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CLINICAL ARTICLE

A randomized trial of sublingual misoprostol to augment routine third-stage management among women at risk of postpartum hemorrhage

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ABSTRACT

Objective: To assess whether a combination of misoprostol and oxytocin is more beneficial than oxytocin alone in reducing blood loss after vaginal delivery among women with known risk factors for postpartum hemorrhage (PPH). *Methods:* A randomized, double-blind trial was conducted in a medical college in eastern India among women aged at least 18 years who had known high-risk factors for PPH. Using a computer-generated random number sequence (block size 6–8), participants were randomly assigned to receive 400 μg misoprostol or matched placebo tablets sublingually, in addition to 10 units of oxytocin, after vaginal delivery. The primary outcomes were postpartum blood loss at 1 hour and frequency of PPH. Analyses were by intention to treat. *Results:* Both groups contained 144 participants. Postpartum blood loss at 1 hour after delivery was significantly lower among women who received misoprostol than among those who received placebo (225.8 ± 156.7 mL vs 302.4 ± 230.3 mL; $P < 0.001$). The frequency of moderate PPH (500–999 mL) was significantly lower in the group receiving misoprostol than in the placebo group (5 [3.5%] vs 15 [10.4%] participants; $P = 0.03$). *Conclusion:* As compared with oxytocin alone, misoprostol with oxytocin more effectively reduced blood loss after vaginal delivery among women at risk of PPH.

Clinical Trial Registry India: CTRI/2014/03/004491

1. Introduction

Postpartum hemorrhage (PPH) is the single major cause of maternal mortality and serious maternal morbidity in low-income countries [1]. Most cases of PPH (almost 80%) occur because the uterus fails to contract [2], and might be avoided by anticipation of risk factors, active management of the third stage of labor (AMTSL), and prompt intervention. Multiple pregnancy, polyhydramnios, grand multiparity, severe pre-eclampsia, prepartum hemorrhage, prolonged and obstructed labor, augmented labor, obesity, anemia, and known previous PPH are some of the risk factors for atonic PPH [3].

The use of uterotonic drugs in the form of oxytocin (10 IU intramuscularly) within 1 minute of delivery of the newborn has been recommended by WHO as an essential component of AMTSL for all deliveries [4]. Misoprostol (600 μg orally), a prostaglandin E1 derivative, has been recommended as the alternative uterotonic drug in settings where oxytocin is unavailable [5]. However, a meta-analysis [6] found that PPH still occurs even after administration of the "gold standard first line oxytocic". This finding could be important for women with one or more of the risk factors for PPH. Although oxytocin has a rapid onset of action (within 3–7 minutes of intramuscular injection), its clinical effect lasts for only approximately 1 hour owing to its short half-life of 4–7 minutes [7].

Misoprostol, which has beneficial properties (e.g. stability at room temperature, low cost, long shelf-life, and non-parenteral routes of administration), has been widely evaluated as an alternative to oxytocin for prophylaxis and treatment of PPH [8]. Its onset of action after sublingual administration—the quickest of all routes—is about 30 minutes and its duration of action is not less than 6 hours [9,10].

Oxytocin and misoprostol act through oxytocin and prostanoid receptors, respectively, in the myometrium. Poor response to one uterotonic could be due to individual variation in the receptor population. Although a synergistic action between oxytocin and misoprostol has not been reported so far, a combined uterotonic regime could be beneficial by enabling maximum utilization of the available receptors. The dose and the dose-related adverse effects of an individual uterotonic might also be reduced with a combined approach.

The combination of misoprostol and oxytocin has been compared with oxytocin alone for PPH prophylaxis among women undergoing both cesarean delivery [11–14] and vaginal delivery [15–19]. Although women at high risk of PPH are more likely to benefit from the combined uterotonics, only one of the previous studies included exclusively high-

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risk women [17]. Evidence is therefore lacking with respect to requirement of uterotonics for the subset of women with known risk factors for PPH. Any intervention that would lessen the risk of blood loss for these women would be beneficial from the global point of view by averting not only maternal death but also morbidity in terms of additional surgical intervention, blood transfusion, and postpartum anemia.

Against this background, the aim of the present study was to evaluate whether augmentation of routine third-stage management with sublingual misoprostol would be beneficial for women at risk of PPH.

2. Materials and methods

The present prospective, randomized, double-blind study was conducted in the Department of Obstetrics and Gynaecology, Nilratan Sircar Medical College and Hospital, Kolkata, India, a tertiary-care teaching hospital in eastern India. The study included women aged 18 years or older who delivered vaginally between October 1, 2012, and May 31, 2014, and who had one or more of the following known risk factors for PPH: multiple pregnancy; polyhydramnios; induced and augmented labor; prolonged labor, defined in accordance with standard guidelines via a partogram; obesity, defined as a body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) above 30; grand multiparty (≥4); severe pre-eclampsia or eclampsia; anemia, defined as a hemoglobin level less than 80 g/L; and known previous PPH. The study excluded women who had cesarean delivery or instrumental vaginal delivery; known hypersensitivity to misoprostol and/or oxytocin; major cardiovascular, hepatic, or hematologic disorders; or intrauterine fetal death or stillbirth. The protocol was approved by the Institutional Ethical Committee and was registered with Clinical Trial Registry India (Registration No. CTRI/2014/03/004491). All participants in the study provided written informed consent.

On admission to the labor ward, women were screened for eligibility by interview, clinical examination, and review of recent investigations. Those who fulfilled the selection criteria were approached for participation during the first stage of labor and consent was obtained. Labor was monitored by partogram, and women who needed augmentation of labor or had prolonged labor were also enrolled on providing consent.

When delivery was imminent with crowning of the presenting fetal part, each participant was randomized by computer-generated random number sequence and block randomization (blocks of 6–8) to receive either two 200-μg tablets of misoprostol (Zitotec; Sun Pharmaceutical Industries Ltd, Mumbai, India) or two tablets of placebo (with the same color, size, and shape) using sealed, opaque, and sequentially numbered packets. Randomization and maintenance of confidential records were done by residents who were not involved in the trial. Preparation of the sealed packets, allocation, and administration of the drugs were done by the labor room midwife. Participants, investigators, and data analysts were masked to group assignment.

All deliveries were conducted by residents. The packets were opened and misoprostol/placebo was administered sublingually within 1 minute of delivery of the newborn (or second newborn in the case of twins) by the labor room midwife. Simultaneously, each participant received 10 IU of intramuscular oxytocin (Syntocinon; Novartis India Ltd, Mumbai, India). Additional oxytocic drugs were administered on the basis of clinical judgement by the senior resident. Blood transfusions were given to women who were hemodynamically unstable and/or had a postpartum hemoglobin concentration of less than 60 g/L, in line with the hospital protocol.

Linens soaked with amniotic fluid were removed soon after delivery of the newborn, and a pre-weighed thick cotton pad with plastic lining was placed under the buttocks. All blood clots were removed from the vagina and kept in a plastic bag. The pad was replaced if completely soaked during the 1-hour observation period. Episiotomies were repaired immediately after complete delivery of the placenta, and cotton swabs used during this procedure were not included in the blood loss assessment. The difference in weight between the soaked and dry pad was added to the weight of blood clots to calculate the total blood loss (1 mL was considered equal to 1 g given the specific gravity of blood of 1.08).

Vital signs were recorded every 15 minutes. Hemoglobin was measured before delivery and 24 hours after delivery.

The primary outcomes were the measured postpartum blood loss (from delivery of the newborn to 1 hour after delivery) and the incidence of PPH. The secondary outcomes were postpartum drop in hemoglobin (24 hours after delivery), requirement of additional oxytocic (1 hour), need for blood transfusion (before discharge), additional surgical intervention for PPH (24 hours), maternal complications (before discharge), and adverse effects related to the uterotonic (1 hour).

A power calculation was used to determine the sample size. In a previous study, mean postpartum blood loss among women with high-risk factors receiving oxytocin after vaginal delivery was 386 ± 298 mL [17]. Under the assumption that administration of misoprostol would reduce blood loss by 100 mL, 140 women would be required in each group to have a 80% chance of detecting a significant difference at the 5% level. Under the further assumption of approximately 5% loss during follow-up, participants were enrolled until there were a few more than 140 in each group.

Analysis was done by intention to treat. Excel version 7 (Microsoft, Redmond, WA, USA) and MedCalc version 11 (MedCalc Software, Ostend, Belgium) were used for statistical analyses. Results were reported as mean ± SD, number (percentage), and median (range). Student *t*, Mann–Whitney *U*, χ^2, and Fisher exact tests were performed to compare variables. Mean and median differences with 95% confidence intervals (CIs) and relative risks with 95% CIs were calculated for outcome parameters as appropriate. $P < 0.05$ was considered statistically significant.

3. Results

During the study period, 750 women admitted to the labor ward were screened for eligibility. In total, 364 had one or more risk factors for PPH and were enrolled in the study. A further 78 women, who were initially screened and found to be ineligible because of a lack of risk factor, were subsequently enrolled because they needed augmentation of labor or showed evidence of prolonged labor. After exclusion of 154 women, 288 women underwent randomization and received the assigned drug (Fig. 1).

The two groups had similar baseline demographic and obstetric characteristics (Table 1). The various risk factors for PPH were observed in similar proportions in the two groups (Table 2).

Mean postpartum blood loss at 1 hour after delivery was significantly lower among women who received adjunct misoprostol with oxytocin than among those who received oxytocin alone ($P < 0.001$) (Table 3). The amount of blood loss was initially divided into three categories (<500 mL, 500–999 mL, and ≥1000 mL). However, blood loss was less than 500 mL for most women in both groups; as the result, the first category was subdivided into two (<150 mL and 150–499 mL). A significantly greater proportion of women on adjunct misoprostol lost less than 150 mL of blood as compared with women on oxytocin alone ($P < 0.001$) (Table 3). The incidence of moderate PPH (500–999 mL) was also significantly lower in the group receiving adjunct misoprostol than in the group receiving placebo ($P = 0.03$) (Table 3). However, there was no significant difference in the incidence of severe PPH (≥1000 mL) between the two groups (Table 3).

The mean postpartum drop in hemoglobin was significantly lower among women who received adjunct misoprostol with oxytocin than among those who received oxytocin alone ($P = 0.004$) (Table 4). It was also observed that more women in the combined uterotonic group had a postpartum drop in hemoglobin of less than 5 g/L ($P < 0.001$) (Table 4). Additional uterotonic drugs and blood transfusion were required slightly less frequently for women who received adjunct misoprostol than for those who received placebo, although the differences were not significant (Table 4).

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