

TRANEXAMIC ACID PLUS OXYTOCIN PROPHYLAXIS IN REDUCING BLOOD LOSS AND PREVENTING POSTPARTUM HEMORRHAGE DURING CESAREAN SECTION

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ABSTRACT

Objective: To find the efficacy of prophylactic tranexamic acid and Oxytocin in preventing postpartum hemorrhage during cesarean section as compared to uterotonic alone.

Materials and Methods: A randomized clinical trial that was single-center, double-blind placebo-controlled was conducted in the Department of Obstetrics and Gynaecology, Khyber Teaching Hospital, between 1st July 2021 to 31st December 2021. A total of 280 patients undergoing cesarean section were randomized to group A receiving tranexamic acid and uterotonic (oxytocin) and control group B having placebo and uterotonic(oxytocin) within three minutes of delivery of the baby. Blood loss after the cesarean section was calculated from blood volume and pre and post-operative hematocrit. The main outcome of the study was to establish the efficacy of tranexamic acid in decreasing the number of women with calculated estimated blood loss > 1000 ml. Secondary outcomes included differences in mean calculated blood loss, peripartum change in hematocrit, and postoperative blood transfusion in both groups. Data was analyzed by statistical package for social sciences(SPSS) version 23.0. Mean and standard deviation were calculated for numerical data and percentages, and frequencies for categorical variables. To see the effects of modifiers, post stratified t-test was used. P-value <0.05 was considered statistically significant.

Results: Both the groups were comparable for maternal age (28.4 ± 4.5 , 28.8 ± 4.9) gestational age (37.71 ± 1.61 , 37.70 ± 1.56), and parity (1.79 ± 1.5 , 2 ± 1.6). Tranexamic acid significantly reduced the number of women with estimated calculated blood loss of > 1000 ml in group A to 10%(n=14) as compared to 18.6%(n=26) in group B (p-value<0.005). Secondary outcomes like mean calculated blood loss and postoperative blood transfusion were statistically insignificant between the two groups.

Conclusion: Pregnant women who received prophylactic uterotonic agents and tranexamic acid treatment within three minutes of cesarean delivery, resulted in a lesser number of women with calculated estimated blood loss > 1000 ml than placebo.

Key Words: Primary postpartum hemorrhage, Tranexamic acid, Cesarean section, Blood loss.

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INTRODUCTION

Primary post-partum hemorrhage remains the leading cause of maternal mortality and morbidity. Despite improvements in antenatal and obstetric care. It has traditionally been defined as blood loss of > 500ml after vaginal delivery and > 1000ml during cesarean delivery of the baby.^{1, 2} As per the World Health Organization 2012 report, nearly 100000 mothers die every year because of PPH and 99% of these deaths occur in middle,

low-income countries. In Pakistan, the prevalence of PPH is 34% leading to considerable morbidity and mortality of parturient mothers.³

The practice of cesarean delivery is increasing day by day with rates rising to 25-30%.⁴ Globally, studies have shown that blood loss during vaginal delivery is considerably lesser as compared to cesarean section.⁵ French studies showed that cesarean deliveries were associated with > 1000 mL blood loss in 11.6% of cases.⁶

World Health Organization (WHO) recommends prophylactic uterotonics such as oxytocin to prevent PPH. But PPH is unpredictable and the majority of the cases occur in the absence of risk factors. Uterotonic(oxytocin) alone might not effectively prevent PPH, secondary to other causes.⁷

Following the results from the World Maternal Antifibrinolytic Trial (WOMAN Trial) which established the

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therapeutic efficacy of tranexamic acid in reducing bleeding-related mortality in parturient mothers, the WHO has recommended the use of Tranexamic Acid (TXA) for the treatment of PPH.⁵

An antifibrinolytic drug, tranexamic acid acts on plasminogen molecules by blocking their lysine binding sites. After the delivery of the baby, tranexamic acid arrests bleeding by stopping the fibrinolytic system that is activated during placental separation.^{6,7} During placental delivery fibrinolytic system is activated, and the effect persists for 6-10 hours postnatally, causing more bleeding that can be dealt with effectively by administering tranexamic acid. TXA not only reduces postpartum blood loss but also the need for blood transfusion and anemia.⁸ The Royal College of Obstetricians and Gynaecologists currently recommends considering the use of prophylactic TXA only in women at high risk for PPH undergoing cesarean section (CS).⁹ However, there is limited evidence for definitive recommendations of prophylactic TXA use in women of all risk profiles undergoing cesarean section.¹⁰ Further high-quality randomized trials are required to confirm the safety and efficacy of TXA in preventing PPH in all women undergoing cesarean section.

Our study aim was to evaluate the effectiveness of prophylactic tranexamic acid administration along with conventional oxytocin in reducing calculated blood loss during cesarean section. Locally no such randomized clinical trial, using a validated method for measuring postpartum blood loss has been conducted. We hypothesize that tranexamic acid could be used in conjunction with traditional uterotonic drugs for preventing PPH in women undergoing cesarean delivery. Our study will help in yielding local data on the prophylactic efficacy of tranexamic acid in reducing postpartum blood loss & update the current guidelines on preventing PPH.

MATERIALS AND METHODS

A randomized control clinical trial was conducted in the Department of Obstetrics and Gynecology, Khyber teaching hospital between 1st July 2021-31 December 2021, after getting approval from the research & ethical review board (814/DME/KMC). A total of 405 patients were enrolled by the non-probability consecutive sampling method. The sample size was calculated using WHO sample size calculator version 2.0 taking 28.0 ± 5.53 mL blood loss in the tranexamic acid group vs. 37.12 ± 8.97 mL in the control group, along with a 95% confidence level of significance with 90% power of the test.¹³ Pregnant women undergoing elective and emergency cesarean section were screened for eligibility by a research assistant who received training from the lead investigator before the start of the study. Study participants were informed that they could withdraw voluntarily from the trial at any time.

Predesigned proformas were filled out for each

patient after taking informed written consent before and after the operation. The proforma included information on age, parity, weight, period of gestation, and an indication of elective and emergency cesarean section. Prenatal and post-natal hemoglobin and hematocrit were also recorded. Women having severe medical disorders, thrombocytopenia, anemia, allergy to tranexamic acid, history of venous thromboembolism, placenta-previa, abruption, and severe pre-eclampsia, failed operative vaginal delivery, retained the second twin were excluded from the study. Eligible patients, who consented were randomly allocated into two groups of 140 each by lottery method. Study group A(n=140) received 1 gm tranexamic acid (available at hospital pharmacy free of cost) intravenously within three minutes of delivery of the baby along with routine 10 IU intravenous oxytocin and control group B(n=140) received routine intravenous 10 IU oxytocin and placebo(10ml normal saline intravenously). The nurse practitioner supervised the randomization process. The anesthetist was instructed to administer oxytocin and tranexamic acid or normal saline/placebo depending on group allocation, followed by two hours of oxytocin infusion as per WHO protocol. Neither the lead investigator and operating obstetrician nor the patient knew about the group allocation. Post-operatively women were transferred from the operating theatre to the post-anesthesia recovery unit where the parturient mothers stayed for one hour before shifting to the postnatal chamber. Preoperative hematocrit was the hematocrit measured within \leq seven days before delivery. Hematocrit obtained by venous blood sampling on postpartum day 2 was labeled as postoperative hematocrit. Any potential side effects of TXA were recorded during the patient's stay in the hospital's post-natal ward.

The main outcome of the study was to find the percentage of the patient in the study and placebo group with a calculated blood loss < 1000 mL using a validated formula. The imprecision of blood loss estimation during cesarean deliveries using a gravimetric method like pre-weighed pads, suction container volume, and visual estimation, lead us to search for some other validated methods to calculate blood loss. The amount of blood loss in milliliters was calculated by the formula used in a French trial, as calculated estimated blood loss = estimated blood volume \times (preoperative hematocrit-postoperative hematocrit/preoperative hematocrit (where estimated blood volume (mL) = weight (kg) \times 85).¹⁴ Secondary outcomes included peripartum change in hematocrit, mean calculated blood loss & postoperative blood transfusion in both groups. Data was analyzed by statistical package for social sciences (SPSS) version-23. Frequencies and percentages were calculated for categorical variables, and mean and standard deviation were calculated for numerical data. To see the effects of modifiers, post stratified t-test was used. P-value < 0.05 was considered statistically significant.

RESULTS

Subject characteristics were similar in both groups (statistically insignificant differences between the two groups). The mean age was 28.4 ± 4.5 in Group A and 28.8 ± 4.9 in Group B. Mean parity and gestational age were 1.79 ± 1.5 & 37.71 ± 1.61 respectively in Group A. While group B showed mean parity of 2 ± 1.6 and gestational age of 37.70 ± 1.56 . Tranexamic acid significantly reduced the number of women with estimated calculated blood loss of > 1000 ml in group A (10%) as compared to 18.6% ($n=26$) in group B ($p\text{-value} < 0.005$). Blood transfusion on Day 2 was seen in 14 patients in tranexamic acid group A as compared to 20 patients in placebo group B. Mean Calculated estimated blood loss in Tranexamic group A was 626.8 ± 472 ml and 699 ± 489 ml in placebo group B with a mean difference of 73 ml. Peripartum change in hematocrit was statistically insignificant.

DISCUSSION

Globally, cesarean section rates are soaring day by day ranging from 25-40%.² Obstetric hemorrhage is one of the most commonly occurring complications with significant maternal mortality and morbidity.^{3, 4}

The WOMAN trial endorsed the effective role of TXA in treating PPH, during vaginal delivery & cesarean section^{5, 6, 11}. Sixteen randomized trials have shown decreased blood loss in pregnant women who receive prophylactic tranexamic acid, during elective cesarean section, excluding emergency cesarean where blood loss is significantly higher.^{12, 13, 14}

Our study showed that 10% of patients in the study group had postpartum blood loss of > 1000 ml as compared to 18.6% in the control group. These results are somewhat comparable to RCT in Karachi which showed a 10% incidence of postpartum hemorrhage in the study group as compared to 33% in the control group, despite of the difference in trial methodology.¹⁵ A descriptive study in Peshawar endorsed the prophylactic efficacy of TXA

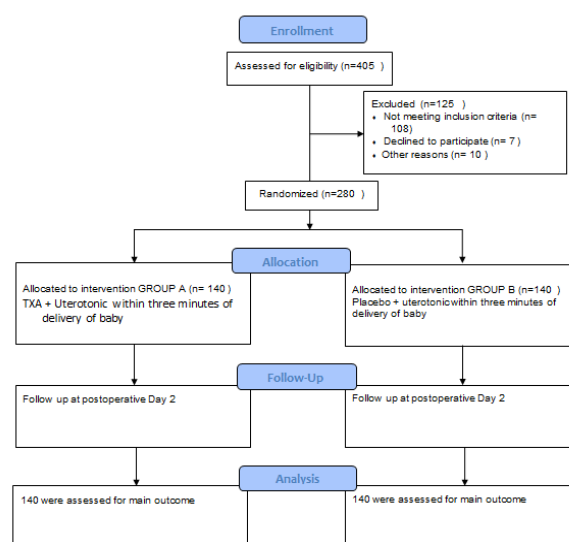


Fig 1: Randomization & Treatment: CONSORT Flow Diagram

Table 1: Baseline characteristics of patients (N=280)

Patient Characteristics	Group A (N=140)	Group B (N=140)	P-value
Mean Age \pm SD	28.4 ± 4.5	28.8 ± 4.9	0.510
Mean Parity \pm SD	1.79 ± 1.5	2 ± 1.6	0.168
Mean Gestational age in weeks \pm SD	37.71 ± 1.61	37.70 ± 1.56	0.941
Mean Weight \pm SD	78.9 ± 11	78.7 ± 13	0.913
Type of caesarean section			
Emergency	60	65	
Elective	80	75	

Table 2 Clinical Outcomes of Trial

Clinical Outcomes	Group A (N=140)	Group B (N=140)	P-value
Main Outcome			
PPH=No Of Patients/Total number Calculated Blood Loss > 1000 ml	14(10%)	26(18.6%)	0.040
Secondary Outcomes			
Mean Calculated blood loss in ml \pm SD	626.8 ± 472	699 ± 489	0.210
Mean peripartum change in hematocrit \pm SD	3.30 ± 2.64	3.38 ± 2.68	0.802
Additional Uterotonics for excessive bleeding-- no/total no.(%)	3(2%)	7(5%)	0.198
Blood transfusion by day 2	14(10%)	20(14%)	0.272

during cesarean section for breech presentation, but the study design and gravimetric method of blood loss calculation differed significantly from our study.¹⁶ A Turkish RCT also endorsed our study results by showing that 2.1% of patients in TXA had postpartum blood loss >1000ml as compared to 5.8% in the placebo group.¹⁷

It is important to ascertain the methodology used in different trials for assessing postpartum blood loss during & after cesarean section.^{17,18} Gravimetric methods like suction container volume or weighted pads for measuring postpartum blood loss are imprecise and prone to subjective bias.²⁰⁻²²

To circumvent such methodological flaws, we used a validated formula used in the French trial, for assessing blood loss. The reduction in the proportion of patients having blood loss of >1000ml in the study versus the control group in the TRAAP-2 trial (26.7% vs. 31.5%) is somewhat comparable to our study (10% vs. 18.6%) despite our small sample size. Both studies showed a reduced need for additional uterotonic drugs and blood transfusion in the study versus the control group.¹⁸

In contrast to our study, a mean difference of 141.6 ml between the study and control group was published in the meta-analysis by Wang et al.¹⁹ Two Iranian studies showed a significant difference (132.7ml) in mean blood loss between tranexamic and control groups but used gravimetric methods to calculate blood loss.²⁰ Similar to these studies, our trial showed that the mean estimated calculated blood loss was 626.8 ± 472 ml in tranexamic acid group A as compared to 699 ± 489 ml in placebo or control group B, with a mean difference of 73 ml. Although our mean difference in blood loss between the two groups is not statistically significant as reported in other studies possibly because of methodological differences (timing and dosage of TXA, type of cesarean section) and sample size variation. Nevertheless, the proportion of women undergoing cesarean delivery with calculated blood loss of more than 1000 ml, the need for blood transfusion, and supplementary uterotonic drugs are more or less comparable to the TRAAP-2 trial, employing a similar trial methodology.

The strength of our study is that it was a randomized clinical trial using a validated method to calculate postpartum blood loss. Our trial will contribute to the growing body of research suggesting the use of tranexamic acid along with time-tested uterotonic agents immediately after childbirth to prevent postpartum hemorrhage. Several limitations of the study need to be acknowledged which include the exclusion of anemic and high-risk obstetric women and the inclusion of emergency cesarean section in the trial. Extrapolation from single-center & small sample-sized studies would be possible only if multi-center and larger sample-size-driven studies are planned and executed across the globe for unified consensus and rec-

ommendation.

CONCLUSIONS

Prophylactic TXA & oxytocin should be considered in women undergoing cesarean section to reduce blood loss. Further studies are required to validate the role of TXA in women at high risk of PPH. Ideal dosing and timing of TXA administration, its cost-effectiveness, and adverse effect profile remain important associations to be explored in the future.

REFERENCES

1. Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323–33.
2. WHO Recommendations for the Prevention and Treatment of Postpartum Haemorrhage. WHO guidelines approved by the guidelines review committee. Geneva: World Health Organization; 2012.
3. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patient with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet*. 2010;376:23–32.
4. Afridi, F., Zubaida Akhtar, Ayesha Afridi, Qudsia Qazi, & Jamila M Naib. (2022). determining the indications of c-section based on WHO Robson classification—an experience in a tertiary care hospital in Peshawar. *Journal of Medical Sciences*, 30(02)
5. WHO Recommendation on Tranexamic Acid for the Treatment of Postpartum Haemorrhage. WHO guidelines approved by the guidelines review committee. Geneva 2017.
6. Sentilhes L, Merlot B, Madar H, Brun S, Sztark F, Deneux-Tharaux C. Postpartum hemorrhage: prevention and treatment. *Expert Rev Hematol*. 2016;9:1043–1061. DOI: 10.1080/17474086.2016.1245135.
7. Misme H, Dupont C, Cortet M, Rudigoz RC, Huissoud C. Distribution of blood loss during vaginal delivery and cesarean section. *J Gynecol Obstet Biol Reprod*. 2016;45:71–79. DOI: 10.1016/j.jgyn.2015.01.004
8. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: a systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054.
9. Sentilhes L, Lasocki S, Ducloy-Bouthors AS, Deruelle P, Perrotin F, Goffinet F, et al. Tranexamic acid for the prevention and treatment of post-partum hemorrhage. *Brit J Anaesth*. 2015;114:576–587. doi: 10.1093/bja/aeu448.
10. Alam A, Choi S. Prophylactic use of tranexamic acid for postpartum bleeding outcomes: a systematic review and meta-analysis of randomized controlled trials. *Transfus Med Rev*. 2015;29(4):231–41
11. WOMAN Trial Collaborators. Effect of early tranexamic acid administration on mortality, hysterectomy, and other co-morbidities in women with post-partum hemorrhage (WOMAN): an international, randomized, double-blind, placebo-controlled trial. *Lancet* 2017;389:2105-16.

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;287:463-468. DOI: 10.1007/s00404-012-2593-y.
13. Sekhawat L, Tabtabai A, Dalili M, Farajkhoda T, Tafti DA. Efficacy of tranexamic acid in reducing blood loss after cesarean section. *Journal of Maternal-Fetal and neonatal medicine*, January 2009; 22(1):72-75
14. Sentilhes L, Winer N, Azria E, Sénat MV, Le Ray C, Vardon D, for the Groupe de Recherche en Obstétrique et Gynécologie (GROG) et al. Tranexamic acid for the prevention of blood loss after vaginal delivery. *N Engl J Med*. 2018;379:731-742.
15. Afshan Shahid and Ayesha Khan. Tranexamic Acid in Decreasing Blood Loss During and after Caesarean Section. *Journal of the College of Physicians and Surgeons Pakistan* 2013, Vol. 23 (7): 459-462
16. Bibi S, Syed W, Khan AA. Efficacy of Tranexamic Acid in Reducing the Blood Loss During Cesarean Section in Primigravida Patients with Breech Presentation. *Journal of Gandhara Medical and Dental Science*. 2022 Apr 6;9(2):3-7.
17. Kemal Gungorduk, Gokhan Yildirim, Osman Asicioğlu, Ozgu Celikkol Gungorduk, Sinem Sudolmus, Cemal Ark. Efficacy of Intravenous Tranexamic Acid in Reducing Blood Loss after Elective Cesarean Section: A Prospective, Randomized, Double-Blind, Placebo-Controlled Study. *Am J Perinatol* 2011; 28(3): 233-240 DOI: 10.1055/s-0030-1268238
18. L.Sentilhes et al. Tranexamic Acid for the Prevention of Blood Loss after Cesarean Delivery. *N Engl J Med* 2021; 384:1623-1634
19. Yongjun Wang, Siyuan Liu, Li He. Prophylactic use of tranexamic acid reduces blood loss and transfusion requirements in patients undergoing cesarean section: A meta-analysis. *J Obstet Gynaecol Res*. 2019 Aug;45(8):1562-1575.
20. Naeiji Z, Delshadiyan N, Saleh S, Moridi A, Rahmati N, Fathi M. Prophylactic use of tranexamic acid for decreasing the blood loss in elective cesarean section: A placebo-controlled randomized clinical trial. *J Gynecol Obstet Hum Reprod*. 2021 Jan;50(1):101973.
21. Urooj H, Shah M, Bukhari B, Rahim R. Comparison of the therapeutic effectiveness of oxytocin versus oxytocin plus tranexamic acid in the prevention of post-partum hemorrhage. *journal of postgraduate medical institute*. 2021 Jun 30;35(2):80-4.
22. Bibi S, Syed W, Khan AA. Efficacy of Tranexamic Acid in Reducing the Blood Loss During Cesarean Section in Primigravida Patients with Breech Presentation. *Journal of Gandhara Medical and Dental Science*. 2022 Apr 6;9(2):3-7.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Bangash AG: Concept, Critical appraisal, and Discussion Writing

Riaz S: Data collection, compilation of results, formatting of the article

Akhtar Z: Data Collection, Manuscript writing

Naz T: Manuscript Writing, Bibliography

Naib JM: Supervision, Critical appraisal

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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