig-6]: Percentage of participants with >500 ml blood loss and >10% decline in haemoglobin.				

* 17 subjects in Study group and 1 subject in Control group had rise in haemoglobin postoperatively. Chi square test used

Use of additional uterotonics intraoperatively was also taken into account. In the control group, there was excessive bleeding in 9 subjects that additional oxytocins were given to them: 20 units of oxytocin was added to drip (at 60ml/hour for 3 hours), injection Methergin 0.2mg was given intra-venously. In the study group, 3 subjects needed additional oxytocins, out of which for 1 subject there was uterine angle extension intra-operatively which contributed to the increased blood loss. There was no need for blood transfusion in either of the groups postoperatively.

There were no adverse effects or immediate postpartum and neonatal complications in this study.

DISCUSSION

Tranexamic acid competitively blocks the lysine binding site of plasminogen, thereby, prevents the lysis of the formed clot. Its onset

of action is 5 - 15 minutes and duration of action is for 3 hours. It binds more avidly to the plasminogen molecule than aminocaproic acid. TXA was discovered by Utako Okomoto in 1950s. It was the outcome of her research work along with her husband after the second Sino-Japanese war [20]. In early nineties, oral TXA was listed as an anti-fibrinolytic agent on the Pharmaceutical Benefits Schedule. In 2010, Pfizer Australia was granted approval by the Therapeutic Goods Administration (TGA) to supply TXA (Cyklokapron) solution for injection. It was then approved by the US Food and Drug Administration. According to the CRASH-2 (Clinical Randomization of Antifibrinolytic in Significant Haemorrhage) trial, there was significant reduction in all- cause mortality in acute trauma by early administration of TXA [21]. WHO has recommended using TXA in situations where the bleeding is not controlled with oxytocin and other uterotonics or if the bleeding is due to refractory atonicity/ trauma- related bleeding. Its effectiveness in reducing PPH is being evaluated in the WOMAN trial (World Maternal Antifibrinolytic trial -London school of Hygiene and Tropical medicine) [22].

PPH contributes much to the maternal morbidity and mortality. More-over, there is increase in the risk of infection, need for blood products, hospital stay and cost. Hence steps towards reducing the blood loss are of immense concern especially in developing countries where there is lack of awareness and resources. After delivery there is exaggerated fibrinolytic activity as a counter action to the acute trauma to blood vessel. Hence, TXA can effectively control the bleeding by arresting fibrinolysis.

This was a randomized, prospective, interventional study comparing the efficacy of TXA in reducing blood loss during caesarean section, between Study and Control arms. Intra-operative blood loss was estimated by gravimetric method. Other methods used for blood loss estimation are visual, direct and photometric methods. Visual method is the most inaccurate but is the most commonly used. Photometric is considered most accurate but it is complex and costly [23]. WHO (2012) recommends that no method is superior to one another. Post-operatively vital parameters were recorded and patients were carefully monitored for any adverse effects. Visual abnormalities, often poorly characterized, represent the most frequently reported post marketing adverse reaction of TXA in Sweden (if drug was continued for several days). Convulsions have been reported, particularly in patients receiving tranexamic acid during cardiovascular surgery and in inadvertent administration into the neuraxial system. But, all the reference studies quoted here [8-16] have not shown any evidence of thrombogenic effect of TXA on pregnant women. Gastrointestinal disturbances (nausea, vomiting and diarrhoea) may occur.

This study showed that there was significant difference in the amount of blood loss and in the percentage of fall in haemoglobin between the two groups. 60% of subjects in control arm had >500 ml of blood loss, whereas, only 3.33% of subjects in study arm had increased bleeding. 38.9% of subjects in control arm had >10% difference in pre and post-operative haemoglobin whereas it is only 9.3% in the study arm. This study is comparable to few other similar studies [8-16]. A study by Movafegh et al., showed there was significantly lesser mean blood loss in the study group (TXA 10mg/kg) for both intraoperative and post-operative period [8]. Oxytocin administration was also lesser in the study group (this was not recorded in this study). Goswami et al., formed three groups- 2 study groups (10mg/kg Vs 15mg/kg dose) and 1 control [11]. There was significant difference between pre and post-operative haemoglobin. Abdel Aleem et al., randomized 740 subjects and showed significant reduction in mean blood loss during and for 2 hours postoperatively [15]. Gungorduk and colleagues observed TXA can be given safely before LSCS and that it also reduced need for additional uterotonics [9]. Gai et al., randomized 180 Primi Parous women and proved its safety and efficacy [16]. Gohel and colleagues randomized 100 women undergoing LSCS and proved same effect. There was no significant difference with regard to duration of surgery and indication for surgery

between the two groups in this study [10]. Senturk et al., conducted similar study with 20 ml of TXA diluted with 20 ml of 5% dextrose. There was significant reduction in blood loss in study arm [14]. Need for iron replacement post-operatively was analysed in a study by Yehia and colleagues. Vaginal bleeding was calculated for first 6 hours after surgery, which was lesser in study arm. Incidence of PPH in study arm was significantly less compared to control arm (31.1% versus 63.2% respectively) [24]. Wang et al., conducted meta analysis of 11 RCTs to evaluate efficacy of TXA and showed there was significant difference in mean blood loss, difference in haemoglobin and the need for blood transfusion between the groups [25]. There were no adverse effects in all above studies.

Viswanathano and colleagues give caution regarding potential risks to the neonate. It says that as neonates are more sensitive o low drug levels, there can be a potency for seizures and concludes that high quality RCTs are necessary before widespread usage of TXA can be supported [26]. An adequately powered multicenter randomized, double-blind, placebo-controlled trial (4000 participants) compares the effect of a low dose of TXA (1 g) after vaginal delivery in the 2 min after the child's delivery and after prophylactic oxytocin administration [27]. Its aim is to clarify current uncertainties regarding efficacy and adverse effects of TXA on parturient. It was approved in 2014, with an estimated duration of study of 34 months.

LIMITATION

There were limitations in this study. First is the gravimetric method of estimation of blood loss. Blood volume collected was only approximate. Blood absorbed over the drape sheets could not be accounted for. This problem was faced in all the participants in both the groups. Second one is that long term effects of the drug were not taken into account.

CONCLUSION

TXA significantly reduced the amount of blood loss during LSCS. Pregnancy is a hypercoagulable state, hence the risk of thrombotic events are more during pregnancy. Nevertheless the use of this antifibrinolytic was not associated with any side effects or complications in the immediate postpartum period. Hence, TXA can be used safely and effectively in subjects undergoing LSCS.

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