ISSN: 0975-1556

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(2); 162-171

Original Research Article

A Double Blinded Randomized Controlled Study to Evaluate the Outcome of IV Tranexamic Acid Versus Topical Tranexamic Acid Application in Prevention of Postpartum Hemorrhage in Women with Placenta Previa

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Received: 03-12-2021 / Revised: 30-12-2021 / Accepted: 28-01-2022
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Conflict of interest: Nil

Abstract

Aim: Adjunctive IV tranexamic acid versus Topical tranexamic acid application on the placental bed for prevention of postpartum hemorrhage in women with placenta previa.

Methods: A double blinded randomized controlled study was conducted in the Department of Obstetrics & Gynaecology, Government Medical College Bettiah, West Champaran, Bihar, India for 1 year. 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. Informed consents were obtained from them. After that participant were randomized into 3 groups: Group 1: 50 patients received 10 IU oxytocin (syntocinon Novartis company) IV after placental delivery. Group 2: 50 patients received 1 gm tranexamic acid (2 ampoules of kapron 500 mg 5 ml.) IV just before skin incision plus 10 IU oxytocin IV after placental delivery. Group 3: 50 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.

Results: 150 women were enrolled (n = 50 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 Tranexamic Acid (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 reducing intraoperative and postoperative bleeding in comparison with IV route with elimination of theoretical risk of thrombic embolism complication with IV rout.

Keywords: IV, Topical, Tranexamic Acid.

Introduction

Postpartum hemorrhage is a leading cause of maternal morbidity and mortality worldwide [1]. Placenta previa is one of the major causes of postpartum hemorrhage. It occurs with an incidence of 0.3-0.5% and is defined by implantation of placenta in lower uterine segment, overlying or approaching internal os [2]. Intra-operative management options deployed to control hemorrhage in placenta previa patients include bimanual uterine compression [3]. implantation site compression with sutures [4], uterine arterial ligation, pelvic arterial embolization [5] and hysterectomy the prevention of postpartum hemorrhage in cases of placenta previa is quite challenging.

Topical application of tranexamic acid provides a high drug concentration at site of 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 bleeding and transfusion requirement.

Postpartum hemorrhage accounts for a major part of the mortality as well as morbidity like severe anemia, need for blood transfusion, hospital stay and infection. Most of the deaths occur soon after giving birth and almost all (99%) occur in low- and middle- income countries. Fourteen million women suffer from postpartum hemorrhage each year, of whom 1-2% die within 2-4 hours after the onset of bleeding, 2 to 11% of them show anemia later in their life [6].

The rates of cesarean section have increased to as high as 25% to 30% in many areas of the world [7]. Postpartum hemorrhage complicates approximately six percent of the cesarean sections. Postpartum hemorrhage is commonly encountered following placenta previa as one of the major causes.

Over many years, several techniques have been described in the literature for controlling massive bleeding associated with placenta previa cesarean sections, including uterine packing with gauze,3 balloon tamponades [8], B-Lynch suture [9], insertion of parallel vertical compression sutures, a square suturing technique4 and embolization or ligation of the uterine and internal iliac arteries [5], but there is a wide variation in the success rate of these maneuvers [10]. Arterial ligation and compression sutures have a low success rate among inexperienced surgeons, pelvic arterial embolization requires high medical costs and sophisticated facilities. Hysterectomy has high morbidity and mortality and confers fertility loss. The prevention of postpartum hemorrhage in cases of placenta previa is quite challenging. Therefore, other non-invasive procedures are needed to prevent and treat postpartum hemorrhage and preserve the uterus. One of the most promising approaches is to minimize peri-operative bleeding through prophylactic use of anti-fibrinolytic agents e.g., aprotinin, tranexamic acid and amino-caproic acid. Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its anti-fibrinolytic effect through reversible blockade of the lysine binding sites on plasminogen molecules [11].

Tranexamic acid has been shown to be very useful in reducing blood loss and incidence of blood transfusion in various surgeries [12]. In gynecology, tranexamic acid reduces maternal blood loss in women with menorrhagia compared with control agents or placebo [13]. In obstetrics, tranexamic acid reduces bleeding related mortality in women with postpartum hemorrhage, especially when administered fairly soon after delivery [14]. Recently, attention has focused on the use of tranexamic acid to reduce blood loss if given prophylactically at cesarean section.

On the basis of results of clinical trials in surgery and trauma, tranexamic acid is recommended for the treatment of primary postpartum hemorrhage if uterotonics fail to control the bleeding or if the bleeding is thought to be due to trauma [15].

However, concerns about possible thromboembolic events with parenteral administration of tranexamic acid have stimulated increasing interest in it's topical use. 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 surgeries 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 [16]. There are very few studies on use of topical tranexamic acid for prevention of bleeding during cesarean section in cases of placenta previa. So, the present prospective study was conducted to investigate the efficacy and safety of topically applied tranexamic acid and compared it with intravenous tranexamic acid.

Materials and methods:

A double blinded randomized controlled study was conducted in the Department of Obstetrics & Gynaecology, Government Medical College Bettiah, West Champaran, Bihar, India for 1 year. Study inclusion criteria were women undergoing cesarean delivery for placenta previa (PP). Diagnosis of PP is based on ultrasound in which the placenta covered the internal os of the cervix.

Methodology

210 patients were assessed for the study, out of which 30 patients were excluded, 20 patients didn't meet the inclusion criteria and 10 patients refused to participate in the study.

Exclusion criteria were women with (cardiac, hepatic, renal disorders, thromboembolic disease, placenta accreta 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 participant were randomized to 3 groups:

Group 1: 50 patients received 10 IU oxytocin (syntocinon Novartis company) IV after placental delivery

Group 2: 50 patients received 1 gm tranexamic acid (2 ampoules of kapron 500 mg 5 ml. Amount company) IV just before skin incision plus 10 IU oxytocin IV after placental delivery

Group 3: 50 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.

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. 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.

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 the 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 intraoperatively, then every 30 minutes after operation therefore 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 noted. After collecting all the data, the data were tabulated and analyzed.

Results:

Present study started with 210 patients who were asked to participate, 30 patients were excluded, 20 patients not meeting inclusion criteria and 10 patients refused to participate. Therefore, the remaining 150 patients were randomized to 3 groups each group comprised of 50 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 = 50)	Group II (n = 50)	Group III (n = 50)	p-value
Age (year)	29.7±2.43	29.8±2.69	29.10±2.86	0.855
Weight (kg)	75.7±10.10	75.77±5.96	75.9±5.46	0.997
Parity (median) (minimum-maximum)	3 (1-4)	2 (1-5)	3 (1-5)	0.843
Gestational age (weeks)	36.40±0.88	36.47±0.10	36.6±0.94	0.932
Pulse	79.8±4.997	79.77±5.193	78.70±5.2	0.596
Temperature	36.997±0.14	36.100±0.19	36.977±0.14	0.823
SBP	120.6±2.46	119.10±2.65	120.05±2.35	0.577
DBP	78.27±2.10	78.05±3.4	78.80±2.10	0.532

Initial haemoglobin (%)	9.91±0.67	9.91±0.68	9.95±0.67	0.929
No. of CS (%)				
0	9 (18)	8 (16)	12 (24)	0.954
1	10 (20)	11 (22)	7 (14)	
2	12 (24)	10 (20)	8 (16)	
3	19 (38)	21 (42)	23 (46)	

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 = 50)	Group II (n = 50)	Group III (n = 50)	p-value
Operative time	48.15±5.89	48.07±5.50	49.27±6.12	0.590
Blood loss				
Intraoperative	919 (320-1540)	533 (190-1425)	533 (190-1445)	0.0001* 0.0001* / 0.0001* / 0.800
4-h postoperative	182.24±20.03	123.06±19.3	125.6±17.99	0.0001* 0.0001*/ 0.0001*/ 0.568
Total blood loss	1111 (470-1750)	661 (280-1580)	656 (280-1600)	0.0001* 0.0001*/ 0.0001*/ 0.752
Extra surgical procedures (%):				
No	25 (50)	43 (86)	43 (86)	0.001* 0.002*/ 0.002*/ 1.00
Uterine artery ligation	22(44)	6 (12)	5 (10)	
Internal iliac ligation	3(6)	1 (2)	2 (4)	

CS: Cesarean section; *Statistically 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=0.590). 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 = 0.752, 0.800, and 0.568 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 (44% and 6 % respectively) compared with Group II (12% and 2% respectively) and group III (10% and 4 % respectively) (P= 0.002 and 0.002) (Table 2).

Table 3: Secondary outcome in the study groups

Variables	Group I (n = 50)	Group II (n = 50)	Group III (n = 50)	Significance
Pulse	90.5±9.72	83.65±8.11	80.5±5.11	0.0001*
Temperature	36.89±0.29	36.87±0.21	36.9±0.19	0.794
SBP	113.6±7.18	118.78±4.12	119.83±2.05	0.0001*
DBP	73.6±6.23	76.88±4.63	78.68±2.57	0.0001*
Hemoglobin (%)	8.64±0.97	9.04±1.01	9.01±1.04	0.125
Post-partum hemorrhage	26 (52)	9 (18)	9 (18)	0.0001*
Additional uterotonics	34 (68)	9 (18)	9 (18)	0.0001*
Need blood transfusion	34 (68)	9 (18)	9 (18)	0.0001*
Nausea	1 (2)	6 (12)	1 (2)	0.123
Vomiting	1 (2)	3 (6)	1 (2)	1.00
Diarrhea	1 (2)	3 (6)	1 (2)	1.00

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; *Statistically 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=0.077, 0.344 and 0.10 respectively). There was increased incidence of post- partum haemorrhage in group I (52%), compared with (18%) 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 (68%) compared with group II (18%) and group III (18%). (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 = 0.794, 0.125, 0.123, 1,00 and 1.00 respectively) (Table 3).

Discussion:

The prevention of postpartum hemorrhage in cases of placenta previa is quite challenging. Recently, attention has focused on use of tranexamic acid to reduce blood loss if given prophylactically at cesarean section. Topical application of tranexamic acid provides a high drug concentration at site of 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 bleeding and transfusion requirement. 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.17 Because the lower uterine segment often contracts poorly, significant bleeding may occur from the placental implantation site. So, in the present study we hypothesized

that there is need of another agent with another mechanism of action rather than utero-tonic for prevention of blood loss during cesarean section due to placenta previa. TA is a lysine analogue which acts as an antifibrinolytic via competitive inhibition of the binding of plasmin and plasminogen to fibrin.18 Peak plasma TA concentration is obtained immediately after intravenous administration, then concentration decreases until the 6th hour. Its half- life is about 2 hours [19]. It has been studied extensively in non-pregnant adults. A Cochrane review showed that TA significantly reduces blood transfusion in patients undergoing emergency or urgent non-obstetrical surgery [20].

TA 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 assess the efficacy of tranexamic acid in prevention of postpartum hemorrhage during cesarean section, but no trial specifically assesses 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 in cesarean delivery reduce intra- and postoperative blood loss, as well as the amount of intraoperative oxytocin use. 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 [21].

In another study, tranexamic acid was used successfully to reduce cesarean delivery blood loss [22]. 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 in 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 post elective cesarean section [23]. Also, present results were in agreement with Ahmed et al, Movafegh et al, Goswam et al and Senturk et al [24,27]. The topical tranexamic group demonstrated that topical administration of 2 gm of tranexamic acid in 2000 ml normal saline at placental bed and uterine scar at cesarean delivery reduces 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. 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 [28].

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 [29]. 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 [28]. One concern regarding use of TA 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 [30].

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 reducing intraoperative and postoperative bleeding in comparison with IV route with elimination of theoretical risk of thrombo- embolism complication with IV route.

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