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CLINICAL ARTICLE

Sublingual misoprostol as an adjunct to oxytocin during cesarean delivery in women at risk of postpartum hemorrhage

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ABSTRACT

Objective: To evaluate whether a combination of misoprostol and oxytocin more effectively reduces blood loss during and after cesarean delivery than does oxytocin alone among women with known risk factors for postpartum hemorrhage (PPH). *Methods:* A prospective, randomized, double-blind, placebo-controlled trial was performed at a tertiary care center in Kolkata, India, between October 2012 and December 2013. Women were eligible if they were undergoing emergency cesarean under spinal anesthesia and were at high risk for PPH. Participants were randomly assigned (1:1) to receive 400 μg misoprostol or matched placebo sublingually after delivery of the newborn using a computer-generated random number sequence (block size eight). Participants and providers were masked to assignment. All participants received 20 IU oxytocin. The primary outcomes were intraoperative and postoperative blood loss. *Results:* Both groups contained 198 women. Mean intraoperative blood loss was significantly lower in the misoprostol group (505.4 ± 215.5 mL) than in the placebo group (587.3 ± 201.5 mL; $P < 0.001$). Mean postoperative blood loss was slightly lower in the misoprostol group (96.9 ± 57.3 mL) than in the placebo group (103.4 ± 58.4 mL; $P = 0.07$). Shivering and pyrexia were more frequently associated with misoprostol ($P < 0.05$ for both). *Conclusion:* Misoprostol as an adjunct to oxytocin seemed to more effectively reduce blood loss than did oxytocin alone.

Clinical Trial Registry India: CTRI/2013/05/003645.

1. Introduction

Cesarean delivery is the most frequently performed major surgical procedure worldwide [1]. Compared with women delivering vaginally, women undergoing cesarean have an increased risk of high blood loss and so are more likely to need a blood transfusion [2–4]. The global rise in the incidence of cesarean delivery in the past decade has possibly contributed to the resurgence of postpartum hemorrhage (PPH) in high-income countries [5,6]. The risk of PPH is further increased in the presence of risk factors such as multiple pregnancy, polyhydramnios, grand multiparity, severe pre-eclampsia, prepartum hemorrhage, prolonged and obstructed labor, augmented labor, obesity, and anemia [2–4].

Oxytocin—the gold standard oxytocic agent—is widely used during cesarean delivery to prevent PPH, even though some studies [7,8] have raised concerns about its efficacy and adverse effects. Misoprostol has been evaluated as an alternative to oxytocin [9–12] during cesarean delivery, and has also been used in combination with oxytocin [13–19]. Two meta-analyses [20,21] concluded that misoprostol was as effective as oxytocin and that the combination of the misoprostol and oxytocin is better than is oxytocin alone for the prevention of PPH. However, women with known risk factors for PPH, who are expected to benefit from an alternative or additional oxytocic agent, were totally or partially excluded from several of the studies [14–16,18,19]. Thus, the existing evidence on the optimal uterotonic agent during cesarean for high-risk women is insufficient.

The present study was conducted to establish whether the combination of misoprostol and oxytocin more effectively reduces blood loss during and after cesarean delivery than does oxytocin alone in women with known risk factors for PPH.

2. Materials and methods

Between October 1, 2012, and December 31, 2013, a prospective, randomized, double-blind, placebo-controlled study was conducted in the Department of Obstetrics and Gynaecology at the Nilratan Sircar Medical College and Hospital, a tertiary care teaching hospital in Kolkata, East India. Women were eligible for inclusion if they were undergoing emergency cesarean under spinal anesthesia and had at least one risk factor for PPH (multiple pregnancy, polyhydramnios, prolonged labor or dystocia [according to the partogram], augmented

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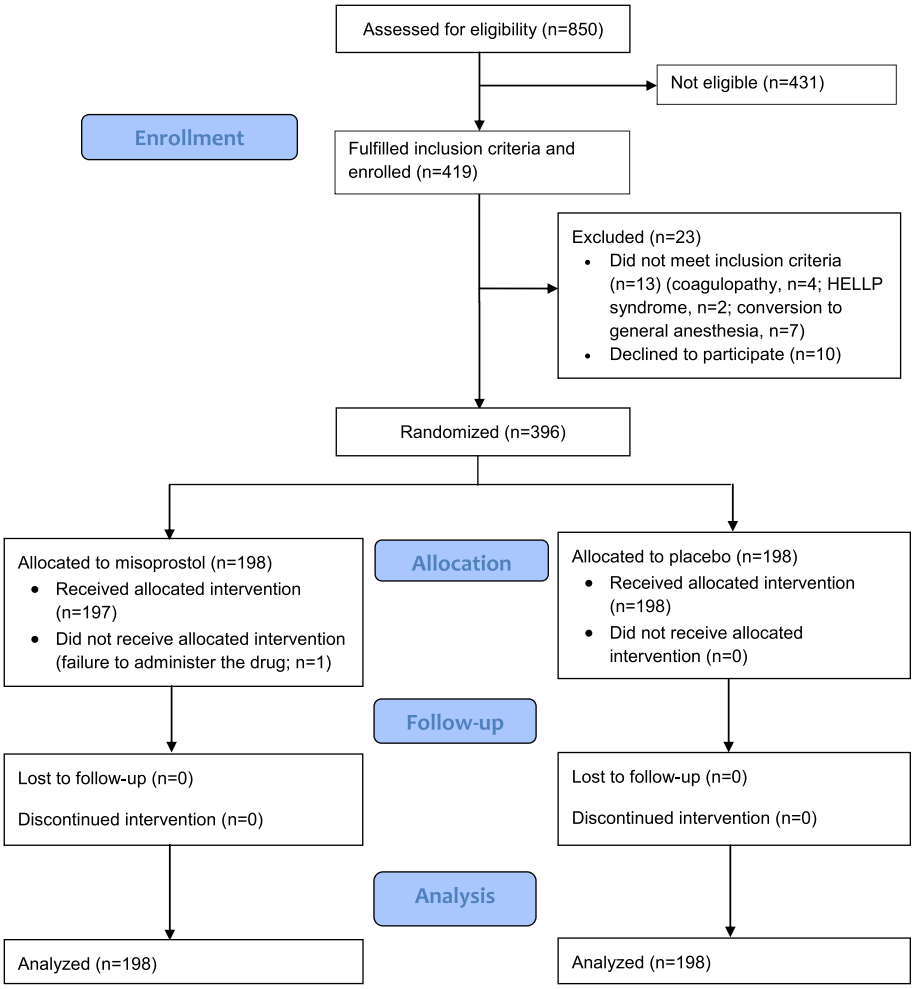

Fig. 1. Flow of participants through the study. Abbreviation: HELLP, hemolysis, elevated liver enzymes, and low platelet count.

labor, obesity [body mass index >30, calculated as weight in kilograms divided by the square of height in meters], grand multiparity [parity ≥4], prepartum hemorrhage, severe pre-eclampsia/eclampsia, anemia [hemoglobin <80 g/L and known previous PPH). Women with any contraindication for the use of misoprostol or oxytocin (e.g. known hypersensitivity) and those with cardiovascular, hepatic, or hematologic disorders were excluded. Conversion to general anesthesia also made women ineligible. The protocol was approved by the Institutional Ethics Committee of Nilratan Sircar Medical College and Hospital.

Eligibility was assessed by interview, clinical examination, and review of recent investigations among women scheduled for emergency

Table 1
Demographic and obstetric characteristics of participants.[a]

Variable	Misoprostol (n = 198)	Placebo (n = 198)	*P* value
Age, y	25.0 ± 5.5	24.5 ± 5.3	0.4[b]
Parity	0 (0–5)	0 (0–5)	0.7[b]
Primipara	129 (65.2)	120 (60.6)	0.4[c]
Grand multipara[d]	5 (2.5)	4 (2.0)	>0.9[e]
Pregnancy duration, wk	37.9 ± 1.8	37.8 ± 1.8	0.7[b]
BMI	23.1 ± 3.2	23.2 ± 3.2	0.7[b]
Birth weight, kg	2.7 ± 0.5	2.6 ± 0.5	0.5[b]
Preoperative hemoglobin, g/L	110.1 ± 10.4	100.9 ± 10.5	0.2[b]
Number of risk factors			
1	177 (89.4)	181 (91.4)	0.5[c]
≥2	21 (10.6)	17 (8.6)	0.5[c]
Number of previous cesarean deliveries			
1	28 (14.1)	21 (10.6)	0.3[c]
≥2	5 (2.5)	3 (1.5)	0.7[e]

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters).
[a] Values are given as mean ± SD, median (range), or number (percentage).
[b] *t* test.
[c] χ^2 test.
[d] Parity ≥4.
[e] Fisher test.

Table 2
Risk factors for postpartum hemorrhage.[a,b]

Variables	Misoprostol (n = 198)	Placebo (n = 198)	*P* value
Multiple pregnancy	34 (17.2)	29 (14.6)	0.5[c]
Polyhydramnios	14 (7.1)	18 (9.1)	0.5[c]
Prepartum hemorrhage	22 (11.1)	17 (8.6)	0.4[c]
Severe pre-eclampsia/eclampsia	39 (19.7)	31 (15.7)	0.3[c]
Anemia [d]	9 (4.5)	13 (6.7)	0.4[c]
Prolonged/obstructed labor	27 (13.6)	34 (17.2)	0.3[c]
Labor augmented by oxytocin	50 (25.3)	47 (23.7)	0.7[c]
Obesity[e]	10 (5.1)	8 (4.0)	0.8[f]
Grand multiparity[g]	5 (2.5)	4 (2.0)	>0.9[f]
Known previous postpartum hemorrhage	12 (6.1)	16 (8.1)	0.4[c]

[a] Values are given as number (percentage).
[b] Some women had more than one risk factor.
[c] χ^2 test.
[d] Hemoglobin <80 g/L.
[e] Body mass index (calculated as weight in kilograms divided by the square of height in meters) >30.
[f] Fisher test.
[g] Parity ≥4.