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ORIGINAL ARTICLE

Sublingual Misoprostol to Reduce Blood Loss at Cesarean Delivery

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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 seventy-four women undergoing elective or emergency cesarean delivery were assigned randomly to receive either 400 μg misoprostol or placebo sublingually at the time of cord clamping. An intravenous infusion of 20 units of oxytocin was started in all women at the same time. 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, and high-risk factors were similar between the two groups. Mean intraoperative blood loss was significantly less in misoprostol group as compared with placebo group (595 ± 108 vs. 651 ± 118 ml, $P = 0.025$). Fewer women needed additional uterotonic agents in misoprostol group (22.2 vs. 42.8 %; $P = 0.0035$; RR 0.52, 95 % CI 0.33–0.82). Perioperative Hb fall was significantly less in misoprostol group (0.87 ± 0.29 vs. 1.01 ± 0.26 g, $P = 0.0018$).
Conclusion Sublingual misoprostol decreases intraoperative blood loss and the need for additional uterotonic agents at cesarean delivery.

Keywords Sublingual misoprostol · Blood loss · Cesarean delivery

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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 [1, 2]. Secondary uterotonic agents such as methyl ergometrine or 15-methyl prostaglandin $F_{2\propto}$ 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 [3]. 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. Though dose of misoprostol used in these trials has widely varied, most of them found misoprostol as effective as [1, 5–8] and—in one case more effective than—oxytocin [4].

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 Military Hospital Jhansi, Uttar Pradesh. 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 400 μg misoprostol or placebo sublingually at the time of cord clamping. Randomization was by computer-generated random numbers and the randomized allocations were kept secure in sequentially numbered opaque, sealed envelopes made at pharmacy containing either 400 μg misoprostol or placebo, which were opened in the operation room. At no time before the data analysis were the group assignments made available to anyone but the pharmacy.

All uterine incisions were low transverse type. At cord clamping, the medication was placed in the patient's sublingual space by the anesthesiologist. Simultaneously, for all women, an intravenous infusion of oxytocin 20 U in 1,000 ml saline solution was started at 10 ml/min for 30 min, which was followed by 2.0 ml/min for 6 h. Placenta was removed by controlled traction after spontaneous separation. Uterus was exteriorized after delivery of placenta, and all women received uterine massage. The surgeon requested additional uterotonic agents on the basis of the clinical findings during surgery. At the discretion of the obstetrician, additional oxytocin was added to the standard oxytocin infusion before secondary uterotonic agents were requested. Additional oxytocin was considered additional uterotonic intervention for purposes of data analysis. Inj Methyl ergometrine 0.2 mg IM and Inj 15-methyl prostaglandin $F_{2\propto}$ 250 μg IM were used as secondary uterotonic agents.

Uterine incision was closed in two layers with No 1 polyglactin. Visceral and parietal peritoneum was not closed. Rectus sheath was approximated with No 1 polypropylene. Skin was approximated with subcuticular closure. Prophylactic antibiotic Inj Cefazolin 2.0 g IV was given at cord clamping, except in women already on antibiotics.

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, and hospitalization period.

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 uterotonic 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. Operation time was abstracted from operation notes. The length of postoperative hospital stay was calculated from medical records.

Statistical Methods

A sample size and power analysis were undertaken before study. Ninety women were required in each arm to show a reduction in additional uterotonic therapy from 40 to 20 % with misoprostol (Power = 0.80, $\alpha = 0.05$ and $\beta = 0.2$). Based on estimated blood loss in women during cesarean section, taking mean blood loss 650 ml with a SD of 120 ml, 88 women were required in each arm to show a reduction of blood loss of 50 ml with misoprostol (Power = 0.80, $\alpha = 0.05$ and $\beta = 0.2$). Student's unpaired t tent was used for analysis of continuous variables. Categorical variables were analyzed by Chi square test or Fisher exact test if numbers were small. $P < 0.05$ was considered as the level of significance. Relative risk (RR) and 95 % confidence intervals (95 % CI) were calculated for categorical data. Statistical software Epi Info Version 3.2.2 (Center for Disease Control and Prevention Atlanta, Georgia, USA) was used for statistical analysis of data.

Results

From June 2003 to July 2005, a total of 174 women were recruited for the study. Ninty were randomly assigned to

misoprostol group and 84 to placebo group. All women received allocated intervention, completed follow up and were analyzed 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 (Tables 2, 3).

Mean intraoperative blood loss was significantly less in misoprostol group as compared to placebo (595 ± 108 vs. 651 ± 118 ml, $P = 0.025$). Proportion of women with blood loss between 500 and 1,000 ml was lesser with misoprostol. (74.4 vs. 87.0 %, $P = 0.038$, RR 0.86, 95 % CI 0.74–0.99) However, there was no difference in proportion of women with blood loss of 1,000 ml or more or the need for blood transfusion. Fewer women in misoprostol group needed additional uterotonic agents in misoprostol group (22.2 vs. 42.8 %; $P = 0.0035$; RR 0.52, 95 % CI 0.33–0.82). Mean postoperative Hb (g) was significantly higher in the misoprostol group (9.79 ± 0.99 vs. 9.51 ± 0.56, $P = 0.023$). Perioperative Hb fall was significantly less in misoprostol group (0.87 ± 0.29 vs. 1.01 ± 0.26 g, $P = 0.0018$). Perioperative Hb fall of 1 g or more was lesser in misoprostol group (64.4 vs. 86.9 %, $P = 0.00059$, RR 0.74, 95 % CI 0.62–0.88) (Table 4).

Shivering was significantly more with misoprostol (21.1 vs. 9.5 %, $P = 0.034$, RR 2.22, 95 % CI 1.03–4079). However, there was no significant difference in incidence of pyrexia, nausea, or vomiting. Similarly, there was no difference in endomyometritis or hospitalization period (Table 5).

Table 2 Indications for cesarean delivery

Data: number (percentage)			
	Misoprostol ($N = 90$)	Placebo ($N = 84$)	P
Post cesarean	26 (28.9)	22 (26.2)	NS, $P = 0.69$
Dystocia	23 (25.6)	18 (21.4)	NS, $P = 0.52$
Fetal distress	15 (16.7)	16 (19.0)	NS, $P = 0.68$
Breech	14 (15.6)	14 (16.7)	NS, $P = 0.84$
Others	12 (13.2)	14 (16.7)	NS, $P = 0.54$

Values in parentheses indicate percentage

None of the differences was significant

S Significant, *NS* Not significant

Discussion

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 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)

Table 1 Maternal demographics and procedure statistics

Data: mean ± SD or number (percentage)			
	Misoprostol ($N = 90$)	Placebo ($N = 84$)	P
Maternal age (yr)	26.0 ± 4.3[a]	25.5 ± 3.6	NS, $P = 0.36$
Parity	2.0 ± 0.8[a]	1.9 ± 0.6	NS, $P = 0.45$
Gestational age (wk)	38.2 ± 1.6[a]	37.7 ± 1.9	NS, $P = 0.06$
Preoperative Hb (g/dl)	10.67 ± 0.90[a]	10.53 ± 0.49	NS, $P = 0.19$
Cesarean			
Primary	61 (67.8)	53 (63.0)	NS, $P = 0.51$
Repeat	29 (32.2)	31 (37.0)	
Cesarean			
Emergency	57 (63.3)	58 (69.0)	NS, $P = 0.43$
Elective	33 (36.7)	26 (31.0)	
Anesthesia			
Spinal	85 (94.4)	78 (92.8)	NS, $P = 0.67$
Epidural	05 (5.6)	06 (7.2)	

All differences were not significant

S Significant, *NS* Not significant

[a] Mean ± SD, Values in parentheses indicate percentage

Table 3 High-risk factors

Data: number (percentage)			
	Misoprostol ($N = 90$)	Placebo ($N = 84$)	P
Previous cesarean	26 (28.9)	22 (26.1)	NS, $P = 0.69$
Induced/augmented labor	23 (25.5)	27 (32.1)	NS, $P = 0.34$
Hypertensive disorders	15 (16.7)	10 (11.9)	NS, $P = 0.37$
Premature rupture of membranes	15 (16.7)	18 (21.4)	NS, $P = 0.42$
Chorioamnionitis	06 (6.6)	04 (4.8)	NS, $P = 0.74$
Antepartum hemorrhage	05 (5.6)	03 (3.7)	NS, $P = 0.72$

Values in parentheses indicate percentage

None of the differences was significant

S Significant, *NS* Not significant

Table 4 Operative factors

Data: mean ± SD or number (percentage)				
	Misoprostol ($N = 90$)	Placebo ($N = 84$)	P	RR (95 % CI)
Estimated Blood Loss				
Total (ml)	595 ± 108[a]	651 ± 118[a]	S, $P = 0.0015$	
<500 ml	17 (18.9)	07 (8.3)	S, $P = 0.044$	2.27 (0.99–5.19)
500–1,000 ml	67 (74.4)	73 (87.0)	S, $P = 0.038$	0.86 (0.74–0.99)
>1,000 ml	06 (6.7)	04 (4.7)	NS, $P = 0.748$	1.40 (0.41–4.79)
Additional uterotonic therapy	20 (22.2)	36 (42.8)	S, $P = 0.0036$	0.52 (0.33–0.82)
Blood transfusion	03 (3.3)	02 (2.4)	NS, $P = 1.00$	1.40 (0.24–8.17)
Postoperative Hb (g/dl)	9.79 ± 0.99	9.51 ± 0.56	S, $P = 0.023$	
Perioperative Hb fall				
g/dl	0.87 ± 0.29	1.01 ± 0.26	S, P = 0.0016	
1.0 g/dl or more	58 (64.4)	73 (86.9)	S, $P = 0.00059$	0.74 (0.62–0.88)
Operating time (min)	32.98 ± 6.9	32.03 ± 4.24[a]	NS, $P = 0.23$	

S Significant, *NS* Not significant

[a] Mean ± SD, Values in parentheses indicate percentage

Table 5 Perioperative morbidity

Data: mean ± SD or number (percentage)				
	Misoprostol ($N = 90$)	Placebo ($N = 84$)	P	RR (95 % CI)
Shivering	19 (21.1)	8 (9.5)	S, $P = 0.034$	2.22 (1.03–4079)
Pyrexia	10 (11.1)	6 (7.1)	NS, $P = 0.365$	1.56 (0.59–4.09)
Nausea	10 (11.1)	8 (9.5)	NS, $P = 0.731$	1.17 (0.48–2.82)
Vomiting	5 (5.6)	3 (3.6)	NS, $P = 0.721$	1.56 (0.38–6.31)
Hospitalization Period (days)	6.71 ± 0.83	7.35 ± 1.01	NS, P = 9.9	

S Significant, *NS* Not significant

[a] Mean ± SD, Values in parentheses indicate percentage

found misoprostol more effective in the reduction of postpartum bleeding. Acharya et al. [1] comparing the effectiveness of 400 μg 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 μg 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 μg 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]. However, some studies have reported no difference [1, 6, 8]. 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 photo spectrometry [9]. In the present study to obviate the

above limitation, 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 [6]. Some others have reported no difference [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 [1].

Significant trend toward lesser perioperative Hb fall, which was found in this study, is similar to that reported in a recent study [10], in which concomitant oxytocin infusion was given to all women, as in the present study. In studies reporting no difference, misoprostol was either compared with oxytocin [1, 7, 8], or a lower dose of misoprostol was used [6].

Shivering, pyrexia, nausea vomiting, and diarrhea are common adverse effects of misoprostol and are dose related. The increased incidence of shivering found in the present study is similar to that reported elsewhere [7]. However, there was 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 [1, 6, 7].

Dose of misoprostol in various studies has ranged from 200 to 800 mcg [1, 4–8]. As the side effects are dose related, a dose of 400 mcg was chosen in the present study to minimize maternal adverse effects with optimal therapeutic benefit. In a recent review, 400 mcg of misoprostol was found to be safer than 600 mcg and just as effective [11].

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), and the highest area under the curve (AUC) of misoprostol acid, the active metabolite of misoprostol [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 [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 [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, 400 mcg by sublingual route appears to be promising. Two recent trials have confirmed efficacy of sublingual misoprostol in reducing blood loss at cesarean delivery [10, 18].

Post hoc power analysis showed that the present study (with an α of 0.05) had 78.9 % power to detect reduction in uterotonic therapy from 42.8 to 22.2 % and 92.5 % power to detect a difference of mean blood loss of 56 ml. In the present study, sample size was relatively small. Blood loss estimated may not have true approximation of the actual loss. Though perioperative Hb fall was also studied, better methods involving measurement of actual blood loss may be more accurate. Larger studies with primary outcome measures such as incidence of postpartum hemorrhage and the need of blood transfusion are needed, to validate the efficacy of misoprostol and to find the optimal dose and route of administration at cesarean delivery.

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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