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The Clinical Outcome of Intravenous Single Bolus 0.5gm of Tranexamic Acid for Reducing Blood Loss Following an Elective Cesarean Delivery: A Randomized Controlled Trial

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Abstract

Objective: **To assess the effectiveness and safety of intravenous single bolus 0.5 gm Tranexamic acid (TA), compared with 1 gm TA and placebo in reducing blood loss during and after cesarean delivery in women who have at least one risk factor for postpartum hemorrhage(PPH).** ***Subjects and Methods:*** **A randomized clinical trial, at a tertiary University Hospital between November 1, 2018, and July 30, 2020, (: NCT03710330) was conducted on 360 pregnant women at term (37–40 weeks) gestation scheduled for elective cesarean delivery, who were assigned to either 0.5 gm,1 gm, or, placebo(saline). The main outcome measures were blood loss at and 6 hours after cesarean delivery, the need for any additional oxytocic drugs, and TA-related side effects.** ***Results:*** **The mean overall blood loss was (609.33 ± 211.5), intraoperative was (465.58 ± 191) and post-operative was (143.75 ± 33.33) in group 2 compared with (829.7 ± 293.3), (665.5 ± 272.2), (165.83 ± 36.59) in group 1 respectively and (751 ± 208.09), (587.75 ± 190.6), (164.08 ± 32.53) in group 3 respectively , so group 2 showed great significant reduction in overall estimated blood loss either intraoperative or post-operative compared with group 1 ,(p = 0.0001,0.0001,0.0001) and group 3, (p= 0.0001,0.0001,0.0001).** ***Conclusion:*** **Both 0.5 gm and 1 gm TA may be more effective than a placebo in reducing total blood loss during and after CD, but 1gm TA may be more effective than 0,5 gm TA in reducing blood loss during and after CD in women who have a minimum of one risk factor for postpartum hemorrhage, for instance, twin pregnancy, macrosomia, and history of PPH, etc.**

Keywords: ***c****esarean section, postpartum hemorrhage, cesarean section, uterine atony.*

Introduction

Excessive blood loss after delivery could also be a complication which will occur suddenly and remain one among the leading causes of obstetric morbidity and mortality throughout the planet. Timely management strategies are urgently needed wherever women deliver. Despite significant progress in obstetric care, 125,000 women die from obstetric hemorrhage annually on the planet[1] The incidence of cesarean delivery (CD) is increasing, and thus the typical blood loss during CD (1000 mL) is double the number lost during vaginal delivery (500 mL). CD rate is as high as 25-30% in many areas of the planet[2]. Despite the varied techniques to prevent excessive hemorrhage following CD, post-partum hemorrhage (PPH) continues to be the foremost common complication seen in around one-fifth of the cases and related to approximately one-quarter of maternal deaths worldwide, leading to increased maternal morbidity and mortality. Primary PPH is estimated to occur in 2% to 6 of all

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births worldwide[3]. Fibrinolytic activity is elevated during and after placental delivery and should continue for 6–10 hours after delivery[4]. The current research agenda must now address the need for interventions to prevent post-partum hemorrhage, particularly in high-risk groups. In 2015 and 2016, two systematic reviews identified 12 and 26 trials of tranexamic acid for the prevention of postpartum hemorrhage, respectively[5,6]. The lysine derivative TA with a relative molecular mass of 157 exerts its antifibrinolytic effect in an indirect way by binding and thereby blocking the lysine-binding sites on the plasminogen molecules. TA acts during a reversible and competitive manner, and thus the blocking results in a reduced affinity of plasminogen to bind to fibrin, and thus the activation of plasminogen to plasmin is decreased. [7]. For several decades, tranexamic acid has been wonted to scale back surgical bleeding in some patients undergoing various kinds of surgery including orthopedic; cardiac; cranial; hepatic; ear, nose, and throat, and gynecological operations. A scientific review and meta-analysis of 129 trials that included 10,488 patients found that tranexamic acid reduced the danger of transfusion by over one-third (RR ¼ 0.62, 95% CI 0.58e0.65; p < 0.001)[8]. In 2011, the CRASH-2 trial[9] showed that early administration of tranexamic acid significantly reduces mortality in trauma patients with hemorrhage. As a results of this trial, the drug was included within the WHO Model List of Essential Medicines[10]. The use of tranexamic acid for the management of postpartum hemorrhage is widely accepted. Nevertheless, there are concerns regarding potential risks of its use, modality, and way of application, right time of infusion and during a particular dose of TA applied is typically different in each work[11]. However, questions persist regarding optimal dosing, as, no defined safe prophylactic intravenous TA dose being found in searching literature having a plus over other doses in reducing total blood loss especially at CD[12]. The minimal effective dose of TA to reduce the speed of postpartum hemorrhage during CD isn't known. We hypothesis that a 0.5-g dose is sufficient to inhibit the foremost common fibrinolytic activity in CD. Our hypothesis is that 0.5gm is effective as 1 gm TA in reducing blood loss during CD. The current study compares the efficacy of two doses of TA,0.5gm versus1 gm compared with placebo in reducing blood loss during and after CD in women who have a minimum of 1 risk factor for postpartum hemorrhage.

Subjects and Methods

A prospective, double-blinded, randomized placebo-controlled study (ClinicalTrials.gov: NCT03710330) was performed at the obstetrics and gynecology department of Aswan university hospital, (Aswu/203/2/18), Egypt, between November 1, 2018, and July 30, 2020. Women with full-term pregnancies who were scheduled to undergo an elective lower-segment cesarean and had a minimum of 1 risk factor for postpartum hemorrhage were eligible for inclusion. Women who met the selection criteria of the study were invited to participate after signing informed written consent. This trial was conducted and reported according to the CONSORT updated guidelines for reporting parallel group randomized trials[13], and according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting randomized clinical trials.

Sample size

The sample size was calculated to support the primary outcome (blood loss in women after cesarean delivery), taking mean blood loss with the use of oxytocin as 974 mL with a typical deviation of 285 mL[11]. If

TA effective in reducing blood loss by 125mL, 120 participants in each group will have > 85% power at 5% significance to detect such a difference (Epi-info: Centers for Disease Control and Prevention, Atlanta, GA, USA).

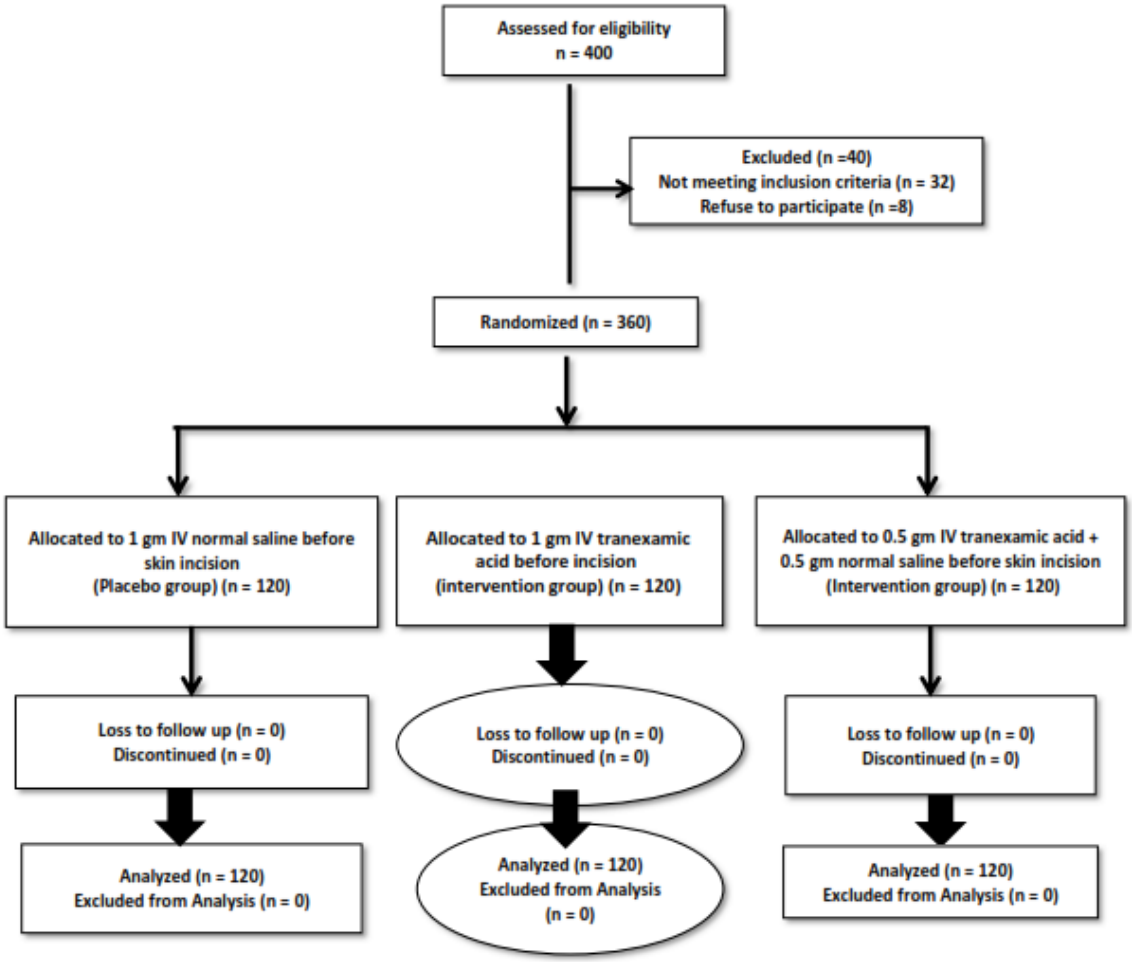

Figure 1: Consort flowchart showing enrolment of participants

Eligible Participants

Study inclusion criteria were women who scheduled for elective CD and had risk factors for postpartum hemorrhage. For example, women with a history of PPH, macrosomia, twin pregnancy, polyhydramnios, etc. Exclusion criteria were: 1-Patients with, cardiac, preeclampsia, renal, hepatic, or thromboembolic disease. 2-patients with antepartum hemorrhage .3-patients had an allergy to tranexamic acid. 400 patients were asked to participate, 40 patients were excluded,30 patients did not meet inclusion criteria and 10 patients refused to participate. Therefore, the remaining 360 patients were included in the study. All participants underwent detailed history, general, and obstetric examinations, weight, and Hight were calculated, preoperative hemoglobin was finished for all participants then an abdominal ultrasound examination was undertaken. The participants who fulfilled the eligibility criteria were explained about the study with

the beneficial and possible adverse effects of tranexamic acid. Informed written consent was obtained from them then participants were randomized into three groups, the placebo group (group 1), (The standard TA dose group (group 2), and the low TA dose group (group 3).

Randomization

Patients were randomized into 3 groups, each compromised of 120 patients consistent with a three-blocked randomization list which was coded (I or II or III) at a 1:1:1 ratio. The three parallel groups were prepared to employ a Computer-generated randomization system. The allocated groups are going to be concealed in serially numbered sealed opaque envelopes which will only be opened after recruitment. Patient allocation is going to be performed before the induction of spinal anesthesia by an independent person, who will not rather be involved during this study. The trial is going to be appropriately blinded; the participants, outcome assessors, and therefore the surgeon performing the procedure are going to be blinded to the medication type, and dose, which can be used.

Intervention

Eligible participants were allocated to one of the three groups quarter-hour before induction of spinal anesthesia. The placebo (group 1) 110 ml normal saline IV quarter-hour before skin incision. The high (group 2) received 1 gm tranexamic acid (2 ampoules of Capron 500 mg /5 ml; Cairo, Egypt) plus 100 ml normal saline quarter-hour before skin incision The low TA (group 3) 0.5 gm tranexamic acid (1 ampoule of Capron 500 mg /5 ml; Cairo, Egypt) plus 105 ml normal saline IV quarter-hours before skin incision. Following delivery, patients in both groups received an intravenous bolus of 10 IU oxytocin (Syntocinon, Novartis, Basel, Switzerland), 1 mL (0.2 mg) intramuscular ergometrine (Methergin, Novartis, Basel, Switzerland), and 10 IU oxytocin in 500 mL lactated Ringer's solution (infused at a rate of 125 mL/h). Fluid monitoring was performed through the rate of infusion and urine output. An entire blood count test was performed 24 hours after delivery. Additional oxytocic therapy was given if the uterine tone was inadequate.

Blood loss estimation

Intraoperative blood loss was measured by adding the quantity of the contents of the suction bottle after delivery of the baby and placenta and therefore the difference in weight (in grams) between the dry and therefore the soaked operation sheets and towels (1gram= 1ml.). Post-operative blood loss was measured through vaginal blood loss during the primary 24 hours post-operative by calculating the difference in weight (in grams) between the dry and therefore the soaked vaginal pads (1gram = 1ml). Then the estimated total blood loss was calculated by the addition of intraoperative and postoperative blood loss.

Study Outcome

The primary outcome was the estimation of blood loss during and 6 hours after cesarean delivery. The secondary outcome measures included the necessity for any additional oxytocic drugs, postoperative Hemoglobin concentration, the incidence of postpartum hemorrhage, operative time, and incidence of side effects (unpleasant taste, fever, shivering, nausea, vomiting, and diarrhea).

Ethical Considerations

Approval from the western Municipality and Faculty of Medicine was obtained. The ethical review board approved the study by a grant number of (Aswu/203/2/18) as a clinically registered randomized, double-blind, clinical trial (ClinicalTrials.gov: NCT NCT03710330). Every patient enrolled in

the study was counseled about the intervention and written informed consent was taken from each woman before performing any intervention.

Statistical Analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. A Chi-square test was used for comparison between groups. Quantitative data were described as means (SD) or medians, as appropriate. They were tested for normality by the Kolmogorov-Smirnov test. within the normally distributed variables, independent samples t-test was used for comparison between groups. within the non-normally distributed variables, the Mann Whitney test was used for comparison between groups. Odds ratios and their 95% confidence interval were calculated. "p-value ≤0.05" was statistically significant.

Results

Four hundred patients were asked to participate in our study,40 patients were excluded as 8 patients refuse to participate and 32 patients not meeting the inclusion criteria. Therefore 360 patients participated. The participants were randomized to three groups each group comprised of 120 patients. Group 1: (received 110 ml IV normal saline before skin in scion), Group 2:(received 1 gm tranexamic acid IV before skin incision in 100ml normal saline), and Group 3 (received 0.5 gm tranexamic acid in 105 ml normal saline IV before skin incision). There was no significant difference with reference to the demographic criteria between the three studied groups in sort of their age, weight, height, body mass index (BMI), parity, fetal age, initial hemoglobin, and an indication of CS. (Table 1). The mean overall blood loss was (609.33±211.5), intraoperative was (465.58 ±191) and post-operative was (143.75± 33.33) in group 2 compared with (829.7 ± 293.3), (665.5± 272.2), (165.83± 36.59) in group 1 respectively and (751± 208.09), (587.75 ± 190.6), (164.08 ± 32.53) in group 3 respectively , so group 2 showed great significant reduction in overall estimated blood loss either intraoperative or postoperative compared with group 1, (p= 0.0001 each) and group 3, (p=0.0001 each). Also, intraoperative blood loss in group 2 showed a significant reduction compared to group 1 (p=0.012) but no significant difference between group 3 and group 1 in reference to postoperative bleeding, (p= 0.692) however the general estimated blood loss in group 2 was significantly reduced compared with group 1 (p=0.007) (Table 2). Group 2 showed a big decrease in the incidence of postpartum hemorrhage, 4 (3.3%) patients compared with 23 (19.2%) patients in group 2and 11(9.2%) patients in group 3, (p=0.0001 and 0.003) respectively. Also, group 2 showed a significant reduction in the incidence of PPH compared with group 1, (p= 0.006). The necessity for additional uterotonics was a significant decrease in group 2, 9 (7.5%) patients compared to 40(33.3%) patients in group 1, and 34 (28.3%) patients in group 3, (p=0.0001 and 0.0001). However, no significant difference between group 3 and group 1 within the got too extra uterotonics (p=0.301). Patients who needed extra surgical intervention was a significant increase in group1, 15(12.5%) compared to 2(1.7%) patients in group 2 and 5(4.2%) patients in group 3, (p=0.0001 and 0.0001). However, no significant difference between group 2 and group 3 within the gotto extra surgical intervention, (p=0.213).

Table (1): Demographic Criteria of pregnant women in the study groups				
Parameters	**Group I** (n = 120)	**Group II** (n = 120)	**Group III** (n = 120)	**P-value**
Age (year)	30.4 ± 4.9	31.03 ± 5.1	31.7 ± 4.9	0.122
Weight (kg)	69.47 ± 6.25	69.97 ± 6.79	69.8 ± 7.41	0.847
Height (cm)	163.18 ± 4.16	163.35 ± 4.32	163.06 ± 4.23	0.866
BMI	26.08 ± 2.02	26.19 ± 2.11	26.21 ± 2.2	0.874
Parity (median) (min. – max.)	2 (0 – 6)	2 (0 – 5)	2 (0 – 6)	0.476
Gestational age (weeks)	38.5 ± 1.02	38.46 ± 1.09	38.41 ± 1.2	0.813
Initial Hemoglobin	10.66 ± 0.78	10.58 ± 0.73	10.65 ± 0.72	0.655
indication of CS (%) **repeated CS** **breech** **twin** **macrosomia** **patient request**	64(53.3) 17(14.2) 14(11.7) 16(13.3) 9(7.5)	66(55) 16(13.3) 16(13.3) 15(12.5) 7(5.8)	68(56.7) 13(10.8) 18(15) 13(10.8) 8(6.7)	0.988

BMI (body mass index), CS (Cesarean Section), # Variables are presented as mean and standard deviation, median (minimum-maximum), and number (percentage).

Also, group 1 showed a significant increase in the incidence of blood transfusion,18 (15%) patients compared with 3 (2.5%) patients in group 2, and 3 (4.2 %) patients in group3. (P= 0.0001 and 0.004) respectively. However, no significant difference between group 2 and group 3 with reference to the incidence of transfusion. (p=0.350). Lastly no significant difference with reference to postoperative hemoglobin, hospital stay, operative time, and postoperative complication as nausea, vomiting, and diarrhea between the three groups (P= 0.884, 0.186, 0.122, 0.948, 1.00, 1.00) respectively. (Table 3).

Discussion

In the best of our knowledge, this study is the first double-blind randomized placebo-controlled trial examine the effectiveness of intravenous 0.5 gm in comparison with 1 gm, and placebo for diminishing blood loss for pregnant ladies who are experiencing CD. The outcomes demonstrated that preoperative intravenous administration of a single bolus dose of 0.5 or 1 gm tranexamic acid is an efficient method for reduction of blood loss during CD in ladies who has a minimum of one risk factor for postpartum hemorrhage compared with placebo. During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products increase thanks to the activation of the fibrinolytic system. This activation can last up to 6–10 h postpartum, causing more bleeding. consistent with this activation of the fibrinolytic system, we decided to use tranexamic acid in this trial. We chose a population of women submitted to CS to work out if TA therapy is effective in reducing postoperative blood loss. The rapid release of tissue plasminogen activator with subsequent fibrinolysis after skin incision[12], and, during placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen active tors and fibrin degradation products increase. This activation causes more bleeding postpartum[8]. As in the current study, preoperative use of 1 g tranexamic acid was shown to reduce blood loss during and after elective cesar

ean among women with full-term singleton pregnancies in a previous investigation[14]. Another study[15-17] confirmed these findings. A meta-analysis of nine trials with 2365 women showed, that women who received TA had significantly less postpartum blood loss, a lower drop in hemoglobin, and a lower incidence of postpartum hemorrhage and severe postpartum hemorrhage compared with controls.

Table (2): blood loss in the study groups				
Blood loss	**Group I** (n = 120)	**Group II** (n =120)	**Group III** (n = 120)	**P value**
Intraoperative	665.5 ± 272	465.58 ± 191	587.75 ± 90.6	0.0001* 0.0001* / 0.007* / 0.0001*
postoperative	165.83 ± 36.59	143.75 ±33.33	164.08 ± 32.53	0.0001* 0.0001*/ 0.692/ 0.0001*
Total blood loss	829.7 ± 293.3	609.33 ± 211.5	751.0 ± 208.09	0.0001* 0.0001*/ 0.012*/ 0.0001*

** Statistically Significant Difference (Group I Versus Group II / Group I Versus Group III / Group II Versus Group III), # Variables are presented as mean and standard deviation.*

Table (3): operative and postoperative outcome in the study groups: -				
Variables	Group I (n = 120)	Group II (n = 120)	Group III (n = 120)	**P value**
Post hemoglobin	9.74 ± 0.64	9.79 ± 0.65	9.75 ± 0.69	0.844
Operative time	68.21 ± 19.18	63.99 ± 15.78	64.46 ± 17.1	0.122
Hospital stay	4.25 ± 0.6	4.13 ± 0.53	4.25 ± 0.57	0.186
Post-partum hemorrhage (%)	23 (19.2)	4 (3.3)	11 (9.2)	**0.0001*** **0.0001* / 0.006* / 0.003***
Additional Uterotonics (%)	40 (33.3)	9(7.5)	34 (28.3)	**0.0001*** **0.0001* / 0.301 / 0.0001***
Need Blood Transfusion (%)	18 (15)	3 (2.5)	5 (4.2)	**0.0001*** **0.0001*/ 0.004*/ 0.350**
Extra surgical intervention (%)	15 (12.5)	2 (1.7)	5 (4.2)	**0.0001*** **0.0001*/ 0.0001*/ 0.213**
Nausea (%)	7 (5.8)	7 (5.8)	6 (5)	0.948
Vomiting (%)	3 (2.5)	2 (1.7)	3 (2.5)	1.000
Diarrhea (%)	3 (2.5)	4 (3.3)	3 (2.5)	1.000

**Statistically Significant Difference (Group I Versus Group II / Group I Versus Group III / Group II Versus Group III). # Variables are presented as mean and standard deviation and number (percentage).*

Moreover, the number of women who needed additional uterotonic agents was significantly lower in the TA group than in controls. The percentage of women who required blood transfusions at, or immediately after, cesareans was significantly lower in the intervention group than in the controls[18]. But no study in this meta-analysis examines the efficacy of 5gm TA. A meta-analysis examines the prophylactic use of tranexamic acid reduce blood loss and transfusion requirements in patients undergoing cesarean section and highlights that, more high-quality research is needed to determine the optimal dose of the drug[19]. In our study the mean blood

loss was 829 ml in the control group, and this agrees with the result from Hemapriya et al[20]. The mean overall blood loss was significantly decreased in the 1gm TA group in comparison with the 0.5 gm TA group or placebo group. So, 1 gm TA is more effective than 0.5 gm TA in reducing blood loss during and after CD. One randomized controlled study showed that one gm TA significantly decreases blood loss. Hemoglobin and hematocrit measured 24 h after surgery were also significantly higher in the study population, which concur with our results[21]. This reduction agrees with the pooled estimation reported in a meta-analysis of 104 studies assessing the value of tranexamic acid in the reduction of postoperative blood loss[22]. Another meta-analysis of 34 articles (5 randomized controlled trials, 7 observational studies, and 22 case reports) [23] showed that tranexamic acid use reduced blood loss by 32.5 mL compared with placebo. Nevertheless, two cases of pulmonary embolism were identified in that meta-analysis, although the possible involvement of tranexamic acid in these thrombotic episodes could neither be confirmed nor excluded. Also mean overall blood loss was significantly decrease in 0.5 gm TA group compared with placebo group.so 0.5 gm TA is effective in reduce blood loss during CD but 1gm TA is more effective without increase side effect. The 1gm TA group showed a significant decrease within the incidence of post-partum hemorrhage, 4 (3.3%) patients compared with 23 (19.2%) patients in placebo group and 11(9.2%) patients in 0.5 gm TA group, (p=0.0001 and 0.003) respectively. Also group 0.5 gm TA showed a significant reduction within the incidence of postpartum hemorrhage compared with placebo group. One limitation of our study was a single- center study, and we use gravimetric method foe measure blood loss in state of alkaline hematin method which is a validated method for accurate measurement of blood loss. However, Marcel H et al 2004 conclude that Estimation of blood loss using a gravimetric method is an accurate and objective tool to evaluate intraoperative blood loss[23]. Another limitation of our study, the inclusion criteria include only women with risk factor for postpartum hemorrhage, and further studies needed to evaluate the efficacy of 0.5gm TA in low-risk women undergoing cesarean section. One of the strengths of our investigation was that a double-blind randomized trial adequately powered to compare the effect of intravenous 0.5 on the amount of perioperative blood loss. Another quality of the investigation lies in its simplicity of use of TA can bring about a clinically significant decrease in intraoperative blood loss.

Conclusion

Both 0.5 gm and 1 gm TA may be more effective than a placebo in reducing total blood loss during and after caesarean delivery, but 1gm TA may be more effective than 0,5 gm TA in reducing blood loss during and after caesarean delivery in women who have a minimum of one risk factor for postpartum hemorrhage, for instance, twin pregnancy, macrosomia and history of PPH, etc.

Conflicts of interest: None

Author contributions All authors agree to be accountable for all aspects of the work. NS: design, literature review, manuscript preparation. HS: conception and design, literature review, manuscript preparation. HS: manuscript preparation.

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