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Study Of Prevention Of Post-Partum Haemorrhage After Caesarean Section With Use Of Tranexamic Acid.

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Abstract

Postpartum haemorrhage (PPH) is one of the leading cause of maternal mortality and morbidity. Haemostatic imbalance due to tissue plasminogen activator (tPA) release, subsequently leading to hyper fibrinolysis is said to have an important role in the pathogenesis of PPH. Antifibrinolytics such as tranexamic acid (TXA) is commonly used in haemorrhagic disorders with the above pathogenesis. Thus TXA use is a part of PPH treatment recommended, and recently, studies have assessed the effectiveness of prophylactic use of TXA in reducing the incidence and severity of PPH. This prospective comparative study was conducted in Dr. Vitthalrao Vikhe Patil Foundation's Medical College and Memorial Hospital, Ahmednagar, after permission from ethical committee, in the period from January 2021 to January 2022 and included a total of 200 pregnant women with a previous caesarean section (para1-CS), who were randomized into two groups of 100 pregnant women each and who underwent elective caesarean section under spinal anaesthesia. The amount of blood loss was significantly lower in the study group than in the control group (416.1289.95 and 688.68134.77, respectively). Also, the 24-h postoperative haemoglobin was significantly higher in the study group (11,660.79 mg/dl) compared to the control group (10,531.07 mg/dl), and the 24-h postoperative hematocrit was significantly higher in the study group (34.992.40) compared to the control (31.623.22). Prophylactic administration of tranexamic acid reduces intraoperative and postoperative bleeding from cesarean sections and the incidence of postpartum haemorrhage.

Keywords: Postpartum haemorrhage, caesarean section**,** tranexamic acid.

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INTRODUCTION

Postpartum haemorrhage (PPH) is a leading cause of maternal morbidity and mortality. PPH is responsible for around 25% of maternal mortality worldwide, 143,000 deaths per year, reaching up to 60% in some developing countries (Alam et al. 2017; Sentilhes et al. 2020). PPH has been characterized as blood loss of more than 500 ml after a vaginal delivery and more than 1000 ml after a lower segment cesarean section. However, the ACOG has proposed a total PPH blood loss >= to 1000 mL or blood loss associated with signs or symptoms of hypovolaemia in the first 24 h after delivery, regardless of delivery route (Committee on Practice Bulletins-Obstetrics 2017). B. shock, acute renal failure, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), hysterectomy and fertility loss (Committeeon Practice Bulletins-Obstetrics 2017 Solomon et al.2012).TXA is a synthetic lysine analogue that competitively inhibits the conversion of plasminogen to plasmin . It prevents the proteolytic effect of plasmin on fibrin threads thus resulting in inhibition of fibrinolysis and stabilization of existing blood clots, reducing the risk of bleeding (Pabinger et al. 2017). TXA has been found to reduce intra- and postoperative bleeding such as cardiac surgery, scoliosis corrective surgery, liver transplants, prostatectomies, arthroplasty, and urinary tract surgeries (Pabinger et al. 2017). The use of TXA has been shown to be beneficial in trauma patients as it reduces the risk of bleeding and the need for blood transfusion when used within 3 h post injury (Roberts et al. 2013). Extensive guidelines have suggested the use of uterotonic drugs in obstetric procedures. In contrast, hemostatic agents are not routinely used as a first-line intervention for PPH (Neb et al. 2017). Our study objective was to evaluate the efficacy of tranexamic acid in reducing blood loss during and after cesarean sections in the lower segments and reducing the risk of postpartum haemorrhage.

MATERIAL AND METHODS

This prospective comparative study was conducted in Dr. Vitthalrao Vikhe Patil Foundation's Medical College and Memorial Hospital, Ahmednagar, after permission from ethical committee, in the period from January 2021 to January 2022 and included a total of 200 pregnant women with a previous caesarean section (para1-CS), who were randomized into two groups of 100 pregnant women each and who underwent elective caesarean section under spinal anaesthesia. The study group included 100 pregnant women who received 2 g tranexamic acid (TXA) with induction of spinal anaesthesia plus 10 IU oxytocin at delivery of the baby; the control group received only 10 I.U. oxytocin. Both groups were compared for the amount of blood loss, which was calculated mathematically.

Inclusion Criteria

Singleton pregnancy, P1-CS (previous section after failed consent to attempt work after CS), age 18 to 39 at time of consent, term 37 weeks gestation, elective CS, spinal anaesthesia, and written informed consent.

Exclusion Criteria

Failed spinal anaesthesia (more than 2 attempts), multiple pregnancy, grand multipara, placenta previa, abruptio placentae, polyhydramnios, fever, rupture of the membranes, patient on anticoagulants or antiplatelet agents, eclampsia or preeclampsia in the current pregnancy, history of cardiovascular diseases such as ischemic heart disease or myocardial infarction, repaired or unrepaired congenital heart disease, unstable arrhythmia or congestive heart failure, or the patient had a contraindication to TXA administration as a history of venous thromboembolism, active thromboembolic disease, thrombophilia (eg, protein C deficiency) .), allergy to TXA, pre-existing hematuria or history of renal insufficiency.

A thorough medical history with careful examination (general and obstetric) and complete preoperative investigations (Rh typing, complete blood count, activated partial thromboplastin time, prothrombin time and concentration, liver and renal function tests) were performed on all patients. All patients were fasted 8 h preoperatively, in the induction room, a G18 gauge IV cannula was inserted and monitors were attached, pulse oximetry, electrocardiogram and non-invasive arterial blood pressure. All patients were continuously monitored during the caesarean section. The routine preoperative fluid preload was in the form of 1L of Ringer's solution over 30 min. If spinal anaesthesia was unsuccessful, general anaesthesia was used instead, and the patient was excluded from the study.

- Group A (study group) included (100) pregnant women who received 2 g tranexamic acid (20 mL volume) diluted in 50 mL normal saline 0.9% (70 mL volume) as a slow IV infusion with induction of spinal anaesthesia. 10 IU of oxytocin was given immediately after the baby was born.

- Group B (control group) included (100) pregnant women who received 20 mL of 0.9% saline diluted in 50 mL of normal saline 0.9% (70 mL volume) with induction of spinal anaesthesia and 10 IU of oxytocin immediately after birth of the baby.

The primary outcome of our study is the blood loss amount during and after CS, estimated by calculating blood loss using standard equations using preoperative and 24-h postoperative hematocrit as follows (Butterworth et al. 2013).

Statistical Analysis

Data were collected, edited, coded and entered into Med-Calc software (version 19.1.0; MedCalc software, Ostend, Belgium) and Social Science Statistics Package, version 25.0 (SPSS Inc., Chicago, IL, USA).). The quantitative data were presented as means, standard deviations and ranges. In addition, qualitative variables were presented as numbers and percentages.

Sample Size

Using the PASS program version 15, setting the alpha error to 5% and the power to 90%, result of a previous study by Salem et al. (Salem et al. 2016) showed that the incidence of postpartum haemorrhage was 24.9% in the tranexamic group and 59% in the placebo group; On this basis, the required sample is 200 pregnant women, each group consists of 100 participants.

RESULTS

There is no statistically significant difference between the two groups in terms of demographics. There was a statistically significant difference in blood loss between the two groups (p-value < 0.001); blood loss in the study group (with TXA) was less than in the control group (416.1289.95 and 688.68134.77, respectively). The mean decrease in 24-h postoperative hematocrit and haemoglobin levels was significantly less in the TXA group than in the control group. The 24-hour postoperative haemoglobin was significantly higher in the study group (11,660.79 mg/dl) compared to the control group (10,531.07 mg/dl), and the 24-hour postoperative hematocrit was significantly higher in the study group (34,992 .40) compared to the control (31.623.22).

Table 1: Patient Demographics.

	Age (mean = SD)	Weight (mean = SD)
Study group (n=100)	27.60 = 4.03	71.28 = 6.15
Placebo (n=100)	26.88 = 4.55	71.76 = 6.02

Table 2. Total Volume of RBC lost and Amount of Blood Loss

	Vol. of RBC lost		Total Blood Loss	
	Range	Mean = SD	Range	Mean = SD
Study Group (n=100)	82-193	138.9 = 29.73	250ml-575ml	416.12=89.95
Control group (n=100)	131- 325	230.92=45.73	393ml-975ml	688.68=134.77

DISCUSSION

TXA is a powerful antifibrinolytic that prevents binding of plasminogen and plasmin to fibrin molecules. TXA has been used in various medical and surgical settings to reduce bleeding and the need for blood transfusion (Pabinger et al. 2017). The clinical randomization of an antifibrinolytic in Significant Haemorrhage (CRASH-2) study, in which approximately 20,000 patients with acute traumatic bleeding participated, showed that the early administration of TXA within 3Fahmy et al. Injury significantly reduces mortality from bleeding (Roberts et al. 2013). The World Maternal Antifibrinolytic (WOMAN) study, conducted in patients with established PPH, showed results similar to the (CRASH-2) study in the obstetric context; They found that administration of TXA within 3 hours after PPH to treat hyperfibrinolysis reduced blood loss and mortality in bleeding patients (Shakur et al. 2017). In both studies, CRASH-2 and WOMAN, administration of TXA beyond 3 hours of trauma or delivery was associated with an increase in mortality compared to placebo (Lier et al. 2019). Activation of the fibrinolytic system has been demonstrated during the labor process. Elevated levels of tissue plasminogen activator (tPA) and D-dimer are indicators of activation of fibrinolysis (Ducloy-Bouthorset al. 2018)

When the placenta separates, there is a rapid reduction in the level of infibrinogen, with the production of fibrin threads leading to a reduction in the level of plasminogen, which in turn stimulates the fibrinolytic system (Ducloy-Bouthors et al. 2018). The endothelium produces more tPA and expresses more thrombomodulin receptors that interact with the resulting thrombin, which activates the coagulation system leading to protein C activation (Pacheco et al. 2019). Protein C activation leads to inhibition of plasminogen activator inhibitor 1 (PAI-1) with unrestricted activity of tPA. This results in increased fibrinolysis with rapid destruction of established fibrin clots. Therefore, the use of TXA appears to reduce blood loss (Pacheco et al. 2019).

In cases of severe PPH, shock leading to tissue hypoxia, hypoperfusion, and acidosis can result in excess release of tissue factor from damaged cells, causing a disturbance in the balance between the coagulation and fibrinolytic systems thus worsening state of hyperfibrinolysis. Inhibition of hyperfibrinolysis by TXA restores the balance of the hemostatic system (Pabinger et al. 2017).

Our study was included 200 pregnant women enrolled for elective CS, randomly divided into two groups; one group received prophylactic 2 g TXA with induction of anaesthesia and 10 units of oxytocin after the baby was born, while the control group received placebo and 10 units of oxytocin. There was a statistically significant difference in blood loss between the two groups (p-value < 0.00)1; blood loss in the study group (TXA) was less than in the control group (416.1289.95 and 688.68134.77, respectively). The mean decrease in 24-h postoperative hematocrit and hemoglobin levels was significantly lower in the TXA group than in the control group. The 24-ha postoperative haemoglobin was significantly higher in the study group (11,660.79 mg/dl) compared to the control group (10,531.07 mg/dl), and the 24-hour postoperative hematocrit was significantly higher in the study group (34,992.40). for control (31.623.22). Thus, TXA reduces intraoperative and postoperative bleeding. Traditional methods of assessing blood loss during and after CS are not easy and inaccurate, since blood is mixed with amniotic fluid in the suction reservoir. Estimating blood loss after CS by inspecting vaginally soaked wipes or even by weighing is a subjective method; he tends to overestimate or underestimate blood loss (Kandappan and Anand 2016). Our study estimated the blood loss mathematically using preoperative and 24-h postoperative haematocrit values.

We chose this method as a quantitative objective measure for estimating blood loss. Similar postoperative results of the current study were observed in a prospective randomized study by Kandappan and B. This study shows that a single intravenous dose of TXA (15 mg/kg body weight) given intraoperative significantly decreases blood loss both during and after caesarean section in the lower segment in multigravida pregnant women and its use was not associated with serious side effects (Kandappanand Anand 2016). However, this study used subjective methods to estimate blood loss. Blood was collected via a suction catheter, the volume was weighed, and soaked gauze and pads were also weighed using an electronic balance. Another prospective randomized study supporting the results of our current study was published by Xu et al. The study was conducted on 174 pregnant women undergoing CS. A dose of 10 mg/kg TXA was given to 88 pregnant women just prior to CS, who were compared to 86 others who received placebo. Blood loss from placental separation to 2 h postpartum was significantly

reduced in the TXA study group than in the control group. But, the amount of blood loss was collected subjectively through a suction container, soaked gauze, wet bandages, and towels (Xu et al. 2013).

Abdel-Aleem et al. pointed to similar results in their prospective randomized study comparing preoperative injection of 1 g TXA in elective caesarean section; the mean total blood loss was significantly less in the TXA group than in the control group. However, they also used a subjective methods of collecting blood losses; the weight of dry towels was subtracted from the weight of wet towels, and the weight of blood was converted to volume using the formula, taking into account that blood is slightly denser than water, so weigh volume of blood = 0.9 (Abdel-Aleem et al 2013). In addition, another study by Sentrk et al. performed on 223 pregnant women registered for caesarean section; half of them received 1 g TXA compared to the placebo group. Blood loss was determined using the following formula by measuring the wet and dry weight of the patient's pads and tampons.

Blood loss volume = wet weight of the pad or tampon− dry weight of the pad or tampon/1.05. Sentrk et al. found that preoperative administration of TXA reduced intraoperative and postoperative blood loss without increasing thromboembolic side effects (Sentrk et al. 2013). Our study revealed only mild side effects of TXA such as hypersensitivity, nausea, vomiting and hypotension that were not statistically significant between the two groups.

Limitations

The study has a few limitations. One of the more notable ones being that a fixed dose of 2g of Tranexamic acid was administered to every patient without considerations for the body weight of the patient. No considerations were made to distinguish between intra-operative bleeding and post-operative bleeding. Other notable risk factors for PPH such as primiplacenta acreta, placenta previa, abruptsio placenta, use of ART regimes, were not considered in the study.

The study did not include methords to acurately measure blood loss greater than 1000ml such as in the case of severe PPH or its further complications. The safety of this drug has been observationally proven in both pregnant and non-pregnat women by older studies hence such considerations to overlook these factors may be made.

CONCLUSION

Use of tranexemic acid phophylactcally reduced the total blood loss during both, the post-operative period as well as the intra-operative period during the caesarean section. A marked reduction was also noted in the incidence of post-partum hemorrhage.

REFERENCES

[1] Abdel-Aleem H, Alhusaini TK, Abdel-Aleem MA, Menoufy M, Gülmezoglu AM (2013) Effectiveness of tranexamic acid on blood loss in patients undergoing elective cesarean section: randomized clinical trial. J Matern Neonatal Med 26(17):1705-1709 [cited 2021 Jan 101

[2] Alam A, Bopardikar A, Au S, Barrett J, Callum J, Kiss A et al (2017) Protocol for a pilot, randomised, double blinded, placebo controlled trial of prophylactic use of tranexamic acid for preventing postpartum hemorrhage (TAPPH-1).

[3] BMJ Open 7(10):1=8

[4] Butterworth J, Mackey DC, Wasnick J (2013) Chapter 51. Fluid Management & Blood Component Therapy. In Morgan & Mikhail's clinical anesthesiology, 5e | AccessMedicine McGraw-Hill Medical [Internet]. [cited 2021 Jan 10].

[5] McGraw-Hill, New York, p 1168

[6] Committee on Practice Bulletins-Obstetrics (2017) Practice bulletin no. 183: postpartum hemorrhage. Obstet Gynecol 130(4)e168- e186.

[7] Ducloy Bouthors A 5, Jeanpierre F, Said 1, Baptiste A.S, Simon E, Lannoy D et al (2018) TRAnexamic acid in hemorrhagic Cesarean section (TRACFS) randomized placebo controlled dose-ranging pharmacobiological ancillary trial: study protocol for a randomized controlled trial. Trials 19(1):1-16.

[8] Kandappan G, Anand B (2016) Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section in multigravida parturients: a case controlled prospective study. J Evid Based Med Health 3(48):2419 2425

[9] Lier H, Maegele M, Shander A (2019) Tranexamic acid for acute hemorrhage: a narrative review of landmark studies and a critical reappraisal of its use over the last decade. Anesth Anal 129(6):1574-1584.

[10] Neb H, Zacharowski K. Meybohm P (2017) Strategies to reduce blood product utilization in obstetric practice. Curr Opin Anaesthesiol 30(3):291-299.

[11] Pabinger I, Fries D, Schöchl H, Streif W, Toller W (2017) Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr129(9-10):303-316. https://doi.org/10.1007/s00508-017-1194-y

[12] Pacheco L.D, Hankins GDV, Saad AF, Costantine MM, Chiossi G, Saade GR (2017) Tranexamic acid for the management of obstetric hemorrhage. Obstet Gynecol130(4):765-769.

[13] Pacheco LD, Saade GR, Hankins GDV (2019) Medical management of postpartum hemorrhage: an update. Semin Perinatol 43(1):22. 26. https://doi.orq/10.1053/ isemperi.2018.11.005

[14] Roberts I. Shakur H. Coats T, Hunt B, Balogun E, Barnetson L, Cook L, Kawahara T, Perel P, Prieto-Merino D, Ramos M, Cairns J, Guerriero C (2013) The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess 17(10):1-79. https://doi.org/10.3310/hta17100

[15] Salem M. Mohamed M, Salem A, Abbas A (2016) Tranexamic acid as prophylactic therapy for intra and post partum hemorrhage, randomized controlled trial. Br J Med Med Res 17(2):1-7. https://doi.org/10.9734/BJMMR/2016/26288

[16] Sentilhes L., Daniel V, Deneux-Tharaux C (2020) TRAAP2-TRAnexamic acid for preventing postpartum hemorrhage after cesarean delivery: a multicenter randomized, doubleblind, placebo-controlled trial- a study protocol. BMC Pregnancy Childbirth 20(1):1-11

[17] Sentürk MB. Cakrak Y, Yildiz G, Yildiz P (2013) 'Tranexamic acid for cesarean section: a double blind, placebo controlled, randomized clinical trial. Arch Gynecol Obstet 287(4):641-645. https//doi.org/10.1007/500404-012-2624-8

[18] Shakur H, Roberts 1, Fawole B, Chaudhri R, El-Sheikh M. Akintan A et al (2017)

[19] Effect of early tranexamic acid administration on mortality, hysterectomy. and other morbidities in women with post-partum hemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial, Lancet. 389(10084).2105-2116.

[20] Solomon C, Collis RE, Collins PW (2012) I laerostatic monitoring during postpartum hemorrhage and implications for management. Br J Anaesth 109(6):851-863.

[21] Xu J, Gao W, Ju Y (2013) Tranexamic acid for the prevention of postpartum hemorrhage after cesarean section: a double-blind randomization trial. Arch Gynecol Obstet 287(3):463- 468.