Original Article: The Function of Preventive Tranexamic Acid in Minimizing Blood Loss During Elective Caesarean Section

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ABSTRACT

Introduction: TXA may lessen the need for hysterectomy, lessen the risk of developing severe anemia, and prevent the need for blood transfusions, all of which could significantly advance the objective of lowering maternal mortality, according to several RCTs that have examined the prophylactic role of the drug (described in the discussion). **Material and Methods:** To make TXA injection, 1 gram (10ml) of TXA was diluted in 100ml of sterile saline. To those in the study group, TXA was infused intravenously for more than 15 minutes, at least 20 minutes before making a skin incision. The control group received no medication at all. All of the participants received spinal anesthesia. Surgery was performed by assistant professors with an MD degree and at least three years of experience. **Results:** Primary outcomes included blood loss from placental delivery to the conclusion of surgery and the percentage of hemoglobin difference, while secondary outcomes included the length of surgery and the percentage of patients who lost more than 500 ml of blood. There was a significant difference between the two groups in these primary and secondary outcomes. **Conclusion:** TXA significantly decreased the amount of blood lost during LSCS. Being in a hypercoagulable state during pregnancy increases the risk of thrombotic events. However, there were no negative side effects or complications in the first few weeks after delivery when this antifibrinolytic was used. So, when subjects are undergoing LSCS, TXA can be applied effectively and safely.

Introduction

Worldwide, more than 5 lac women pass away each year from pregnancy- and delivery-related causes. The primary cause of mortality as well as morbidities like severe anemia, the need for blood transfusions, hospital stays, and infections is postpartum hemorrhage (PPH).

In order to achieve Millennium Development Goal 5's target of reducing maternal mortality by 75% by 2015, a reduction of 5% must be made each year. Only a small percentage of all

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maternal deaths are caused by individuals at high risk of PPH. Most cases of morbidity and mortality occur in people who have no risk factors and are unpredictable. 9 point 2 percent of 1620 rural Indian women who participated in the analysis of PPH reported having it. Though the incidence of early PPH (occurring within 24 hours of delivery) is lower in caesarean section than vaginal delivery, the latter is a major surgery and causes greater blood loss. Maternal or sociodemographic factors did not differ between women with PPH and those without. Consequently, it is crucial to effectively and practically stop the blood loss, which is why this study is necessary.

Pharmacologic management, in addition to obstetric, surgical, and radiologic interventions, is crucial in this regard. The main cause of PPH is uterine atony. In addition to intravenous ergometrine, intramuscular carboprost, and misoprostol, oxytocin is the first line of treatment for PPH. To the well-established uterotonics, especially oxytocin, prohaemostatic drugs like TXA offer a complementary biochemical haemostatic effect(Fig 1).

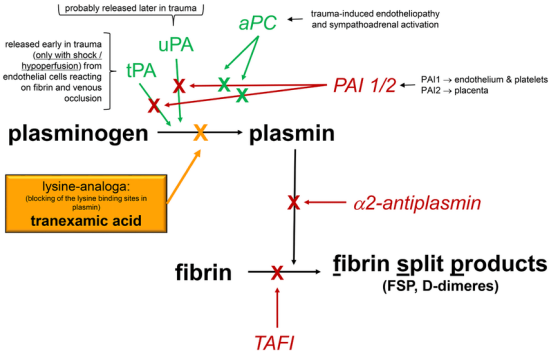

Figure 1: Tranexamic Acid mechanism

Surgery frequently makes use of systemic anti-fibrinolytic drugs. The results showed that aprotinin decreased the risk of blood transfusion by 34% and the risk of TXA by 39%. A systematic review of 211 randomised controlled trials of anti-fibrinolytic agents in elective surgical patients found 211 randomised controlled trials. By binding to plasminogen in a competitive manner, TXA, a lysine analogue, prevents fibrinolysis.

By preventing plasminogen and plasmin activation, it stops the lysis of the formed clot. It has been demonstrated that TXA, which is ten times more potent than amino-caproic acid, can decrease uterine blood loss without surgery. A randomized controlled trial evaluating TXA for the treatment of PPH revealed that a high dose of TXA reduces blood loss in women with PPH. The study examined women with menorrhagia and found that those treated with TXA experienced a significant decrease in mean menstrual blood loss.

TXA may lessen the need for hysterectomy, lessen the risk of developing severe anemia, and prevent the need for blood transfusions, all of which could significantly advance the objective of lowering maternal mortality, according to several RCTs that have examined the prophylactic role of the drug (described in the discussion).

Material and Methods

Over the course of a year, from June 2018 to May 2020, the study was conducted among patients at the PSG hospital who were scheduled to have elective caesarean sections. The formula used to determine sample size was 2 SD2 (Z2 + Z2)2 M2 - M1. Reference was taken from a RCT carried out in Karachi to determine the incidence of PPH in the study and control arms. In this study, PPH

incidence was 30% in the placebo group compared to 13% in the TXA group.

The study's power was set at 80%, and the two-sided confidence interval at 95%. Given these factors, 58 women in each group were the bare minimum required to generate statistically significant results, so a total of 120 subjects—60 in each group—were chosen for the study.

Twenty-one term, multiparous (parity not to exceed two), singleton pregnant women who were scheduled to have an elective LSCS delivery were enrolled. By using a computer-generated random number table, they were split into two groups as the control and study groups. Each group had 60 participants. The study wasn't blinded; it was open-label. The gestational age ranged from 37 to 42 weeks, and subjects between the ages of 19 and 34 were included.

Exclusion criteria for the study included participants with coagulation disorders, renal disease, severe pre-eclampsia, chronic hypertension, and gestational hypertension. Subjects who were allergic to TXA, had a history of thromboembolic disorders, were more likely to experience increased bleeding due to abnormal placentation, multiple pregnancies, polyhydramnios, or previous cesarean sections, as well as those who had received blood transfusions as a result of anemia, were all excluded from the study.

Following the subjects' informed consent, they were assigned to one of the two groups using a straightforward randomization process. Both groups estimated their preoperative hemoglobin levels. Previous LSCS studies have either used a 1gm or 10mg/kg intravenous bolus [9,10,16] as their dose. A study mentioned that a 15mg/kg dose was more efficient without increasing side effects. For this study, a dose of 1 gram was chosen, with the average antenatal woman weighing 70 kg.

To make TXA injection, 1 gram (10ml) of TXA was diluted in 100ml of sterile saline. To those in the study group, TXA was infused intravenously for more than 15 minutes, at least 20 minutes before making a skin incision. The control group received no medication at all. All of the participants received spinal anesthesia. Surgery was performed by assistant professors with an MD degree and at least three years of experience. Both groups received routine care following the delivery of the neonate. 10 units of oxytocin were added to ringer lactate and allowed to flow at a rate of 75 to 100 ml/hour for three hours following surgery. There were no study participants who were dropped. Following placental delivery and up until the conclusion of the procedure, the blood loss was quantified using a gravimetric method. The suction container had blood accumulating in it, it was observed.

Prior to and following surgery, wet mops and the perineal sheet from the operating table were weighed using an electronic scale. The total amount of blood loss (in milliliters) was calculated as the product of the following factors: 1) Blood absorbed by wet mops (wet weight of used mop - dry weight + 2) Blood absorbed by perineal sheets during vaginal squatting (wet weight - dry weight + 3) Blood collected in suction container. The amount of blood lost prior to placental delivery and amniotic fluid were excluded from the study. A mg weight was assumed to be equal to 1 ml of blood . Calculations only took into account intraoperative blood loss; they excluded postoperative bleeding.

Although the gravimetric method is thought to be the most practical, it only provides approximations . The time between the skin incision and skin closure was used to calculate the length of the procedure. Patients (in both arms) were observed for 4 hours following surgery.

Monitoring revealed stable vital signs, including heart rate, blood pressure, and oxygen saturation. For all patients, hemoglobin estimation was performed 24 hours following

surgery so that the results could be compared to the preoperative value. Urinary catheters were removed after 12 hours, input-output charts were kept, and patients were watched for any increased vaginal bleeding. Up until the day of discharge, participants were watched. There were no immediate postpartum or neonatal complications.

Ethical Considerations: This study has been approved by the committee of Alborz University of Medical Sciences(Ethic No: IR.ABZUMS.REC.1401.146)

Results

Age, weight, height, parity, gestational age, baseline hemoglobin levels for all participants, gestational diabetes, hypothyroidism, asthma, and fetal compromise were not statistically different between the two groups . Previous cesarean section, malpresentation, gestational diabetes, hypothyroidism, asthma, and fetal compromise were not statistically different between the two groups dot(Fig 2).

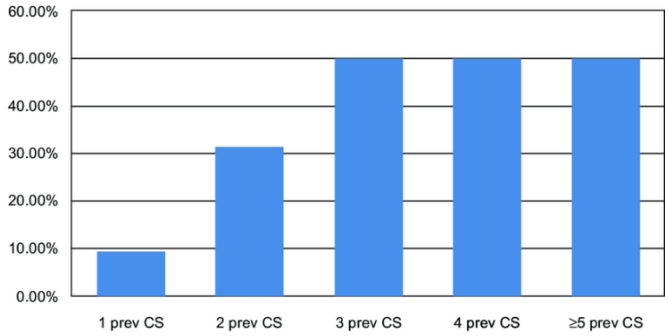

Figure 2: Blood lose rate after Intervention

Primary outcomes included blood loss from placental delivery to the conclusion of surgery and the percentage of haemoglobin difference, while secondary outcomes included the length of surgery and the percentage of patients who lost more than 500 ml of blood. There was a significant difference between the two groups in these primary and secondary outcomes(Fig 3).

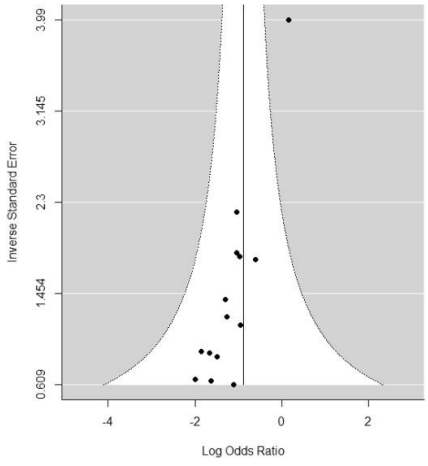

Figure 3: hemoglobin rate after intervention

It was also considered whether to use more uterotonics intraoperatively. 9 subjects in the control group experienced excessive bleeding, necessitating the administration of additional oxytocins: 20 units were added to the drip (at a rate of 60 milliliters per hour for three hours) and an intravenous injection of Methergin 0.2 mg. Three of the study group's subjects required additional oxytocins, and one of them had a uterine angle extension during surgery, which

increased blood loss. In neither of the groups postoperatively, blood transfusion was required. In this study, there were no negative outcomes or immediate postpartum and neonatal complications.

Discussion

The lysine binding site of plasminogen is competitively blocked by tranexamic acid, preventing the lysis of the clot that has formed. It begins working within 5 to 15 minutes and keeps working for 3 hours. It binds to the plasminogen molecule with greater vigor than amino-caproic acid. By Utako Okomoto in the 1950s, TXA was found. It was the product of their joint research efforts following the Second Sino-Japanese War.

On the Pharmaceutical Benefits Schedule from the early 1990s, oral TXA was listed as an anti-fibrinolytic drug. The Therapeutic Goods Administration (TGA) authorized Pfizer Australia to sell TXA (Cyklokapron) solution for injection in 2010. After that, the US Food and Drug Administration gave its approval.

Early TXA administration significantly reduced all-cause mortality in acute trauma, according to the CRASH-2 (Clinical Randomization of Antifibrinolytic in Significant Haemorrhage) trial . The WHO has advised using TXA in cases where bleeding cannot be controlled by oxytocin and other uterotonics or if the bleeding is caused by refractory atonicity or trauma-related bleeding. The WOMAN trial (World Maternal Antifibrinolytic trial - London School of Hygiene and Tropical medicine) is assessing its efficacy in lowering PPH. Maternal morbidity and mortality are significantly impacted by PPH. Infection risk, blood product requirements, hospital stays, and costs are also on the rise.

Therefore, efforts to reduce blood loss are extremely important, especially in developing nations where there is a lack of knowledge and resources. Exaggerated fibrinolytic activity occurs after delivery as a protective measure against the acute trauma to blood vessels. By stopping fibrinolysis, TXA can therefore effectively control bleeding. Between the Study and Control arms, this randomized, prospective, interventional study compared the effectiveness of TXA in reducing blood loss during caesarean section. Through the use of gravimetry, intraoperative blood loss was estimated. The estimation of blood loss can also be done visually, directly, or photometrically.

The most popular method is the visual one, which is also the most inaccurate. The most accurate method is thought to be photometric, but it is also the most complicated and expensive .WHO (2012) advises that there is no method that is superior to another. Vital signs were monitored postoperatively, and patients were closely watched for any negative side effects. The most common post-marketing adverse reaction of TXA in Sweden is visual abnormalities, which are frequently poorly characterized (if the drug was taken for a few days). Convulsions have been documented, especially in patients receiving tranexamic acid during cardiovascular surgery and when the medication was accidentally administered into the neuraxial system. But there is no evidence of a thrombogenic effect of TXA on pregnant women in any of the reference studies cited here . Diarrhea, vomiting, and other gastrointestinal disturbances could happen.

This study demonstrated a significant difference between the two groups in terms of both the amount of blood lost and the percentage of hemoglobin falling. Only 3% of subjects in the study arm experienced increased bleeding, compared to 60% of subjects in the control arm who lost more than 500 ml of blood. Only 9.3 percent of subjects in the study arm experienced a >10% difference in pre- and post-operative hemoglobin, compared to 38.9 percent of subjects in the control arm.

This study and a select few others are comparable. a research study by Movafegh et al,

which covered the intraoperative and postoperative periods, revealed that the study group (TXA 10mg/kg) experienced significantly less mean blood loss. In the study group, there was also less oxytocin administered (this was not tracked in the study).

"Goswami et al.", divided the subjects into two study groups (10 mg/kg vs 15 mg/kg dose) and one control group . Between pre- and post-operative haemoglobin, there was a sizable difference. Abdel Aleem and other people, which randomly assigned 740 subjects, revealed a significant decrease in mean blood loss during and for 2 hours after surgery. TXA can be administered safely before LSCS, and Gungorduk and colleagues found that it also decreased the need for additional uterotonics. Gai and others., which tested the safety and effectiveness of the treatment on 180 Primi Parous women .

Gohel and colleagues demonstrated the same effect after randomizing 100 women undergoing LSCS. In this study, there was no discernible difference between the two groups in terms of the length of the procedure or the reason for the surgery. Senturk and associates. conducted a similar study using 20 ml of TXA diluted with 20 ml of 5 percent dextrose.

Blood loss in the study arm was significantly reduced. Yehia and colleagues examined the post-operative need for iron replacement in their study. The first six hours after surgery were used to calculate vaginal bleeding, which was lower in the study arm.

PPH incidence in the study arm was significantly lower than in the control arm (31 percent versus 63 percent, respectively) . Wang and others. conducted a meta analysis of 11 RCTs to assess the efficacy of TXA and found that there were significant differences in mean blood loss, haemoglobin levels, and the need for blood transfusions between the groups.

In the studies mentioned above, there were no negative effects. Regarding potential risks to the neonate, Viswanathano and colleagues advise caution. It claims that because neonates are more susceptible to the effects of low drug concentrations, there may be a potential for seizures [26] and concludes that high quality RCTs are required before the widespread use of TXA can be deemed to be supported.

A low dose of TXA (1 g) after vaginal delivery in the two minutes following the child's delivery and prophylactic oxytocin administration are compared in an adequately powered multicenter randomized, double-blind, placebo-controlled trial with 4000 participants . Its purpose is to address current questions about the effectiveness and unfavorable effects of TXA on pregnant women. It had a 34-month estimated study period when it was approved in 2014.

Conclusion

TXA significantly decreased the amount of blood lost during LSCS. Being in a hypercoagulable state during pregnancy increases the risk of thrombotic events. However, there were no negative side effects or complications in the first few weeks after delivery when this antifibrinolytic was used. So, when subjects are undergoing LSCS, TXA can be applied effectively and safely.

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