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Comparative study of topical and intravenous tranexamic acid for prevention of postpartum haemorrhage in placenta praevia cesarean section

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Abstract
Introduction: Topical application of tranexamic acid provides a high drug concentration at site of wound and a low systemic concentration. Intravenous tranexamic acid has been shown to be very useful in reducing blood loss and incidence of blood transfusion.
Aims and Objectives: To compare topical and intravenous tranexamic acid for prevention of postpartum haemorrhage in placenta praevia cesarean section.
Material and Methods: Group 1: Patients who received 1 gram (10 ml) tranexamic acid intravenous before skin incision plus 10 IU oxytocin intravenous infusion after placental delivery.
Group 2: Patients who received 10 IU oxytocin intravenous infusion after placental delivery plus 2 grams (20 ml) topical tranexamic acid applied on placental bed after delivery of baby.
Results: The mean age was similar in both groups i.e. 27.31 ± 5.62 years in group 1 and 28.06 ± 6.73 years in group 2. Mean body weight was 63.20 ± 6.12 kg in group 1 and 61.49 ± 6.12 kg in group 2. The mean systolic blood pressure in group 1 and 2 was 112.74 ± 8.79 and 113.49 ± 10.57 mmHg respectively, mean diastolic blood pressure was 75.37 ± 8.21 and 76.34 ± 6.70 mmHg and mean pulse rate was 91.77 ± 6.74 and 92.17 ± 7.49 per minute respectively. Maximum number of women had unscarred uterus i.e. 80% in group 1 and 77.1% in group 2. Mean pre-operative hemoglobin was 9.59 ± 1.35 g/dl in group 1 and 9.30 ± 1.33 g/dl in group 2. Mean INR was 0.99 ± 0.14 in group 1 and 0.97 ± 0.15 in group 2. The mean platelet count was 2.01 ± 0.39 lac in group 1 and 1.97 ± 0.42 lac in group 2. Only 8.6% in group 1 and 14.3% in group 2 required blood transfusion. Mean requirement of intra-operative blood transfusion was 0.457 ± 0.730 units in group 1 and 0.085 ± 0.279 units in group 2. Intra-operative mean blood loss was 464.86 ± 28.00 ml in intravenous tranexamic acid group and 420.46 ± 69.75 ml in topical tranexamic acid group. The requirement of additional uterotonics in form of misoprostol and/or carboprost was 17.1% in group 1 and 5.7% in group 2.A total of 22.9% women showed nausea and vomiting in group 1while none of the women showed nausea, vomiting or any other side-effects in topical tranexamic acid group. A total of 20% women in group 1 and 5.7% women in group 2 developed postpartum hemorrhage. Mean post-operative hemoglobin was 8.85 ± 1.26 g/dl in group 1 and 8.75 ± 1.30 g/dl in group 2. The mean decline in hemoglobin concentration was 0.734 ± 0.35 g/dl in group 1 and 0.569 ± 0.25 g/dl in group 2. Mean requirement of post-operative blood transfusion was 0.20 ± 0.575 units in group 1 and 0.057 ± 0.232 units in group 2. Mean birth weight of neonates was 2.41 ± 0.52 kg in group 1 and 2.42 ± 0.57 kg in group 2. Perinatal complications like low birth weight, NICU transfer, respiratory distress syndrome and severe birth asphyxia were not significantly different in both groups.
Conclusion: From our study, it is concluded that tranexamic acid used prophylactically intravenously before skin incision or topical application on placental bed after placental delivery in patients undergoing cesarean section for placenta praevia significantly reduces intra-operative blood loss. Tranexamic acid use also reduces incidence of postpartum hemorrhage, need for blood transfusion, and need of additional uterotonics or additional surgical interventions in form of hemostatic sutures, balloon tamponade, uterine artery ligation or cesarean hysterectomy.

Keywords: Topical, intravenous tranexamic acid, postpartum haemorrhage, placenta praevia, cesarean section

Introduction
Postpartum hemorrhage is a leading cause of maternal morbidity and mortality worldwide [1]. Placenta praevia 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 the 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 technique [4] 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 approach 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 is 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.

Material and Methods

This prospective interventional randomized controlled study was conducted on women with placenta previa who attended the labour room in the department of Obstetrics & Gynecology at Pt. B. D. Sharma, PGIMS, Rohtak, Haryana. The study was conducted over a period of one year.

Women with placenta praevia undergoing cesarean section were included in the present study and women with cardiac, hepatic, renal, thromboembolic disease, placenta accreta and allergy to tranexamic acid were excluded.

Method of recruitment

Subjects were enrolled in the study after taking written informed consent and explaining in details about the study protocol. The diagnosis of placenta praevia was made on the basis of ultrasonography. Participants were randomized into two groups based on computerized generated method:

Group 1: Included patients who received 1 gram (10 ml) tranexamic acid intravenous before skin incision plus 10 IU oxytocin intravenous infusion after placental delivery.

Group 2: Included patients who received 10 IU oxytocin intravenous infusion after placental delivery plus 2 grams (20 ml) topical tranexamic acid applied on placental bed.

Intervention

10 IU oxytocin intravenous infusion in 500 ml normal saline over 30 minutes was given in both the group. One gram (10 ml) tranexamic acid was given by slow intravenous injection just before skin incision. The detailed history and thorough clinical examination of all subjects was done. All were subjected to investigations namely haemoglobin, blood group, HIV, HBsAg, VDRL, glucose challenge test, TSH, complete urine examination and ultrasonography. Patients' blood pressure and pulse were taken. Hemoglobin concentration was done preoperatively and 24 hours postoperatively and change in hemoglobin concentration was noted. The patients were followed up till discharge. Any maternal morbidity and mortality were also noted.

Primary outcome was measured in terms of blood loss: Quantity of blood loss in ml = [weight of gauze pads used after surgery – weight of gauze pads used before surgery] + volume of blood in suction bottle after placental delivery.

Secondary outcome was measured in terms of need for blood transfusion, need of uterotonics and need of additional surgical intervention like uterine artery ligation or uterine compression sutures.

Statistical analysis

At the end of the study, all data was compiled and the statistics were analyzed with SPSS version 21. Continuous variables were presented as mean ± SD or median for the unevenly distributed data. Categorical variables were expressed as frequencies and percentages. Association between two or more variables was compared using chi-square test. For all statistical tests, a p-value less than 0.05 was considered statistically significant.

Observations

In this study, mean age was 27.31 ± 5.62 years in group 1 and 28.06 ± 6.73 years in group 2 (p>0.05). Most women in our study were nullipara where 48.6% in group 1 and 40% in group 2 (p>0.05). Mean body weight was 63.2 ± 6.12 kg in group 1 and 61.49 ± 6.12 kg in group 2 (p >0.05). Mean systolic blood pressure in group 1 and 2 was 112.74±8.79 and 113.49±10.57 mmHg respectively (p>0.05), mean diastolic blood pressure was 75.37 ± 8.21 and 76.34 ± 6.70 mmHg (p >0.05) and mean pulse rate was 91.77 ± 6.74 and 92.17 ± 7.49 per minute respectively (p>0.05). It is concluded from the data that there is no statistically significant difference between groups in terms of pre-operative vitals. Majority of the women presented with bleeding per vaginum with 77.1% in group 1 and 2 each (p>0.05). It also showed that the percentage of women who presented with labour pains was 11.4% and 8.6% in group 1 and 2 respectively (p>0.05). In both cases, this observation was found to be statistically insignificant. A few women presented only with amenorrhea without bleeding per vaginum and/or labour pains. Women who had no previous cesarean section in group 1 and 2 were 80% and 77.1% respectively. No woman in the study gave history of any other surgery. The difference in the number of previous cesarean section between groups does not show any statistical significance (p >0.05). In the present study, 8.6% women in group 1 and 11.4% women in group 2 included in the study were having previous history of dilatation and curettage (p>0.05). Present study shows that 25.7% women in group 1 and 17.1% women in group 2 presented with malpresentation. Malpresentation included breech, oblique and transverse lie.

A total of 2.9% women in group 1 and none in group 2 had absent fetal heart sound on ultrasonography indicating intrauterine death of fetus at the time of presentation. Women who underwent cesarean section had major degree placenta previa. Most women presented with type IV placenta previa followed by type III and type IIb. Women with type IV placenta previa were 48.6% in group 1 and 54.3% in group 2 (p>0.05)

Pre-operative hemoglobin level in most women was in range of 9.0–10.9 g/dl that includes 71.4% in group 1 and 57.1% in group 2. In our study, 8.6% in group 1 and 5.7% in group 2 were found to be severely anemic. The mean pre-operative hemoglobin level was 9.59 ± 1.35 g/dl in group 1 and 9.30±1.33 g/dl in group 2. No statistically significant difference was found between groups in terms of mean pre-operative hemoglobin level (p >0.05). Mean INR was 0.99±0.14 in group 1 and 0.97±0.15 in group 2 (p>0.05). The mean platelet count was found to be 2.01±0.39 lac in group 1 and 1.97±0.42 lac in group 2 (p>0.05) which is also statistically insignificant. Majority of the women in our study did not require pre-operative blood transfusion. Mean requirement of pre-operative blood transfusion was 0.143±0.486 units in group 1 and 0.171±0.446 units in group 2. The difference was found to be statistically insignificant (p >0.05). Mean gestational age at delivery was 36.69 ± 2.35 weeks in group 1 and 35.86 ± 2.35 weeks in group 2. No statistically significant difference was observed between groups in terms of gestational age at delivery (p >0.05).

Table 1: Intra-operative mean blood loss in three groups

Blood loss after placental delivery (ml)	Group 1 Frequency (%) (n = 35)	Group 2 Frequency (%) (n = 35)	p value
200 – 400	19 (54.3%)	26 (74.3%)	0.164 [95% CI = 108.03 to 272.77]
400 – 600	10 (28.6%)	8 (22.9%)	
600 – 800	4 (11.4%)	1 (2.9%)	
800 – 1000	2 (5.7%)	0 (0%)	
>1000	0 (0%)	0(0%)	
Total	35 (100%)	35 (100%)	
Mean ± SD	464.86 ± 28.00	420.46 ± 69.75	0.388

Table 1 shows that the mean intra-operative blood loss was 464.86±28.00 ml in group 1 and 420.46±69.75 ml in group 2. The blood loss measured in group 1 was 54.3% in range of 200-400 followed by 28.6% in range of 400-600 ml. Maximum women (74.3%) were having blood loss in range of 200-400 ml in group 2. Blood loss in group 2 was comparatively lesser than that in group 1 but this difference was not found to be statistically significant (p=0.164).

Table 2: Distribution of women according to the requirement of intra-operative blood transfusion

Intra-operative blood transfusion (Packed cell)	Group 1 Frequency (%) (n = 35)	Group 2 Frequency (%) (n = 35)	P value
No	23 (65.7%)	32 (91.4%)	0.058 [95% CI = -0.57 to1.54]
1-unit	9 (25.7%)	3 (8.6%)	
2-units	2 (5.7%)	0 (0%)	
3-units	1 (2.9%)	0 (0%)	
Total	35 (100%)	35 (100%)	
Mean ± SD	0.457 ± 0.730	0.085 ± 0.279	

Table 2 illustrates mean requirement of intra-operative blood transfusion was 0.457±0.730 units in group 1 and 0.085±0.279 units in group 2. When compared among groups, no statistical significant difference found (p=0.058).

Present study shows that 11.4% women in group 1 and 5.7% women in group 2 required additional medical intervention in form of misoprostol and 5.7% in group 1 and none in group 2 in the form of misoprostol + carboprost. No statistical significance was observed on comparison between group 1 and group 2 as far as need of additional medical intervention is concerned (p >0.05). Study illustrates that in group 1, 17.1% women required additional surgical intervention intraoperatively while none in group 2 with a p-value of 0.001 which is statistically highly significant while no statistically significant difference was observed during comparison between group 1 and group 2 (p=0.161).

Table 3: Side effects of tranexamic acid

Side effects	Group 1 Frequency (%) (n = 35)	Group 2 Frequency (%) (n = 35)	p value
Nausea	8 (22.9%)	0 (0.0%)	<0.001 HS
Vomiting	8 (22.9%)	0 (0.0%)	<0.001 HS

HS = highly significant.

Table 3 illustrates that 22.9% women in intravenous tranexamic acid group showed nausea and vomiting post-operatively. None

of the women showed nausea, vomiting in topical tranexamic acid group. No other side effects like thromboembolism till hospital stay or seizure episodes noted in both groups. This observed difference was statistically highly significant (p<0.001).

In the present study, 20% women developed postpartum hemorrhage (blood loss >500 ml) in group 1 and 5.7% in group 2. The p-value was found to be <0.001 in terms of postpartum hemorrhage as maternal complication which is statistically highly significant. No significant difference was found on comparison between group 1 and group 2 for postpartum hemorrhage (p=0.151).

Table 4: Post-operative hemoglobin level

Postoperative hemoglobin (g/dl)	Group 1 Frequency (%) (n = 35)	Group 2 Frequency (%) (n = 35)	P value
4.0 - 6.9	3 (8.6%)	2 (5.7%)	0.357 [95% CI = -0.65 to 0.85]
7.0 - 8.9	9 (25.7%)	14 (40.0%)	
9.0 - 10.9	22 (62.9%)	16 (45.7%)	
≥11	1 (2.9%)	3 (8.6%)	
Total	35 (100%)	35 (100%)	
Mean ± SD	8.85 ± 1.26	8.75 ± 1.30	0.983

Table 4 illustrates mean post-operative hemoglobin was 8.85±1.26 g/dl in group 1 and 8.75±1.30 g/dl in group 2. No statistically significant difference was observed on comparison between group 1 and group 2 (p=0.357).

Mean change in hemoglobin concentration from pre-operative hemoglobin to post-operative hemoglobin was 0.734±0.35 g/dl in group 1 and 0.569±0.25 g/dl in group 2. No statistically significant difference was observed on comparison of the same between group 1 and group 2 (p=0.080). 11.4% women in group 1 and 5.7% in group 2 required blood transfusion post-operatively. Mean requirement of post-operative blood transfusion was 0.20±0.575 units in group 1 and 0.057±0.232 units in group 2. There was no statistical significance observed on comparing group 1 and group 2 in terms of post-operative blood transfusion (p=0.183).

Mean birth weight was 2.41±0.52 kg in group 1 and 2.42±0.57 kg in group 2 (p>0.05). Apgar score of neonates at 1 minute and 5 minute shows 2.9% in group 1 while none in group 2 were having score less than 7 (p>0.05). Similarly, 2.9% in group 1 while none in group 2 were having Apgar score at 5 minute less than 7 (p>0.05). No statistically significant difference was observed on comparing Apgar scores at 1 minute and at 5 minute in the two groups. No Neonate in group 1 and 2.9% in group 2 were born with very low birth weight with no significant difference statistically. On other hand, 45.7% in group 1 and 51.4% in group 2 were having low birth weight. Neonates born premature were 45.7% in group 1 and 68.7% in group 2. Total 14.3% neonates were transferred to NICU in group 1 and 17.1% in group 2. The observed difference was statistically insignificant with a p-value of >0.05. Mean hospital stay was 4.31±2.53 days in group 1 and 4.14±3.18 days in group. The difference was found to be statistically insignificant on comparing group 1 and group 2 (p=0.992).

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.

Mean age was 27.31±5.62 years in group 1 and 28.06±6.73 years in group 2. This observation was found to be statistically insignificant. In study by Sekiguchi *et al.* [17], mean age was 33.5±4.4 and 33.4±4.4 years in complete and incomplete placenta previa groups respectively which is higher than mean age in our study.

Most women in our study were nullipara where 48.6% in group 1 and 40% in group 2 (p>0.05). Similar finding was observed by Sekiguchi *et al.* [17] which concluded that most women with placenta previa were nulliparous (42%). Kaur *et al.* [18] also found that more than 50% of the women having placenta previa were multiparous. In study by Naik *et al.* [19], maximum number of cases of placenta previa were found to be multigravida (79.26%).

Mean body weight was 63.2±6.12 kg in group 1 and 61.49±6.12 kg in group 2 with no statistically significant difference (p >0.05). Mean body weight was similar in two groups (66.58±7.02 kg versus 64.50±9.22 kg) with no statistically significant difference (p=0.27) in study conducted by Shahid *et al.* [20].

In the present study, mean pre-operative systolic blood pressure was 112.74±8.79 and 113.49±10.57 mmHg in group 1 and 2 respectively, while diastolic blood pressure was 75.37±8.21 and 76.34±6.70 mmHg respectively. Mean pre-operative pulse rate was 91.77±6.74 and 92.17±7.49 per minute in group 1 and 2 respectively. The difference was statistically insignificant in terms of pre-op vitals (p=0.864, 0.261).

The findings are in agreement to the study conducted by Salem *et al.* [21] were similar in study group and control group. Mean systolic blood pressure was 115±10.24 versus 113±12.06 mmHg, diastolic blood pressure was 78.90±5.18 versus 80.09±4.00 mmHg and pulse rate was 85±5.7 versus 84±4.9 per minute in study group and control group respectively with no statistically significant difference.

In our study, majority of the women presented with bleeding per vaginum among all groups with 77.1% in group 1 and 2 each (p=0.201). Women presented with labour pains were 11.4% in group 1 and 8.6% in group 2 (p=0.137). This observation was found to be statistically insignificant. Only 6.66% women presented with labour pains as opposed to 35.8% in the study done by Sekiguchi *et al.* [17] in 2013. Lower incidence in our study may be due to the fact that minor degree placenta previa cases delivered vaginally.

Prior cesarean delivery is a risk factor for placenta previa. In present study, 20% women in group 1 and 22.9% women in group 2 had previous cesarean delivery with no statistical significance (p=0.878). There was no history of other surgeries like myomectomy in our study. The incidence of prior cesarean delivery was 11.7% in the study by Sekiguchi *et al.* [17], 12.05% in study by Sushma *et al.* [22] and 20.75% in study by Naik *et al.* [19].

In the present study, in 8.6% women in group 1 had history of previous D&C and 11.4% in group 2 (p>0.05). Sekiguchi *et al.* [17] in a study observed that previous history of D&C was found in 35.8% of women with placenta previa. Previous history of D&C in our study was lesser as compared to this study which may be due to the fact that majority of women in our study were primigravida.

Present study shows that 25.7% women in group 1 and 17.1% women in group 2 presented with Malpresentation.

Malpresentation included breech, oblique and transverse lie. This result is comparable to previous studies by Sushma *et al.* [22] (14.81%), Kaur *et al.* [18] (21.05%) and Naik *et al.* [19] (18.87%).

A total of 2.9% women in group 1 and none in group 2 had absent fetal heart sound on ultrasonography indicating intrauterine death of fetus at the time of presentation. This is comparable to the stillbirth rate of 5.26% in the study by Kaur *et al.* [18].

In our study, most of the women who underwent cesarean delivery had type IV placenta previa i.e. 48.6% in group 1 and 54.3% in group 2 (p>0.05). The findings are comparable to the study by Kaur *et al.* [18] who observed 81.58% women with major degree placenta previa.

In the present study, mean pre-operative hemoglobin level was 9.59 ± 1.35 g/dl in group 1 and 9.30±1.33 g/dl in group 2 (p>0.05). In study by Yehia *et al.* [23] found that pre-operative hemoglobin level was 11.8±1.5 g/dl in study group and 11.9±1.2 g/dl in control group with no statistical significance (p=1.000).

In our study, the mean pre-operative INR was 0.99±0.14 in group 1 and 0.97±0.15 in group 2 (p>0.05). The mean pre-operative platelet count was 2.01±0.39 and 1.97±0.42 lac in group 1 and 2 respectively (p>0.05).

In present study, 8.6% in group 1 and 14.3% in group 2 required pre-operative blood transfusion in the form of packed cell. Mean requirement of pre-operative blood transfusion was 0.143±0.486 units in group 1 and 0.171±0.446 units in group 2 (p>0.05).

Some patients necessitate preterm cesarean section for life-threatening hemorrhage. Mean gestational age at delivery was 36.69±2.35 weeks in group 1 and 35.86±2.35 weeks in group 2 with no statistical significance among groups (p >0.05). Similarly, Shady *et al.* [24] observed that the mean gestational age was 36.45±0.90 weeks in group 1 and 36.40±0.93 weeks in group 2 with no statistical significance (p >0.05).

In our study, mean blood loss was 464.86±28.00 ml in group 1 and 420.46± 69.75 ml in group 2. A study by Shahid *et al.* [20] concluded that intravenous tranexamic acid significantly reduced the quantity of blood loss from placental delivery to the end of cesarean section which was 356.44±148.20 ml in tranexamic acid group versus 710.22±216.72 ml in placebo group (p<0.001).

In our study, 34.3% in group 1 and 8.6% in group 2 required blood transfusion intra-operatively. Mean requirement of intra-operative blood transfusion was 0.457±0.730 units in group 1 and 0.085±0.279 units in group 2. Our study shows that the use of tranexamic acid in cesarean section reduces the need of intra-operative blood transfusion. Reducing intra-operative blood loss would lower the risks and cost associated with blood transfusion. Our findings are in agreement with that of study by Shahid *et al.* [20] and Goswami *et al.* [25] Shahid *et al.* [20] observed that 33% women required blood transfusion in placebo group as compared to intravenous tranexamic acid group in which only 8% women required blood transfusion.

In our study, it was observed that majority of women in tranexamic acid group (both group 1 and 2) did not require additional medical intervention intra-operatively in form of uterotonics like misoprostol or misoprostol plus carboprost. The difference was found to be statistically insignificant (p=0.232). Our study is comparable to the study conducted by Sujata *et al.* [26] in which 83% women in control group and 23% women in intravenous tranexamic acid group needed additional uterotonics intra-operatively (p<0.001). This study concluded that intravenous tranexamic acid administered at least 10 minutes before skin incision or topical application on placental bed significantly reduced the requirement for additional uterotonic drugs.

In group 1, 17.1% women required additional surgical interventions, however, none required in group 2. This observation was statistically highly significant (p=0.001). Our findings are comparable to that of previous study by Shady *et al.* [24] in which 52.5% women in control group required additional intra-operative surgical interventions in form of uterine artery ligation and internal iliac artery ligation while 17.5% required surgical intervention in each intravenous and topical tranexamic acid group. The difference observed was statistically significant (p=0.001).

Tranexamic acid administered intravenously caused nausea and vomiting in 22.9% women. None of them showed nausea, vomiting or any other side-effects like thromboembolic episode in topical tranexamic acid group. This observed difference was statistically significant (p<0.001). Our results are in accordance with study done by Shady *et al.* [24] which concluded that the incidence of nausea and vomiting was higher in intravenous tranexamic acid group (22.5%) than topical (7.5%) with a p value of 0.122.

Incidence of postpartum hemorrhage was 20% in group 1 and 5.7% in group 2 with a p-value of <0.001. The difference observed is statistically significant. These findings are similar to study done by Salem *et al.* [21] in which incidence of postpartum hemorrhage was 59.3% in control group versus 24.9% in intravenous tranexamic acid group which was statistically highly significant (p<0.001).

Mean post-operative hemoglobin was 8.85±1.26 g/dl in group 1 and 8.78±1.30 g/dl in group 2. In the study by Shady *et al.* [24], mean post-operative hemoglobin was 9.04±1.01 g/dl and 9.01±1.04 g/dl in group 1 and 2 respectively (p>0.05). Yehia *et al.* [23] observed that post-operative hemoglobin level was 11.2±1.5 g/dl in study group and 9.6±1.2 g/dl in control group with statistically significant difference (p=0.01).

Mean decline in hemoglobin concentration was 0.734±0.35 g/dl in group 1 and 0.569±0.25 g/dl in group 2 with p<0.001. Similar to our study, Roy *et al.* [27] had comparable results in which decline in hemoglobin concentration was 0.26±0.22 g/dl in tranexamic acid group and 0.99±0.48 in control group. This study observed that the use of tranexamic acid in cesarean section led to less decline in hemoglobin concentration post-operatively (p<0.001).

It was observed in our study that 11.4% women in group 1 and 5.7% women in group 2 required blood transfusion post operatively. Mean requirement of post-operative blood transfusion was 0.20 ± 0.575 units in group 1 and 0.057 ± 0.232 units in group 2. Hence use of tranexamic acid either intravenously or topically significantly reduced the need for post-operative blood transfusion. This is because of the fact that tranexamic acid reduced perioperative blood loss and incidence of postpartum hemorrhage.

In the present study, 45.7% in group 1 and 54.3% in group 2 were having low birth weight. Mean birth weight was 2.41±0.52 kg in group 1 and 2.42±0.57 kg in group 2 (p>0.05).

The safety of giving tranexamic acid intravenously while the fetus was still in utero was a key concern. As a consequence, the neonatal outcome was meticulously evaluated by a neonatologist. In the present study, Apgar score of less than 7 at 1-minute and 5-minute was observed in 2.9% neonates in group 1 and none in group 2 (p >0.05). Similarly, study conducted by Roy *et al.* [27] found that the mean Apgar score at 1-minute and 5-minute were 7.06±1.25 and 8.66±1.00 in the study group and 7.18±1.35 and 8.64±0.98 in the control group respectively.

There was no significant difference in the Apgar scores between study and control group (p=0.559 and p=0.910).

Various perinatal complications like low birth weight, prematurity, NICU admissions, respiratory distress syndrome and birth asphyxia were found to be similar in both groups. In our study, 14.3% neonates in group 1 and 17.1% neonates in group 2 were transferred to NICU (p>0.05). Most neonates (37.2%) were transferred to NICU due to low birth weight, 2.9% neonates due to respiratory distress syndrome and 2.9% neonates due to severe birth asphyxia. Mean hospital stay in our study was 4.31±2.53 days in group 1 and 4.14±3.18 days in group 2.

In the present study, it was observed that tranexamic acid significantly reduced intra-operative blood loss. It also reduced the incidence of postpartum hemorrhage, need of additional uterotonics, need for intra-operative surgical interventions, intra and post-operative blood transfusion and led to less decline in hemoglobin concentration post-operatively. Tranexamic acid had no effect on Apgar score, perinatal outcome, NICU transfer, low birth weight or respiratory distress syndrome. Topical tranexamic acid use was not associated with adverse events like nausea and vomiting as opposed to intravenous use. Hence the study concluded that prophylactic adjunctive tranexamic acid application on placental bed in patients undergoing cesarean for placenta previa reduced the incidence of postpartum hemorrhage.

Conclusion

From the present study, it is concluded that tranexamic acid used prophylactically intravenously before skin incision or topical application on placental bed after placental delivery in patients undergoing cesarean section for placenta previa significantly reduces intra-operative blood loss. Tranexamic acid use also reduces incidence of postpartum hemorrhage, need for blood transfusion, need of additional uterotonics or additional surgical interventions in form of hemostatic sutures, balloon tamponade, uterine artery ligation or cesarean hysterectomy. Topical use of tranexamic acid on placental bed in patients with placenta previa undergoing cesarean section is equally effective in reducing the intra-operative blood loss and need for blood transfusion without increasing the risk of nausea, vomiting and theoretical risk of thromboembolism associated with intravenous route. Thus, topical tranexamic acid can be safely and effectively used on placental bed during cesarean section for placenta praevia to reduce blood loss.

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