Effect of Intravenous Administration of Tranexamic Acid in Reducing Blood Loss During and After Caesarean Section

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ABSTRACT
Objective: To determine the effectiveness and safety of intravenous tranexamic acid in reducing blood loss during and after caesarean section.

Methods: A prospective randomised control study in which sixty subjects of caesarean deliveries who were included in the study were divided into two groups: Tranexamic acid (TXA) group – subjects who received tranexamic acid; and Control group - subjects who did not receive tranexamic acid. Intravenous tranexamic acid (Tranostat) 10mg/kg was administered 10 minutes prior to skin incision slowly over 5 minutes in the tranexamic acid group and 10ml of normal saline was administered in the placebo control group over 5 minutes intravenously. The amount of blood loss was measured on two occasions. The first period was from placental delivery to abdominal wound closure (in ml) and the second period from the end of LSCS to 2 hours after surgery (in ml).

Results: Tranexamic acid significantly reduced bleeding from the time of placental delivery to abdominal wound closure in LSCS with blood loss of 339.0 ± 18.4 ml in tranexamic acid (TXA) group compared to blood loss of 377 ± 24 ml in control group. The reduction in blood loss was statistically significant (p value = 0.000). The blood loss from abdominal wound closure to 2 hours post delivery in TXA group and control group were 48.7 ± 9.1 ml and 58.4 ± 9.7 ml respectively and the difference was statistically significant (p value = 0.001). Thus the mean total blood loss was 388.0 ± 22.8 ml and 432.4 ± 30.8 ml in the TXA group and the control group, respectively. The result was found to be highly significant (p value = 0.001).

Conclusion: Tranexamic acid significantly reduced the amount of blood loss during and after lower segment caesarean section. It was not associated with any adverse drug reaction or thrombosis; hence it can be used safely in women undergoing LSCS.

Keywords- Tranexamic acid, Caesarean Section, placental delivery, closure, thrombosis

INTRODUCTION
Caesarean delivery is a common surgical procedure in Obstetrics and has increased worldwide \(^{112}\). Towards the end of pregnancy; the uterus is perfused at a rate of 500-750 ml/min with an average blood loss of approximately 1000 ml during caesarean section (CS) \(^3\). The blood loss in caesarean delivery varies from less than 500 ml to more than 1000 ml \(^4\). Tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid), a synthetic derivative of the amino acid lysine is an antifibrinolytic, thus prevents fibrinolysis and the breakdown of clot \(^5\).
Caesarean section (CS) rates had increased to as high as 20–30% in countries such as: Canada, USA and Brazil by 1990 [6]. By 2001 it was 21.4% in England and Wales, a five-fold increased since 1971, continuing a rising trend [7]. The United States statistics (2006) estimated that, 31.1% of all deliveries were by caesarean section and the number of vaginal birth after caesarean births had dropped dramatically. Caesarean deliveries on maternal request (CDMRs) are estimated to make up 4% to 18% of all caesareans today [8]. Brazil had recorded the highest CS rate (54%) in the world by 2014. The rate is as high as 88% in private sector, with some hospitals recording 100% [9]. The caesarean delivery rate of U.S. peaked in 2009 with 32.9% after increasing every year since 1996(20.7%) [10], whereas it was 32.2% in 2014 [11]. The CS rate was 36.9% at Government Maternity Hospital, Hyderabad, India by December 2010 [12], whereas the rate was 25.66% at Government Victoria Hospital, Visakhapatnam, Andhra Pradesh in 2014 [13].

A “perfect storm” of medical, legal, and personal choices and financial benefits has contributed to an uncontrolled rise in the rate of CS [14]. Caesarean section is associated with complications like haemorrhage, infection, pulmonary embolism and problem in subsequent pregnancies. The risk of a mother requiring hysterectomy is 10 times greater following CS compared to vaginal delivery and the risk of mortality is increased up to several folds when compared to vaginal delivery [14]. One of the most common complications of CS is primary or secondary postpartum haemorrhage (20%), which leads to increased maternal mortality and morbidity [15]. In the United States haemorrhage and hypertensive disorders contribute 12.5% and 12.3% of maternal deaths respectively [1].

The main purpose of TXA is the reduction of perioperative bleeding and transfusion requirements in both cardiac and non-cardiac surgery [16]. The aim of the study was to determine the effectiveness and safety of intravenous tranexamic acid in reducing blood loss during and after caesarean section.

**MATERIALS AND METHODS**

This prospective randomized control study was conducted in the department of Obstetrics and Gynaecology, Regional Institute of Medical Sciences, Imphal, Manipur during one and half calendar years commencing from October 2013 to March 2015. The study protocol was approved by Institutional Ethics Committee. Inclusion criteria were: 1) Women aged 20-40 years with singleton pregnancy at between 38+5 days and 40 weeks’ gestation, who were categorized as class 1 (normally healthy) according to American Society of Anaesthesiologists (ASA) and were scheduled to undergo LSCS under spinal anaesthesia. 2) Malpresentation, contracted pelvis, foetal distress and patients’ request. 3) First time caesarean section. Exclusion criteria were: 1) Patient not willing to participate in study. 2)Previous history of caesarean delivery or intra-abdominal surgery; polyhydramnios, oligohydramnios, macrosomia, pre-eclampsia or abnormal placenta; thrombophilia, anaemia, or coagulopathy; cardiovascular, renal, or liver disorders; or contraindication to any drug used in the study. Sixty subjects of caesarean deliveries fulfilling the inclusion criteria were included in the study. The subjects were divided into two groups: Tranexamic acid (TXA) group (n=30) – subject who received tranexamic acid and Control group (n=30) - subject who did not receive tranexamic acid. The sample size of 30 in each group is according to the rule of thumb for high powers. Intravenous tranexamic acid (Tranostat) 10mg/kg was administrated 10 minutes prior to skin incision slowly over 5 minutes in the tranexamic acid group and normal saline (10 ml) was also administrated in the placebo control group over 5 minutes intravenously 10 minutes prior to skin incision. Every alternate or odd number of the subjects was given intravenous tranexamic acid. Following delivery of the neonate, the mother was given 10 units of oxytocin by intramuscular route.
immediately and 20 units oxytocin in a pint of Ringer’s Lactate intravenously for 2 hours in both the group. Quantity of blood loss from placental delivery to abdominal wound closure (in ml) = [weight of used materials in both the periods (before and after the surgery) – weight of the materials prior to the surgery] + the volume sucked in the suction bottle after placental delivery (ml). Quantity of blood loss 2 hours after surgery (in ml) = weight of the pads used after the surgery – weight of the pads prior to the surgery. Nova KS-1303 weighing scale (silver) [made in China] was used in weighing materials. Blood pressure, heart rate and respiratory rate were assessed immediately after the delivery of the placenta, 1 hour and 2 hours after the surgery. Haemoglobin was investigated after 24 hours of the surgery.

The observations of the study were recorded in a data base programme namely IBM SPSS Statistics 21 developer (SPSS, Inc., Chicago, IL, USA). Descriptive statistics like percentage, mean and standard deviation were used. Analytical statistics like t-test, Chi-square test and Mann Whitney U test were used.

RESULTS
Sixty subjects enrolled in the study were randomised in the 2 groups and there was no significant difference in age, weight, height and preoperative blood pressure statistically (p>0.05; Table 1). Cephalopelvic disproportion (CPD) was the most common indication for LSCS and this is same in both the groups.

Table 1: Distribution based on characteristics of the respondents

| Characteristics          | TXA group (Mean ± SD) | Control group (Mean ± SD) | p-value |
|--------------------------|-----------------------|---------------------------|---------|
| Age in years             | 26.6±5.0              | 28.8±4.7                  | 0.08    |
| Weight in Kg             | 58.850±2.51           | 58.783±2.18               | 0.501   |
| Height in cm             | 158.150±2.20          | 158.153±1.78              | 0.436   |
| Preoperative systolic BP | 120.60±11.04          | 125.20 ±12.02             | 0.746   |
| Preoperative diastolic BP| 79.16 ±7.09           | 80.72 ±7.09               | 0.878   |

Tranexamic acid significantly reduced bleeding from the time of placental delivery to abdominal wound closure in LSCS with blood loss of 339.0 ± 18.4 ml in tranexamic acid (TXA) group compared to blood loss of 377 ±24 ml in control group (p value< 0.001). The blood loss from abdominal wound closure to 2 hours post delivery in TXA group and control group were 48.7 ± 9.1 ml and 58.4 ± 9.7 ml respectively and the difference was statistically significant (p value<0.001). Thus the mean total blood loss was 388.0±22.8 ml and 432.4±30.8 ml in the TXA group and the control group, respectively. The result was found to be highly significant (p value< 0.001) (Table 2).

Table 2: Distribution of the respondents by amount of blood loss

| Blood loss                                      | TXA             | Control         | t-test  |
|------------------------------------------------|-----------------|-----------------|---------|
| Placental delivery to wound closure in ml       | 339.0 ± 18.4    | 377 ± 24.0      | t=6.96  |
|                                                |                 |                 | p=0.000 |
| Wound closure to 2 hours in ml                  | 48.7 ± 9.1      | 58.4 ± 9.7      | t=-4.0  |
|                                                |                 |                 | p=0.000 |
| Total blood loss ml                             | 388.0±22.8      | 432.4±30.8      | t=-6.330|
|                                                |                 |                 | p=0.000 |
Preoperative haemoglobin level (in gm%) was almost same in both the groups (TXA group=11.67±0.85, control group=11.82±0.85; p=0.501). Post operative haemoglobin was higher in TXA group (11.15±0.7 gm%) than control group (10.98 ± 0.9 gm%) but the finding was statistically insignificant (p=0.436). But there was a significantly less fall in haemoglobin among the TXA group (TXA=0.52±0.2 gm%, control=0.84±0.2 gm%; p<0.05).

The duration of CS is reduced among study cases (42.00±5.00 mins) than that of control cases (47.40±3.90 mins) and the finding is statistically significant (p<0.001) (Table 3). In the TXA group the duration of CS was 5 minutes shorter when compared to the controls.

Table 3: Distribution of the respondents by duration of CS

| Variable                  | TXA         | Control     | Mann Whitney u test |
|---------------------------|-------------|-------------|---------------------|
| Duration of CS in minutes | 42.00±5.003 | 47.40±3.900 | T=-4.662 p-0.000    |

There was no significant difference in blood pressure statistically in between the two groups when measured during the time of placental delivery, 1 hour and 2 hours post-operative periods.

Heart rate during placental delivery was same in both the groups but it was increased among TXA group after 1 hour and 2 hours post operative periods and this finding was statistically significant (p<0.05) (Table 4). But there was no significant change in respiratory rate during placental delivery and post operative periods in both the groups statistically.

Table 4: Distribution of the respondents by heart rate (HR) and respiratory rate (RR)

| Variables                     | TXA            | Control        | Mann Whitney U test |
|-------------------------------|----------------|----------------|---------------------|
| HR During placental delivery  | 83.73±7.216    | 83.80±5.810    | Z=-0.010 p-0.917    |
| HR 1 Hr Post operative       | 94.13±6.410    | 81.73 ± 10.154 | Z=-4.96 p-0.000    |
| HR 2 Hr post operative       | 91.20±6.359    | 80.13±5.656    | Z=-4.77 p-0.000    |
| RR During Placental Delivery | 19.30±1.236    | 19.60±0.932    | Z=-0.847 p-0.387   |
| RR 1 Hr Post operative       | 19.10±1.647    | 19.20±1.424    | Z=-0.065 p-0.945   |
| RR 2 Hrs Post operative      | 18.80±1.126    | 19.10±0.885    | Z=-1.087 p-0.277   |

Nausea and its association with vomiting were common in both the groups but there was no difference in the complications between the two groups and were statistically insignificant. The Apgar scores in both the groups were statistically insignificant.

DISCUSSION

As tranexamic acid exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules and inhibits endometrial plasminogen activator and thus prevents fibrinolysis and the breakdown of clot. Tranexamic acid bearing a molecular weight of 157.21 g/mol crosses the placental barrier with the cord blood concentration of about 30 mg per L, after an intravenous injection of 10 mg per kg to pregnant women. Tranexamic acid is proved to be a better drug under its class for various purposes, as well as the safest haemostatics with minimum side effects. It has been considered in patients with major haemorrhage in Obstetrics and other specialties in an attempt to control massive haemorrhage. The main purpose of TXA is the...
reduction of perioperative bleeding and transfusion requirements in both cardiac and non-cardiac surgery\cite{5,16,17}.

Under normal conditions, fibrinolysis provides an important mechanism to limit propagation of intravascular thrombosis. Tissue plasminogen activator (t-PA), from vascular endothelium, converts plasminogen to plasmin that impairs the haemostatic process by a number of mechanisms including degradation of cofactors Va and VIIIa, proteolysis of platelet adhesive receptors, consumption of alpha 2-antiplasmin, and the degradation of fibrin and fibrinogen\cite{18}.

The study showed that tranexamic acid significantly reduced blood loss both from the time of placental delivery to abdominal wound closure in LSCS (p<0.001) and from the time of abdominal wound closure to 2 hours post delivery (p<0.001). Thus the mean total blood loss was significantly less in the TXA group (p value<0.001). Blood loss of \(\geq 500\) ml were not observed in either of the TXA group or control group. Novikova N and Hofmeyr GJ\cite{19} also demonstrated that blood loss greater than 400 ml was less common in women who received TXA intravenously (1 gram or 0.5 gram) during vaginal birth or caesarean section.

The results were comparable with a study by Gai MY et al with a total blood loss of 351.57±148.20 ml in the TXA group and 439.36±191.48 ml in the control group (P=0.002). The blood loss from the end of CS to 2 hours post delivery of 42.75±40.45 ml in the TXA group versus 73.98±77.09 ml in the control group (P=0.001) was also comparable\cite{20}. The blood loss in the two periods was also significantly reduced in the TXA group according to Xu J et al\cite{21} and Mayur G et al\cite{22}.

According to a study conducted by Movafegh A et al\cite{23} the mean blood loss was significantly less in the tranexamic acid group compared to the control group for both intraoperative 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.

In our study, there was significantly lesser fall of haemoglobin level in the TXA group postoperatively (p<0.05). The fall in haemoglobin was 0.32 g/dl less in TXA group as compared to control group. Halder S et al\cite{24} in their study also found out that the fall of haemoglobin in the TXA group was 1.214 g/dl in comparison to 1.7256 g/dl in the control group that was statistically significant (p < 0.0001). The duration of CS in the study was five minutes shorter in the TXA group when compared to that of the control group and the finding was statistically significant (p<0.05). This had not been documented in any other studies that we came across. The shorter duration of CS was probably due to a better field of vision for the surgeon by the use of tranexamic acid.

Heart rate during placental delivery was similar in both the groups, but it was significantly increased in the TXA group when compared to the control group following 1 hour and 2 hours of post delivery (p<0.05). However blood pressure (BP) and respiratory rate (RR) were comparable in both the groups. There was no significant alteration in the vital signs in the studies by Gai MY et al\cite{20}, Mayur G et al\cite{22}, Halder S et al\cite{24} and Sekhavat L et al\cite{25} following tranexamic acid administration.

No sign of thrombosis were not observed in any of the patients in our study. Dunn C J and Goa K L\cite{26} in their review on the use of tranexamic acid in surgery, increased risk of thrombosis with the drug were not demonstrated in the clinical trials. In a similar study, Mayur G et al\cite{22} did not demonstrate the increase in the risk of thrombosis among 100 patients. In another study, Shahid A and Khan A\cite{27} while determining the effectiveness of tranexamic acid (TXA) in reducing blood loss during and after caesarean section (CS), the increased in the risk of thrombosis was not reported. Similar studies by Sentürk MB et al\cite{28} in 220 patients and Gungorduk K et al\cite{29} in 660 patients, the incidence of thromboembolic events were not increased.
The side effects of tranexamic acid such as nausea, vomiting and diarrhoea were statistically not significant in both the groups in this study and were consistent with previous studies. There was no difference in Apgar score between the two groups immediately following delivery in our study. The similar result was found in a study conducted by Gai MY et al [20]. Thus, tranexamic acid had no effect on the Apgar score of the baby. Tranexamic acid is inexpensive and treatment would be considered highly cost effective in high, middle and low income countries, thus it has been included in the WHO list of essential medicines. Its use can be considered very promising in reducing blood loss during caesarean section.

**CONCLUSION**

Tranexamic acid significantly reduced the amount of blood loss during and after lower segment caesarean section. The used of tranexamic acid was not associated with any adverse drug reaction like nausea, vomiting, diarrhea or thrombosis. Foetal outcome was not adversely affected by the use of tranexamic acid as evaluated by Apgar score. The duration of CS was five minutes shorter in the TXA group when compared to that of the control group.

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