Prophylactic Use of Tranexamic Acid in Reducing Blood Loss during Elective Cesarean Section

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ABSTRACT

Background: Primary postpartum hemorrhage (PPH) plays a major role in maternal mortality and morbidity like severe anemia, blood transfusion requirement, hospital stay and infection. Tranexamic acid is now recommended in treatment of PPH, yet its prophylactic use before delivery is still not recommended.

Objective: To assess the efficacy of preoperative administration of Tranexamic acid in decreasing blood loss during elective cesarean section.

Patients and Methods: The study was conducted at Department of Obstetrics and Gynecology of Menoufia University Hospitals. It included 100 pregnant females who went through elective cesarean section with age >18 and < 35 years and singleton alive fetus. They were randomly allocated to two groups: the study group of which women received 1 gm of tranexamic acid 20 minutes before skin incision and the control group who did not receive tranexamic acid. The assessment included the following: measurement of blood loss amount and estimation of postoperative 1st day hemoglobin and hematocrit value.

Results: There was highly statistically significant difference between both groups regarding the amount of blood loss during cesarean delivery and blood loss 2 hours from end of CS ($p \leq 0.001$). This was reflected in the percentage of difference of preoperative and postoperative hemoglobin and hematocrit values, which showed highly significant statistical difference ($p \leq 0.001$).

Conclusion: Tranexamic acid administration before elective cesarean section was effective in decreasing intraoperative and postoperative bleeding. And in turn reduces the incidence of PPH with no immediate maternal or neonatal side effects.

Keywords: Cesarean section, Postpartum hemorrhage, Tranexamic acid.

INTRODUCTION

Cesarean section (CS) is considered one of the most common surgeries in the entire world [(1)]. In the last three decades, increased cesarean delivery rates has been a worldwide concern , witnessed in both developing and developed conutries. In Egypt, women with less than 3 living children were twice more likely to go through caesarean birth than women with more parity [(2)]**.** Primary postpartum hemorrhage (PPH) plays a major role in maternal mortality and morbidity like severe anemia, blood transfusion requirement, hospital stay and infection [(3)]**,** with about 295 000 women died during childbearing and follwing parturition. About 94% of these deaths took place in settings with poor resources, with about 65% (two thirds) occurred in the World Health Organization (WHO) African region [(4)]**.**

In 2017, WHO recommended that tranexamic acid (TXA) should be given in the first 3 hours following delivery in-patient with established diagnosis of PPH, alongside basic established care for all patients either with PPH delivered vaginally or by cesarean section [(5)]**.** For this reason, we designed this prospective randomized control trial to analyze effect of prophylactic administration of TXA in decreasing bleeding during caesarean section.

PATIENTS AND METHODS

This prospective randomized clinical study was carried out in Department of Obstetrics and Gynecology, Menoufia University Hospital in the period from March 2019 to March 2020. The study included 100 pregnant women who underwent elective cesarean section.

After excluding patients who did not meet inclusion criteria and those who declined to participate, the patients were randomized into two groups. Group (A) (study group): pregnant women who received 1 gm of tranexamic acid 20 minutes before skin incision and Group (B) (control group): pregnant women who did not receive tranexamic acid. Sealed, consecutively numbered envelopes containing computer-generated number (Randomization Generator Version 1.0) were opened when the women were recruited. The allocation ratio was 1:1. The Patients were blinded to the groups.

A full general examination, including blood pressure (BP), pulse, height, and weight, was done first. Then, body mass index (BMI) was calculated and recorded. Ultrasound was done to ensure viability and to determine the gestational age, the presenting part, the position of the placenta and the amniotic fluid. Preoperative routine investigation CBC, PT, ABO & Rh typing was done.

Preoperative administration of 1 gm of tranexamic acid [AMOUN company, as 5 mL ampoule containing 500 mg (100 mg/mL solution) that is, 1 g/10 mL] intravenously over 10 min at a rate of 1 mL/min, about 20 min before skin incision in the study group with no drug is given to control group. 1 gram of TXA

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was chosen for this study, as per Updated WHO Recommendation on Tranexamic Acid for the Treatment of Postpartum Hemorrhage [5]. All CS were done under spinal anesthesia and all the surgeries were performed by assistant lecturer or higher stuff. In both groups 20 units of oxytocin (Syntocinon, Novartis CO., Egypt) in 500 mL of normal saline was infused intravenously over 20 to 30 minutes after delivery of fetus. Additional 20 units of oxytocin was given postoperatively (10 U in each bottle of IV fluid for two consecutive bottles over a period of 12 hours).

Assessment of blood loss intraoperative and 2 hours postoperative using gravimetric measurement. It constitutes placing an absorbable sheet under the patients. Weighting of these absorbable sheets after cesarean section as well as materials such as soaked pads and gauzes on a sensitive scale and subtracting the known dry weights of these materials to determine the achieved weight, which represent the actual blood loss [6].

- The achieved weight = (weight of absorbable sheets, soaked pads, soaked gauzes) – (dry weights of these materials). Volume of blood loss (ml) = the achieved weight (gm) ÷1.06

Postoperative Hb and HCT estimation was done within 24 h after the surgery (after discontinuation of IV fluids) for all the women and compared to the preoperative value. All cases were monitored for 2 hours postoperatively.

Vitals (heart rate, blood pressure, oxygen saturation, urine output, uterine contractility status, and side effects if any was noted at regular intervals. Apart from routine postoperative care, all women were observed for any increased bleeding per vagina and additional pre weighed pads were provided along with measures to reduce bleeding if needed.

Ethical and patients' approval: The study was approved from the Ethical Committee, Faculty of Medicine, Menoufia University and written informed consent was obtained from all cases.

Statistical analysis

Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 23. The used tests of significance included: Student t-test, Paired t-test and Preason correlation. P value at 0.05 was used to determine significance where P-value ≤ 0.05 is statistically significant.

RESULTS

There was no statistically significant difference between the both groups regarding demographic data including age, gravidity, gestational age in weeks and parity ($p > 0.05$) (Table 1).

This study showed highly statistically significant difference in blood loss during cesarean delivery and blood loss 2 hours after end of CS between study group and control group ($p < 0.001$). The total amount of blood loss ranged between (318-556 ml) in study group compared to control group, which ranged between (463-769 ml) which is highly statistically significant ($p \leq 0.001$) (Table 2).

None of both study & control group women had PPH (blood loss >1000 ml) and about 22% only of study group had blood loss > 500 ml and about 86% of control group had blood loss > 500 ml. Additionally, a highly significant statistical difference ($p \leq 0.001$) was shown between the two groups in the secondary outcomes.

Percentage of difference in hemoglobin and hematocrit values pre & postoperative; with a mean preoperative Hb level 10.36 gm/dl in study group and 10.26 gm/dl in control group before onset of CS (Table 3). There was no blood transfusion required in either of the groups postoperatively nor additional surgical interventions in both groups.

There were no adverse effects, admission to ICU or immediate postpartum and neonatal complications. All patients were discharged alive.

Table (1): Comparison of age, parity, GA and anthropometric measurement of studied groups No=100

Mean ± standard deviation	Group A No=50	Group B No=50	t-test	P value
Age (years)	21.46 ± 2.71	21.46 ± 2.71	0.282	0.778
Median	21.50	21.50		Ns
Gestational age (weeks)	39.34 ± 0.47	39.28 ± 0.45	0.643	0.521
Median	39	39		NS
Parity	0.66 ± 0.47	0.72 ± 0.45	0.643	0.521
Median	1	1		NS
Weight (kg)	73.88 ± 6.32	71.96 ± 6.72	1.47	0.145
Median	76	70		NS
Height (cm)	159.7 ± 4.09	159.8 ± 4.65	0.137	0.891
Median	159.50	159		NS
BMI (kg/m^2)	29.01 ± 2.23	28.22 ± 2.06	1.84	0.069
Median	29.35	27.50		NS

Group A=study group Group B=control group NS=non-significant S=significant

Table (2): Comparison of blood loss between studied groups no=100

Mean ± standard deviation	Group A No=50	Group B No=50	t-test	P value
Blood loss during cesarean delivery (ml)	286.82 ± 47.42	406.74 ± 60.56	11	<0.001
Median	282.5	403		HS
Blood loss from end of C.S to 2 hours after (ml)	143.46 ± 23.61	203.36 ± 30.30	11.02	<0.001
Median	141	201		HS
Total amount of blood loss (ml)	430.28 ± 71.03	610.10 ± 90.87	11.02	<0.001
Median	424	604		HS

Group A=study group Group B=control group HS=High-significant

Table (3): comparison of Hb and HCT between studied groups no=100

Mean ± standard deviation	Group A No=50	Group B No=50	t test	P value
Hb Pre- operative	10.36±0.66	10.26±0.76		0.525
Median	10.40	10.35	0.638	NS
Hb post- operative	9.79±0.67	9.22±0.76	3.95	<0.001
Median	9.80	9.35		HS
HCT pre –operative	31.06±2.006	30.79±2.30	0.620	0.537
Median	31	31		
HCT post –operative	29.37±2.056	27.63±2.29	3.98	<0.001
Median	29.40	28		HS

HS=High-significant

DISCUSSION

TXA is known for a long time as

an antifibrinolytic agent discovered by Utako Okomoto in 1950s [(7)], but its prophylactic use in prevention of postpartum hemorrhage through reduction of blood loss during & after cesarean section or vaginal birth is quite new.

It is known that during placental delivery there is release of coagulant factors along with hyperfibrinolysis and fibrinogen depletion owing to vascular injury and these physiological events can last for several hours postpartum [(8)]. During CS, there is extensive tissue injury during the procedure, which leads to further increase in fibrinolysis and resultant bleeding [(9)]. Therefore, TXA can effectively control the bleeding by arresting fibrinolysis.

This study was a randomized, prospective, interventional control study, which compared the efficacy of TXA administration preoperatively in decreasing blood loss during elective C.S between study and control groups. Blood loss was estimated intraoperatively using gravimetric method. Postoperatively, vital parameters were recorded and patients were monitored for any side effects. TXA reaches its highest plasma concentration within 1 hour after intravenous administration and its therapeutic levels can be maintained for approximately 8 hours after operation, which covers the period of hyperfibrinolysis. This explain the efficacy of TXA in decreasing mean blood loss significantly intraoperative and up to 2 hours postpartum as shown in this study alongside other previous studies. A meta-analysis included around 40138 bleeding patients (traumatic and post-partum hemorrhage), concluded that early administration of TXA improved survival by more than 70% and 10% decrease in survival rate occur with every 15 min delay in treatment administration during the first 3 hours with no benefit gained after 3 hours [(10)].

In our study, we used TXA at a fixed dose of 1 gm in 10 mL (100 mg/mL) IV at 1 mL per minute, thereby taking 10 min for the drug administration (as per recent WHO recommendation of use of tranexamic acid for the treatment of postpartum hemorrhage) [(5)]. This was done about 20 min before skin incision, as the onset of action of TXA is 5-15 mins. TXA should not be administrated through a line with blood, or mixed with solutions containing penicillin. [(11)].

In present study, the mean blood load was significantly less in study group compared to control group for intraoperative bleeding (286.82 ± 47.42 ml Vs 406.74 ± 60.56 ml) as well as postoperative bleeding (from end of CS to 2 hours postpartum) (143.46 ± 23.61 ml Vs 203.36 ± 30.30 ml; $p < 0.001$) respectively. This difference in mean blood loss in each group was reflected in the difference of mean HB% and HCT value after surgery in the two groups which was high statistically significant.

Movafegh *et al.* [(12)] used TXA in dose of 10 mg/kg, given 20 min before skin incision at caesarean delivery. Mean blood loss was significantly less in the

study group compared with 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. These results are consistent with our study**.** A study by **Abdel Aleem et al. [13]** included the blood loss from the beginning of CS until two hours postpartum inclusive of amniotic fluid and showed significant reduction in mean blood loss during and for 2 hours postoperatively after randomization of 740 subjects, which is similar to our results**.** One trial used 2 different doses of TXA by forming three groups (2 study groups and one control group) one Group received 10mg/kg of TXA in 20 ml of 5% dextrose, given intravenously, while the second group received 15mg/kg and the third group (control group) was given a placebo. There was no significant difference in postoperative blood loss in all three groups. Pre- and post-operative hemoglobin levels differed significantly when compared to control group **[14].** Another randomized, double blinded, case-controlled study by **Xu *et al.* [15]** was conducted on around 174 primipara underwent C.S, during which study group (88 women) was given 10mg/kg of TXA just before C.S. There was significant less blood loss in the period between the end of CS and 2 h postpartum in the study group than the control group ($p < 0.01$), with no significant decrease in blood loss from placental delivery to the end of C.S ($p = 0.17$)**.** Two hundred and twenty-three (223) women who underwent elective C.S were included in **Yehia *et al.*, [16]** study during which 1 gm of TXA was given over 2 minutes to study group along with induction of anesthesia. TXA significantly reduced the amount of blood loss during CS with decreasing postpartum requirements of iron replacement **[16].** A study by **Sahu *et al.*[17]** showed that there was significantly lesser total blood loss (intraoperative as well as postoperative) in study group versus control group ($P < 0.05$), with only three women (6%) had PPH in control group. No side effects were noted in women or neonates**. Novikova *et al.*[18],** conducted a systematic review of twelve trials involving 3285 women undergoing elective C.S (nine trials, 2453 participants) or spontaneous vaginal birth (three trials, 832 participants) and found that TXA use in addition to uterotonic medications was effective in decreasing blood loss greater than 1000 ml in C.S but not vaginal birth. Blood loss greater than 400 ml or 500 ml was more apparent in women having vaginal birth than in women undergone C.S. It also prevents occurrence of PPH postpartum and blood transfusion in women at low risk of PPH following both C.S and vaginal delivery.

The limitation of our study is that the long-term side effect of TXA use were not taken into account. A large upcoming multicenter randomized, double-blind, placebo- controlled trial included 4524 women with cesarean deliveries and seeked to determine if the benefits of the routine prophylactic use of tranexamic acid after cesarean delivery significantly overcome its potential side effects in the 3 months after delivery **[19].**

The poor nutritional and antenatal care status of most pregnant women attending our hospital is reflected in the demographic data of this study with mean preoperative hemoglobin levels of 10.36 g/dl. In most cases of PPH, there is no identifiable risk factor with most women have low risk pregnancies. Therefore, prevention of postpartum hemorrhage and possible postpartum blood loss is essential besides improving antenatal care and treating anemia as this may reduce the morbidity associated with PPH.

TXA is an antifibrinolytic agent which is widely available, cheap, safe and easy to store (unlike oxytocin), which does not need maintenance of cold chain. However, long-term side effect of the drug on the mother and her baby was difficult in our settings due to poor follow up.

CONCLUSION

Prophylactic administration of tranexamic acid, an antifibrinolytic agent, prior to cesarean section was effective in reducing intraoperative, postoperative blood loss and subsequently reduces the incidence of postpartum hemorrhage as well as reduces blood transfusion requirement and its related complication without any immediate maternal or neonatal adverse events.

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