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Original Research Article

Adjunctive IV tranexamic acid versus topical tranexamic acid application of the placental bed for prevention of postpartum hemorrhage in women with placenta previa: a randomized controlled trial

Nahla W. Shady*, Hany F. Sallam

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

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***Correspondence:**
Dr. Nahla W. Shady,
E-mail: nahlagyn@yahoo.com

ABSTRACT

Background: Placenta previa one of the famous etiology of excessive blood loss during and after cesarean section. The objective of this study was to determine the effect of prophylactic adjunctive IV versus topical tranexamic acid (TA) on calculated and measured blood loss during and after caesarean section due to placenta previa compared with standard IV oxytocin alone.
Methods: In this double-blind randomized controlled trial, 120 women were undergoing caesarean delivery for placenta previa (PP) were randomly allocated to receive 10 IU oxytocin IV after placental delivery, or receive 1 gm tranexamic acid IV just before skin incision plus 10 IU oxytocin IV after placental delivery or received 10 IU oxytocin IV after placental delivery plus 2 gm topical tranexamic acid applied on placental bed. The main outcome was to measure blood loss during and 4-hour post caesarean delivery.
Results: 120 women were enrolled (n = 40 in each group). Both groups of women received IV tranexamic acid (Group II) and topical tranexamic acid (Group III) showed great reduction in intraoperative and 4 hours post-operative blood loss compared with (Group I) which received 10 IU oxytocin only (P = 0.0001, 0.0001, 0.0001, 0.0001), so the overall estimated blood loss in group II and III showed highly reduction compared with group I (P = 0.0001, 0.0001).
Conclusions: Prophylactic adjunctive TA topical application on the placental bed or iv administration reduces blood loss during and after caesarean delivery in women with a placenta previa. novel application of topical tranexamic acid on the placental bed is effective in reduce intraoperative and postoperative bleeding in comparison with IV route with elimination of theoretical risk of thrombi embolism complication with IV rout.

Keywords: Oxytocin, Placenta previa, Post-partum hemorrhage, Tranexamic acid

INTRODUCTION

Obstetric haemorrhage is one of the leading causes of maternal morbidity and mortality throughout the world. Haemorrhage following delivery is the leading reason for an obstetric admission to the intensive care unit (ICU), and it is responsible for about 30% all pregnancy-related deaths in both high- and low-income countries.[1] Most of the deaths occur soon after giving birth and almost all (99%) occur in low-income and middle-income countries.[2] Placenta previa is defined as the presence of placental tissue over or adjacent to the cervical os. Traditionally, four variations of placenta previa were recognized, complete, partial, marginal, and low lying.[3]

Improved ultrasound technology and precision have allowed for more accurate assessments of the placental location in relation to the cervical os. Recent revised classification of placenta previa consists of two variations: true placenta previa, in which the internal cervical os is covered by placental tissue, and low-lying placenta, in which the placenta lies within 2 cm of the cervical os but does not cover it.[3]

Caesarean delivery is indicated for all women with sonographic evidence of placenta previa and most women with low-lying placenta. When performing a caesarean delivery for placenta previa, the surgeon should be aware of the potential for rapid blood loss during the delivery process.

Once the placenta separates, bleeding is controlled by the contraction of uterine myometrial fibres around the spiral arterioles. Because the lower uterine segment often contracts poorly, significant bleeding may occur from the placental implantation site.[4]

Early activation of fibrinolysis is also recorded after childbirth. Within 1 h of giving birth, the serum concentration of tissue plasminogen activator doubles, possibly because of tissue damage during childbirth thereafter, the concentration falls.[5] On the basis of results of clinical trials in surgery and trauma, tranexamic acid is recommended for the treatment of primary post-partum haemorrhage if uterotonics fail to control the bleeding or if the bleeding is thought to be due to trauma.[6]

Recently, attention has focused on the use of tranexamic acid (TXA) to reduce blood loss if given prophylactically at caesarean section. This is not a uterotonic agent; TXA is an anti-fibrinolytic agent better known to gynaecologists for oral use as treatment of menorrhagia, and to trauma surgeons where it has been shown to reduce blood loss.[7]

Topical application of tranexamic acid provides a high drug concentration at the site of the wound and a low systemic concentration. Studies from cardiac and orthopedic surgery have shown an equal or superior effect of topical compared with intravenous tranexamic acid on both bleeding and transfusion requirement. Topical treatment is cost-effective, and adverse effects or drug interactions have not been reported.[8] There are several published clinical trials for the use of TXA in the obstetric setting as well, but no consensus on its use or guidelines for management.[7]

In the view of limited, good-quality evidence is available to inform on the best practices for prevention of bleeding at caesarean section due to placenta previa. Present study aimed at evaluating role of adjunctive IV Tranexamic acid versus topical Tranexamic acid infusion of the placental bed for prevention of postpartum haemorrhage in women with placenta previa.

METHODS

This study was a double blinded randomized controlled study conducted at Aswan University Hospitals from August 2015 to August 2017.

Departmental ethical review board approved the study. Study inclusion criteria were women undergoing cesarean delivery for placenta previa (PP). Diagnosis of PP based on ultrasound in which the placenta covered the internal os of the cervix.

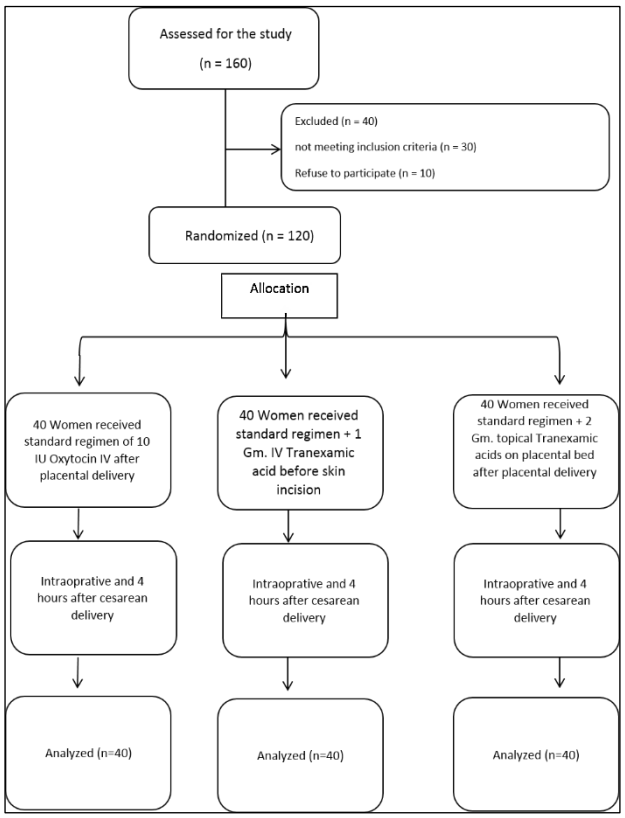

Figure 1: The study flowchart.

Exclusion criteria were women with (cardiac, hepatic, renal disorders, thromboembolic disease, placenta accrete and allergy to Tranexamic acid). The participants who fulfilled the eligibility criteria were explained about the study with the beneficial and possible adverse effects of tranexamic acid.

Informed consent was obtained from them, after that participants were randomized to 3 groups:

- Group 1: 40 patients received 10 IU oxytocin (syntocinon Novartis company) IV after placental delivery
- Group 2: 40 patients received 1 gm tranexamic acid (2 ampoules of kapron 500 mg 5 ml. Amoun company) IV just before skin incision plus 10 IU oxytocin IV after placental delivery

- Group 3: 40 patients received 10 IU oxytocin IV after placental delivery plus 2 gm topical tranexamic acid (4 ampoules of kapron 500 mg 5 ml) applied on placental bed.

Randomization will be performed using a computer-generated randomization system. The allocated groups will be concealed in serially-numbered sealed opaque envelopes that will only be opened after recruitment. Patient allocation will be performed prior to the induction of anesthesia by an independent person, who will not otherwise be involved in this study.

The trial will be appropriately blinded; the participants, outcome assessors and the surgeon performing the procedure will be blinded to the medication type, which will be used.

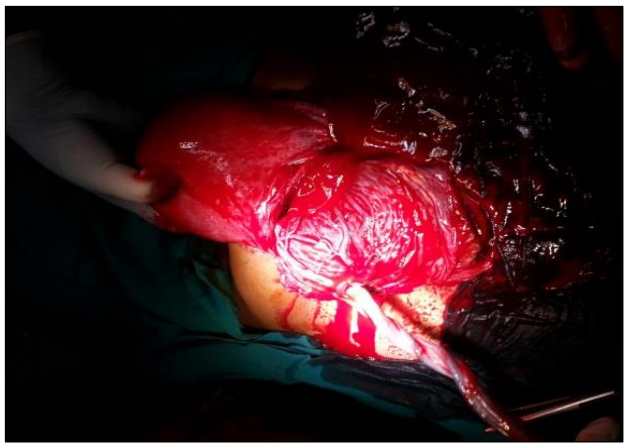

Figure 2: Placenta previa.

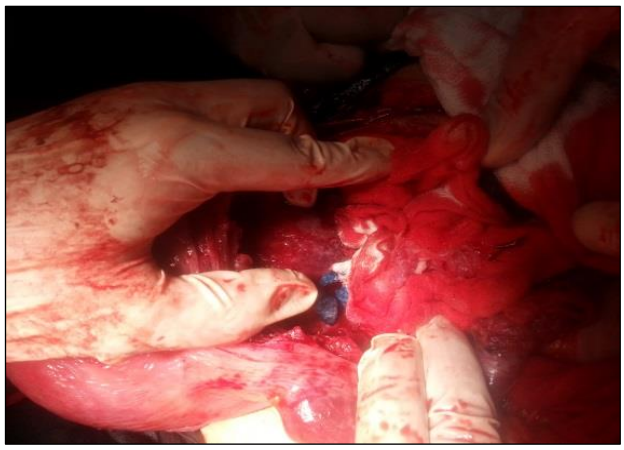

Figure 3: Topical tranexamic acid application to the placental bed.

All participants, were performed under general anesthesia. They received 1-gram Tranexamic acid (10 ml) in 100 ml saline infusion or placebo by slow intravenous injection at an approximate rate of 1 mL per min just before skin incision. The standard technique of trans peritoneal lower segment cesarean section was adopted, after removal of the placenta, we gave standard regimen of 10 IU of oxytocin intravenously and lastly, a towel soaked with 2g Tranexamic acid (20 ml) diluted in 100 ml of sodium chloride 0.9% or placebo (120 ml of sodium chloride 0.9%.) used to compress the placental bed for 5 minutes. To ensure a sufficiently high concentration, the tranexamic acid was diluted only to a volume sufficient to moisten a fairly large wound surface 32:20 ml moistens at least 1500 cm^2.

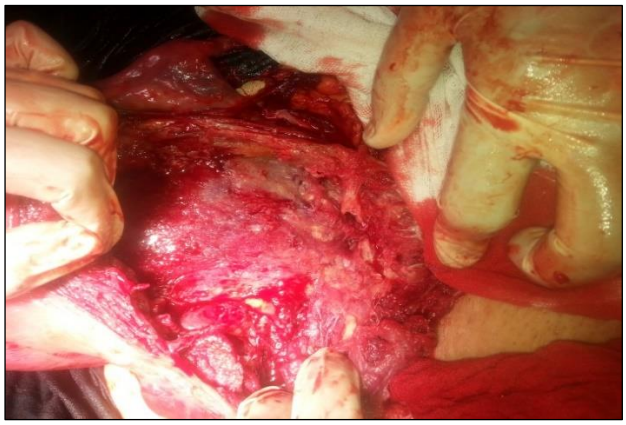

Figure 3: Placental bed after topical Tranexamic acid application.

The primary outcome of the present study was estimation of blood loss after delivery of the placenta to the end of the cesarean section which was measured by adding the volume of the contents of the suction bottle which was changed after delivery of placenta to avoid being mixed with amniotic fluid and blood from parities and the difference in weight (in grams) between the dry and the soaked operation sheets and towels (1 gram = 1 ml), at the end of the operation a new pre-weighted pads were used and blood loss from the end of cesarean section to 4 hours post-operative was measured by weighing the soaked pads (in grams) and subtracting the weight of dry pads (in grams) from it (1gram =1 ml).

The secondary outcome was measuring additional blood transfusion, need for uterotonics in the form of oxytocin infusion, Inj. methyl ergometrine, Inj. carboprost and sublingual misoprostol tab 600 mcg. Also use of additional surgical interventions to control post-partum hemorrhage in form of uterine artery ligation with or without internal iliac artery ligation were done when needed.

The patient's pulse rate, blood pressure and temperature were recorded preoperative and continuously intraoperative, then every 30 minutes after operation therefor the mean were calculated and recorded postoperative. Also, Hemoglobin concentration was done in all patients preoperative and 24 hours postoperative and the change in concentration was noted, any side effects such as nausea, vomiting, diarrhea were noted and lastly maternal death or severe maternal morbidity such

as seizure, thromboembolic events, need for intensive care unit admission, hysterectomy were recorded.

After collecting all the data, the data were tabulated and analyzed. Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. Chi-square test and Monte Carlo test were used for comparison between groups, as appropriate. Quantitative data were described as means (SD) or medians, as appropriate. They were tested for normality by Kolmogorov-Smirnov test. In the normally distributed variables, one-way ANOVA test was used for comparison between groups.

In the non-normally distributed variables, Kruskal-Wallis test and Mann Whitney test were used for comparison between groups, as appropriate. Odds ratios and their 95% confidence interval were calculated. p value ≤0.05" was considered to be statistically significant.

RESULTS

Present study started with 160 patient who were asked to participate, 40 patients were excluded, 30 patients not meeting inclusion criteria and 10 patients refuse to participate. therefor the remaining 120 patients were randomized to 3 groups each group comprised of 40 patients. Group I: (received the standard regimen of 10 IU oxytocin IV after placental delivery), Group II: (received standard regimen plus 1 gm tranexamic acid IV before skin incision), and Group III: (received the standard regimen plus 2 gm topical tranexamic acid after placental delivery at the placental bed).

There was no significant difference with respect to their age, weight, parity, gestational age, pre-operative pulse, systolic blood pressure (SBP), diastolic blood pressure (DBP), temperature, initial haemoglobin and number of previous caesarean sections (CS) (Table1).

Table 1: preoperative characteristics of pregnant women in the study groups.

Parameters	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	Significance
Age (year)	29.5±2.42	29.6±2.68	29.8±2.85	0.854
Weight (kg)	75.5±10.09	75.75±5.95	75.7±5.45	0.996
Parity (median) (minimum-maximum)	3 (1-4)	2 (1-5)	3 (1-5)	0.842
Gestational age (weeks)	36.38±0.87	36.45±0.9	36.4±0.93	0.931
Pulse	79.6±4.996	79.75±5.192	78.68±5.1	0.595
Temperature	36.995±0.13	36.98±0.18	36.975±0.13	0.822
SBP	120.4±2.45	119.8±2.64	120.03±2.34	0.576
DBP	78.25±2.9	78.03±3.3	78.78±2.9	0.531
Initial haemoglobin (%)	9.89±0.66	9.89±0.67	9.93±0.66	0.928
No. of CS (%)				
0	7 (17.5)	6 (15)	9 (22.5)	0.952
1	8 (20)	9 (22.5)	6 (15)	
2	9 (22.5)	8 (20)	7 (17.5)	
3	16 (40)	17 (42.5)	18 (45)	

SBP: (Systolic Blood Pressure); DBP: (Diastolic Blood Pressure); CS: (Cesarean section); #Variables are presented as mean and standard deviation, median (minimum – maximum) and number (percentage).

Table 2: Operative time, blood loss during and after CS and extra surgical procedures in the study groups.

Side effects	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	Significance
Operative time	48.13±5.88	48.05±5.49	49.25±6.11	0.589
Blood loss				
Intraoperative	918 (320-1540)	532 (190-1425)	532 (190-1445)	0.0001* 0.0001* / 0.0001* / 0.799
4-h postoperative	182.23±20.02	123.05±19.2	125.5±17.98	0.0001* 0.0001*/ 0.0001*/ 0.567
Total blood loss	1110 (470-1750)	660 (280-1580)	655 (280-1600)	0.0001* 0.0001*/ 0.0001*/ 0.751
Extra surgical procedures (%):				
No	19 (47.5)	33 (82.5)	33 (82.5)	0.001* 0.002*/ 0.002*/ 1.00
Uterine artery ligation	18(45)	6 (15)	5 (12.5)	
Internal iliac ligation	3(7.5)	1(2.5)	2(5)	

CS: Cesarean section; *Statistical significant difference (Group I versus Group II / Group I versus Group III / Group II versus Group III); # Variables are presented as mean and standard deviation, median (minimum-maximum) and number (percentage)

Also, no significant difference with respect to operative time (p=0.589). Both Group II and Group III showed great reduction in intraoperative and 4 hours post-operative blood loss compared with Group I, (P = 0.0001, 0.0001, 0.0001, 0.0001), so the overall estimated blood loss in group II and III showed highly reduction compared with group I (P = 0.0001, 0.0001). However no significant difference in overall estimated blood loss either intraoperative or 4 hours post-operative between group II and III, (P = 0.751, 0.799, and 0.567 respectively). There was statistically significant decrease in the incidence of extra-surgical procedures in form of (uterine artery ligation, with or without internal iliac artery ligation) in Group I (7.5% and 45% respectively) compared with Group II (2.5% and 15% respectively) and group III (5% and 12.5 % respectively) (P= 0.002 and 0.002) (Table 2).

Table 3: Secondary outcome in the study groups.

Variables	Group I (n = 40)	Group II (n = 40)	Group III (n = 40)	Significance
Pulse	90.4±9.71	83.65±8.11	80.5±5.11	0.0001* 0.0001* / 0.0001* / 0.076
Temperature	36.88±0.19	36.87±0.21	36.9±0.19	0.793
SBP	113.5±7.17	118.78±4.12	119.83±2.05	0.0001* 0.0001* / 0.0001* / 0.343
DBP	73.5±6.22	76.88±4.63	78.68±2.57	0.0001* 0.002* / 0.0001* / 0.09
Hemoglobin (%)	8.63±0.96	9.04±1.01	9.01±1.04	0.124
Post-partum hemorrhage	21 (52.5)	7 (17.5)	7 (17.5)	0.0001* 0.001* / 0.001* / 1.00
Additional uterotonics	27 (67.5)	7 (17.5)	7 (17.5)	0.0001* 0.0001* / 0.0001* / 1.00
Need blood transfusion	27 (67.5)	7 (17.5)	7 (17.5)	0.0001* 0.0001*/ 0.0001*/ 1.00
Nausea	1 (2.5)	5 (12.5)	1 (2.5)	0.122
Vomiting	1 (2.5)	2 (5)	1 (2.5)	1.00
Diarrhea	1 (2.5)	2 (5)	1 (2.5)	1.00

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; *Statistical significant difference (Group I versus Group II / Group I versus Group III / Group II versus Group III); # Variables are presented either mean and standard deviation and number (percentage)

There was a significant decrease in post-operative pulse in group I compared with Group II and III (P= 0.0001 and 0.0001). Also, there was significant decrease in both post-operative SBP and DBP in group I compared with group II (P=0.0001 and 0.002 respectively) and group III (P= 0.0001 and 0.0001). However no significant difference with respect to post-operative pulse, SBP, DBP, between group II and III (P=0.076, 0.343 and 0.09 respectively). There was increased incidence of post-partum haemorrhage in group I (52.5 %), compared with (17.5%) in both group II and III, (P = 0.001 and 0.001), hence the incidence of blood transfusion and additional utero-tonics were highly increased in Group I (67.5%) compared with group II (17.5%) and group III (17.5%). (P = 0.0001, 0.0001, 0.0001, 0.0001). However, the incidence of post-partum haemorrhage, the need for blood transfusion and additional utero-tonics were not changed between Group II and III. There was no significant difference between the three groups with respect to post-operative temperature, 24-hour post-operative haemoglobin concentration, nausea, vomiting and diarrhoea (P = 0.793, 0.124, 0.122, 1,00 and 1.00 respectively) (Table 3).

DISCUSSION

The American College of Obstetricians and Gynecologists (ACOG) revitalize program defines postpartum hemorrhage as cumulative blood loss greater than or equal to 1,000 ml or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (includes intrapartum loss) regardless of route of delivery.[9] In the 2015 Agency for Health Research and Quality systematic review, there was no consistent evidence for benefit in severe postpartum hemorrhage, transfusion, hysterectomy, intensive care unit admission, or mortality from standardized protocols.[10] Management of cesarean section with placenta previa and prevention of intraoperative and postpartum hemorrhage is still challenging. Prophylactic oxytocin, by dilute intravenous infusion (bolus dose of 10 units), or intramuscular injection (10 units), remains the most effective medication with the fewest adverse effects for prevention of postpartum hemorrhage during cesarean section the main action is the contraction of uterine myometrial fibers around the spiral arterioles.[11] Because the lower uterine segment often contracts poorly,

significant bleeding may occur from the placental implantation site.

So, in the present study we hypo sized that there is need of another agent with another mechanism of action rather than uteri-tonic for prevention blood loss during cesarean section due to placenta previa

TXA is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin.[12] Peak plasma TXA concentration is obtained immediately after intravenous administration, then concentration decreases until the 6th hour. Its half-life is about 2 hours.[13] It has been studied extensively in non-pregnant adults. A Cochrane review showed that TXA significantly reduces blood transfusion in patients undergoing emergency or urgent non-obstetrical surgery.[18]

TXA is safe in pregnancy, being FDA category B. It is therefore unsurprising that there is interest in its role in the prevention of postpartum hemorrhage.

In the best of our knowledge many trials asses the efficacy of tranexamic acid in prevention of postpartum hemorrhage during cesarean section but no trial specifically asses the role of tranexamic acid in cesarean section for placenta previa more over we claim that our study was the first to evaluate the novel topical application of tranexamic acid on the placental bed and uterine scar during cesarean section for the aim of prevention of intraoperative and post-partum hemorrhage.

The present work demonstrates superiority of adjunctive intravenous and topical tranexamic acid regarding decrease obstetric hemorrhage during cesarean section for placenta previa.

The intravenous tranexamic group demonstrated that intravenous administration of 1 gm of tranexamic acid at skin incision at cesarean delivery reduced intra- and postoperative blood loss, as well as the amount of intraoperative oxytocin used. Hemoglobin level showed a non-significant decrease in the control group

In a multicenter study, the efficacy of tranexamic acid to reduce post-placental delivery blood loss and post-operative blood loss 2 hours after surgery was assessed. The intervention led to less bleeding 2 hours postoperatively; however, it failed to decrease post placental delivery blood loss However, unlike in the present study, tranexamic acid was administrated per kilogram body weight in our study all patients received 1 g of tranexamic acid regardless of their weight. Tranexamic acid was administered only 10 minutes before skin incision in this study.[14]

In another study, tranexamic acid was used successfully to reduce cesarean delivery blood loss.[15] A reduction in postoperative bleeding of around 17% at 2 hours was found in the intervention group, which was significantly less than the almost 25% in IV group tranexamic acid and 23% reduction topical tranexamic group in postoperative blood loss found in the present study

Aleem A et al in double blind case control trial who conduct their work upon 740 patients and concluded that the use of tranexamic acid before elective cesarean section is associated with reduced post-partum hemorrhage during and pot elective cesarean section.[16]

Also, present results were in agreement with Ahmed et al, Movafegh et al, Goswam et al and Senturk et al.[20-23]

The topical tranexamic group demonstrated that topical administration of 2 gm of tranexamic acid in in 2000 ml normal saline at placental bed and uterine scar at cesarean delivery reduced intra- and postoperative blood loss, as well as the amount of intraoperative oxytocin used. Hemoglobin level showed a non-significant r decrease in the control group

There was no study in the literature address the role of topical tranexamic acid during cesarean section although Two case reports on the use of topical tranexamic acid to control postoperative local bleeding in 2 women with clotting disorders who were undergoing gynecologic procedures.[17]

A 51-year old woman with essential thrombocytopenia underwent an uneventful total abdominal hysterectomy and sapling-oophorectomy; however, the patient experienced continuous loss of blood from drains placed in the peritoneal cavity and sub rectal space. After multiple failed attempts to stop the bleeding with pressure dressings, a pressure dressing soaked in 5 mL of tranexamic acid (100 mg/mL) was applied. Bleeding decreased within a few minutes, and 2 additional applications were used over a 48-hour period, which allowed the patient to be discharged with no further complications on postoperative day.[6]

In the second case, a 75-year-old female with a history of severe factor XI deficiency underwent a vaginal hysterectomy and vaginal wall repair. Postoperatively, the vaginal vault oozed blood which could not be controlled with vaginal packs. The bleeding was better controlled once a vaginal pack soaked in 15 ml of tranexamic acid (100 mg/ml) was applied, with a reduction in bleeding observed the following day. The patient was subsequently initiated on oral tranexamic acid, given as 1 g daily for 7 days, and was discharged on postoperative day 6 with no further complications.[17]

One concern regarding use of TXA in pregnancy is the potential for thromboembolic events in a population at already high baseline risk of thrombosis.[18] In the present study no case reported to complicated with DVD or pulmonary embolism post-operative in the early postoperative period.

The WOMAN trial results show that the effect of TA in post-partum hemorrhage is consistent with the effect recorded in surgery and trauma. There was a significant reduction in death due to bleeding and laparotomy to control postpartum hemorrhage with tranexamic acid and no evidence to increased risk of thromboembolic disease.[19]

CONCLUSION

Prophylactic adjunctive TA topical application on the placental bed or iv administration reduces blood loss during and after caesarean delivery in women with a placenta previa. novel application of topical tranexamic acid on the placental bed is effective in reduce intraoperative and postoperative bleeding in comparison with IV route with elimination of theoretical risk of thrombi embolism complication with IV route.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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