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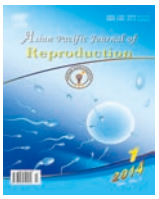

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Tranexamic acid reduces blood loss during and after cesarean section: A double blinded, randomized, controlled trial

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ABSTRACT

Objective: To evaluate the efficacy of tranexamic acid in reduction of blood loss during and after cesarean section. **Methods:** Women included in the current double blinded, randomized, controlled trial were recruited from women attending for elective cesarean section and randomized into two groups; study group: received tranexamic acid with induction of anesthesia plus 10 IU of oxytocin injection after delivery of the baby. Control group: received only oxytocin 10 IU injection after delivery of the baby. **Results:** Twenty four hours post-operative hemoglobin level was significantly higher in study group (11.2 ± 1.5 mg/dL) compared to control (9.6 ± 1.2 mg/dL), also 24 hours post-operative hematocrit was significantly higher in study group (30.2 ± 6.6) compared to control (29.2 ± 2.8). Calculated total blood loss from placental delivery till end of cesarean section was significantly less in study group compared to control (369.5 ± 198.0 versus 606.8 ± 193.0 mL; respectively), also, calculated vaginal bleeding during first 6 hours post-operative was significantly less in study group compared to control (85.0 ± 30.7 mL versus130.8 ± 49.3 mL, respectively). The incidence of post-partum hemorrhage was significantly less in study group compared to control (31.1% versus 63.2%; respectively), also the need for iron replacement therapy was significantly less frequent in study group compared to control (0.9% versus 6.6%, respectively). **Conclusions:** Tranexamic acid can be used safely to reduce blood loss during cesarean section. Reduced blood loss after tranexamic acid was associated with improvement of post-operative hemoglobin, hematocrit and with reduction of post-partum need for iron replacement.

1. Introduction

Obstetric hemorrhage remains one of the major determinants of maternal death in both developed and developing countries. Because of its weight as a leading cause of maternal mortality and morbidity, obstetric hemorrhage (ante-partum and post-partum hemorrhages) must be investigated for national guideline development [1]. Haemostatic drugs are not usually used as first-line treatment in post-partum hemorrhage (PPH) [2]. It was authenticated that extensive tissue injury can direct the haemostatic equilibrium toward increased fibrinolysis, leading to coagulopathy and bleeding [3]. Anti-fibrinolytic drugs, namely tranexamic acid (TXA) have been recognized to decrease blood loss and transfusion needs in various elective surgeries [4]. Furthermore, the Clinical Randomization of an Anti-fibrinolytic in Significant Haemorrhage (CRASH-2) study concluded that tranexamic acid decreases the risk of death in bleeding trauma patients [5]. Tranexamic acid decreases post-partum blood loss after vaginal birth and after cesarean section based on two randomized controlled trials (RCTs) [6].This study was

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designed to evaluate the efficacy of TXA in reduction of blood loss during and after cesarean section (CS).

2. Materials and methods

This double blinded, randomized, controlled trial was conducted at Ain Shams University, Maternity Hospital, from September 2012 to March 2013, after approval of the study by institute ethical committee.

Two hundred and twenty three (223) women attending the labor ward for elective CS were included in the study after informed consent and randomized into 2 groups; group 1 (study group): women who received 1 gram of TXA (kapron®, Amoun, Egypt) with induction of anesthesia by slow intravenous injection over 2 minutes in addition to 10 IU of oxytocin (syntocinon®, NOVARTIS, Egypt) injection after delivery of the baby were included. Group 2 (control group): women who received only oxytocin 10 IU of oxytocin injection after delivery of the baby were included. Six women in group I and five women in group II were excluded from this study (either due to uterine contraction before elective CS or no available suction set in the operative room), so 106 women were finally analyzed in each group. All CS were done under spinal anesthesia, by lecturer of the causality (lecturer of the causality; who had passed the residency program for 3 years and having an experience for 3 years as assistant lecturer, with MD degree), assisted by a registrar of the causality. A plan of interventions was sealed in closed envelops, numbered in accordance with the randomization tables. Packing, sealing and numbering were all performed by two independent doctors other than the investigator. Surgeons and investigators were not aware whether patient received TXA or not (double-blinding). Randomization coding tables were concealed from investigators till the end of the study. Women who had medical disorders with pregnancy, bleeding tendency, risk of thromboembolism, known allergy to TXA, ante-partum hemorrhage, abnormal site of the placenta (detected by ultrasound), macrosomic baby, twin pregnancy, polyhydramnios were excluded from this study. All women were subjected to history taking, general, abdominal examination and pre-operative investigations (complete blood count, prothrombin time, activated partial thromboplastin time, liver and kidney function tests).

2.1. Primary outcome measures

Blood loss during CS after delivery of placenta; which was estimated by using soaked towels and suction bottle and was estimated by anesthesiologists attended the cesarean section to avoid potential surgeon bias. Blood loss from uterine incision and soaked towels before placental delivery were not added to blood loss measurements. Soaked towel = 150 mL. while semi-soaked towel = 75 mL. [7].

2.2. Secondary outcome measures

(1).Vital data during first 2 post-operative hours; (2). Vaginal bleeding during first 6 post-operative hours (amount of vaginal bleeding was calculated according to number of soaked pads used after cesarean section - each soaked pad = 50 mL); (3). 24 hours post-operative hemoglobin and hematocrit values (4). Need for other surgical measures to stop bleeding (B-lynch, uterine artery ligation, internal iliac artery ligation, hysterectomy and/or transfusion of blood or blood products) (5). Maternal and neonatal side effects of medications given.

2.3. Sample size justification

Sample size was calculated using data from previous studies [8, 9], data from Cochrane systematic review that showed the risk of post-partum blood loss > 400 mL was 14.44% in women who received TXA, in contrast to 32.38% in women who did not [6], and EpiInfo version 7.0, setting the power at 80%, the two-sided confidence level at 95% and 10% patients drop rate. Calculation according to these values, the minimal number of women needed to produce a statistically acceptable figure was 98 in each group. Therefore, two hundred and twenty women (223) were recruited in the beginning of the current study to be randomized into two groups.

2.4. Statistical analysis

Data were collected, tabulated then statistically analysed using the Statistical Package for Social Sciences (SPSS) computer software version 18. Numerical variables were presented as mean and standard deviation (±SD), while categorical variables were presented as number and percentage. *Chi*-square test (χ^2) was used for comparison between groups as regard qualitative variables. Student *t*-test was used for comparison between groups as regard quantitative variables. A difference with a P value <0.05 was considered statistically significant.

3. Results

The two studied groups were matched with no significant difference between the study and control groups regarding; mean age, body mass index (BMI) and gestational age (Table 1).

Table 1
Demographic data of the two studied groups.

Variables	Group 1 (n =106)	Group 2 (n =106)	P value
Age (Years)	28.4 ± 4.9	28.6 ± 4.7	0.47
Parity	2.0 ± 1.5	1.8 ± 1.3	0.84
BMI (kg/m^2)	27.2 ± 1.6	27.5 ± 2.0	0.11
Gestational age (Weeks)	39.1±1.1	39.0±1.2	0.73

Analysis using Independent Student's t-test, BMI body mass index [calculated as weight (in kilograms) divided by squared height (in meters)], Group 1= Study group and group 2 = Control group; Data were expressed as Mean ± SD.

No significant difference regarding pre-operative hemoglobin and pre-operative hematocrit value was found, but the 24 hours post-operative hemoglobin was significantly higher in study group (11.2 ± 1.5 mg/dL) compared to control group (9.6 ± 1.2 mg/dL, P<0.05), also, 24 hours post-operative hematocrit value was significantly higher in study group (30.2 ± 6.6) compared to control (29.2 ± 2.8, P<0.05) (Table 2).

Calculated total blood loss from placental delivery till end of CS was significantly less in study group compared to control group (369.5 ±198.0 versus 606.8 ± 193.0 mL, respectively), also, calculated vaginal bleeding during first 6 hours post-operative was significantly less in study group compared to control (85.0 ± 30.7 versus 130.8 ± 49.3 mL, respectively), and calculated total blood loss from placental delivery till 6 hours post-operative was significantly less in study group compared to control (454.5 ± 201.0 versus 737.6 ± 217.0 mL, respectively) (Table 2)

The incidence of post-partum hemorrhage was significantly lower in study group compared to control group (31.1% versus 63.2%, respectively), also, the need for iron replacement was significantly less frequent in study group compared to control (0.9% versus 6.6%, respectively, P<0.05). No blood transfusion was needed in study group, while it was needed in two cases in control group (this difference was not statistically significant), no other surgical measures were needed to stop post-partum bleeding in both studied groups, no side effects or thrombotic events or neonatal adverse outcomes were recorded in both studied groups.

Table 2
The measured outcome in both studied groups.

Variables	Group 1 (n =106) (Mean ± SD)	Group 2 (n =106) (Mean ± SD)	P value significance (Test used)
Calculated total blood loss from placental delivery till end of CS (mL)	369.5 ±198	606.8 ± 193	0.001(<0.05) (χ^2)
Calculated vaginal bleeding during first 6 hours post operative (mL)	85.0 ± 30.7	130.8 ± 49.3	0.02 (<0.05) (χ^2)
Calculated total blood loss from placental delivery till 6 hours post-operative (mL)	454.5 ± 201	737.6 ± 217	0.002 (<0.05) (χ^2)
Immediate post-operative pulse rate (/minute)	91.1 ± 5.8	95.8 ± 5.5	0.8 (>0.05) (χ^2)
Two hours post-operative pulse rate (/ minute)	83.9 ± 5.7	90.2 ± 5.2	0.7 (>0.05) (χ^2)
Immediate post-operative systolic blood pressure (mmHg)	113.1 ± 7.3	108.8 ± 5.9	0.8 (>0.05) (χ^2)
Two hours post-operative systolic blood pressure (mmHg)	121.0 ± 4.7	123.0 ± 4.7	1.0 (>0.05) (χ^2)
Immediate post-operative diastolic blood pressure (mmHg)	70.4 ± 3.3	68.7 ± 4.07	1.0 (>0.05) (χ^2)
Two hours post-operative diastolic blood pressure (mmHg)	80.4 ± 6.0	76.8 ± 6.2	0.8 (>0.05) (χ^2)
Pre-operative hemoglobin level (mg/dL)	11.8 ± 1.5	11.9 ± 1.2	1.0 (>0.05) (t test)
24 hours post-operative hemoglobin level (mg/dL)	11.2 ± 1.5	9.6 ± 1.2	0.01 (<0.05) (t test)
Pre-operative hematocrit value (%)	33.0 ± 3.7	33.1 ± 3.1	1.0 (<0.05) (t test)
24 hours post-opertive hematocrit value (%)	30.2 ± 6.6	29.2 ± 2.8	0.002 (<0.05) (t test)

(χ^2) = Chi-square test, Group 1= Study group and group 2 = Control group

4. Discussion

Pregnant women with singleton fetus planned to have elective CS at ≥37 weeks gestation were randomized to receive 1 g TXA intravenously before elective CS group or not and blood loss was measured during and for two hours after operation by Abdel-Aleem and colleagues [8]. Abdel-Aleem and colleagues; concluded that the pre-operative use of TXA is associated with reduced blood loss during and after elective CS [8]. Also, women undergoing lower segment cesarean section (LSCS) were randomized to receive either TXA or distilled water just before the surgery in Shahid *et al* study [9]. Shahid *et al*, found that TXA significantly reduced the quantity 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 to 2 hours post-partum. Shahid *et al*, concluded that TXA can be used safely and effectively in women undergoing LSCS to reduce intra-operative blood loss [9].

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 [10]. Gungorduk and colleagues found that TXA significantly reduced bleeding during CS and reduced the need for additional uterotonic

agents [10]. Another randomized, double-blind, case-controlled study was conducted on 174 primipara undergoing CS by Xu *et al* (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 [11]. Xu *et al*, found that the blood loss in the period between the end of CS and 2 hours post-partum 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 [11].

In this study; the incidence of post-partum hemorrhage was significantly less in study group compared to control group, also, the need for iron replacement was significantly less frequent in study group compared to control, and no blood transfusion was needed in study group, while it was needed in two cases in control group (this difference was not statistically significant). No side effects or thrombotic events or adverse neonatal outcomes were recorded in both studied groups.

Gungorduk and colleagues, concluded that TXA can be used safely and effectively to reduce CS bleeding and to reduce the need for uterotonic agents [10]. Also, One hundred and eighty (180) primiparas were randomized into two groups; 91 in study group (received TXA immediately before CS) and 89 in control group (did not receive TXA) by Gai *et al*, to explore the efficacy and safety of TXA at CS [12]. Gai *at al* concluded that TXA can be used safely and effectively to reduce bleeding resulting from CS [12].

Hundred and twenty-three (223) women (101 study group & 122 control) were included in Sentürk & colleagues double-blind, controlled, randomized clinical trial, to detect the effect of TXA on blood loss during and after CS [13]. Sentürk & colleagues found that TXA reduced intra-operative and post-operative blood loss and they did not observe any complications caused by TXA such as venous thromboembolism, gastrointestinal problems and hypersensitivity [13]. Also, Yang et al, concluded that TXA can be used safely and effectively to reduce post-partum blood loss following vaginal delivery [14].

The current double-blind randomized trial concluded that TXA can be used safely without any maternal or neonatal side effects to reduce blood loss during and after CS. The reduced blood loss during and after CS following TXA administration was associated with improvement of post-operative hemoglobin, hematocrit values and with reduction of post-partum need for iron replacement.

Conflict of interest statement

No actual or potential conflict of interest in relation to this article exists.

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