Italian Journal of
Gynæcology & Obstetrics
September 2024 - Vol. 36 - N. 3 - Quarterly - ISSN 2385 – 0868

The adjunctive role of temporary uterine packing combined with topical tranexamic acid for reducing blood loss during haemorrhagic caesarean delivery: a randomized controlled trial

Nahla W. **Shady**, Ahmed A. **Taha**, Hany F. **Sallam** *

Department of Obstetrics and Gynecology, Aswan Faculty of Medicine, Aswan University, Aswan Governorate, Egypt.

ARTICLE INFO

History
Received: 28 September 2023
Received in revised form: 18 December 2023
Accepted: 09 January 2024
Available online: 20 September 2024

DOI: 10.36129/jog.2024.151

Key words
Postpartum haemorrhage; tranexamic acid; caesarean delivery.

***Corresponding author:** Hany F. **Sallam**, Professor. Department of Obstetrics and Gynecology, Aswan University Hospital, Aswan University, 81528, Al kornish St., Aswan, Egypt.
Email: nahlagyn@yahoo.com.
ORCID 0000-0003-3368-8414.

ABSTRACT

Objective. To explore the efficacy and safety of temporary uterine packing combined with topical tranexamic acid (TA) as an adjunct for reducing blood loss during a haemorrhagic caesarean delivery (CD), compared with placebo.
Materials and Methods. A prospective, open label randomized controlled trial was performed at an Obstetrics and Gynecology Department of a tertiary University Hospital, Egypt, between January 1, 2019, and July 1, 2023. Women were eligible if they underwent elective caesarean under spinal anaesthesia and were bleed around 700 ml by visual analogue estimation and gravimetric measures. Participants were randomly assigned (1:1) to receive 400 μg misoprostol sublingually plus temporary uterine packing with topical tranexamic or matched placebo. the first outcome was the percentage of patients for whom haemorrhage was controlled with just the trial regimen.
Results. A total of 180 women fully completed the protocol (90 in each group). Extra needs of uterotonic or surgical procedures were performed in 26 (28.9%) women within the TA group and in 59 (65.6%) controls. Blood loss between enrolment and 6 hours later was significantly lower within the TA group (1,005.9 ± 141.3), than within the control group (1,254.2 ± 228.5, $p = 0.001$). Within the TA group, bleeding duration was shorter and progression to severe PPH and PRBC transfusion was less frequent than in controls ($p < 0.01$).
Conclusions. Uterine packing combined with topical tranexamic acid applied at the placenta bed, appeared to be more effectively reduce blood loss than did placebo during haemorrhagic CD.

INTRODUCTION

Postpartum haemorrhage (PPH) may be a total blood loss greater than 1,000 mL with signs and symptoms of hypovolemia within 24 hours of the birth process, no matter the route of delivery [1].
Caesarean delivery is that the most often performed major operative procedure worldwide. The worldwide rise in the incidence of caesarean delivery (CD) within the past decade has possibly contributed to the increased rate of PPH [2].
Approximately over a quarter of all the lower segment, CS deliveries are complicated by primary PPH. So estimated blood loss of quite 700 mL should alert the obstetrician to possible excessive bleeding [3].
Blood loss after delivery could also be a complication that will occur suddenly and remain one

of the leading causes of obstetric morbidity and mortality throughout the planet. Timely management strategies are urgently needed wherever women deliver. Although there's great progress in obstetric care, 125,000 women die from blood loss associated with delivery annually within the planet [4].

There is a worldwide commitment to decrease the speed of PPH to satisfy the need of the Millennium Development Goal (MDG) of reducing maternal deaths by three-quarters by the year 2015, as PPH account for 25% of maternal mortality worldwide [5].

The competitive mechanism of actions of TA should be effective when applied in a topical fashion because it avoids fibrin degradation, TA acts directly at active bleeding and clot formation sites and not within the circulation. It had been previously supposed that this achieves a better therapeutic concentration at the location of bleeding, effectively limiting blood loss [6].

The current research goals must now address the role of topical application of TA to decrease the speed of postpartum haemorrhage, particularly in high-risk groups. Thus, TA should tend early and empirically as soon as a PPH is diagnosed, and before severe haemorrhage.

Due to the paucity of trials comparing the use of topical tranexamic acid, it remains unclear whether the efficacy of topical TA administration in CD for reducing blood loss within the high-risk groups for postpartum haemorrhage is capable or but that of IV administration [7, 8].

Our hypothesis is that temporary uterine packing with topical TA effective than placebo in reducing postpartum blood loss during haemorrhagic CD.

The current study compares the efficacy of temporary uterine packing combined with topical tranexamic with placebo in reducing blood loss during and after haemorrhagic CD.

MATERIALS AND METHODS

This study was an open label, randomized controlled trial conducted after an ethical committee agreement at a university hospital from January 1, 2019, to July 1, 2023. We prospectively filed it at clinicaltrials.gov (NCT03778242). We adherence to the CONSORT guidelines for randomized trial reporting. Study inclusion criteria were patients who were admitted for an elective or non-emergency CS during labour and exposed to intraoperative bleeding about 700 ml diagnosed by visual analogue estimation and gravimetric method thanks to atonic uterus. Women with a medical disorder, placenta previa, placenta accrete, allergy to TA, and intraoperative bleeding thanks to causes aside from uterine atony were excluded from the study. Patients over 40 or who have pre-existing coagulation disorders, red blood cell disease, which is understood to cause abnormal blood coagulation also to exclude from the study.

Eligible participants

There were 2,349 pregnant women at term (37:40 weeks) gestation scheduled for low segment CD under were invited for this study. 349 not meeting inclusion criteria and 321 refused to participate. 1,679 women undergoing elective caesarean delivery, 1,442 women were excluded as they didn't reach 700 ml intraoperative bleeding, and 237 women who reach about 700 ml intraoperative bleeding were included and continued the study. 57 women were excluded during CD thanks to excessive mechanical tears during the extraction of the baby. 180 patients complete the study.

All participants underwent detailed history, general, abdominal, and ultrasound examinations. The participants who fulfilled the eligibility criteria were explained about the study with the beneficial and possible adverse effects of TA. Informed written consent was obtained from them.

Randomization

Patients were randomized into two groups, each compromised of ninety patients consistent with a two-blocked randomization list which was coded (1 or 2) at a 1:1 ratio. The randomization scheme was computer-generated. The allocated groups are going to be concealed in serially numbered sealed opaque envelopes which will only be opened after recruitment. Patient allocations are going to be performed during CS by an independent person, who won't rather be involved during this study. The trial was an open label.

Intervention

All women performed CS by using spinal anaesthesia, Pfannenstiel incision of the skin, open of

abdomen in layers, lower uterine segment transverse incision. After delivery of the baby 10 IU of oxytocin intravenous infusion administered by the anaesthesiologist then delivery of the and placenta, during CS, intraoperative bleeding was estimated, if bleeding around 700 ml and thanks to atonic uterus then temporary uterine packing for five minutes, with gauze of the dimensions soaked with 2 g tranexamic diluted in 60 ml saline acid or placebo, plus 400 mc sublingual misoprostol. For all haemorrhagic CD cases, blood loss was recorded at five minutes intervals: at treatment, 5 mint-, 10 mint-, 20 mint, and end of the operation. If the lady was stable, providers were asked to attend 10 min after administering trial treatment before considering additional interventions for the PPH, although the administration of any additional intervention at any time point was documented. Additional interventions and therefore the explanation for PPH (as determined by the provider) were documented. At the time of discharge from the hospital, participants were asked about side effects.

Blood loss estimation

Intraoperative blood loss was measured by adding the quantity of the contents of the suction bottle which was changed after delivery of the placenta to avoid being mixed with amnionic fluid and blood from gauze which was strictly kept for weighing, and therefore, the reform the difference in weight (in grams) between the dry and the soaked operation sheets and towels (1 g = 1 ml).
Post-operative blood loss was measured by calculating the difference in weight (in grams) between the dry and therefore the soaked pads (1 g = 1 ml). Then, the entire blood loss was calculated by the addition of intraoperative and postoperative blood loss.

Study outcome

The primary outcome was the proportion of patients for whom haemorrhage was controlled with just the trial regimen (placebo or 2,000 mg TA, followed by 400 mcg misoprostol) without recourse to additional treatment. The secondary outcome measures included estimation of intraoperative, postoperative, and total blood loss (ml), need for transfusion, other surgical interventions, additional uterotonics, and operative time. Also, haemoglobin concentration was wiped out all patients preoperatively and 24 hours postoperative, and therefore the change in concentration was noted. Any side effects like fever, shivering, unpleasant taste, nausea, vomiting, and diarrhoea were recorded.

Calculation of sample size

The primary outcome was the proportion of women for whom bleeding was controlled with just the trial regimen (placebo or 2,000 mg TA, followed by 400 mcg misoprostol) without recourse to additional treatment. Controlled bleeding was subject to provider assessment. We hypothesized that bleeding would stop among 89% of women within the placebo group (misoprostol alone), as demonstrated in previous trials on the efficacy of misoprostol to treat PPH [9]. We estimated that a further 10% of women who received the TA additionally to the misoprostol would experience cessation of bleeding with no other intervention. Supported these assumptions (89% *vs* 99%), a sample of 180 PPH cases (90 per group) was required for a one-sided test with 80% power, alpha = 0.05.

Statistical analysis

Data were entered and statistically analysed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. The 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 Kolmogorov-Smirnov test. Within the normally distributed variables, an independent sample 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 considered statistically significant.

RESULTS

Out of 2,349 eligible women delivered by CS, 180 women were consented to participate and continued the study. They were randomized into two

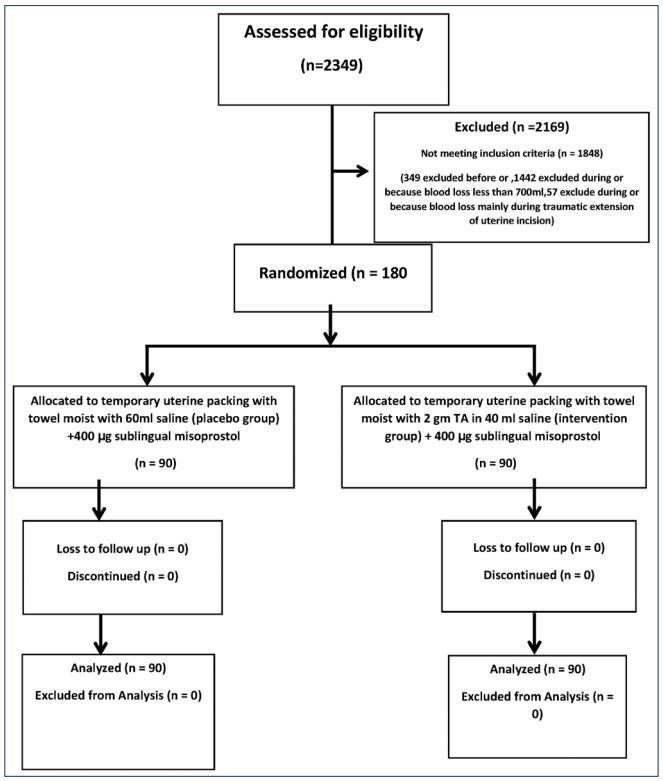

Figure 1. *Flow chart of the study.*

Table 1. *Preoperative characteristics of pregnant women in the study groups.*

Parameters	Group I (n = 90)	Group III (n = 90)	Test of significance
Age (year)	29.6 ± 2.2	30.2 ± 2.6	t = 1.8, p = 0.07
Weight (kg)	68.6 ± 6.9	68.3 ± 6.7	t = 0.3, p = 0.7
Height (cm)	163.9 ± 4.2	163.5 ± 4.3	t = 0.7, p = 0.5
BMI	25.5 ± 2.3	25.5 ± 2.2	t = 0.05, p = 0.96
Parity (median) (minimum-maximum)	2 (0-6)	2 (0-6)	*Z = 0.5, p = 0.7
Gestational age (weeks)	38.3 ±0.8	38.3 ± 0.9	t = 0.5, p = 0.6
Initial haemoglobin	10.6 ± 0.8	10.6 ± 0.7	t = 0.05, p = 0.96
Indication of CS (%)			
Breech	17 (18.8)	17 (18.8)	
Patient request	17 (18.8)	16(17.7)	
Previous CS	12 (13.3)	13 (14.4)	χ^2 = 0.3, p = 0.99
Twin	14 (15.3)	16 (17.7)	
Failure to progress	9 (10)	8 (8.8)	
Macrosomia	21 (23.3)	20 (22.2)	

BMI: body mass index; CS: caesarean section; all measures are described as mean ± SD except parity as median (range); *Z of Mann-Whitney test.

groups: tranexamic acid group and placebo group (**Figure 1**).

There was no significant difference between the 2 groups with reference to their age, weight, gestational age, parity, number of CS, an indication of CS, and initial haemoglobin (**Table 1**).

There was a significant reduction in intraoperative blood loss within the TA group (900.4 ± 123.3) compared with the placebo group (1,068.3 ± 180.2; p = 0.001). However, there was a significant difference in postoperative bleeding between the 2 groups (p = 0.001).

The all-estimated blood loss during CS and 24 hours postoperative was significantly lower within the TA group (1,005.9 ± 141.3) than that within the placebo group (1,254.2 ± 228.5; p = 0.001) (**Table 2**).

The incidence of transfusion was increased within the placebo group of 64 (71.1%) women compared with 27 (30.0%) women within the TA group (p = 0.001). More women within the placebo group 59 (65.6%) than in TA group 28 (31.1%) required additional uterotonics (p = 0.0001). Also, more women within the placebo group 25 (27.7%) than in TA group 9 (10%) required more surgical intervention (p = 0.0001). There was a significant difference in operative time within the TA group (69.4 ± 10.6) compared with the placebo group (69.4 ± 10.6) (p = 0.002).

There was no significant difference in reference to 24-hour post-operative haemoglobin concentration between the 2 groups (0.844) (**Table 3**).

About the side effect, there was no significant difference between the 2 groups in reference to nausea, vomiting, and diarrhoea (p = 0.8, 1.1, respectively) (**Table 3**).

DISCUSSION

This trial demonstrates that temporary uterine packing with topical application of TA adminis-

Table 2. *Surgical outcome in the study groups.*

Blood loss	Group I (n = 90)	Group II (n = 90)	Test of significance
Intraoperative	1,068.3 ± 180.2	900.4 ± 123.3	p < 0.001, t = 7.3
Postoperative	185.9 ± 55.6	105.6 ± 23.5	t = 12.6, p < 0.00
Total blood loss	1,254.2 ± 228.5	1,005.9 ± 141.3	t = 8.8, p < 0.001
Additional Uterotonics (%)	66 (73.3)	28 (31.1)	χ^2 = 32.2, p < 0.001

Variables are presented as mean and standard deviation and number (percentage).

Table 3. *Operative and postoperative outcome in the study groups.*

Variables	Group I (n = 90)	Group III (n = 90)	Test of significance
Post haemoglobin (gm/ dL)	9.7 ± 0.7	9.8 ± 0.7	t = 1.2, p = 0.2
Operative time(min)	74 ± 9.1	69.4 ± 10.6	t = 3.1, p = 0.002
Hospital stays	3.8 ± 0.8	3.8 ± 0.7	t = 0.1, p = 0.9
Post-partum haemorrhage (%)	59 (65.6)	26 (28.9)	$\chi^2 = 24.3$, p < 0.001
Need blood transfusion (%)	64 (71.1)	27 (30.0)	$\chi^2 = 30.4$, p < 0.001
Extra surgical intervention (%)	25 (27.7)	9 (10)	$\chi^2 = 9.8$, p = 0.007
Uterine artery ligation	15 (16.7)	4 (4.4)	
B-Lynch suture	10(11.1)	5 (5.6)	
Nausea (%)	7 (7.8)	6 (6.7)	$\chi^2 = 0.1$, p = 0.8
Vomiting (%)	9 (10.0)	4 (4.4)	$\chi^2 = 2.1$, p = 0.2
Diarrhoea (%)	5 (5.6)	3 (3.3)	Fisher's Exact test, p = 0.7

Variables are presented as mean and standard deviation and number (percentage).

tered to women with haemorrhagic CD decreases blood loss, and cases diagnosed with PPH. In addition, TA-treated women decrease the need for extra uterotonic and extra surgical procedures in the form of uterine artery ligation and B-Lynch compression sutures to hold the bleeding, with the only minor, transient side effects.

In our study, we test the application of temporary uterine packing with topical TA for secondary prevention of postpartum haemorrhage during haemorrhagic CD when estimated blood loss reaches 700 ml. Such a strategy implies that the drug must be administered only to the patient at risk for postpartum haemorrhage and not to every woman, as routine prophylaxis's from PPH as many patients experienced CD, not suffer from blood loss more than 500 ml. Our trial entails that topical application of TA is an option that may decrease the rate of PPH and the need for extra uterotonic and extra surgical manoeuvres to decrease blood loss during CD.

Also, in our study, we shoe to explore the role of topical application of TA instant of the intravenous route to try to decrease the potential theoretical complication from IV route application. The use of other routes of administration of TA should has a priority, as recommended by the WHO [10].

The purpose of this study was to explore the potential for reducing bleeding by administering temporary uterine packing with topical application of TA in women with haemorrhagic CD. The studied population was selected based on active haemorrhage of more than 800 mL when its clinical course might be life-threatening. The 800-mL threshold for the definition of haemorrhagic CD. This selection of patients required a specific procedure for measurement and verification of blood loss at each time point.

Our study the first type addresses the role of topical application of TA to hold the haemorrhagic CD. CRASH-2 study revealed that TA safely reduces the danger of death in bleeding trauma patients when administered within 3 hours [11]. Within the field of obstetrics, three randomized, controlled trials have suggested that TA administration in women after vaginal or elective caesarean delivery reduces blood loss and therefore the incidence of PPH [12-14].

Instead of acute severe haemorrhage, postpartum bleeding is usually steady. In order that estimated blood loss is usually only approximately half the loss. If atony persists, bleeding may appear to be only moderate at any given instant but may continue until serious hypovolemia develops [15].

In our study, we chose to interfere early with the use of temporary uterine packing with topical TA for prevention of postpartum haemorrhage during the caesarean delivery when estimated blood loss is about 700 ml.

Urgent treatment of haemorrhagic CD with tranexamic acid is important for two reasons. First, women with postpartum haemorrhage bleed to death unnoticed and vastly. Most deaths due to haemorrhage occur soon after childbirth, with more than half occurring within 8 h. If treatment is delayed, many women who could have benefited will have complicated with morbidity and mortality of haemorrhage. Second, tranexamic acid is most effective when topically applied.

Tranexamic acid should be always readily available in emergency obstetric care facilities: it is cost-effective, heat-stable, and widely available, with a long shelf life.

There are 3 trials within a Cochrane review of TA used for the treatment of PPH, explore that TA effectively reduce blood loss [11].

One trial randomly allocated 152 women with postpartum haemorrhage, defined as blood loss > 800 mL following vaginal delivery, to receive high-dose tranexamic acid (a loading dose of 4 g over 1 h followed by an infusion of 1 g over 6 h) or standard care [16].

A meta-analysis of 20,172 women, showed that tranexamic acid reduces the risk of death due to bleeding (RR = 0.81, 95%CI 0.65-1.00), with early treatment being more effective. Based on this review, the WHO updated its recommendation on the use of tranexamic acid for the treatment of postpartum haemorrhage [17].

The result of our study agrees that topical application of TA may be a safe, effective, and affordable treatment for haemorrhagic CD. The present research agenda must address the necessity for interventions to stop postpartum haemorrhage, particularly in high-risk groups. Tranexamic acid should be used in addition to all usual treatments for the management of HCD including medical, non-surgical, and surgical interventions.

In 2015 and 2016, two systematic reviews identified 12 and 26 trials of tranexamic acid for the prevention of postpartum haemorrhage, respectively [18, 19].

One trial includes 4,079 women explore that, there was no reduction in PPH, however, there was a one quarter reduction in clinically significant PPH [20]. Assess the effectiveness of preventive TXA treatment to decrease PPH in women who underwent CD in one meta-analysis using 50 RCTs. They discovered that giving TA to low-risk individuals likely decreased their chance of experiencing blood loss larger than 1,000 millilitres, and that this reduction was substantially higher in high-risk patients. Additionally, they discovered that TA may lessen the average total blood loss in people at low risk and may lessen it more in patients at high risk. When compared to administration before to skin incision, which resulted in significant reductions in blood loss > 1,000 mL and need for blood transfusion, TXA given after cord clamping was linked to a minor reduction in blood loss > 1,000 mL and had no effect on the need for blood transfusion [21-24].

One of the strengths of our study was that the randomized study provides evidence that temporary uterine packing with the appliance of topical TA as an adjunct to secondary prevention of postpartum haemorrhage could seem to reduce blood loss more effectively than did placebo with oxytocin alone. Another strength of our study is that the temporary uterine packing with the appliance of topical TA easy procedure, easily achievable, no need for classy manoeuvre, to supply a big decrease of blood loss and cases with PPH in cases with haemorrhagic CD.

Potential limitations, first, the main weakness of this randomized, controlled study is its open label, unblinded character. Therefore, the results are in danger of bias. We select this protocol to enable the medical team ready to know the drug given to the patient during this emergent situation. However, centralized randomization and strict data concealment were followed.

A second limitation is that the planning of this study wasn't powered to point out decreases during several invasive procedures, which are the most aim of management. Nevertheless, we observed a trend toward a decrease in the rate of surgical procedures. From this attitude, the study produced encouraging data that support the necessity for further work, like large sample size, multicentral, power enough to explore the efficacy of temporary uterine packing with topical tranexamic acid in reducing maternal morbidity and mortality in cases with haemorrhagic CD.

CONCLUSIONS

This study is the first to demonstrate that uterine packing combined with topical tranexamic acid applied at the placenta bed, appeared to be more effectively reduce blood loss than did placebo during haemorrhagic CD.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

All authors contributed equally to this work.

Funding

None.

Study registration

We prospectively filed the study at clinicaltrials.gov (NCT03778242): https://clinicaltrials.gov/ct2/show/NCT03778242.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

All study procedures were carried out according to the Declaration of Helsinki, and the study was approved by the institutional ethical committee. The study protocol was approved by the Ethics Committee of Aswan University Faculty of Medicine (Aswu/276/7/18).

Informed consent

All patients signed an informed consent.

Data sharing

Data are available under reasonable request to the corresponding author.

REFERENCES

1. Main EK, Goffman D, Scavone BM, Low LK, Bingham D, Fontaine PL, et al. National Partnership for Maternal Safety: Consensus Bundle on Obstetric Hemorrhage. Obstet Gynecol. 2015;126(1):155-62. doi: 10.1097/AOG.0000000000000869.
2. Kandil M. The Skyrocketing rate of cesarean section in Egypt. Glob Drugs Therap. 2018;3(4). doi: 10.15761/GDT.1000153.
3. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum hemorrhage (WOMAN): an international, randomized, double-blind, placebo-controlled trial. Lancet. 2017;389(10084):2105-16. doi: 10.1016/S0140-6736(17)30638-4.
4. Dilla AJ, Waters JH, Yazer MH. Clinical validation of risk stratification criteria for peripartum hemorrhage. ObstetGynecol. 2013;122(1):120-6. doi: 10.1097/AOG.0b013e3182941c78.
5. Primm AN. Fibrinolysis, Antifibrinolytic Agents, and Perioperative Considerations. Essentials of Blood Product Management in Anesthesia Practice. 2021:37-49.
6. Li B, Miners A, Shakur H, Roberts I; WOMAN Trial Collaborators. Tranexamic acid for treatment of women with post-partum hemorrhage in Nigeria and Pakistan: a cost-effectiveness analysis of data from the WOMAN trial. Lancet Glob Health. 2018;6(2):e222-8. doi: 10.1016/S2214-109X (17)30467-9.
7. Jia J. Combined use of intravenous and topical tranexamic acid in patients aged over 70 years old undergoing total hip arthroplasty. J Orthop Surg Res. 2019;14(1):345. doi: 10.1186/s13018-019-1384-6.
8. Lechien A, Faraoni D, Van der Linden P. Effective tranexamic acid concentration for 95% inhibition of tissue-type plasminogen activator-induced hyperfibrinolysis in full-term pregnant women: a prospective interventional study. Blood Coagula Fibrinolysis. 2021;32(3):186-93. doi: 10.1097/MBC.0000000000001015.
9. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials. BMC Med. 2010;8:18.doi: 10.1186/1741-7015-8-18.
10. Vogel JP, Oladapo OT, Dowswell T, Gülmezoglu AM. Updated WHO recommendation on intravenous tranexamic acid for the treatment of post-partum haemorrhage. Lancet Glob Health. 2018;6(1):e18-9. doi: 10.1016/S2214-109X(17)30428-X.
11. Shakur H, Beaumont D, Pavord S, Gayet-Ageron A, Ker K, Mousa HA. Antifibrinolytic drugs for treating primary postpartum haemorrhage. Cochrane Database Syst Rev. 2018;2:CD012964. doi: 10.1002/14651858.CD012964.
12. Xu J, Gao W, Ju Y. Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomization trial. Arch Gynecol Obstet. 2013;287:463-8. doi: 10.1007/s00404-012-2593-y.
13. Zargar M, Nikbakht R, Ahmadi M. The Effect of Tranexamic Acid on Preventing Post-partum Hemorrhage Due to Uterine Atony: A Triple-blind Randomized Clinical Trial. Curr Clin Pharmacol. 2018;13(2):136-9. doi: 10.2174/1574884713666180507101002.
14. Sekhavat L, Tabatabaii A, Dalili M, Farajkhoda T, Tafti AD. Efficacy of tranexamic acid in reducing blood loss after cesarean section. J Matern Fetal Neonatal Med. 2009;22(1):72-5. doi: 10.1080/14767050802353580.
15. Ducloy-Bouthors AS, Jude B, Duhamel A, Broisin F, Huissoud C, Keita-Meyer H, et al. High-dose tranexamic acid reduces blood loss in postpartum haemorrhage. Crit Care. 2011;15(2):R117. doi: 10.1186/cc10143.
16. Ducloy-Bouthors AS, Duhamel A, Kipnis E, Tournoys A, Prado-Dupont A, Elkalioubie A, et al. Postpartum haemorrhage related early

increase in D-dimers is inhibited by tranexamic acid: haemostasis parameters of a randomized controlled open labelled trial. Br J Anaesth. 2016;116(5):641-8. doi: 10.1093/bja/aew021.

17. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron FX, Roberts I; Antifibrinolytic Trials Collaboration. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet. 2018;391(10116):125-32. doi: 10.1016/S0140-6736(17)32455-8.
18. Ker K, Shakur H, Roberts I. Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials. BJOG. 2016;123(11):1745-52. doi: 10.1111/1471-0528.14267.
19. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum haemorrhage. Cochrane Database Syst Rev. 2015;(6):CD007872. doi: 10.1002/14651858.CD007872.pub3.
20. Sentilhes L, Winer N, Azria E, Sénat MV, Le Ray C, Vardon D, et al. Tranexamic Acid for the Prevention of Blood Loss after Vaginal Delivery. N Engl J Med. 2018;379(8):731-42. doi: 10.1056/NEJMoa1800942.
21. Visconti F, Quaresima P, Rania E, Palumbo AR, Micieli M, Zullo F, et al. Difficult caesarean section: A literature review. Eur J Obstet Gynecol Reprod Biol. 2020;246:72-8. doi: 10.1016/j.ejogrb.2019.12.026.
22. Cheema HA, Ahmad AB, Ehsan M, Shahid A, Ayyan M, Azeem S, et al. Tranexamic acid for the prevention of blood loss after cesarean section: an updated systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol MFM. 2023;5(8):101049. doi: 10.1016/j.ajogmf.2023.101049.
23. Saccone G, Nazzaro G, Miranda M, Gragnano E, Locci M. Use of tranexamic acid at the time of delivery. Ital J Gynaecol Obstet. 2024;36(1)70-6. doi: 10.36129/jog.2023.107.
24. Shady NW, Farouk HA, Sallam HF. The effect of intravenous (IV) tranexamic acid plus buccal misoprostol on blood loss during and after cesarean delivery: a randomized double-blind study. Ital J Gynaecol Obstet. 2022;34(1):35-42. doi: 10.36129/jog.34.01.06.