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Role of Tranexamic Acid in patients with increased risk for Postpartum Hemorrhage Undergoing Cesarean Delivery in a Tertiary Care South Indian Teaching Hospital

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Conflicts of interest: No conflicts of interest to declare.

Abstract:

Background: Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality worldwide PPH responds to uterotonic drugs, including Oxytocin, Methyl Ergometrine, and Prostaglandins. Tranexamic acid is a synthetic lysine analog that exerts its effect by competitively blocking the lysine binding sites on plasminogen molecules, thus inhibiting the activation of plasminogen into plasmin, and acting as a fibrinolysis inhibitor. Consequently, clot breakdown is inhibited and excessive or recurrent bleeding is controlled.

Objective: To assess the effects of tranexamic acid among patients undergoing cesarean delivery who were at high risk of postpartum hemorrhage.

Methodology: A Randomized control trial was conducted in a tertiary care teaching hospital of South India. Women undergoing an elective or emergency cesarean delivery who were at high risk for postpartum hemorrhage were enrolled for the study. They were randomly assigned using sealed, opaque envelopes to receive 10 mg/kg tranexamic acid or normal saline 10 min before skin incision. The primary outcome was need for additional uterotonic drugs within 24 h after delivery.

Results: 50 patients were assigned to each group.P value <0.05 was considered to be significant after obtaining a chi square value.

Conclusion: As Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality worldwide more aggressive measures are needed for its prevention and control Intravenous tranexamic acid, administered before skin incision, significantly reduced the requirement for additional uterotonics among women at increased risk for postpartum hemorrhage.

Keywords: Tranexemic Acid, Post Partum Hemohhrage, Cesarean.

Introduction: Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality worldwide with the need for more aggressive measures for its prevention and control [1, 2]. PPH responds to uterotonic drugs, including Oxytocin, Methyl Ergometrine, and Prostaglandins though many adverse effects are associated with these drugs [3,4,5,6], oxytocin-receptor down regulation and desensitization following exposure to oxytocin leads to a lack of further improvement in uterine contractions irrespective of increased doses [7]. Oxytocin induced desensitization depends on the duration of oxytocin exposure over 4.2 h [4]. Hence, prolonged oxytocin labor augmentation makes the uterus refractory. In cases of abnormal placentation and retained placenta, the lower uterine segment fails to contract [3]; thus these does not respond well to uterotonic drugs because the lower uterine segment is poor in oxytocin receptors [8]. Uterine bleeding due to

hypertensive disorders and cholestasis of pregnancy [9] is caused by poor platelet quality or low plasma levels of coagulation factor, and therefore does not respond well to incremental doses of uterotonics. Thus, pharmacological interventions to prevent and control PPH should be beyond the use of uterotonic drugs [6]. Tranexamic acid is an inexpensive, antifibrinolytic drug long used to control bleeding due to surgery, menorrhagia or trauma [10,11]. Additionally, tranexamic acid has been shown to reduce bleeding during cesarean delivery as well as the need for additional uterotonic agents, albeit to a minimal degree. However, previous studies have been performed only in women with a standard risk for PPH and have not focused on assessing the effects of tranexamic acid in high-risk women[12,13]. The main aim of the present study was to assess the effects of tranexamic acid in women at high risk of PPH following cesarean delivery. The need for additional uterotonic drugs during the first 24 h was the primary endpoint.

Materials and Methods

Study population and Study duration: A randomized controlled trial was conducted at Owaisi Group of Hospitals , Hyderabad, India, between December 2014 to December 2016. Pregnant women who had at least one risk factor for PPH and who underwent elective or emergency cesarean delivery formed the **inclusion criteria**. The **Variables** considered were pregnancy-induced hypertension, use of oxytocin augmentation for at least 4 hrs, more than two previous cesarean deliveries, chorioamnionitis, oral temperature > 38.5 °C with a high leukocyte count after ruling out other sources of infection, general anesthesia, placenta previa, polyhydramnios (amniotic fluid index >95th percentile for the length of pregnancy as reported on prenatal ultrasonography), fibroids, multiparity (parity >4),multiple pregnancy, cholestasis, acrosomia (estimated birth weight >4 kg), and genital-tract injury. Patients were enrolled once the decision to undertake cesarean delivery (elective or emergency) was taken. Patients not willing to give informed consent for elective delivery, pregnant women with history of ischemic cardiac disease, hemodynamic instability, bleeding disorders, and known allergy to tranexamic acid, history of any thrombogenic episodes, anticoagulant use, and a history of kidney disease, and an operating surgeon with fewer than 10 years of experience formed the **exclusion criteria** of the study population. **Estimation of sample size**:previous studies involving normal obstetric populations showed that the incidence of additional uterotonic drug use in conjunction with [13] or without [15] tranexamic acid was 8.5% and 40%, respectively. Therefore, 40 patients were recruited to the present study to ensure an 80% power to detect a decrease in the primary outcome measure from 40% in the control group to 8.5% in the experimental group at a 5% level of significance.

Randomization, Masking and Plan of Work: The selected envelope was opened by the anesthesiologist in charge of the case, who then prepared the appropriate drug. Patients, obstetricians, and data analysts were masked to group allocation. Demographic characteristics, the indication for cesarean delivery, and preoperative hematocrit levels within the 24 h before delivery (in the absence of significant preoperative bleeding) were recorded.According to the allocated group, patients were given 10 mg/kg intravenous tranexamic acid (500 mg cyclocapron per 5 mL ampoule) diluted to 10 mL with normal saline (group T) or 10mL normal saline (Group C) 10 min before skin incision. Standard patient monitoring, including non invasive blood pressure measurement, electrocardiography, and pulse oximetry, was performed using an Intellivue MP 20 G5-M1019A monitor. Anesthesia was administered according to the

anesthesiologist's instructions. Any hypotension likely to be due to the anesthetic agents was treated by intravenous ephedrine as required. As soon as the umbilical cord was clamped after delivery, all patients received 5 IU intravenous oxytocin diluted to 5 mL with normal saline over 30 s (timed by stopwatch). All patients also received an infusion of 20 IU oxytocin in 450 mL normal saline over 3 h, followed by 10 IU oxytocin in 500 mL normal saline over the next 5 h. Following placental delivery by controlled cord traction, the uterus was exteriorized and massaged. Five minutes after the bolus administration of oxytocin, the obstetrician was allowed to request additional uterotonic drugs at any time during the surgery (in case of increased capillary ooze or unsatisfactory uterine tone towards the end of uterine closure) or within the first 24 h after delivery (in case of increased postoperative vaginal bleeding, defined as a change of more than three fully soaked pads in any one hour). In case of increased bleeding, additional oxytocin doses were administered according to the PPH protocol followed at our Hospital (Table 1). The endpoint for uterotonic drug administration was determined by the surgeon's clinical judgment. The requirement for additional uterotonics was recorded from the time of delivery for 24 h.

Method of quantification of blood loss: Blood loss was estimated by the difference in hemoglobin values assessed before delivery and 48 h after delivery according to the following formula [14]: {[(Hbpre−Hb48) ⁄ Hbpre] x [(0.3669 H3) + (0.03219 x W) + 0.6041]} + {(V x18)/ Hbpre}, Where Hb pre is the preoperative hemoglobin in g/dL, Hb48 is the postoperative hemoglobin at 48 h in g/dL, W is the patient's weight in kilograms, H is the height in meters, V is the total volume of blood transfused, and 18 is the hemoglobin concentration of the packed red blood cell units available at our Hospital. The need for perioperative blood transfusion (after excessive perioperative bleeding or postoperative hemoglobin < 8 g/dL), postoperative hemoglobin at 48 h, or any neonatal adverse events or thrombogenic events in the mother were also noted.

The primary outcome was the need for additional uterotonic drugs within the first 24 h after delivery.

Data Analysis: Data with a normal distribution were summarized as mean ± standard deviation. The $\chi 2$ test was used to compare the differences in variables between the two groups. A two-sided $P < 0.05$ was considered statistically significant.

Ethical approval was provided by the Hospital Ethics Committee. All participants provided written informed consent. After providing informed consent, participants were randomly assigned in a 1:1 ratio to receive tranexamic acid (group T) or to a control group (group C). Women were requested to randomly choose an envelope from a container of sealed, opaque envelopes. At the beginning of the study, the container was filled with opaque envelopes, each containing one sheet of paper with either a T or a C written on it.

Results & Discussion

Table 1 illustrates the order of drugs to be given in case of increased bleeding**.** Both groups contained 50 participants, their socio demographic characteristics are listed in Table 2.The two groups were similar in terms of the risk factors for PPH and patient demographics as shown in Table 2 and Figure 1 , and the indications for cesarean delivery depicted in Table 3 and Figure 2, Five patients in group C received tranexamic acid on the first day of surgery due to continued bleeding.

Nevertheless, they were not excluded from the study and was analyzed in the group to which she was originally assigned (group C) as treating a patient is rather more important than grouping them. Additional uterotonic drugs were required in significantly more patients group C than

in group T (P <0.05) illustrated in Table 5 and Figure 3.The chi square statistic was performed using SPSS Software and the chi square value was found to be 21.2519.P Value was calculated as 0.000282 significant at p<0.05. Each type of uterotonic drug was used significantly more in group C than in group T. Hemoglobin and hematocrit levels 48 h after delivery were found to be lower in group C than in group T. The estimated blood loss at 48 h was lower in group T than in group C. But no patients in group T had an estimated blood loss of more than 1000 mL, more than one-fourth of the patients in group C bled more than 1000 mL in the preoperative period. There was no significant difference in the proportion of patients who required a blood transfusion as depicted in Table 5. One of the patients in group C—who had a postoperative hemoglobin level of 7 g/L—refused the blood transfusion.

One neonate in group T developed seizures within the first 24 h due to maternal chorioamnionitis and was diagnosed with early neonatal sepsis.The present results suggest that the use of tranexamic acid among women at high risk of PPH after cesarean delivery reduces the need for additional uterotonic drugs. Furthermore, the median estimated blood loss 48 h after delivery was considerably lower among patients who received tranexamic acid than among those in the control group.*Gungorduk et al.* [13] performed a randomized, doubleblind, placebo-controlled study to assess the efficacy of tranexamic acid in blood loss reduction following an elective cesarean delivery in 660 women, and found that the mean estimated blood loss at 48 h was significantly when compared with the lower among women treated with tranexamic acid than among those in the placebo group (499.9 ± 206.4 mL vs. 600.7 ± 215.7 mL, respectively; P< 0.001). The blood loss among patients assigned to tranexamic acid was similar in the present study, but that in group C was much higher than that recorded by *Gungorduk et al.* [13]. This difference is probably attributable to the fact that women at increased risk of peripartum bleeding were excluded by *Gungorduk et al.* [13], whereas only women at a high risk of hemorrhage were included in the present study. Additionally, *Gungorduk et al.* [13] observed that the proportion of women given tranexamic acid who had an estimated blood loss of more than 1000 mL was significantly lower than that of the placebo group (7 [2.1%] vs. 19 [5.8%]), but the difference was not significant.With regard to additional uterotonic drugs, they were administered to more women in the present study than in that of *Gungorduk et al.* [13] (48 [14.5%] of 330 women in the control group and 28 (8.5%) of 330 in the tranexamic acid group received additional uterotonic drugs in the previous investigation), probably because only high-risk cases were included in the present study.Nevertheless, the tranexamic acid group of our study had a lower incidence of uterotonic use and the number of drugs used was also significantly lower than reported by *Gungorduk et al.* [13]. In 2006, *Balki et al*. [16] recommended a minimum oxytocin dose of 3 IU following cesarean delivery for labor dystocia.In the present study, however, a 5 IU dose was administered according to the center's protocol. Nevertheless, despite the higher dose, 5 patients in the control group still experienced increased bleeding. Of these 5 patients, only one responded to additional oxytocin, may be due to down regulation and desensitization of the oxytocin receptors leading to additional doses of oxytocin being ineffective [7].

A common mechanism underlying numerous causes of PPH is activation of the fibrinolytic system following placental delivery, leading to rapid degradation of fibrinogen and fibrin and an increase in plasminogen activators [8], which can last up to 10 h and worsen the bleeding. Tranexamic acid is a synthetic lysine analog that exerts its effect by competitively blocking the lysine binding sites on plasminogen molecules, thus inhibiting the

activation of plasminogen into plasmin, and acting as a fibrinolysis inhibitor. Consequently, clot breakdown is inhibited and excessive or recurrent bleeding is controlled [8]. Thus, tranexamic acid can reduce blood loss independent of its etiology. Tranexamic acid has been deemed a category B drug by the US Food and Drug Administration, and its use is safe during breastfeeding [8].Tranexamic acid is known to cause hypersensitivity reactions, this known fact about the drug lead to limitation of the study group to be small. Tranexamic acid was found to be safe for the fetus and did not increase the risk for thrombogenic episodes in the mother.

Tables & Figures

Table 1: Order of drugs to be given I case of increased bleeding

Steps	Drug Intervention	Time
1	Doubling the rate of oxytocin infusion	5 min after oxytocin bolus
2	Methylergometrine (200µg, intravenous)	10 min after step 1
3	Carboprost (250 µg, intramuscular)	10 min after step 2
4	Carboprost (250 µg, intramuscular)	15 min after step 3
5	Carboprost (250 µg, intramuscular)	15 min after step 4
6	Misoprostol (800 µg, sublingual)	15 min after step 5

Table 2: Socio demographic characteristics

Characteristics	**Group T n=50(%)**	**Group C n=50(%)**
Age		
16-20	16(32)	6(12)
21-25	12(24)	10(20)
26-30	10(20)	14(28)
31-35	7(14)	8(16)
36-40	5(10)	2(4)
Gravida		
Primi	24(48)	28(56)
Second	16(32)	17(34)
Multi	10(20)	15(30)
Pregnancy Outcome		
Live Birth	48(96)	48(96)
Males	26(52)	30(60)
Females	20(40)	17(34)
IUGR	2(4)	1(2)
Still Births	1(2)	1(2)
IUD	1(2)	1(2)
Drugs Prescribed		
Methylergometrine	2(10)	8(40)
Carboprost	3(15)	4(20)
Misoprost	2(10)	8(40)
Tranexemic Acid	50(100)	5(25)

Table 3: Risk Factors for Post Partum Haemohhrage.

Risk Factors for PPH	Group T n=50(%)	Group C n=50(%)	RR (95%CI)
Hypertension of pregnancy	5(10)	4(8)	1.25 (0.35-4.38)
Oxytocin augmentation over 4 h	4(8)	3(6)	1.33 (0.31-5.65)
< 2 previous cesarean Deliveries	8(16)	5(10)	1.60 (0.56-4.55)
Chorioamnionitis	2(4)	2(4)	1.00 (0.14-6.82)
General anesthesia	5(10)	2(4)	2.5 (0.50-12.2)
Placenta previa	6(12)	6(12)	2.5 (0.50-12.28)
Polyhydramnios	4(8)	8(16)	0.5 (0.16-1.55)
Fibroids	3(6)	5(10)	0.60 (0.15-2.37)
Multiparity	3(6)	6(12)	0.50 (0.13-1.88)
Twin pregnancy	3(6)	4(8)	0.75 (0.17-3.18)

Cholestasis of pregnancy	3(6)	1(2)	3.00 (0.32-27.87)
Macrosomia	3(6)	3(6)	1.00 (0.21-4.71)
Genital-tract injury	1(2)	1(2)	1.00 (0.06-15.54)
RR: Relative Risk 95%CI:95% confidence interval			

Figure 1: Risk Factors for Post Partum Haemohhrage

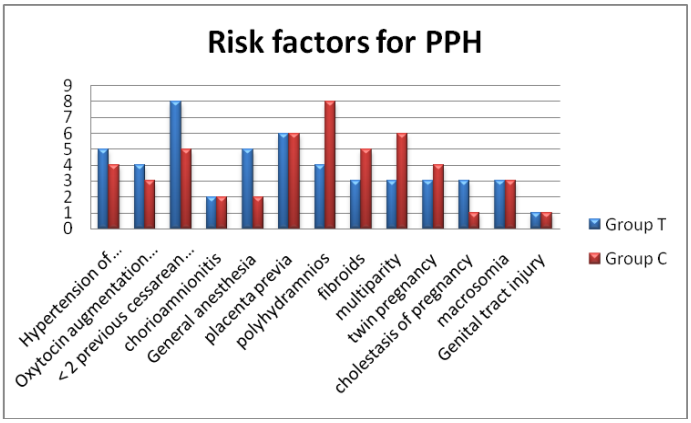


Table 4: Indication of Cesarean Delivery

Indication	Group T n=50(%)	Group C n=50(%)	RR (95% CI)
High blood pressure	8(16)	7(14)	1.14 (0.44-2.91)
Fetal distress	4(8)	6(12)	0.66 (0.20-2.21)
Impending uterine rupture	2(4)	4(8)	0.50 (0.09-2.60)
Non-progress of labor	12(24)	18(36)	0.66 (0.36-1.22)
Placenta previa	6(12)	4(8)	1.50 (0.45-4.99)
Failed Induction	6(12)	6(12)	1.00 (0.34-2.89)
Fibroid	2(4)	1(2)	2.00 (0.18-21.35)
Macrosomia	2(4)	1(2)	2.00 (0.18-21.35)
Previous cesarean delivery	6(12)	2(4)	3.00 (0.63-14.15)
Twin Pregnancy	2(4)	1(2)	0.64 (0.12-3.31)
RR:Relative Rsisk 95%CI:95% confidence interval			

Figure 2: Indication of Cesarean Delivery

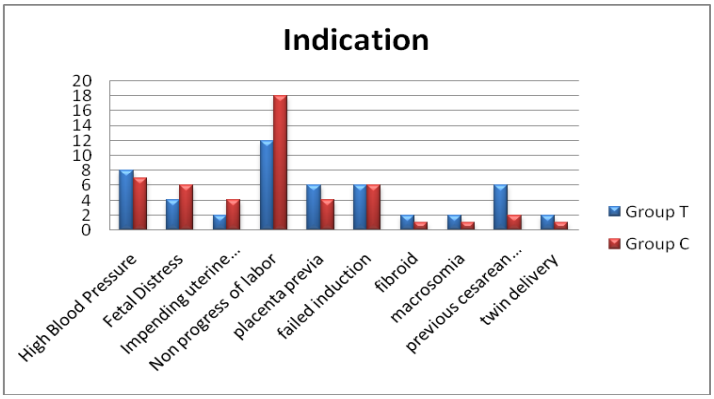


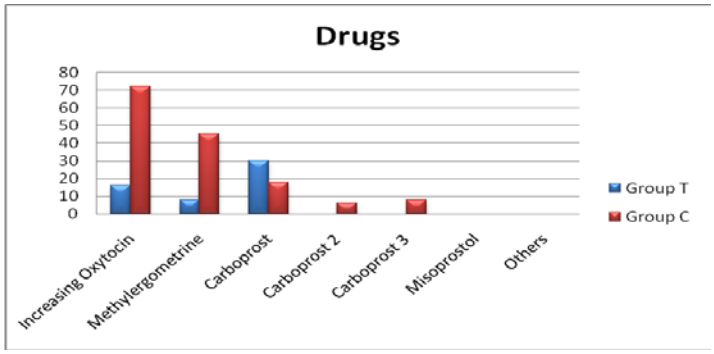
Table 5: Surgical Outcome

Outcome	Group T	Group C
Estimated Blood Loss, ml	547	942
Blood Loss > 1000 ml	12	23
Required Blood Transfusion	7	12
Additional Uterotonics	2	5

Table 6: Additional Uterotonic Drugs used

Drug	Group T	Group C
Increasing Oxytocin	16 (23.41)[2.31]	72(64.69)[0.85]
Methylergometrine	8(14.10)[2.64]	45(38.90)[0.96]
Carboprost	30(12.77)[23.25]	18(35.23)[8.43]
Carboprost 2	0(1.60)[1.60]	6(4.40)[0.58]
Carboprost 3	0(2.13)[2.13]	8(5.87)[0.77]
Misoprostol	0	0
Others	0	0

Figure 3: Additional Uterotonic Drugs used



The chi square statistic is 43.545.

The P value is 0.00001

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Conclusion

Postpartum hemorrhage (PPH) is one of the leading causes of maternal morbidity and mortality worldwide and more aggressive measures for its prevention and control are needed.Our study concluded that the intravenous tranexamic acid, administered at least 10 min before skin incision significantly decreases the requirement of an additional uterotonic drugs and perioperative blood loss during cesarean delivery among women at increased risk for postpartum hemorrhage.

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