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CLINICAL ARTICLE

Randomized controlled trial of tranexamic acid among parturients at increased risk for postpartum hemorrhage undergoing cesarean delivery

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ABSTRACT

Objective: To assess the effects of tranexamic acid among patients undergoing cesarean delivery who were at high risk of postpartum hemorrhage. *Methods:* Between August 1, 2012, and April 30, 2013, a randomized controlled trial was performed at a tertiary care center in India. Women undergoing an elective or emergency cesarean delivery who were at high risk for postpartum hemorrhage were enrolled. They were randomly assigned using sealed, opaque envelopes to receive 10 mg/kg tranexamic acid or normal saline 10 min before skin incision. Anesthesiologists were not masked to group assignment, but patients and obstetricians were. The primary outcome was need for additional uterotonic drugs within 24 h after delivery. Analyses were by intention to treat. *Results:* Thirty patients were assigned to each group. Additional uterotonic drugs were required in 7 (23%) patients assigned to tranexamic acid and 25 (83%) patients in the control group ($P < 0.001$). *Conclusion:* Intravenous tranexamic acid, administered before skin incision, significantly reduced the requirement for additional uterotonics among women at increased risk for postpartum hemorrhage.
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1. Introduction

Postpartum hemorrhage (PPH) is the leading cause of maternal morbidity and mortality worldwide [1,2], and there is an urgent need for more aggressive measures for its prevention and control. The most common etiology for PPH is uterine atony, which responds to uterotonic drugs, including oxytocin, methylergometrine, and prostaglandins [3]. However, several adverse effects are associated with these drugs [3–6], and oxytocin-receptor downregulation and desensitization following exposure to oxytocin leads to a lack of further improvement in uterine contractions irrespective of dose increases [7]. Oxytocin-induced desensitization is dependent on the duration of oxytocin exposure and occurs over a clinically relevant time frame of 4.2 h [4]. Thus, prolonged oxytocin labor augmentation makes the uterus refractory to its effects.

Another cause of PPH is genital-tract trauma, for which the management is surgical. In cases of abnormal placentation and retained placenta, the lower uterine segment fails to contract [3]; these cases do not respond well to uterotonic drugs because the lower uterine segment is poor in oxytocin receptors [8]. Uterine bleeding due to other etiologies—e.g. 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 have to go beyond the sole use of uterotonic drugs [6].

Tranexamic acid is an inexpensive, antifibrinolytic drug long used to control bleeding due to surgery, menorrhagia [10], or trauma [11]. Additionally, tranexamic acid has been shown to reduce bleeding during cesarean delivery [12] as well as the need for additional uterotonic agents [13], 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.

The 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.

2. Materials and methods

A randomized controlled trial was conducted at Max Hospital, New Delhi, India, between August 1, 2012, and April 30, 2013. Pregnant women who had at least one risk factor for PPH and who were to undergo elective or emergency cesarean delivery were eligible for inclusion in the study. The risk factors considered were pregnancy-induced hypertension, use of oxytocin augmention for at least 4 h, 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

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index >95th percentile for the length of pregnancy as reported on prenatal ultrasonography), fibroids, multiparity (parity >4), multiple pregnancy, cholestasis, macrosomia (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 who had go undergo a category-1 emergency cesarean delivery (urgent threat to the life or the health of the mother or fetus) were not enrolled because informed consent could not be obtained. Other exclusion criteria were a history of ischemic cardiac disease, hemodynamic instability, bleeding disorders, known allergy to tranexamic acid, history of any thrombogenic episodes, anticoagulant use, a history of kidney disease, and an operating surgeon with fewer than 10 years of experience. Ethical approval was provided by the Max Healthcare Scientific and 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. 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; Pfizer Ltd., Puurs, Belgium) diluted to 10 mL with normal saline (group T) or 10 mL 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 (Philips, Boeblingen, Germany). 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 (wotocin 5 U/mL; Wochkardt Ltd., Aurangabad, India) 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 Max 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.

Table 1
Order of drugs to be given in case of increased bleeding.

Step	Drug/intervention	Time
1	Doubling the rate of oxytocin infusion	5 min after oxytocin bolus
2	Methylergometrine (200 μg, 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

Blood loss was estimated by the difference in hemoglobin values assessed before delivery and 48 h after delivery according to the following formula [14]:

$$\left\{\left[\left(Hb^{pre} - Hb^{48}\right)/Hb^{pre}\right] \times \left[\left(0.3669 \times H^3\right) + (0.03219 \times W) + 0.6041\right]\right\} + \left\{(V \times 18)/Hb^{pre}\right\},$$

where Hb^{pre} is the preoperative hemoglobin in g/dL, Hb^{48} 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 Max Hospital.

The need for perioperative blood transfusion (after excessive perioperative bleeding or postoperative hemoglobin <80 g/L), 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. The secondary objectives were the estimated blood loss, blood transfusion requirements, and any neonatal adverse events or thrombogenic episodes in the mother.

Two 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, 60 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.

An intention-to-treat analysis was performed using the SPSS version 17.0 program for Windows (SPSS Inc, Chicago, IL, USA). A Shapiro–Wilk test was conducted to verify the distribution of the data. Data with a normal distribution were summarized as mean ± standard deviation, whereas those with a skewed distribution were described as median (interquartile range). The χ^2 test was used to compare the differences in variables between the two groups. The Student *t* test was used for continuous, normally distributed variables. The Mann–Whitney test was used to test independent relationships between the variables that did not demonstrate normality. A two-sided $P < 0.05$ was considered statistically significant.

3. Results

Both groups contained 30 participants (Fig. 1). The two groups were similar in terms of the risk factors for PPH (Table 2), patient demographics (Table 3), and the indications for cesarean delivery (Table 4). One patient in group C received tranexamic acid on the first postoperative day because of continued bleeding. Nevertheless, because an intention-to-treat analysis was used, she was not excluded from the study and was analyzed in the group to which she was originally assigned (group C).

Additional uterotonic drugs were required in significantly more patients group C than in group T ($P < 0.001$) (Table 5). Each type of uterotonic drug was used significantly more in group C than in group T (Table 6). Hemoglobin and hematocrit levels 48 h after delivery were significantly lower in group C than in group T ($P = 0.001$ and $P = 0.011$, respectively) (Table 5).

The estimated blood loss at 48 h was lower in group T than in group C ($P < 0.001$) (Table 5). Whereas no patients in group T had an estimated blood loss of more than 1000 mL, more than one-fifth in group C bled more than 1000 mL in the perioperative period ($P = 0.011$) (Table 5). There was no significant difference in the proportion of patients who required a blood transfusion (Table 5). One of the patients in group C—who had a postoperative hemoglobin level of 69 g/L—refused the blood transfusion.

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