Study on use of Sublingual Misoprostol to Reduce Blood Loss at Caesarean Delivery in Tertiary Care Centre

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Abstract
Objective: This prospective randomized controlled study was carried out with the purpose of assessing the efficacy of sublingual misoprostol in decreasing intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery.

Methods: One hundred 110 women undergoing elective or emergency cesarean delivery were assigned randomly to receive either 600 µg misoprostol or placebo sublingually at the time of cord clamping. Simultaneously oxytocin 20 units (10 units in IV drip and 10 Intramuscular) was given. The primary outcome measures were intraoperative blood loss, need for additional uterotonic agents, and perioperative hemoglobin (Hb) fall.

Results: The maternal demographic factors, indications for cesarean delivery were similar between the two groups. Mean intraoperative blood loss was significantly less in misoprostol group as compared with placebo group (510 ± 100 vs. 670 ± 110 ml). Fewer women needed additional uterotonic agents in misoprostol group (20.2 vs. 40.5 %). Perioperative Hb fall was significantly less in misoprostol group (0.77 ± 0.25 vs. 1.05 ± 0.25 g).

Conclusion: Sublingual misoprostol decreases intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery.

Keywords Sublingual misoprostol • Blood loss • Cesarean delivery.

Introduction
Postpartum hemorrhage is the leading cause of preventable maternal mortality in the developing world, and its prevention is assumed to be an important and rational strategy, and has been identified as a key component of safe motherhood. Oxytocin is routinely used to prevent uterine atony and excessive uterine bleeding during cesarean delivery. However, despite its effectiveness, 10-40 % of women need additional uterotonic therapy. Secondary uterotonic agents such as methyl ergometrine or 15-methyl prostaglandin F2 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 uterotonic properties, misoprostol has been evaluated for both the prevention and the treatment of...
postpartum hemorrhage. It is readily absorbed when given by oral, sublingual, buccal, vaginal, or rectal route. Its easy availability, relatively 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 settings in developing countries.

Although misoprostol has been extensively evaluated for prevention and treatment of postpartum hemorrhage following vaginal delivery, there have been a few randomized controlled trials evaluating its efficacy in reducing intraoperative blood loss and additional uterotonic therapy at cesarean delivery. Misoprostol in these trials has been administered by oral, buccal, or sublingual routes and compared mostly with oxytocin administered as IM/IV bolus, IV infusion, or intrauterine injection or with placebo. The present study was undertaken with the aim of assessing the efficacy of sublingual misoprostol in decreasing intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery.

Methods
This prospective randomized placebo controlled trial was conducted at Nalanda Medical College and Hospital, Patna. All women undergoing emergency or elective cesarean section were eligible for the study irrespective of indication, previous cesarean or high-risk factor. Informed consent was taken from all subjects. Women were assigned randomly to receive either 600 µg misoprostol or placebo sublingually at the time of cord clamping. All uterine incisions were low transverse type. At cord clamping, the medication was placed in the patient’s sub-lingual space by the anesthesiologist. Simultaneously, all women were given oxytocin 20 U (10 units by IV drip and 10 units IM) Placenta was removed by controlled traction after spontaneous separation. Uterus was exteriorized after delivery of placenta, and all women received uterine massage.

Uterine incision was closed in two layers with No 1 polyglactin. Parietal peritoneum was closed. Rectus sheath was approximated with No 1 polypropylene. Skin was approximated with subcuticular closure. Prophylactic antibiotic and post-operative antibiotics was given. The primary outcome measures were intraoperative blood loss and the need for additional uterotonic agents and perioperative hemoglobin (Hb) fall. Secondary outcome measures were shivering, pyrexia, nausea, vomiting, operating time, postpartum hemorrhage, blood transfusion, endomyometritis. Intraoperative blood loss was calculated by measuring blood in the suction apparatus and sterile drapes before irrigation and by evaluating the blood in abdominal swabs and gauzes. Additional uterotonic therapy included additional oxytocin requirement or the use of secondary utero-tonic agents. Perioperative fall in Hb was calculated from preoperative and second postoperative days’ Hb estimation. Pyrexia was defined as temperature more than 38.0 °C. Postpartum hemorrhage was defined as estimated loss of at least 1,000 ml. Endomyometritis was diagnosed if uterine tenderness and fever were present.

Results
From August 2013 to March 2014, a total of 110 women were recruited for the study. 60 were randomly assigned to misoprostol group and 50 to placebo group. All women received allocated intervention, completed follow up and were analysed according to group assignment. There was no significant difference between two groups with respect to age, parity, gestational age, and preoperative Hb. Both groups were also similar with respect to primary/repeat or elective/ emergency cesarean section or the type of anesthesia (Table 1). There was no difference between two groups with respect to the indication for cesarean section or various high-risk factors. Mean intraoperative blood loss was significantly less in misoprostol group as compared to placebo.
(510 ± 100 vs. 670 ± 110 ml. Fewer women in misoprostol group needed additional uterotonic agents in misoprostol group. Mean postoperative Hb (g) was significantly higher in the misoprostol group (9.70 ± 0.80 vs. 9.11 ± 0.50). Perioperative Hb fall was significantly less in misoprostol group (0.77 ± 0.25 vs. 1.05 ± 0.25 g).

Shivering was significantly more with misoprostol, However, there was no significant difference in incidence of pyrexia, nausea, or vomiting. Similarly, there was no difference in endometritis.

**Discussion**

Cesarean section is a very 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 which require a cold chain, skilled administration, and have untoward effects in therapeutically effective doses. Further, the drug’s wide availability, low-cost, stability at room temperature, and ease of use make it an ideal drug for use in such settings.

Zhao et al. [4] in their study comparing 600 µg oral misoprostol with oxytocin (20 U intrauterine plus 20 U IV) found misoprostol more effective in the reduction of postpartum bleeding. Acharya et al. [1] comparing the effectiveness of 400 ig oral misoprostol with 10 U IV syntocinon found misoprostol to be as effective as intravenous syntocinon in the reduction of intraoperative blood loss. Lokugamage et al. [5] compared 500 ig oral misoprostol with 10 U IV Syntocinon and concluded that oral misoprostol could be used as an alternative oxytocic agent. Hamm et al. [6] in a placebo controlled study concluded that 200 mcg buccal misoprostol reduced the need for additional uterotonic agents. In another study comparing 400 µg sublingual misoprostol versus 20 U oxytocin infusion, Vimala et al. [7] found sublingual misoprostol to be as effective as oxytocin. In a placebo-controlled double blind study, comparing 800 ig oral misoprostol with 20 U oxytocin infusion after initial administration of 5 U of IV oxytocin, Lapaire et al. [8] found misoprostol to be as effective as oxytocin in reducing postoperative blood loss.

The mean intraoperative blood loss in the present study was significantly less in misoprostol group, which is similar to that reported in two studies [4, 7].

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**TABLE 1 INDICATION FOR CESAREAN DELIVERY**

| Indication       | Misoprostol (N = 60) | Placebo (N = 50) |
|------------------|----------------------|------------------|
| Post Cesarean    | 20                   | 14               |
| Fetal distress   | 15                   | 10               |
| Malpresentation  | 5                    | 5                |
| Prolonged labour | 4                    | 5                |
| Hypertensive disorder | 6               | 5                |
| PROM             | 2                    | 3                |
| APH              | 4                    | 4                |
| Dystocia         | 4                    | 4                |

**TABLE 2 OPERATIVE FACTORS**

|                          | Misoprostol (N = 60) | Placebo (N = 50) |
|--------------------------|----------------------|------------------|
| Estimated Blood Loss     |                      |                  |
| Total (ml)               | 510 ± 100°           | 670 ± 110°       |
| <500 ml                  | 20                   | 07               |
| 500-1,000 ml             | 39                   | 41               |
| >1,000 ml                | 01                   | 02               |
| Additional uterotonic therapy | 10               | 20               |
| Blood transfusion        | 02                   | 01               |
| Postoperative Hb (g/dl)  | 9.70 ± 0.90          | 9.11 ± 0.50      |
| Perioperative Hb fall g/dl | 0.77 ± 0.25          | 1.05 ± 0.25      |

**TABLE 3 PERIOPERATIVE MORBIDITY**

|                      | Misoprostol (N = 60) | Placebo (N = 50) |
|----------------------|----------------------|------------------|
| Shivering            | 15                   | 3                |
| Pyrexia              | 10                   | 2                |
| Nausea               | 8                    | 5                |
| Vomiting             | 2                    | 2                |
However, some studies have reported no difference \cite{1,6,8}. Blood loss at cesarean is difficult to assess accurately. In the present study perioperative change in Hb between preoperative and the second postoperative day was also done to assess the blood loss indirectly.

The need for additional uterotonic agents was significantly less in the present study; this finding is similar to that reported in a similar study in which oxytocin infusion was given to all women \cite{6}. Some others have reported no difference \cite{1,7,8}.

IV Oxytocin injection appears in circulation within 15 s and reaches peak levels in 60 s with a half life of three min. Misoprostol appears in circulation within 20-30 min but stays longer. Thus, it may be useful to combine both drugs using IV oxytocin to achieve initial effect followed by misoprostol for more sustained effect. This may also be helpful in high-risk patients who are at increased risk of bleeding, but have contraindications for the use of secondary uterotonic agents \cite{1}.

Shivering, pyrexia, nausea vomiting, and diarrhea are common adverse effects of misoprostol and are dose related.

Oral, buccal, rectal, and sublingual routes have been used in different studies. Sublingual route was chosen because it avoids oral intake, does not disrupt operative field, and ensures continuous plasma levels of a potent uterotonic agent over a prolonged period. Pharmacokinetic studies on various routes of administration have shown that sublingual route achieved the highest serum peak concentration (C max), the shortest time to peak concentration (T max) of misoprostol acid, the active metabolite of misoprostol \cite{12-14}.

In a Cochrane review on prostaglandins for prevention of postpartum hemorrhage, it was concluded that neither intramuscular prostaglandin nor misoprostol was preferable to conventional injectable uterotonics as part of the active management of the third stage of labor especially for low-risk women \cite{15}. However, in this meta-analysis which included 37 misoprostol trials, only three pertained to cesarean delivery.

Misoprostol has been recommended in a dose of 600 mcg or 400 mcg by oral or sublingual route for prevention of PPH in the absence of active management of third stage of labor or non-availability of injectable conventional uterotonics \cite{16,17}.

Cesarean delivery is carried out in a setting where conventional oxytocics 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 postpartum hemorrhage in high-risk women, where other uterotonic agents are either contraindicated or not available. In the present study, 600 mcg by sublingual route appears to be promising.

**Conclusion**

Sublingual misoprostol reduces intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery. It may have a role as an adjunct to oxytocin in the prevention of postpartum hemorrhage in high-risk women, where other uterotonic agents are either contraindicated or not available.

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