Original Article

Role of intravenous tranexamic acid on cesarean blood loss: A prospective randomized study

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ABSTRACT

Background: Postpartum hemorrhage (PPH) is a major cause of maternal mortality globally. Tranexamic acid, an anti-fibrinolytic agent, is a novel approach to prevent this dreadful complication. This study aims to document the efficacy of intravenous (IV) tranexamic acid in reducing blood loss during and after cesarean section (CS).

Materials and Methods: In this prospective, randomized, placebo-controlled, open-label study, 100 mothers scheduled for elective CS were randomly selected and divided into two groups (study and control) of 50 each. The study group received 1 g IV tranexamic acid and the control group received IV placebo. Following delivery, all mothers received 10 units of oxytocin in 500 mL of normal saline.

Results: The mean intraoperative and postpartum blood loss were significantly lower in the study group than the control group: 499.11 ± 111.2 ml and 59.93 ± 12.5 ml versus 690.85 ± 198.41 ml and 110.06 ± 13.47ml, respectively ($P < 0.001$). Total blood loss was 30% less in the study group ($P < 0.001$). Six mothers had PPH in the control group while none in the study group had PPH. The difference between the preoperative and postoperative hemoglobin values was significantly less in the study group than the control group, 0.26 ± 0.22 g% versus 0.99 ± 0.48 g% ($P < 0.001$).There was no significant difference with respect to other hematologic parameters. There was no added adverse effect or need for NICU admission in the study group.

Conclusion: Preoperative IV tranexamic acid significantly reduced blood loss during elective CS without any significant adverse effects.

Key words: Anti-fibrinolytics; blood-loss; cesarean delivery; postpartum hemorrhage; Tranexamic acid.

Background

Postpartum hemorrhage (PPH) is a major complication after both vaginal and cesarean delivery worldwide, which contributes substantially to maternal mortality and near misses. Each year, approximately 1–2% of mothers with PPH die, with an average interval of approximately 2–4 hours from onset of PPH to death.[1] PPH is defined as the loss of more than 500 mL of blood following normal delivery or more than 1000 mL loss following cesarean section (CS).[2] There are four causes of PPH – uterine atony, trauma to the birth passage, retained placental tissue or membranes, and coagulopathies such as disseminated intravascular coagulation (DIC).[3] PPH can reach disastrous proportions during CS.

Management of hemorrhage after CS may range from administration of oxytocic and blood transfusion to more radical measures such as hysterectomy.[4,5] Use of anti-fibrinolytic agents such as tranexamic acid (TXA),

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however, avoids both the hazards of blood transfusion as well as the long-term side-effects of hysterectomy.

The aim of this study is to assess the effect of intravenous (IV) TXA on blood loss during and after CS.

Materials and Methods

A randomized, placebo-controlled, open-label clinical study was conducted after Institutional Ethics Committee approval from May 2012 to April 2013 with 100 clinically stable singleton antenatal mothers (aged 20–40 years) at term scheduled for elective CS. Pregnancy complications such as pre-eclampsia, polyhydramnios, macrosomia, multiple pregnancy, preterm labor, placenta previa, and abruptio placentae were excluded from the study along with mothers suffering from blood dyscrasias, coagulation disorders, thromboembolic disorders, severe anemia, allergy to TXA, and severe medical and surgical complications involving the heart, liver, or kidney.

Sample size was calculated assuming that a difference of 100 mL of total (intra and postoperative) blood loss would be a clinically important difference between the two groups. It was calculated that 45 participants would be required per group to detect this difference with 80% power and 5% probability of Type 1 error. Standard deviation was assumed to be 190 for control group and 150 for the test group based on an earlier study.[6] Adjusting for 10% dropout rate, recruitment target was set at 50 participants per group. Figure 1 shows a summary of study design.

The selected 100 mothers were randomized into two groups using a computer-generated randomization list to receive either 1 g (in 10 mL) of IV TXA dissolved in 20 mL of 5% dextrose solution (study group; $n = 50$) or IV placebo, i.e. 30 mL of 5% dextrose solution (control group; $n = 50$), 20 minutes before beginning spinal anesthesia. During CS, after draining the amniotic fluid completely and delivery of placenta, blood was drained in a separate suction container. Dry and soaked mops and sheets were weighed by a sensitive weighing machine.

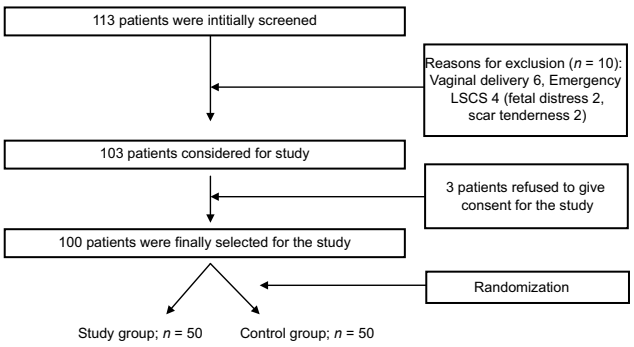

Figure 1: Summary of study design

Mean blood loss from mops and sheets was calculated using the formula used by Gai *et al*.:[7] blood from mops and sheets = (weight of soaked material – weight of dry material)/1.05; where 1.05 is the specific gravity of blood at 37°C. To this, the blood drained in the suction container after delivery of placenta was added to get the total intraoperative blood loss.

After delivery, 10 units of oxytocin in 500 mL of normal saline was infused intravenously every 20 to 30 minutes. Additional 15 units of oxytocin was given postoperatively (5 U in each bottle of IV fluid for three consecutive bottles over a period of 12 hours). Further administration of oxytocin was according to requirement. Two-hour postoperative blood loss was calculated from the soaked pads by the same formula mentioned above.

Two hours postoperative vitals (pulse, systolic and diastolic blood pressure, respiratory rate, and pallor) were compared with the preoperative status in both groups. Pre- and 24-hour postoperative complete blood count, coagulation profile, liver function test, and renal function test were compared between the two groups.

Results

The data was expressed as mean ± SD, frequency, and percentage. A preliminary test of normalcy (Kolmogorov–Smirnov test) was carried out for the distribution of the data. Numerical variables were compared with independent sample *t*-test and Mann–Whitney U test, while categorical variables were dealt with Chi-square test and Fisher's exact test as appropriate. Two-tailed *P* value of <0.05 was considered significant. For data analysis, standard statistical software such as Microsoft Excel and SPSS version 11.5 were utilized.

Table 1 shows that the two groups were equally matched with respect to demographic characteristics (viz. age, weight, height, gravida, parity), period of gestation at which CS was done, indications for elective CS, preoperative vitals (pulse, systolic blood pressure, diastolic blood pressure, respiratory rate, pallor), and preoperative hematological work-up such as complete blood count, liver function tests, and renal function tests.

Table 2 shows that both intraoperative and 2-hour postoperative blood loss were significantly less in the study group than the control group.

Table 3 shows the postoperative status of the study and control groups. Comparison of 2-hour postoperative vitals between the two groups showed that pallor ($P = 0.004$) and pulse rate ($P = 0.000$) were significantly lower in the study group. Systolic blood pressure, diastolic blood pressure, and respiratory rate did not have any significant difference in the two groups postoperatively. Postoperative fall in hemoglobin percent was significantly more in control (0.99 g%) group than study group (0.26 g%) ($P = 0.000$). Other parameters, viz. total count, platelet count, prothrombin time and activated plasma thromboplastin time, bilirubin and liver enzymes, urea, and creatinine did not have any significant difference in the two groups. There was no significant difference in APGAR values at 1 min ($P = 0.559$) and 5 min ($P = 0.910$) between the groups. The incidences of adverse effects such as nausea, vomiting, and diarrhoea were not significantly increased in the study group compared to the control group. There was no evidence of thrombosis in any of the mothers in the study group.

Table 1: Demographic characteristics and pre-operative vitals and blood work-up

Parameters	Study group (mean±SD or %)	Control group (mean±SD or %)	*P*
Age (years)	25.00±4.71	25.88±5.39	0.387*
Weight (kg)	65.22±5.58	64.86±8.476	0.803*
Height (m)	1.55±0.04	1.55±0.04	0.889*
Gravida 1st	28 (56%)	31 (62%)	0.45#
2nd	20 (40%)	19 (38%)	
3rd	2 (4%)	0	
Parity Null	33 (66%)	36 (72%)	0.48#
1st	16 (32%)	14 (28%)	
2nd	1 (2%)	0	
Period of gestation (weeks)	38.92±1.38	39.02±1.42	0.722*
Indications for LSCS			
Postdated pregnancy	14 (28%)	11 (22%)	0.945^
CPD	13 (26%)	14 (28%)	
Previous 1 or 2 LSCS	9 (18%)	11 (22%)	
Malpresentations	9 (18%)	8 (16%)	
Elderly primi	5 (10%)	6 (12%)	
Pallor present	22	29	0.161^
Absent	28	21	
Pulse (per minute)	81.64±8.17	84.04±6.92	0.116*
SBP (mmHg)	117.56±8.25	116.00±8.52	0.355*
DBP (mmHg)	74.12±6.08	73.76±8.72	0.787#
Respiratory rate (per minute)	13.64±1.39	12.92±2.10	0.057#
Hb (g%)	10.33±1.26	9.80±1.34	0.050*
Total count (per cc)	9250.48±1391.16	9149.46±1271.68	0.706*
Platelet count (lacs/cc)	2.1±0.62	2.16±0.62	0.589*
PT (s)	11.86±0.17	11.87±0.17	0.651*
aPTT (s)	31.53±0.93	31.51±0.86	0.894*
Bilirubin (T)	1.00±0.27	1.04±0.25	0.493*
Bilirubin (D)	0.26±0.14	0.28±0.15	0.551#
ALT (IU/ml)	38.34±4.17	38.92±3.99	0.480*
AST (IU/ml)	39.94±4.99	38.18±4.86	0.212*
Urea	22.66±1.80	22.52±1.78	0.655#
Creatinine	0.80±0.20	0.79±0.19	0.805*

P calculated using. *Independent sample *t*-test, #Mann-Whitney U test and ^Chi-square test

Discussion

TXA exerts its antifibrinolytic effect by blocking the lysine binding locus of the plasminogen and plasmin molecules, thereby preventing the binding of plasminogen and plasmin to the fibrin substrate. TXA also inhibits conversion of plasminogen to plasmin.[8] After delivery of the baby, there is transient activation of fibrinolytic cascade for 6 to 10 hours.[7] Hence, the efficacy of an antifibrinolytic agent such as TXA is being evaluated for the prevention of PPH.

The results show that, intraoperatively, mothers in the study group had a mean blood loss of 499.11 ± 111.2 mL, while mothers in control group had a mean blood loss of 690.85 ± 198.41 mL ($P = 0.000$). Two hours postoperatively, the study group had a mean blood loss of 59.93 ± 12.5 mL, while the control group had a mean blood loss of 110.06 ± 13.47 mL ($P = 0.000$). Coupling the two results, mothers in the study group had a mean total blood loss of 559.68 ± 113.80 mL, while mothers in the control group had a mean total blood loss of 800.91 ± 200.26 mL. Thus, in the study group, there was total reduction in blood loss by approximately 30% ($P = 0.000$). Six mothers in the control group required extra 10 U of oxytocin infusion, while only two of the mothers in the TXA group required the same.

Movafegh *et al*.[6] performed their study with intravenous administration of 10 mg/kg of TXA 20 minutes before skin incision at cesarean delivery. Mean blood loss was significantly less in the TXA group compared with the control group for both intraoperative bleeding (262.5 ± 39.6 versus 404.7 ± 94.4 mL) and postoperative bleeding (67.1 ± 6.5

Table 2: Pre and postoperative blood loss estimation

Parameters	Study group (*n*=50) (mean±SD)	Control group (*n*=50) (mean±SD)	Significance
Blood volume in suction (ml)	98.64±28.89	220.80±64.48	*P*<0.001*
Blood volume in mops + sheets (ml)	401.11±112.43	470.05±141.07	*P*<0.01*
Blood loss - intraoperative (ml)	499.75±111.20	690.85±198.41	*P*<0.001*
Blood loss - 2 h postoperative (ml)	59.93±12.5	110.06±13.47	*P*<0.001*
Total blood loss	559.68±113.80	800.91±200.26	*P*<0.001*

P calculated using. *Independent sample *t*-test

Table 3: Postoperative vitals, blood work-up, APGAR score of neonate, and side-effects of drug

Parameters	Study group (n=50) (mean±SD or %)	Control group (n=50) (mean±SD or %)	P
Pallor - present	24 (48%)	38 (76%)	0.004^
Absent	26 (52%)	12 (24%)	
Pulse (per min)	83.76±7.52	91.6±5.07	0.000*
SBP (mmHg)	111.80±8.827	108.6±10.184	0.096*
DBP (mmHg)	68.44±6.011	69.32±7.22	0.753#
Respiratory rate(/min)	14.38±1.22	14.00±1.71	0.493*
Hb% (g%)	10.08±1.18	8.81±1.18	0.000#
Hb% difference (pre-op and post-op)	0.26±0.22	0.99±0.48	0.000*
Total count (per cc)	9354.80±1383.91	9243.20±1267.12	0.675*
Platelet count (lacs/cc)	1.94±0.62	2.03±0.62	0.493*
PT (s)	11.78±0.16	11.79±0.16	0.712*
aPTT (s)	31.78±0.91	31.7±0.83	0.750*
Bilirubin (T)	0.83±0.18	0.86±0.19	0.535*
Bilirubin (D)	0.19±0.09	0.21±0.10	0.573#
ALT	41.18±4.95	41.60±4.84	0.669*
AST	37.8±4.42	38.78±4.39	0.226#
Urea	22.08±1.54	21.96±1.48	0.739#
Creatinine	0.75±0.17	0.75±0.16	0.910#
APGAR score 1 minute	7.06±1.25	7.18±1.35	0.559#
5 minutes	8.66±1.00	8.64±0.98	0.910#
Side effects			
Nausea	16 (32%)	13 (26%)	0.059^
Vomiting	9 (18%)	8 (16%)	0.790^
Diarrhoea	1 (2%)	0 (0%)	0.315^
Thrombosis	0 (0%)	0 (0%)	

P calculated using. *Independent sample *t*-test, #Mann-Whitney U-test and ^Chi-square test

versus 141.0 ± 33.9 mL; $P < 0.001$). Oxytocin administration was significantly less in the TXA group compared with the control group (39 ± 5.8 vs. 43 ± 5.4 units; $P = 0.001$). These results were consistent with the present study.

A similar study was carried out by Gai *et al*.[7] in China by administering TXA 10 min before skin incision. This intervention led to less bleeding 2 hours postoperatively: 42.75 ± 40.45 mL in the study group versus 73.98 ± 77.09 mL in the control group ($P = 0.001$), but did not show any decrease in post-placental delivery blood loss. This was probably due to the fact that TXA was administered only 10 min before the skin incision. Thus, the present study was designed to administer TXA 20 min before spinal anesthesia.

Sekhavat *et al*.[9] conducted a prospective randomized study on 90 primipara mothers which showed that TXA significantly reduced blood loss from the end of CS to 2 hours postpartum; 28.02 ± 5.53 mL blood loss in the tranexamic group versus 37.12 ± 8.97 mL in the control group ($P = 0.000$). These results were comparable to our study although they studied only primipara, whereas our study had no inclusion criteria based on parity.

In our study, postoperatively, there was significantly more pallor in the control group than the study group (38 versus 24) ($P = 0.004$). There was also significant increase in pulse, mean 84/min in study group versus 92/min in control group ($P = 0.000$). Other parameters such as systolic blood pressure, diastolic blood pressure, and respiratory rate did not have any significant difference in the two groups. In the study by Movafegh *et al*.[6] and Gai *et al*.,[7] there was no significant increase in pulse as well as other postoperative vitals.

There was significant difference in postoperative hemoglobin levels between the two groups, mean concentration being 10.0 g% in the study group versus 8.8 g% in the control group ($P = 0.000$). The difference between the preoperative and postoperative hemoglobin values was also significantly less in the study group than the control group (P value = 0.000). Other hematologic and biochemical parameters did not have any significant difference in the two groups. These results were comparable with the study by Movafegh *et al*.[6] and Gai *et al*.[7]

Side-effect profile of TXA such as nausea, vomiting, and diarrhoea was similar in both groups. These results were

similar to previous studies. The incidence of thrombosis during pregnancy and puerperium is 5–6 times higher than that in the general population. When the anti-fibrinolytic drug TXA is administered, the increased risk of thrombosis should be considered, especially in the postpartum LSCS population. In our study, however, none of the mothers developed signs of thrombosis. Svanberg *et al*.[10] reported 67 cases of abruptio placentae being treated by TXA without any signs of thrombosis in any. Similar results were found in other studies.[6,7,9] All data demonstrated that TXA can be used safely without increasing the occurrence of thrombosis, but still more studies are needed in this regard.

The safety of giving TXA (1 g) while the fetus was still *in utero* was a key concern. As a consequence, the neonatal outcome was meticulously evaluated by a neonatologist. In the current study, the mean APGAR scores at 1 and 5 min were 7.06 ± 1.25 and 8.66 ± 1.00 in the study group and 7.18 ± 1.35 and 8.64 ± 0.98 in the control group, respectively. Thus, there was no significant difference in the APGAR values at 1 min ($P = 0.559$) and at 5 min ($P = 0.910$) among the two groups. None of the babies required NICU admission. Results were comparable to previous studies.[6,7,9,11,12]

To conclude, antenatal administration of intravenous TXA 20 min before spinal anesthesia significantly reduces the amount of blood loss during and after lower segment caesarean section without any untoward adverse effects on the mother or the baby.

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Conflicts of interest
There are no conflicts of interest.

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