Tranexamic Acid plus Oxytocin Versus Oxytocin only in Reducing Blood loss after Cesarean Section. A Double Blinded Randomized Controlled Trial

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Abstract

Objective: to assess the efficacy of tranexamic acid in reducing blood loss after cesarean section.

Patients and methods: This was a double blinded randomized controlled trial. One hundred and thirty patients admitted for elective cesarean section were randomized into two groups to receive either tranexamic acid plus oxytocin (group T) or oxytocin only (group A) after obtaining informed consent. The primary outcome of the study was the intraoperative blood loss. Other measures of outcome were the postoperative blood loss, the need for additional uterotonics, postopertative hemoglobin and hematocrit levels, need for blood transfusion and any side effects related to tranexamic acid.

Results: tranexamic acid significantly reduced intraoperative blood loss after CS when combined with oxytocin; 246.5 ± 103.8ml in the tranexamic group versus 525.4 ± 99.4 ml in the oxytocin only group (P=<0.001). Postpartum blood loss was also reduced significantly in the tranexamic acid group; 77.7 ± 11.6 ml in the tranexamic acid group versus 103.3 ± 11.3ml in the oxytocin only group (P=<0.001). Hb 24hrs after cesarean section was significantly greater in the tranexamic group; 11.3±1.0 g/dl versus 10.7±0.9 g/dl in the oxytocin only group (p=0.001). The need for additional uterotonics was significantly reduced among the tranexamic group; 3(4.6%) versus the oxytocin only group; 12(18.5%) with p value = 0.013. Operative time was significantly shorter in the tranexamic group; 65.8±13.0 min versus the oxytocin only group; 79.1±16.3min. No significant difference was found between the two groups regarding the need for blood transfusion and there was no reported neonatal side effects.

Conclusion: tranexamic acid significantly reduced intraoperative and postoperative blood loss after cesarean section and it can be safely used for prophylaxis against postpartum hemorrhage after cesarean section in low risk patients.

Key words: tranexamic acid, cesarean section.

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Introduction

Postpartum hemorrhage (PPH) is considered to be one of the leading causes of maternal morbidity and mortality in the United States and is the most common cause of maternal mortality worldwide (1). According to WHO statistics, PPH is responsible for 60% of maternal mortalities in the developing countries which accounts for more than 100,000 maternal deaths per year worldwide(2).

Primary postpartum hemorrhage is leading form of obstetric haemorrhage. The WHO defines primary PPH as blood loss of 500ml or more during the first 24hours after giving birth (3).

Medical management in the form of uterotonic drugs is the first line treatment for major PPH. When first-line treatment fails, second line therapies consist of surgical or radiological procedures. Hysterectomy is the last choice for controlling bleeding and it's a life saving procedure in severe cases(4).

Oxytocin given either by the intravenous or intramuscular route is recommended for the prophylaxis against PPH for all births. (5). In case of caesarean section, oxytocin (5 iu by slow intravenous injection) should be used to stimulate contraction of the uterus and to decrease blood loss (6)

Tranexamic acid has risen in the past years as another agent which can be used to decrease blood loss following childbirth. Small, single center, randomized, controlled trials have shown significant decrease in postpartum blood loss when prophylactic tranexamic acid is given to women undergoing elective cesarean delivery. Nevertheless, because of methodologic limitations related to blinding, outcome assessment, attrition bias, and absence of postdischarge follow-up, especially for thromboembolic events, the findings in these trials are interpreted as inconclusive, and current guidelines do not advocate routine administration of tranexamic acid after cesarean deliveries.(7)

The aim of this study is to evaluate the efficacy of tranexamic acid in reducing blood loss after cesarean section

Patients and methods

This randomized controlled study was carried out at the labor ward of Ainshams university maternity hospital during the period from August 2020 to April 2021 The study population included pregnant women with singleton fetus admitted for delivery by elective lower segment cesarean section. Age of the included participants was from 20 to 40 years of age with gestational age from 37+0 weeks to 41+0 weeks. Patients with risk factors or history of postpartum hemorrhage, medical disorders as diabetes mellitus or hypertension, contraindications or hypersensitivity to tranexamic acid and women receiving anticoagulant therapy were excluded from the study.

The study participants were divided into two groups; group(T) and group(O); Group sample sizes of at least 65 cases per group achieve 80% power to reject the null hypothesis of zero effect size when the population effect size is 0.50 and the significance level (alpha) is 0.050 using a two-sided two sample equal-variance t-test (8). The Women who fulfilled the criteria for the study will be approached for consenting and will be given a serial number in the study, randomization will be done through a computer generated system For the sake of concealment, cards with either (T) or (O) on them will be kept in sealed envelopes with a serial number. According to the computer system an envelope will be chosen which corresponds to the number of enrollment of the women in the study and then will prepare either the TXA plus oxytocin or oxytocin only according to the card and give it to her. The mean examiner, the surgeon and the analyst will be masked to the given drug. For those in group (T), they will receive 1gm of TXA (1gm/10ml) IV just before skin incision. As soon as the umbilical cord is clamped, all women included in the study group (T) and group (O) will receive 5IU oxytocin IV bolus. Hemoglobin and Hematocrit will be withdrawn before the procedure and will be repeated 24 hours after delivery. Records of primary and secondary outcomes will be tabulated.

The primary outcome of the study was the amount of blood loss after delivery of the placenta and for 2hours after. It was estimated

by measuring the amount of blood in the suction drain, blood absorbed by soaked mops (wet weight of the used mop – dry weight) and blood absorbed by perineal sheet during vaginal toileting (wet weight – dry weight). Soaked mops and operation table perineal sheet were weighed by electronic scale before and after the surgery with one mg weight was taken as equivalent to one ml of blood (9). Other measures of outcome were the amount of blood products transfused, operative time, postoperative hospital stay and neonatal complications if existed.

The analysis will be carried out using the MedCalc 9.3 statistical software. Normal distribution of continuous variables will be assessed using the Kolmogorov-Smirnov test; the chi-square test will be used to analyze categorical variables; the Student's t test will be used for the analysis of normally distributed continuous variables; and the Mann-Whitney U test will be used for abnormally distributed variables. Relative risk with a 95% confidence interval (CI) will be calculated. $P \leq .05$ will be indicated statistical significance.

This study will be done after approval of the ethical committee of the department of obstetrics and gynecology, Faculty of Medicine, Ain shams University. Informed consent will be taken from all participants before recruitment in the study and after explaining the purpose and procedure of the study. The investigator will obtain the written, signed informed consent of each subject before performing any study specific procedure on the subject. The investigator will retain the original signed informed consent form. All laboratory samples, evaluation forms, reports, video recordings and other record that leave the site will not include unique personal to maintain subject confidentiality. The study will be based on the investigator self-funding.

Results

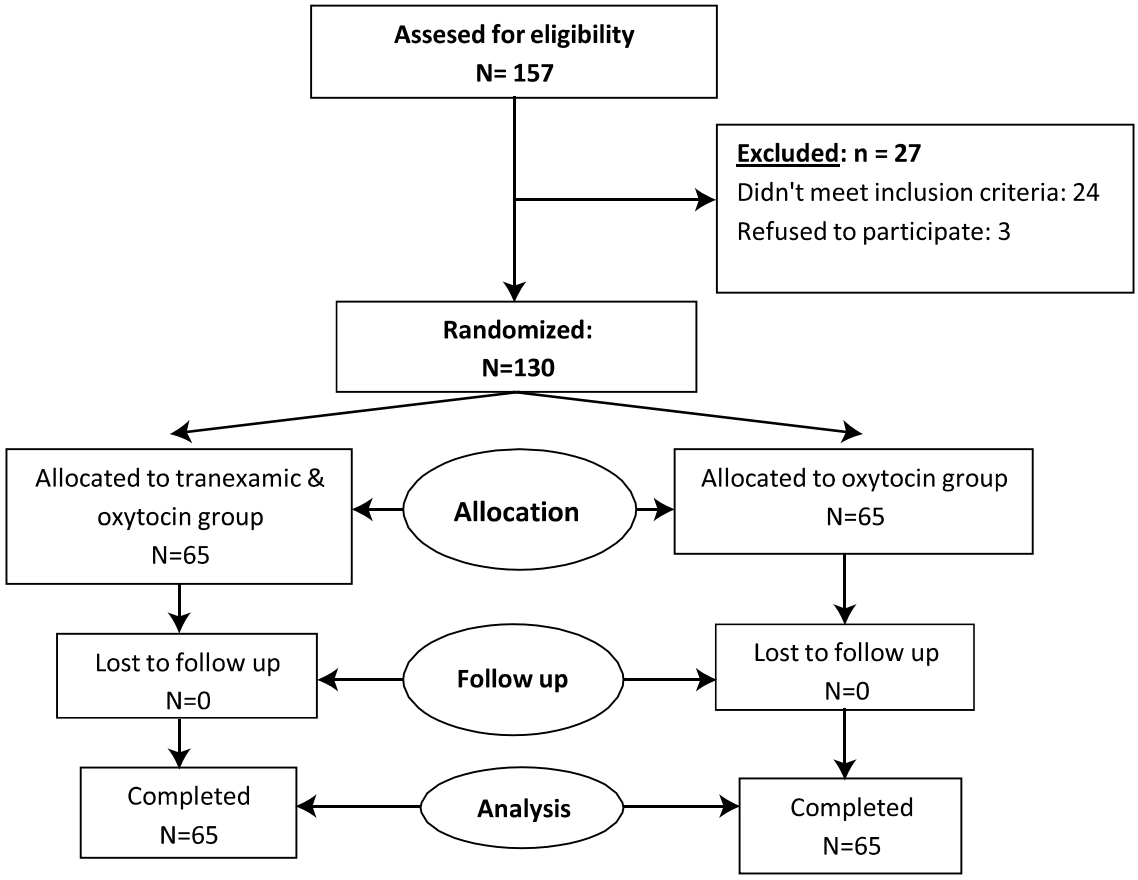

Figure 1: flow chart of the studied cases

Table 1: Demographic data among the studied groups

Items	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Age (years)	**Mean±SD**	29.7±5.8	29.2±6.2	^ 0.621
	Range	20.0–40.0	20.0–40.0	
BMI (Kg/m²)	**Mean±SD**	29.8±2.6	29.8±2.8	^ 0.974
	Range	24.0–35.0	25.0–35.0	
Parity, (n, %)	**Nulli**	9 (13.8%)	10 (15.4%)	# 0.804
	Multi	56 (86.2%)	55 (84.6%)	
GA (week)	**Mean±SD**	38.1±0.9	38.0±1.0	^0.924
	Range	37.0–40.0	37.0–40.0	
ABO	**A**	33 (50.8%)	28 (43.1%)	#0.158
	B	10 (15.4%)	16 (24.6%)	
	AB	3 (4.6%)	8 (12.3%)	
	O	19 (29.2%)	13 (20.0%)	
Rh	**Positive**	52 (80.0%)	58 (89.2%)	#0.145
	Negative	13 (20.0%)	7 (10.8%)	
Previous cesarean section		56 (86.2%)	54 (83.1%)	#0.627

BMI: body mass index, GA: Gestational age, ^ : Independent t-test, # : Chi square test.

Table 2: intraoperative blood loss (mL) among the studied groups

Source	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Sheet	**Mean±SD**	180.8±74.0	275.4±122.2	**<0.001***
	Range	64.0–450.0	104.0–550.0	
Suction	**Mean±SD**	91.7±58.5	229.8±106.0	**0.003***
	Range	50.0–200.0	100.0–400.0	
Towel	**Mean±SD**	57.2±31.0	101.6±44.1	**<0.001***
	Range	11.0–165.0	20.0–234.0	
Total	**Mean±SD**	246.5±103.8	525.4±99.4	**<0.001***
	Range	111.0–550.0	271.0–784.0	

^ : Independent t-test, *: Significant

Table 3: Postoperative blood loss (ml) among the studied groups

Source	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Sheet	**Mean±SD**	77.7±11.6	103.3±11.3	<0.001*
	Range	49.0–106.0	85.0–133.0	
Drains		**No intraperitoneal drains**		

^ : Independent t-test, *: Significant

Table 4: Hemoglobin (gm/dl) among the studied groups

Time	Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Pre-operative	**Mean±SD**	11.8±1.0	11.5±0.9	0.119
	Range	9.4–14.0	9.8–14.1	
Post-operative	**Mean±SD**	11.3±1.0	10.7±0.9	**0.001***
	Range	9.0–13.6	8.8–13.4	
Drop	**Mean±SD**	0.4±0.2	0.8±0.3	**<0.001***
	Range	0.2–1.6	0.3–1.4	

^ : Independent t-test, *: Significant

Table 5: Need for additional uterotonics and blood transfusion and neonatal side effects among the studied groups

Complications	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Uterotonics	3 (4.6%)	12 (18.5%)	**#0.013***
Blood transfusion	1 (1.5%)	2 (3.1%)	§0.999
Neonatal side effects	0 (0.0%)	0 (0.0%)	**Not applicable**

#: Chi square test. §: Fisher's Exact test. *: Significant

Table 6: operative time (minutes) among the studied groups

Measure	Tranexamic & oxytocin group N=65	Oxytocin group N=65	P-value
Mean±SD	65.8±13.0	79.1±16.3	<0.001*
Range	45.0–110.0	45.0–105.0	

^ : Independent t-test. *: Significant

Discussion

This was a double-blinded randomized controlled clinical trial which was conducted at the labor ward of Ain Shams University Maternity Hospital (ASUMH) during the period between November 2019 and December 2021 and it was aiming at comparing the efficacy of tranexamic acid plus oxytocin versus oxytocin alone in reducing blood loss following CS.

One hundred thirty women (130) were included in the study and they were randomized into two groups; Group (O): 65 women received oxytocin only while Group (T): 65 women received oxytocin plus tranexamic acid

Regarding the Demographic data, there was no statistically significant difference between the two groups regarding age, BMI, parity, gestational age, ABO& Rh blood groups and previous cesarean delivery.

As for Intraoperative blood loss, it was estimated by measuring the amount of blood in the suction bottle in addition to weighing the soaked towels and sheets. All measures were summated to estimate the intraoperative blood loss, there was significant difference in the between the study group and the control group favoring the study group and that difference was found in all measures; suction, sheets, towels and the total blood loss (194.6±87.2 VS 485.0±103.5). Regarding Postoperative blood loss, it was estimated by weighing the sheet which was placed beneath the patient immediately after the procedure; the sheet was weighed 2 hours after the procedure. The results showed significant statistical difference

between the two groups favoring the study group (77.7 ± 11.6 VS 103.3 ± 11.3). Our results were consistent with results obtained by Lakshmi & Abraham, who randomized their patients into two groups to receive either tranexamic acid as 20 min before skin incision in addition to 10 units of oxytocin while the other received oxytocin only. There was significant difference between the two groups regarding blood loss favoring the study group (347.17±106.6 VS 517.72±150). Moreover, blood loss over 500cc was significantly different between the study and the control group (2/60 {3.3%} VS 36/60{60%}). However, their measurements were limited to intraoperative blood loss and the postoperative period was not included (9). Our results were also similar to results by Abdelaleem et al., who conducted their study on 740 pregnant women underwent elective CS. The participants were randomized into two groups to receive either tranexamic acid or nothing before the procedure with equal dosage of oxytocin received after delivery. There was significant difference regarding total blood loss between the two groups (241.61±126.02 VS 510.7±144.52). Intraoperative blood loss and up to 2hrs post cesarean section blood loss was measured (10). The study by Movafegh et al., showed similar results as well. The study participants were randomized into two groups to receive either tranexamic acid or normal saline 20 min before procedure and the two groups received the same dosage of oxytocin after delivery of the placenta. The study showed significant difference between the study group and the control group regarding intraoperative blood loss (262.5± 39.6 mL VS 404.7±94.4 mL) and postoperative blood loss (67.1± 6.5 mL vs 141.0±33.9 mL)(11).

Regarding the Hemoglobin difference, there was no significant difference between the two groups in the levels of preoperative hemoglobin (Mean ± SD = 11.8±1 VS 11.5± 0.9 with P value 0.119) while there was statistically significant difference between the two groups regarding postoperative hemoglobin (Mean ± SD = 11.3±1 VS 10.7±0.9 with P value 0.001). Our results were consistent with that obtained by Ray et al., who showed in their study which included two groups who received either 1g intravenous (IV) tranexamic acid or placebo 20 min before beginning of spinal anesthesia and the same dose of oxytocin after delivery that post-operative fall in hemoglobin per cent was significantly more in control (0.99 g%) group than study group (0.26 g%) (p = 0.000). (Ray et al.,2016) (12). Study conducted by Senturk et al., showed similar results as well. The study included two groups who received either 20cc of IV tranexamic acid or placebo 10 minutes before the start of cesarean section and all patients received 20 IU oxytocin IV bolus form after removal of placenta. The results showed significant difference when hemoglobin loss was compared between the two groups with p value of 0.034 (13).

The Need for additional uterotonics during the procedure was also assessed in our study and it was found that the need for additional uterotonics during the procedure was significantly more in the control group (18.5% of the group) compared with that of the intervention group (4.6% of the group) with p value of 0.013. Such results were similar to that obtained by Lakshmi & Abraham as the need for additional uterotonics in the control group was significantly more compared to tranexamic acid group (15% VS 3%)(9).

Gungorduk et al., also showed similar results in their study; significant difference was found between the two groups regarding the need for additional uterotonics with 14.5% of the placebo group required additional uterotonics compared to 8.5% of the active group with p value = 0.02 (14).

Regarding the need for Blood transfusion, there was no significant difference between the two groups. Only 1 patient in the study group (1.5%) and 2 patients (3.1%) needed blood transfusion with P value 0.999. Our results were comparable to that obtained by Senturk et al., who showed no need for blood transfusion in both groups (study and control) included in their study (13). However, results obtained by Shahid & Khan were different as there was significant difference between the two groups regarding the requirement for blood transfusion; 33% of the patients in the control group required blood transfusion with only 8% in the study group. Such difference between results of their study and our study

can be attributed to certain points; the mean preoperative hemoglobin was already in the anemic range in both study and control group of the previously mentioned study (study group: 9.76

± 0.85 VS control group: 9.88 ± 1.26) with further aggravation of such anemia in the postoperative period (study group: 8.67 ± 0.715 VS control group: 8.0 ± 0.94), smaller sample size than our study and the fact that hemoglobin was withdrawn on the third postpartum day in their study which was a better reflection of the actual hemoglobin status of the patient (15).

As for the Operative time, it was significantly shorter among the tranexamic acid plus oxytocin group compared with oxytocin group (Mean ± SD = {65.8±13.0 VS 79.1±16.3}). Such difference in the operative time could be attributed to less time spent in achieving adequate hemostasis in the tranexamic group. Our results were consistent with results obtained by Lakshmi & Abraham who randomized their participants into two groups as well; one was given tranexamic acid as 1gm diluted in 100ml saline 20 min before skin incision in addition to 10 units of oxytocin while the other received oxytocin only. The operative time was significantly shorter among the tranexamic acid group (9). However, Maree and Hassein obtained different results in their study which included 100 women; one group received 10mg/kg of tranexamic acid + 5 IU bolus IV oxytocin after delivery while the other group received 20 IU infusion of oxytocin soon after delivery. There was no significant difference between the two groups regarding the operative time (Mean ± SD = {37.58±1.72 VS 37.1±2.49}). Such difference between this study and our study could be attributed to different sample size between the two studies yielding different results, higher levels of experience among the operating surgeons in the study conducted by Maree & Hassein, higher percentage of previous LSCS in our study (86.2% in the TXA group and 83.1% in the control group) compared with their study (18% in the TXA+ oxytocin and 10% in the control group) and the fact that our study was limited to elective CS while their study included emergency CS for different reasons (16).

Maternal or fetal complications related to tranexamic acid were also assessed and there were no reported complications. However, such outcome needs a much bigger sample size and it wasn't the primary concern of our study.

Our study wasn't without limitations. The major limitations of our study was the small sample size and the fact that side effects of tranexamic acid were not measured and because of its rarity, studies with much bigger sample size will be needed to detect it

Conclusion

Our study showed that tranexamic acid is an effective agent in reducing blood loss during elective cesarean section in low risk patients. It has minimal side effects and it's rarely unavailable. However, further studies are needed to evaluate its effectiveness in patients with risk factors for postpartum hemorrhage i.e high risk patients.

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