

# Sublingual Misoprostol vs Intravenous Tranexamic Acid in reducing Blood Loss during Cesarean Section: A Prospective Randomized Study

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## ABSTRACT

**Introduction:** The increasing incidence of cesarean sections in India has caused a rise in the incidence of postpartum hemorrhage (PPH). There has been expanding interest in the role of misoprostol and tranexamic acid (TXA) in preventing and managing PPH during lower (uterine) segment cesarean section (LSCS). However, the lack of a published study comparing the efficacies of these drugs prompted us to conduct this study.

**Aims and objectives:** To compare the efficacies of sublingual misoprostol (600 µg) and intravenous TXA injection (500 mg) in reducing blood loss during LSCS by assessing intraoperative blood loss, perioperative hemoglobin (Hb) fall, and need for additional uterotonic agents.

**Materials and methods:** A total of 163 pregnant patients undergoing emergency/elective LSCS during the study period from 2013 to 2014 were randomly assigned to two groups – group I (82) received sublingual misoprostol 600 µg and group II (81) intravenous TXA 500 mg at cord clamping. Visual estimation of blood loss was done and 48 hours postoperative Hb and packed cell volume were measured to compare with preoperative values. Need for added uterotonics, blood transfusion, and adverse effects of drugs was assessed. The two groups were again subgrouped based on presence or absence of risk factors for PPH.

**Results:** The TXA significantly reduced blood loss compared with misoprostol (416 vs 505 mL) in patients without high-risk factors for PPH. Misoprostol caused significantly higher minor side effects while TXA reduced operation time.

**Conclusion:** The TXA can be routinely used after cord clamping along with oxytocin in patients undergoing elective/emergency LSCS to reduce perioperative blood loss, especially in those without risk factors for PPH.

**Keywords:** Cesarean section, Hemorrhage, Misoprostol, Tranexamic acid.

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## INTRODUCTION

Obstetric hemorrhage is the leading cause of maternal mortality worldwide, irrespective of mode of delivery. Cesarean section is one of the most commonly performed major operations in women throughout the world, escalating to between 20 and 30% in most developed countries over the past four decades.<sup>1</sup> India is representative of the magnitude of this problem. The increasing incidence of cesarean section has contributed to postpartum hemorrhage (PPH), as the average blood loss during cesarean section is twice that during vaginal delivery.<sup>2</sup>

Although the value of routine oxytocins to reduce PPH after vaginal birth has been well established, their value in cesarean section has received little attention. It has been assumed that the benefits of oxytocins observed at vaginal birth also apply to cesarean section. However, 10 to 42% of women receiving oxytocin were found to require additional oxytocin agents, such as ergot alkaloids and prostaglandins.<sup>3</sup> Moreover, oxytocin may not be the ideal agent for prevention of PPH in patients with preeclampsia, prolonged labor, or cardiac disease.<sup>4,5</sup> In addition, oxytocin is both light and heat sensitive, and requires cold storage, which limits its use in developing countries.

Misoprostol has been proposed as an alternative to injectable uterotonic agents for preventing PPH following vaginal or cesarean delivery. Misoprostol is a prostaglandin E1 analogue, which has strong uterotonic activity through selectively binding E-series prostanoid receptors (Ep2/Ep3) and is also relatively inexpensive and is stable at room temperature with a long shelf-life. As a consequence, the World Health Organization has enlisted it as an essential medicine for primary PPH in 2011, especially for resource-poor countries.<sup>6</sup>

It is well absorbed when administered by oral, buccal, sublingual, vaginal, or rectal routes.<sup>7</sup> A pharmacokinetic

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study found that sublingual misoprostol has the shortest time to peak concentration, the highest peak concentration, and the greatest bioavailability when compared with other routes. The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration, it takes 75 minutes. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first-pass metabolism via the liver. The abundant blood supply under the tongue and the relatively neutral pH in the buccal cavity may be contributing factors. However, sublingual administration, which gives the highest  $C_{max}$  is also associated with the highest incidence of side effects when compared with other routes.<sup>8</sup>

Another popular approach is to minimize perioperative bleeding through the prophylactic use of the antifibrinolytic agent, tranexamic acid (TXA). The TXA is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine-binding sites on plasminogen molecules. There have been studies that showed that TXA injection significantly reduced the blood loss from the placental delivery to 2 hours postpartum without complications of thrombosis.<sup>9-11</sup>

We had gone through various studies regarding drugs used to control blood loss during cesarean section. However, even with the best of our efforts, we could not come across a published study that compared the efficacies of misoprostol and TXA in order to adopt the practice of routinely administering the better of the two along with oxytocin during cesarean section to prevent PPH. It was hoped that an orally/sublingually active drug would be preferred by surgeons against a parenteral injection. It was the dearth of any published data on this matter and the desire to assess difference in efficacies, if any, of these drugs, in patients with and without high-risk factors for PPH undergoing lower (uterine) segment cesarean section (LSCS), which prompted us to conduct this study.

## MATERIALS AND METHODS

This prospective randomized controlled study was conducted in pregnant patients who attended the Department of Obstetrics and Gynecology of the Malabar Institute of Medical Sciences, Calicut, Kerala, India and had undergone emergency or elective cesarean section during the study period from November 2013 to June 2014.

### Inclusion criteria

Consenting women between the ages of 18 and 39 years with singleton pregnancy undergoing emergency or elective cesarean section, irrespective of indication, previous cesarean or high-risk factors for PPH like induced/augmented labor, hypertensive disorders, gestational

diabetes, obesity, premature rupture of membranes, chorioamnionitis, and antepartum hemorrhage.

### Exclusion criteria

Multiple pregnancies, age <18 or >39 years, associated renal/hepatic disorders, thromboembolic/bleeding disorders, cesarean section under general anesthesia, and known hypersensitivity to misoprostol or TXA.

Sample size was calculated using equation  $n = 2 (Z\alpha + Z\beta)^2 \sigma^2 / \delta^2$ , where  $Z\alpha$  is the table value for  $\alpha$ ,  $Z\beta$  the table value for  $\beta$ ,  $\sigma$  is the pooled standard deviation (SD) of blood loss,  $\delta$  is the difference in blood loss between two groups,  $\alpha$  is Type I error,  $\beta$  is the Type II error. The  $\alpha$  was fixed as 0.05 and  $\beta$  as 0.1, so that power was 90% and  $\delta$  was considered to be 50 mL, and thus, the sample size required per treatment group was calculated to be 66.

A total of 163 patients were studied. Ethical clearance was obtained from the ethical committee of the hospital and informed consent was taken from all subjects. Preoperative Hb and packed cell volume (PCV) were checked for all patients. They were then assigned randomly to two groups to receive either of the two study drugs during LSCS, at the time of cord clamping.

Group I (82 patients) received 600  $\mu$ g misoprostol sublingually, while group II (81 patients) received intravenous injection of 500 mg TXA. The drugs were administered by the anesthetist. Simultaneously, all subjects received an intravenous infusion of oxytocin 20 U in 500 mL saline solution at 10 mL/min. The surgeon requested additional uterotonic agents on the basis of the clinical findings during surgery.

## OUTCOME

### Primary Outcome

Analysis of

- Intraoperative blood loss
- Perioperative hemoglobin (Hb) fall
- Need for additional uterotonic agents.

### Secondary Outcome

Assessment of

- Blood loss in presence and absence of high-risk factors for PPH
- Blood loss > 1000 mL (defined as PPH during cesarean section)
- Need for blood transfusion
- Side effects of drugs
- Operating time.

The quantity of blood loss in (mL) = (weight of the used mops – weight of the mops prior to the surgery) + the volume sucked in the suction bottle after placental

delivery. Postoperatively, Hb and PCV were checked 48 hours after the surgery. Randomization was by computer-generated random numbers. Blinding was not possible due to difference in the modes of administration of the two drugs.

### Statistical Methods

Data were analyzed using Statistical Package for the Social Sciences 17.0. Data on continuous measurement were represented as mean with SD. Median was calculated for nonparametric continuous variables. Data on categorical outcome were represented using frequency with percentages. Continuous variables between the treatment groups were compared using independent sample t-test/Mann-Whitney U test according to the normality of the data. Independent sample t-test was assessed using Levene's test for equality of variances and Kolmogorov-Smirnov test for normality. Categorical variables were analyzed using chi-square test for independence. For all tests, a p-value less than 0.05 was considered statistically significant.

### RESULTS

The distribution of the various variables in the two study groups has been depicted in Table 1.

### Confounding Factors

There was no significant difference between the two groups with respect to age, parity, gestational age, and preoperative Hb and PCV. Both groups were also similar with respect to distribution of primary/repeat cesarean

section, the indications for cesarean section, or presence or absence of high-risk factors for PPH.

The comparison of the different outcomes have been tabulated in Table 2.

### Intraoperative Blood Loss

Among patients with no high-risk factors for PPH, TXA significantly reduced blood loss compared with misoprostol (416 vs 505, p-value 0.023). But, in the presence of high-risk factors, the difference in blood loss between the treatment groups was not statistically significant (534 vs 478 mL, p-value 0.23). Overall, irrespective of the presence or absence of high-risk factors, there was a trend toward decrease in mean intraoperative blood loss in the tranexamic group as compared with misoprostol group, but with no statistical significance ( $470.30 \pm 192.548$  vs  $491.74 \pm 200.043$  mL,  $p = 0.487$ ).

### Perioperative Hb and PCV Fall

There was no statistical difference between the two groups regarding the perioperative Hb and PCV fall [TXA vs misoprostol with >10% Hb fall was 30.9 vs 22% (p-value 0.197)]. Mean postoperative Hb for tranexamic vs misoprostol was 11.01 vs 11.36 and mean PCV of 32.77 vs 33.92%.

### Other Parameters

No patient required blood transfusion. The need for additional uterotonics was almost similar in both the treatment groups (p-value 0.957). Mean operation time was significantly reduced in TXA group compared with misoprostol group (43.09 vs 46.77 minutes, p-value 0.023). This could be due to the possibly earlier effect of the

**Table 1:** Distribution of variables between the groups

	Treatment group		p-value
	Tranexamic	Misoprostol	
Age	27.14 ± 4.59	27.07 ± 4.58	0.931
Weight	74.38 ± 11.81	72.00 ± 1.66	0.20
Preoperative Hb	11.93 ± 1.19	12.22 ± 1.02	0.105
Preoperative PCV	36.17 ± 3.48	36.96 ± 2.91	0.118
<b>Parity</b>			
Primi	38 (46.9%)	38 (46.3%)	0.942
Multi	42 (51.9%)	42 (51.2%)	
Grand multi	1 (1.2%)	2 (2.4%)	
<b>Indications</b>			
Previous CS	31 (38.3%)	33 (40.2%)	0.34
PROM/PPROM	3 (3.7%)	0 (0%)	
Fetal distress	14 (17.3%)	8 (9.8%)	
Abnormal Doppler/CTG	3 (3.7%)	3 (3.7%)	
Others	30 (37%)	38 (46.3%)	
<b>High risk factors</b>			
Present	37 (45.7%)	42 (51.2%)	0.479
Absent	44 (54.3%)	40 (48.8%)	

PROM: Premature rupture of membrane; PPROM: Preterm premature rupture of membrane; CTG: Cardiotocography

**Table 2:** Comparison of outcomes between the two groups

	Treatment group		p-value
	Tranexamic	Misoprostol	
Birth weight	2.87 ± 0.54	2.96 ± 0.57	0.329
Blood loss	435 (207)	453 (275)	0.487
Without risk factors	416.0 ± 135.77	505.83 ± 214.94	0.023*
With risk factors	534.86 ± 229.09	478.23 ± 186.37	0.23
Reduction in Hb	0.92 ± 0.73	0.86 ± 0.63	0.576
Reduction in PCV	3.40 ± 2.40	3.04 ± 2.15	0.319
Operation time	40 (15)	45 (20)	0.023*
<b>Required additional uterotonics</b>			
Yes	26 (32.1%)	26 (31.7%)	0.957
No	55 (67.9%)	56 (68.3%)	
<b>Minor side effects</b>			
Yes	36 (44.4%)	51 (62.2%)	0.023*
No	45 (55.6%)	31 (37.8%)	

Continuous variables were presented as mean ± SD or median (IQR); IQR: Interquartile range

\*Significant at 5% level of significance



fibrinolytic action of TXA compared with misoprostol's uterotonic action. However, other possible confounding factors, such as individual surgeon expertise were not included in the assessment. This possibility requires further studies and evaluation.

### Side effects

No major intraoperative or postoperative adverse effects were noted in any group. Minor side effects like nausea, vomiting, and shivering were noted in both groups. Minor side effects were significantly higher in misoprostol group compared with TXA group (p-value 0.023).

### Cost-effectiveness

Misoprostol tablet was a single tablet manufactured by Cipla at a strength of 600 µg at a price of ₹ 52 per tablet. The TXA was an injection manufactured by Ozone, in a 5-mL vial at a strength of 100 mg/mL, and total dose of 500 mg at a price of ₹ 57 per vial. However, keeping in mind the lack of need for refrigeration and free availability in government supplies misoprostol can be more cost-effective in resource-poor settings. A detailed cost analysis would be required in this aspect.

## DISCUSSION

A cesarean section is the most common major operation performed on women worldwide. Despite routine use of oxytocin during cesarean delivery, a number of women, especially those at high risk, may develop uterine atony and hemorrhage either during surgery or in the immediate postoperative period, with serious consequences. Any modality of treatment, which helps in its prevention, will be useful in reducing maternal mortality and morbidity. Misoprostol is an evidence-based alternative to other uterotonic agents due to its wide availability, low cost, stability at room temperature, and ease of use.<sup>12</sup> Intravenous administration of TXA has been routinely used for many years to reduce hemorrhage during and after many surgical procedures. It has also been shown to be effective and safe in women undergoing LSCS.<sup>9,10</sup>

As there were no published studies comparing the efficacies of misoprostol with TXA, we had to analyze our results with existing data comparing misoprostol and oxytocin, and those between TXA and oxytocin infusion.

Blood loss at cesarean is difficult to assess accurately. In a study, visual assessment of blood loss was 33% less than the drape estimate, with the drape estimate correlating well with photospectrometry.<sup>13</sup> In the present study, to obviate the above limitation, perioperative changes in Hb between preoperative and the second postoperative day was also done to assess the blood loss indirectly.

There was a statistically insignificant reduction in blood loss in the TXA group compared with the misoprostol group, irrespective of the presence or absence of high-risk factors (470.30 vs 491.74 mL, p = 0.487). The blood loss in each group correlated with other individual studies. Sood and Singh<sup>14</sup> in their study, comparing 400 µg sublingual misoprostol and 20 U oxytocin with oxytocin alone have shown a mean intraoperative blood loss for misoprostol of 591 mL (n = 100). Our study used misoprostol at a dose of 600 µg as it was readily available as a single tablet and easy to administer in contrast to two tablets of 200 µg. Again, in a study by Gohel et al<sup>9</sup> comparing 1 gm TXA with oxytocin, they showed mean blood losses of 374 vs 472 mL (n = 100). Our study had instead used a 500 mg dose as it was the same strength used by a previous researcher in a pilot study in our institution and was found to significantly reduce blood loss, at a lower dose.

It is worth noting that a statistically significant reduction in blood loss was noted in patients without high-risk factors for hemorrhage in the TXA group vs the misoprostol group (416 vs 505 mL, p-value 0.023). This shows that TXA fares better than misoprostol in uncomplicated primary cesarean sections, which are at low-risk for atonicity and where the amount of hemorrhage relies solely upon the surgical trauma. However, when blood loss in patients with high-risk factors was analyzed, there was not much difference in the reduction in blood loss between the two drugs, which shows that there might be an interplay of various other factors that finally result in blood loss.

Blood loss >1000 mL, perioperative Hb and PCV fall, and requirement of additional uterotonics were similar in both treatment groups. On the contrary, minor side effects had a significantly higher incidence in the misoprostol group compared with the TXA group.

## CONCLUSION

The TXA significantly reduced blood loss compared with misoprostol in patients without high-risk factors for hemorrhage. However, the reduction in blood loss was not significant between the two groups in patients with high-risk factors. In view of the significantly higher incidence of minor side effects of misoprostol, TXA can be routinely used after cord clamping along with oxytocin in patients undergoing elective/emergency LSCS to reduce perioperative blood loss. Further larger sample studies on various dosing regimens of these drugs are possible in future.

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