

Research Article

Role of Prophylactic Tranexamic Acid in Reducing Blood Loss during Elective Cesarean Delivery

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Introduction

Each year, worldwide, about 530,000 women die from causes related to pregnancy and childbirth. Nearly all (99%) of these deaths are in low and middle income countries [1]. Although maternal mortality has become a rare event in developed countries, it nonetheless remains a crucial indicator of the quality of obstetric care and the health status of mothers. Haemorrhage, which usually occurs in the postpartum period, is responsible for between one quarter and one third of obstetric deaths worldwide [2]. About one in five of these haemorrhages progresses to a severe form that may endanger the mother's life or at least her future fertility. Also PPH causes maternal morbidity as blood transfusion (which can transmit blood borne viral infections, adverse reactions), severe anaemia and postpartum pituitary infarction [3]. Primary Postpartum Haemorrhage (PPH) is considered if blood loss within the first 24 hours after delivery (vaginal or cesarean) ≥ 1000 ml or associated with manifestations of hypovolemia in spite of amount of blood loss [4]. Traditional definitions depended on mode of delivery, if estimated blood loss ≥ 500 ml with vaginal delivery and ≥ 1000 ml with cesarean delivery were considered primary postpartum haemorrhage [5]. Prevalence estimates for PPH in the literature vary widely, from 3% to 15% of deliveries [6-8]. This diversity is explained partly by the variety of criteria and methods used to define PPH: definitions are based on haematological indicators or on the volume of blood loss, which in turn can be estimated clinically or measured more objectively by, for example, a blood collection bag. 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.

The most common causes of postpartum haemorrhage are uterine atony, abnormal placentation including placental abruption, lower genital tract lacerations, retained placental tissue, coagulopathies, vessel malformation, and uterine rupture [9]. Risk factors for atonic PPH include primiparity, macrosomia, multiple pregnancy, previous PPH, obesity, prolonged or augmented labor, polyhydramnios, previous cesarean delivery, antepartum haemorrhage, morbid adherent placenta, anaemia, blood disease, coagulation defect, pregnancy induced hypertension, fibromyomata and elective

cesarean section [10]. Nevertheless, most women with PPH have low-risk pregnancies and no identifiable risk factors.

During delivery, when the placenta separates from the uterine wall, sequential physiologic and hemostatic changes occur and reduce bleeding, including strong myometrial contractions, increased platelet activity, and massive release of coagulant factors; at the same time, however, fibrinolytic activity increases [12]. The placental separation is a critical window for the prevention of PPH so; they can be schematically divided into two categories: those involving a mechanical mechanism and those involving prohaemostatic agents. Active Management of the Third Stage of Labour (AMTSL), consisted of a combination of the following interventions: administration of uterotonic agents immediately after delivery of the child, early cord clamping and cutting, Controlled Cord Traction (CCT), and uterine massage [13,14]. It has been shown that the administration of uterotonics, and in particular oxytocin, after birth is the only component of AMTSL that is effective in preventing PPH. However, in addition to this enhancement of mechanical haemostasis, a complementary biochemical haemostatic effect might be expected from the use of prohaemostatic drug such as TXA [13,14].

Tranexamic Acid (TXA) is an amino acid lysine synthetic derivative, it is a potent antifibrinolytic agent that exerts its effect by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own hemostatic mechanisms, so clot breakdown (fibrinolysis) is inhibited and bleeding is reduced [15]. The administration of TXA in planned surgery reduces the risk of blood transfusion, mean transfused volume, and need for re-operation due to bleeding, without increasing thrombotic events [16]. Significant reductions of 26-54% vs placebo or control in mean menstrual blood loss were reported in women with menorrhagia treated with TXA [17]. This result is particularly significant since the efficacy of TXA in menorrhagia suggests that it can reduce uterine blood loss, even of low volume, and in a nonsurgical context. This provides further support for the hypothesis that TXA might be effective for the prevention of PPH after both caesarean and vaginal deliveries. Therefore, during labour the administration of oxytocin enhances the myometrial contraction, and TXA might be able to counter the increased fibrinolytic activity and thus facilitate the hemostatic process.

There is a risk of venous thromboembolism during pregnancy and especially during the puerperium, There is no significant increase in the incidence of thrombotic events related to TXA has been observed in any trial of TXA among pregnant women (n=2228), including RCTs, observational nonrandomized studies and case series [18].

The aim of this study was to assess the efficacy of slowly intravenous administration of antifibrinolytic agent (TXA) on reducing blood loss during elective Cesarean delivery.

Patients and Methods

The study was conducted on 200 women who were admitted at Shatby Maternity University Hospital during the period from January 2019 till November 2019, who were planned to be delivered by elective LSCS. It was Prospective double randomized open(not blind) study. The individual information on the study was given for the women in late pregnancy during prenatal visits and was repeated again during labour, good counselling of each women and then confirmation of her participation and informed written consent before delivery.

Inclusion criteria

Age of patients between 19 and 38 yrs, primiparous/multiparous, singleton full term (gestational age of 37 to 42 wks) pregnancy. They were divided into 2 groups, as control and study groups each one comprised of 100 patients.

Exclusion criteria

History of thromboembolic disorders, any medical disorders(renal, liver, brain or cardiovascular diseases), severe hemorrhagic disease, Eclampsia, HELLP syndrome, anemia, anticoagulant therapy, allergy to TXA, IUFD, macrosomic baby, multiple pregnancy, polyhydraminos, preterm labour, antepartum hemorrhage, morbid adherent placenta.

Full detailed history was taken to exclude the women had exclusion criteria, general physical and obstetric examination and all routine investigations needed for operation as hemoglobin level, haematocrit value, liver, kidney function and coagulation profile, also obstetric ultrasound. Women were classified randomly into two groups using a computer-generated randomization system, to receive either 1 g of TXA or placebo (normal saline). 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 while normal saline was given to the control group. Spinal anaesthesia was done for all participants. After delivery of the neonate, routine care was given to both 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 sheets 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 sucked in special container and not included in the study. One mg weight was taken as equivalent to 1ml of blood [19]. Only the intraoperative blood loss was calculated; postoperative period was not included. Gravimetric method gives only approximate estimation, however it is considered the most practical [20]. Blood clots were weighed separately. Postoperatively patients (in both groups) were monitored for 4 hours, vital signs as heart rate, blood pressure, oxygen saturation were monitored and managed according to need as additional uterotonic drugs, blood transfusion or surgical

Table 1: Demographic data.

Parameter	Study (n=100)	Control (n=60)	p-value
Age (years)	27.14±4.986	26.77±4.942	0.397
BMI (kg/m ²)	32.88±2.76	33.59±3.22	0.138
Parity	1.74±1.461	1.61±1.286	0.27
Gestational age (wks)	37.86±0.81	37.93±0.069	0.735

Table 2: Indications of surgery.

Indication	Study	Control
Previous LSCS	65	67
Pervious uterine scar	7	5
Malpresentation (Breech, Transverse)	12	10
Gestational Diabetes	10	15
Fetal complication (Intra Uterine Growth Retardation)	2	0
CPD	1	2
Elderly primigravida	3	1

intervention as (bimanual uterine compression, uterine ballon, B Lynch, uterine artery ligation, internal iliac ligation, embolization or hysterectomy). Haemoglobin level and haematocrit value were checked pre-operative and 24 hours after the surgery for all the patients to compare the preoperative and postoperative values. 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. Maternal side effects caused by tranexamic acid like visual disturbance, chest pain, calf pain, incoordination were noted. Any surgical intervention or hysterectomy required for failed medical management was noted. Any maternal mortality and cause for it was evaluated.

Results

Table 1,2 As regard amount of blood loss, there was statistically significant difference between both groups where less blood loss in study group, also hemoglobin level and hematocrit value pre-operative and 24hours post-operative were highly statistically significant differences between the two groups where lower values postoperative in control group (Table 3).

There were no changes in the vital signs postoperative in both groups; also, no surgical intervention was needed just extra doses of oxytocin in control group. Nausea was the only side effect was found in study group.

Discussion

PPH is commonly defined as blood loss of ≥500 ml after vaginal delivery of a baby or ≥1000 ml after caesarean section. However, these

Table 3: Comparison of blood loss, hematocrit value and Hemoglobin level.

Group	Study group	Control group	P-value
Amount of blood loss in ml	499.9±206.4	600.7±215.7	
Pre-operative Hb	11.4±0.8	11.3± 0.6	
Pre-operative Hct	33.0±1.7	32.8±1.6	
24 hours Post-operative Hb	10.0±0.8	9.1±0.6	<0.001
24 hours Post-operative Hct	30.7±1.5	30.1±1.0	<0.001

thresholds do not take into account pre-existing health status, and blood loss as little as 200-300 ml can be life threatening for a woman with severe anemia or cardiac disease. Obstetric hemorrhage remains one of the major causes of maternal death in both developed and developing countries. Because of its importance as a leading cause of maternal mortality and morbidity, and because of evidence of substandard care in the majority of fatal cases, obstetric hemorrhage must be considered as a priority topic for national research development [21]. PPH contributes much to the maternal morbidity and mortality. Moreover, 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. During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products increase due to activation of the fibrinolytic system, this activation can last up to 6-10 h postpartum causing more bleeding. 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 [22].

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. 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 mortality in acute trauma by early administration of TXA. WHO has recommended using TXA in situations where the bleeding is not controlled with oxytocin and other uterotonic or if the bleeding is due to refractory atonicity/trauma-related bleeding [23]. Thus, the current study was held to assess the efficiency of use of tranexamic acid in reducing blood loss in patients undergoing cesarean sections.

200 women were enrolled in the study who were planned for elective cesarean section classified randomly into study and control groups, each one included 100 women. In our study, there was no significant difference as regard patient characteristics (age, weight, BMI, parity and gestational age) between the study (TXA) and the control groups (Placebo). Moreover, most common cause for surgery was previous cesarean delivery.

The amount of blood loss from time of placental delivery until closure of skin was 499.9 ± 206.1 versus 600.7 ± 215.7 between Study and Control group respectively. This result agreed with that had been reported with different studies as Gai MY et al., and Sekhavat et al as they assessed the blood loss during cesarean delivery and up to 2 hours postoperative [24,25]. Movafegh et al also found that Mean blood loss was significantly less in the TXA group compared with the control group for both intraoperative bleeding and postoperative bleeding they found also that Oxytocin administration was significantly less in the TXA group compared with the control group, these results were consistent with the present study [26].

In our study, there were no changes in postoperative parameters

such as pulse, systolic blood pressure, diastolic blood pressure, and respiratory rate and did not have any significant difference in both groups. In the study by Gai et al., [24] and Movafegh et al., [25] there was no significant increase in pulse as well as other postoperative vitals.

Mayur et al. showed that tranexamic acid significantly reduced the quantity of blood loss from the end of LSCS to 2 hours postpartum [27].

In this study, postoperative hemoglobin level was significantly higher in the study group (10.0 ± 0.8) than in the control group (9.1 ± 0.6) ($p < 0.001$). Reduction in hemoglobin was significantly less in the study group than in the control group by (0.9 ± 0.2 gm/dl) ($p < 0.001$). In addition, post-operative hematocrit value was significantly higher in the study group (30.7 ± 1.5) than in the control group (30.1 ± 1) ($p < 0.001$). Reduction in hematocrit was significantly less in the study group than in the control group by (0.6 ± 0.5 %) ($p < 0.001$). These results were comparable with the study by Movafegh et al., [26] and Gai et al., [24].

Also meta-analysis of 9RCTs for evaluation the effect of prophylactic TXA in decreasing PPH at cesarean section showed that TXA was associated with a significant reducing postpartum blood loss and lower hemoglobin level drop postoperative [28].

The side effects described with the use of TXA include gastrointestinal symptoms such as diarrhea, nausea and vomiting that occur in about 10% of patients. Rare complications include hypotension, thrombosis, blurred vision, renal cortical necrosis and retinal artery obstruction [29]. There were no mortality and no thrombotic event was reported. The most frequently reported adverse effect of TXA was nausea No complications were reported in either group.

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.

Limitations

There were limitations in this study. First is the gravimetric method of estimation of blood loss. Blood volume collected was only approximate. 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 so there is a need of undertaking multicentre randomized controlled trials to study its effect on thromboembolic event.

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