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Tranexamic Acid as Prophylactic Therapy for Intra and Post Partum Hemorrhage, Randomized Controlled Trial

Mohamed N. Salem[1], Magdy A. Mohamed[1*], Ahmed H. Salem[1] and Ahmed Abbas[2]

[1]Department of OB/GYN, Faculty of Medicine, Sohag University, Egypt.
[2]Department of OB/GYN, Faculty of Medicine, Assuit University, Egypt.

Authors' contributions

This work was carried out in collaboration between all authors. Author MNS designed the stud and wrote the protocol. Author MAM wrote the first draft of the manuscript. Authors AHS and AA managed the literature searches. All authors shared in monitoring of cases and approved the final manuscript.

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ABSTRACT

Objective: To evaluate the role of TXA in minimizing the incidence of postpartum hemorrhage after cesarean delivery.
Methodology: This is a randomized placebo controlled study conducted on 169 patients who subjected to elective CS. Study group include 84 patients who received 2 gm Tranexamic acid before induction of anaesthesia plus 10 u oxytocin. The control group received only 10 U oxytocin. Both group were compared as regard amount of blood loss.
Results: The amount of blood loss was lower in study group than control group (410.33±175.08 ml versus 650.25±180.90 ml). Also the 24 hours post-operative hemoglobin was significantly higher in study group (10.68±0.9 mg/dl) compared to control group (8.2±0.7 mg/dl), as well as, the 24 hours post-operative hematocrit value was significantly higher in study group (37.63±5.4) compared to control (31.19±2.48).

**Corresponding author: E-mail: magdyelkardosy@gmail.com;*

Conclusion: Tranexamic acid could be helpful option in reducing amount of blood loss during elective CS.

Keywords: Tranexamic acid; cesarean section; postpartum hemorrhage.

1. INTRODUCTION

Post partum hemorrhage (PPH) has traditionally been defined as blood loss ≥500 ml within the 24 h following childbirth, with severe PPH defined as blood loss ≥1000 ml. Other definitions specified PPH as blood loss >15% of total blood volume or 10% decline in hemoglobin levels measured peripartum. Postpartum hemorrhage (PPH) is responsible for around 25% of maternal mortality worldwide, reaching as high as 60% in some developing countries [1]. Almost all (99%) of the deaths are in low and middle income countries and most of the deaths occur in the immediate post-partum period. PPH can also be a cause of long-term severe morbidity, and approximately 12% of women who survive PPH will have severe anemia [2].

Causes of postpartum may be conveniently remembered using 4Ts as mnemonic: tone (uterine atony), tissue (retained products), trauma (cervical tear and rupture uterus) and thrombosis (coagulopathy) [3].

There are several factors that predispose to atonic postpartum hemorrhage as over distention of the uterus as in polyhydramnios and multiple pregnancy, obesity, macrosomic baby, retained products of conception, obstructed labor and anemia and previous history of atonic ppH [3].

Different modalities of treatment, either medical and surgical, as well as effective volume replacement and optimal transfusion of blood products are used in management of postpartum hemorrhage [4].

Tranexamic acid (TXA) is an anti-fibrinolytic agent that inhibits clot breakdown by blocking the lysine binding sites on plasminogen molecules [5].

TXA is not a new drug and has been used for many years to treat menorrhagia and dental extraction in people with haemophilia. More recently, it has been used to reduce bleeding in elective surgical patients. Although there are many on-going trials of TXA in elective surgery, the accumulated evidence already shows that TXA reduces bleeding [6].

Detailed guidelines have been suggested the use of uterotonic drugs in obstetric interventions. In contrast, hemostatic drugs are not routinely used as a first-line intervention in PPH [7].

1.1 Aim of the Study

The aim of our study is to evaluate the role of TXA in minimizing the incidence of postpartum hemorrhage after cesarean.

2. PATIENTS AND METHODS

This is a randomized placebo controlled study conducted on 169 patients who attended to OB/GYN emergency unit of Sohag University Hospital in the period from November 2013 to October 2014. All of these patients fulfilling the inclusion criteria and delivered by elective C. S.

Thorough history taking from all patients was done with meticulous examination (general and obstetrical) and full pre-operative investigations (Rh typing, complete blood count, activated partial thromboplastin time, prothrombin time and concentration, liver and kidney function tests) were done. Routine pre-opertive fluid preload was given in form 1 litre normal saline.

- Inclusion criteria:
  - Age: 20-35 years.
  - Singleton pregnancy
  - Term pregnancy.
- Exclusion criteria:
  - Grand multipara (GMP). ○ Multiple pregnancies.
  - Fetal macrosomia.
  - Polyhydramnios.
  - Placenta previa.
  - Anti-coagulants.
  - Pre-eclampsia.
  - Previous history of deep venous thrombosis (DVT).

After approval of the study by the institute of ethical committee and after having a written consent from all patients, the study was

conducted. The patients were randomly grouped into two groups;

Group A (study group) included 84 pregnant women who received 2 gm of Tranexamic acid (4 ampoules of kapron® 500 mg 5 ml- Amoun company) given on 150 ml saline was given with induction of spinal anaesthesia. 10 I.U. oxytocin (syntocinon®. Novartis company) given immediately after fetal extraction.

Group B (control group) included 85 pregnant women who received 10 I.U. of oxytocin immediately after delivery of the baby.

Random tables were used to randomize those patients into two groups (Tranexamic acid group was labeled as letter "A", and placebo group was labeled as letter "B". Both "A" and "B" labels were put in the opaque envelops according to serial ranking obtained from the random tables. After obtaining a written consent from participants women, the corresponding serial envelop was opened and the patient then received the corresponding drug according to the type of label inside "A" or "B".

The main goal of our study was estimation of blood loss during CS after delivery of placenta; which was estimated by using soaked towels and suction graduated bottle and was estimated by the anesthetist who attended the cesarean section to. Blood loss from uterine incision and soaked towels before placental delivery were not added to blood loss measurements. According to Fazel MR, et al. [8] Soaked towel =140-150 ml. while semi-soaked towel = 70-75 ml.

In addition, assessment of Vital signs (pulse, blood pressure, respiratory rate) during first 6 post-operative hours was carried out. Also the amount of vaginal bleeding during first 6 post-operative hours was estimated according to number of soaked pads used after cesarean section - each soaked pad = 50 ml);

24-48 hours post-operative hemoglobin and hematocrit values were measured.

Any complication was reported such as the need for blood transfusion or the need for any surgical measures to stop bleeding.

2.1 Statistical Analysis

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Data were presented by mean ± standard deviation (M±SD). Statistical significance was defined as P value less than 0.05.

3. RESULTS

Both groups are matched with each other as regard anthropometric and obstetric criteria.

Comparison of the two studied groups clinically (as regard vital signs including pulse, blood pressure temperature and respiratory rate) showed no statistically significant difference pre-operatively. Also the same condition can be applied in comparing the two groups from laboratory aspect including measuring hematocrit value and hemoglobin and blood chemistry (random blood sugar, prothrombin time and concentration, liver function tests and kidney function tests (Table 2).

There was statistically significant difference between the two studied groups as regard clinical evaluation (including pulse, blood pressure) of the patients 2 hours, 6 hours and 24 hours after delivery. Also the 24 hours post-operative hemoglobin was significantly higher in study group (10.68±0.9 mg/dl) compared to control group (8.2±0.7 mg/dl), , as well as, the 24 hours post-operative hematocrit value was significantly higher in study group (37.63±5.4) compared to control (31.19±2.48) (Table 3).

Also comparison of the two groups as regard the amount of blood lost during cesarean section calculated after placental extraction up to skin closure showed that it was significantly less in the study group (410.33±175.08 ml) compared to the control group (650.25±180.90 ml). In addition, comparison of estimated amount of post partum vaginal bleeding during first6 hours post-operative was significantly less in the study group (100.67±25.18 ml) than in the control group (75.90±28.9 ml) respectively. According to WHO definition of post partum hemorrhage, the overall incidence of post-partum hemorrhage in study group was significantly less than the control group (24.9% versus 59.3%, respectively), (Table 4).

In addition, the need for blood transfusion occurred in one case only in the study group; while it was needed in four cases in control group (the difference was statistically significant).No case required additional surgical procedure in the study group. Two cases in the control group required surgical intervention (one case required uterine artery ligation and the other case needed B- lynch suture).

Table 1. Anthropometric and obstetric criteria

Criteria	Group A (Study group)	Group B (Control group)	P-value
Number of patients	84	85	N.S.
Age in years (mean ± SD)	23±1.5	22±2.4	N,S.
Locality:			
Rural	39	43	N.S.
Urban	45	42	N.S.
Weight in kg (mean ± SD)	67±5.5	64±3.8	N.S.
Height in cm (mean ± SD)	157±2.5	160±1.4	N.S.
Parity:			
Pgda.	28	33	N.S.
Multipara.	56	52	N.S.
Gestational age in weeks.	37w±3d	38w±4d	N.S.

Table 2. Pre-operative clinical and laboratory criteria the study and control groups

	Group A (Study group)	Group B (Control group)	P value
Clinical criteria:			
Pulse (b/m)	85±5.7	84±4.9	N.S.
Systolic blood pressure (mmHg)	115±10.24	113±12.06	N.S.
Diastolic blood pressure (mmHg)	78.9±5.18	80.09±4	N.S.
Temperature (Celsius)	36.8±0,2	36±0.4	N.S.
Respiratory rate (Cycle/Minute)	16±2	15±4	N.S.
Laboratory:			
Hematocrit value (%).	41.5±2.48	40.9±1.9	N.S.
Hemoglobin level (gm/dl)	11.04±0.8	10.87±1.06	N.S.
AST	19.45±1.61	20±0.7	N.S.
ALT (unit/liter)	21.7±0.94	20.9±1.01	N.S.
Prothrombin time	10±1.02	10.1±0.9	N.S.
Serum creatinine	0,7±0.06	0.69±0,05	N.S.

Table 3. Post-operative clinical and laboratory criteria the study and control groups

Criteria	Group A study group	Group B control group	P-value
Clinical criteria			
Pulse:			
After 2 hours.	95±6.0	100.5±8.9	< 0.05
After 6 hours.	91±5.5	98.5±8.2	< 0.05
After 24 hours	88±3.2	92.04±6.5	< 0.001
Systolic blood pressure:			
After 2 hours.	110±9.8	98.8±7.8	< 0.05
After 6 hours.	105±6.7	90.56±4.5	< 0.05
After 24 hours	116±5.05	95.67±4.7	< 0.001
Diastolic blood pressure:			
After 2 hours	75±10.5	70±4.6	< 0.05
After 6 hours.	70±4.6	65.4±2.3	< 0.05
After 24 hours	77±2.9	70.6±1.8	<0.05
Laboratory criteria (after 24 hours)			
Hemoglobin level (gm/dl)	10.68±0.9	8.2±0.7	< 0.05
Hematocrit value (%)	37.63±5.4	31.19±2.48	< 0.001

Table 4. Comparison of the amount of blood lost during cesarean section, estimated amount of post partum vaginal bleeding and overall incidence of post-partum hemorrhage in the two groups

	Group A (Study group)	Group B (Control group)	P-value
Blood lost during cesarean section (ml)	410.33±175.08	650.25±180.90	< 0.001
Estimated amount of 6- hourspost partum vaginal bleeding	100.67±25.18 ml	75.90±28.9	< 0.05
Incidence of post partum hemorrhage	24.9%	59.3%	< 0.001

4. DISCUSSION

Tranexamic acid (TXA) has an antifibrinolytic effect through inhibition of plasminogen activator that helps in the conversion of plasminogen to plasmin. So, TXA has been widely used to reduce blood loss in elective surgery where it reduces blood transfusion by about one-third of cases studied by [9,10] and in treatment of menorrhagia [11]. Recently, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH- 2) trial has shown that the early administration of TXA significantly reduces mortality in bleeding trauma patients [12,13].

During placental delivery, activation of the fibrinolytic system which could lasts up to 10 hours after delivery occurred, this leads to rapid degradation of fibrinogen and fibrin, resulting n increase in fibrin degradation products (FDP). Therefore, the use of TXA appears to reduce the blood loss.

How to minimize postpartum hemorrhage is the main goal of different researches as this is a main clue in reducing anemia that may predispose to postpartum hemorrhage in following pregnancies and in preventing blood transfusion with its potential hazards including allergic reaction and viral transmission. Economic evaluation has shown that giving TXA to reduce bleeding in elective surgery would be lifesaving in certain localities all over the world where there is a shortage of blood, because more blood will be available for those who need it. In those countries where blood is readily available, the use of TXA will decrease the risk of transfusion-transmitted viral infections because fewer units of blood will be transfused [14].

Our study randomized controlled trial conducted on a group of pregnant women & was planned to have elective CS. The patients were randomized to receive 2 g TXA intravenously before elective CS group or not and blood loss was measured during and for six hours after operation and hemoglobin levels, hematocrit values were measured 24 hours after the operation.

The present study showed that preoperative administration of TXA significantly reduced bleeding from the time of placental delivery up to six hours postpartum in LSCS.

Our results were in agreement with those obtained by Shahid and colleagues in 2013 whose research was conducted on 74 term pregnancies and concluded that preoperative administration of TXA significantly decreased the amount of blood loss from placental delivery to the end of LSCS and it also reduced the quantity of blood loss from the end of LSCS till 2 hours post-partum. Shahid et al. [15] concluded that TXA can be used safely and effectively in women undergoing LSCS to reduce intra-operative blood loss.

Also our results were matched with those of Abdel-Aleem M. and others in 2013, who conducted their work upon 740 patients (373 in study group and 367 in control group) and concluded that the use of TXA before elective cesarean section is associated with reduced blood loss during and after elective CS [16].

Another randomized, double-blind, case controlled study was conducted on 174 primipara undergoing CS by Xu and colleagues (88 given 10 mg/kg TXA immediately before CS were compared with 86 others to whom TXA was not given) to determine the efficacy of TXA in reducing blood loss in patients after CS. Xu et al. [17] found that the blood loss in the period between the end of CS and 2 hours postpartum was significantly lower in TXA group than in the control group and they concluded that TXA is effective in reducing blood loss in patients undergoing CS.

Six hundred and sixty women (660) women who underwent elective CS were included in Gungorduk and colleagues study to determine the efficacy and safety of TXA in reducing blood

loss during elective CS. Gungorduk and colleagues found that TXA significantly reduced bleeding during CS and reduced the need for additional uterotonic agents [18].

Similar study carried out in India by Mayur et al. [9]. It was conducted on 100 patients underwent to LSCS showed comparable results reducing the blood loss in the study group, Blood loss was collected and measured during two periods. The first period was from placental delivery to end of LSCS and second from the end of LSCS to 2 hours postpartum. Hemoglobin, urine analysis, liver and renal functions were tested in both the groups. Another study carried out on 180 primipara by Gai MY, et al. [19], in China showed that TXA significantly reduces bleeding from the time of placental delivery to the end of caesarean section, which was 351 ml in the study group while 440 mL in the control group.

Use of TXA in pregnant women may raise the risk of occurrence of thrombo-embolism. However, previous studies have shown the safety of this drug for use in both pregnant and non-pregnant patients [20]. In our study, thrombo-embolic events were not evaluated because the sample size was too low for adequate power. However, none of the women showed any signs or symptoms of immediate thrombo-embolic events and other side effects like color vision affection, allergic reaction, nausea, vomiting and diarrhea were not statistically significant by difference in the two groups.

5. CONCLUSION

Tranexamic acid could be helpful option in reducing amount of blood loss during elective CS & may give a great benefit as prophylaxis against postpartum hemorrhage.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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