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Role of Sublingual Misoprostol to Reduce Blood Loss at Delivery by Cesarean

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Original Research Article

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Abstract: This prospective randomized controlled study was carried with the purpose of assessing the efficacy of sublingual misoprostol in decreasing intra-operative blood loss and the need of additional uterotonic agents at cesarean delivery.
Keywords: Sublingual misoprostol, Blood loss, Cesarean delivery.

INTRODUCTION

Postpartum hemorrhage is a leading cause of preventable maternal mortality in developing world. Its prevention is important and the key component of safe motherhood.

Oxytocin is routinely used to prevent P.P.H. due to uterine atony. However despite its effectiveness, about 20-25% of women need additional uterotonic therapy [1,2]. Secondary uterotonic agents such as methylergometrin or 15- methyl prostaglandin F2 alpha are associated with adverse effects when administered within a dose range likely to be effective.

Misoprostol is a prostaglandin E1 analogue with good uterotonic properties and few adverse effects at therapeutic dose. Because of its utertonic properties misoprostol has been evaluated for both the prevention and treatment of postpartum hemorrhage [3]. It is readily absorbed when given by sublingual, buccal, oral, vaginal or rectal route. Its easy availability, having low cost, thermo-stability, long shelf life and ease of administration, all of which appear to make it particularly suitable for use in low resource setting in developing countries.

Thus misoprostol has been extensively evaluated for prevention and treatment of postpartal hemorrhage following vaginal and cesarean section delivery.

There are few randomized controlled trials evaluating its efficacy in reducing intra-operative blood loss and additional uterotonic therapy at cesarean delivery.

In present study misoprostol 400 microgram sublingually administered just after cutting the cord and intra-operative blood loss and need for additional uterotonic agents at cesarean delivery.

METHODS

One hundred women undergoing elective or emergency cesarean delivery in labor room at Nalanda Medical College and Hospital, Patna from July 2014 to June 2017 were assigned randomly to receive either 400microgram of misoprostol or placebo sublingually at the time of cord clamping. IV infusion of 20 units of oxytocin was started in all women at the same time. The primary outcome measures were intra-operative blood loss, need for additional uterotonic agents and peri-operative hemoglobin (Hb) fall.

All uterine incisions were low transverse type. At cord clamping, the medications was placed in the patient's sublingual space by the anesthesiologist. At the same time 20 units of oxytocin in 1000ml of saline solution was started at 10-15ml/min for ½ hr. followed by 2-4ml/min for next 2hrs. Placenta was removed by controlled cord traction after spontaneous separation. Uterus was exteriorized and all women received uterine massage. The surgeon requested additional uterotonic agents according to clinical finding during surgery like additional oxytocin was added to the standard oxytocin infusion, injection methyl ergometrine0.2ml IM and injection 15-methyl prostaglandin F2-250microgram IM as secondary uterotonic agents.

Table-1: Indication for cesaran delivery - data: number (percentage)

	Misoprostol No:50	Placebo No:50
Post cesarean	15(30%)	15(30%)
Dystocia	10(20%)	09(18%)
Fetal distress	09(18%)	10(20%)
Breech	09(18%)	07(14%)
Others	07(14%)	09(18%)

Uterine incision was closed in 2 layers with no.1 polyglactin. Visceral peritoneum was not closed. Parietal peritoneum was closed. Rectus sheath was approximated with no.1 polypropylene. Skin was closed by interrupted mattress stitch. Antibiotic injection Ceftriaxone + Sulbactam was given pre-operatively.

The primary outcome measures were intra-operative blood loss and the need for additional uterotonic agents and peri-operative hemoglobin fall.

Secondary outcome measures were shivering, pyrexia, nausea, and vomiting, post partal hemorrhage, blood transfusion, endometritis and hospitalization period.

Table-2: High Risk Factors DATA: Number (Percentage)

	Misoprostol No:50	Placebo No:50
Previous cesarean	15(30%)	15(30%)
Induced/augmented labor	12(24%)	15(30%)
Hypertensive disorder	8(16%)	04(08%)
Prom	8(16%)	10(20%)
Ante partum hemorrhage	04(08%)	04(08%)
Chorioamnionitis	03(06%)	02(04%)

Intra-operative blood loss was estimated by measuring blood in suction apparatus and sterile drapes tetras used. Additional uterotonic therapy included additional oxytocin, requirement, or the use of secondary uterotonic agents. Peri-operative fall in hemoglobin was calculated from pre-operative and second post-operative days hemoglobin estimation.

Pyrexia was considered when temperature more than 38.0 degree Celsius. Post-partal hemorrhage was defined when estimated blood loss at least 1000ml or more. Endomyometritis was estimated if uterine tenderness and pyrexia was present. Operative time was also abstracted from operative note. The length at post-operative hospital stay was calculated from medical records.

RESULTS

From July 2014 to June 2017, a total of 100 women were recruited in the study. Fifty were randomly assigned to misoprostol group and fifty to placebo group. There was no significant difference between two groups in respect to age, parity, gestational age and pre-operative hemoglobin. Both groups were also similar with respect to primary or repeated cesarean section and elective/emergency cesarean section. There was no difference in respect to indication and various high risk factors.

Mean intra-operative blood loss was significantly less in misoprostol group as compared to placebo. Mean intra-operative blood loss was significantly less in misoprostol group as compared to placebo group. Proportion of women with blood loss between 500ml and 1000ml was lesser with misoprostol.

Fewer women in misoprostol group needed additional uterotonics. Mean post-operative hemoglobin (gm) was significantly higher in the misoprostol group. Peri-operative blood loss and hemoglobin % fall was significantly less misoprostol group. Peri-operative hemoglobin fall of above 1gm was lesser in misoprostol group. Shivering was significantly high in misoprostol group. However there was no significant difference in the incidence of pyrexia, nausea and vomiting. Similarly there was no difference in endomyometritis or hospital stay period.

DISCUSSION

Cesarean section is the most common and important operation done on women throughout the world. Inspite of routine use of uterotonic oxytocin in cesarean section may develop uterine atony and hemorrhage during operation or immediately after operation –especially in high risk cases-having serious consequences.

Thus any modality of treatment which helps in its prevention will be useful in reducing maternal mortality and morbidity. Misoprostol is evidence based alternative to other uterotonic agents which may require a cold chain, skilled administration and have untoward effects in therapeutically effective doses. Misoprostol is widely available, low cost, stable at room temperature and ease of use which makes it a useful and ideal drug for use in such settings.

The mean intra-operative blood loss in the present study was significantly reduced in misoprostol group, which is similar to that reported by Zhao *et al*. as shown in table 4 whereas same studies has reported misoprostol to be as effective as oxytocin in reducing post-partal blood loss [4]. Lokugamage *et al.* [5] compared 500microgram oral misoprostol with 10 unit IV Syntocine and concluded that oral misoprostol could be used as an alternative oxytocic agent. In another study comparing 400 microgram sublingual misoprostol vs 20 units oxytocin infusion [6].

Blood loss at cesarean is difficult to assess accurately. In study, visual assessment at blood loss was 35% less than that drape estimate. In the present study peri-operative change in hemoglobin between pre-operative and second post-operative day was also done to assess the blood loss indirectly. In present study the need for additional uterotonic agents was significantly less.

Significant trend towards lesser peri-operative hemoglobin fall, which was found in this study which is similar to study [7] in which concomitant oxytocin infusion was given to all women, as in the present study.

Shivering, pyrexia, nausea, vomiting and diarrhea are common adverse effect of misoprostol and were dose related which is also reported similarly in literature however there is no difference in pyrexia. No difference in other maternal adverse effects such as nausea or vomiting was noted which is similar to that reported in the literature.

Table-3: Peri-operative morbidity - Number (Percentage)

	Misoprostol No:50	Placebo No:50
Shivering	10(20%)	04(08%)
Pyrexia	05(10%)	05(10%)
Nausea	05(10%)	04(08%)
Vomiting	02(04%)	01(02%)
Hospitalization period (in days)	8 days	7 days

In various studies dose of misoprostol ranged from 200 to 800 microgram. As the side effects are dose related, a dose of 400 microgram was chosen in present study to minimize maternal adverse effects with optimal therapeutic benefit. In the recent review 400microgram of misoprostol was found to be safer than 600 microgram [8].

Misoprostol is used by various routes-like oral, buccal, sublingual, rectal and even vaginal. In this study sublingual route was chosen because it avoids oral intake, does not disrupt operative field and ensures continuous plasma levels of this uterotonic agent over the prolonged period. Pharmacokinetic studies on various routes of administration have shown that sublingual route achieves the highest serum peak concentration and the shortest time to peak concentration [9,10].

Cesarean delivery is carried out in a setting where conventional oxytocins are available and active management of third stage of labor is invariably practiced. Misoprostol may have a role as an adjunct to oxytocin in prevention of PPH in high risk women, where other uterotonic agents are either contraindicated or not available. In present study 400 microgram by sublingual route appears to be promising. Several recent trails have confirmed efficacy of sublingual misoprostol in reducing blood loss at cesarean delivery [7,11].

CONCLUSION

Sublingual 400 microgram of misoprostol reduces intra-operative blood loss and the need for additional uterotonic agents at cesarean delivery. It has a role as an adjunct to oxytocin in the prevention of PPH in high risk women where other uterotonic agents are either contraindicated or not available.

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