

Oral Misoprostol Versus Oxytocin in the Management of the Third Stage of Labour

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Abstract

Objective: To compare the effects of oral misoprostol 800 µg with intramuscular oxytocin 10 IU in routine management of the third stage of labour.

Methods: This randomized controlled trial was performed in a rural district hospital in Ghana, West Africa, and enrolled women in labour with anticipated vaginal delivery and no known medical contraindication to prostaglandin administration. Women were randomized to receive oral misoprostol 800 µg or intramuscular oxytocin 10 IU. Blood samples were taken to determine hemoglobin concentration before delivery and at 12 hours post partum. Treatment was administered at delivery of the anterior shoulder. The primary outcome was the change in hemoglobin concentration from before to after delivery. Secondary outcomes included other measures of blood loss and presumed medication side effects.

Results: In total, 450 women were enrolled in the study. Their baseline characteristics were similar. There was no significant difference between the groups in the change in hemoglobin concentration (misoprostol 1.07 g/dL and oxytocin 1.00 g/dL). The only significant secondary outcomes were shivering (80.7% with misoprostol vs. 3.6% with oxytocin) and pyrexia (11.4% with misoprostol, none with oxytocin).

Conclusion: Routine use of oral misoprostol 800 µg appears to be as effective as 10 IU parenteral oxytocin in minimizing blood loss during the third stage of labour, as determined by change in hemoglobin concentration. Misoprostol appears to be a safe, inexpensive, and effective uterotonic for use in rural and remote areas, where intravenous oxytocin may be unavailable.

Résumé

Objectif : Comparer l'effet de l'administration, par voie orale, de 800 µg de misoprostol à l'administration par voie intramusculaire de 10 UI d'oxytocine dans le cadre de la prise en charge du troisième stade du travail.

Méthodes : Cet essai clinique randomisé a été effectué dans un hôpital de district en région rurale du Ghana, en Afrique de l'Ouest.

Key Words: Misoprostol, labour, third stage, postpartum hemorrhage, randomized clinical trial

Competing Interests: None declared.

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Les participantes étaient des femmes en période de travail chez qui l'on s'attendait à pratiquer un accouchement vaginal et dont les antécédents ne montraient aucune contre-indication médicale quant à l'administration de prostaglandine. On a administré à ces femmes, au hasard, 800 µg de misoprostol par voie orale ou 10 UI d'oxytocine par voie intramusculaire. Des prélèvements sanguins ont été effectués afin de déterminer la concentration d'hémoglobine avant l'accouchement et 12 heures après. Le traitement a été administré une fois l'épaule antérieure dégagée. L'issue primaire constatée a été une variation sur le plan de la concentration d'hémoglobine pendant le travail et après l'accouchement. Parmi les issues secondaires, mentionnons d'autres mesures de la perte sanguine et des effets indésirables attribuables aux médicaments administrés qui étaient appréhendés.

Résultats : Au total, 450 femmes ont participé à l'étude. Leurs caractéristiques de base étaient similaires. Il n'existait aucune différence marquée entre les groupes en ce qui a trait à la variation de la concentration d'hémoglobine (misoprostol 1,07 g/dL et oxytocine 1,00 g/dL). Les seules issues secondaires significatives constatées étaient les frissonnements (80,7 % avec le misoprostol par rapport à 3,6 % avec l'oxytocine) et la pyrexie (11,4 % avec le misoprostol, aucun cas avec l'oxytocine).

Conclusion : L'administration courante de 800 µg de misoprostol par voie orale semble être aussi efficace que l'administration de 10 UI d'oxytocine par voie parentérale pour minimiser les pertes sanguines pendant le troisième stade du travail, comme le démontre la variation de la concentration d'hémoglobine. Le misoprostol semble être un utérotonique sûr, abordable et efficace, pouvant être utilisé dans les régions rurales et éloignées où l'administration d'oxytocine par intraveineuse peut ne pas être possible.

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INTRODUCTION

Obstetrical hemorrhage has long been a leading cause of maternal mortality.^{1,2} Active management of the third stage of labour has yielded remarkable reductions in rates of postpartum bleeding, not only in Western societies, but also in the developing world.³ Although cord traction and uterine massage are simple interventions, the administration of a pharmacologic uterotonic may not be possible in many situations. In hospitals and clinics of

developed countries, supplies (e.g., needles and syringes) and facilities (e.g., refrigeration and sterilization) are readily available. In the rural communities of developing countries, however, these things are notably absent. Although great advances have been made in the urban centres of developing nations, little has been done for the women who are still dying of obstetric hemorrhage in their villages. To this end, a working group of the World Health Organization (WHO) recommended in 1989 that "active management of the third stage of labour, including the use of parenteral oxytocin, be carried out at the most peripheral/lowest level of the maternal health care system as possible."⁴ Yet for the women in these villages, an injection of such a lifesaving medication may not be feasible. For these women and their traditional birth attendants, efforts should be made to find an alternative, easy to administer, inexpensive, stable, and effective medication to aid in management of the third stage of labour.

Misoprostol (Cytotec, Searle) is a prostaglandin E₁ analogue that has been marketed internationally for use in the treatment and prevention of gastric ulcer disease induced by non-steroidal anti-inflammatory drugs (NSAIDs).⁵ The use of misoprostol for cervical priming, in the induction of labour and alone or in combination as an abortifacient, has also been described.⁶⁻¹³ El-Refaey et al. first showed that the drug might be effective in preventing postpartum hemorrhage (PPH) in an uncontrolled study of 237 women.¹⁴ They concluded that observed rates of PPH and other measures of blood loss were comparable to rates observed when the third stage of labour is managed using oxytocin-ergometrine and were more favourable than passive management alone. The investigators were encouraged and called for a double-blind randomized trial. A short time later, Walley et al. reported the results of a double-blind placebo-controlled trial, performed in Ghana in women at low risk for PPH.¹⁵ The primary outcome measure was the change in hemoglobin concentration from before to after delivery in an equivalence trial comparing use of oral misoprostol (400 µg) and intramuscular oxytocin (10 IU). They found no difference between the groups in the management of the third stage of labour. Since this time, results from the WHO multicentre randomized trial of misoprostol in the management of the third stage of labour have been made known.¹⁶ This group compared the effect of 600 µg oral misoprostol with 10 IU parenteral oxytocin in 18 459 randomly assigned women undergoing a vaginal delivery. The primary outcome measures were documented blood loss of greater than 1000 mL and the use of additional uterotonics. The findings indicated that 600 µg of oral misoprostol is less effective than parenteral oxytocin both in reducing the incidence of blood loss greater than

1000 mL and in the need for additional uterotonics in settings where active management is the norm.

The present study was designed to extend the findings of Walley et al.¹⁵ and to address some of the points raised by the WHO multicentre trial. The purpose of this study was to test a higher dose of oral misoprostol (800 µg) in the rural area of a developing country to determine whether it is at least as effective as parenteral oxytocin in minimizing blood loss during the third stage of labour, as determined by change in hemoglobin concentration.

METHODS

We recruited women at Holy Family Hospital, Techiman, which is in the Brong Ahafo Region of Ghana, West Africa, between April and October 2002. This hospital conducts approximately 3000 deliveries annually. Many of the women come from local villages: Techiman is at the crossroads of the country, is the location of the largest open market in the nation, and draws many women from the surrounding villages and even from neighbouring countries. Nurse midwives staff the labour ward with backup from a generalist physician (medical officer).

The Human Investigation Committee of the Faculty of Medicine, Memorial University of Newfoundland, and the local health authority in Sunyani, Ghana, approved the research proposal. The nurse midwives informed patients about the study either when they presented to the routine prenatal clinics or when they presented to the labour and delivery ward. Informed consent was obtained from each woman in her own language, using a standardized form, after admission to the labour ward.

When it was clear that a vaginal delivery was highly probable, the next sequentially numbered, opaque, sealed envelope was opened. It contained a standard data sheet and a random, computer-generated assignment to either the intramuscular oxytocin group or the oral misoprostol group. A separate box contained individually packaged treatments, which contained either one vial of oxytocin (10 IU), one syringe, one 22-gauge needle, and an alcohol swab for the control group, or four 200 µg tablets of misoprostol for the treatment group. After consent was obtained, the initial maternal blood sample was drawn to determine hemoglobin concentration.

All women presenting in labour were offered participation in the trial. The only exclusion criterion was any contraindication to prostaglandin administration (known hypersensitivity or medical conditions such as asthma or epilepsy). Women who were perceived to be at high risk for PPH were not excluded, but these factors were recorded on the data sheet. They were as follows: grand multiparity (> para 5), multiple gestation, previous PPH, precipitous labour (< 3

hours), known coagulation abnormality, chorioamnionitis, polyhydramnios, previous Caesarean delivery, and oxytocin induction or augmentation of labour. Women with intrauterine fetal death or stillbirth were allowed participation if it was felt the pregnancy had otherwise reached a viable gestational age, which was greater than 28 completed weeks at this hospital.

At delivery of the anterior shoulder, either 800 µg misoprostol was taken orally with a small glass of water (< 100 mL) or an intramuscular injection of oxytocin 10 IU was given. Blood loss was estimated by the nurse midwife or health officer and recorded but was not objectively measured. If a woman had significant blood loss, the usual hospital protocol was initiated at the discretion of the attending physician. This protocol included use of intravenous oxytocin, attention to lacerations, removal of retained placenta, and blood transfusion as required. The data were collected initially in a hardcover scientific notebook and transferred to the data collection sheet after the delivery had been completed.

At approximately 12 hours post partum, a second blood sample was drawn to determine postpartum hemoglobin concentration. After delivery, women were monitored for additional blood loss and the occurrence of shivering by objective or subjective report. Temperature was monitored and recorded in the data sheet if above 37.5°C. The standard practice at this centre was to discharge multiparous women from hospital within 24 hours if their delivery had been routine.

Training for the midwives took place at an introductory workshop, which discussed trial design, proper technique of medication administration, recording of data including outcomes and side effects, and how to obtain voluntary, informed consent. These nurse midwives were familiar with conducting labour and delivery, including administration of routine oxytocic agents as a part of active management of the third stage of labour. One of the investigators visited the site on a regular basis to answer questions from the staff and to troubleshoot any problem areas.

Sample Size Calculation

We calculated sample size on the basis of findings from a previous chart review of 50 women at Korle-Bu Teaching Hospital in Accra, Ghana. The primary outcome measure was the change in hemoglobin from before to after delivery. A standard deviation (SD) of 0.3 g/dL was calculated from the chart review. A difference between the groups of more than 0.1 g/dL was designated as clinically significant. Using $\alpha = 0.05$ (2-tailed) and $\beta = 0.10$, we found the minimum required sample size to be 191 women per group. We

produced 450 packages for randomization to allow for lost supplies and inadequately completed data sheets.

Statistical Analysis

Data were analyzed on an intent-to-treat basis by parametric and nonparametric tests, using Statistix Version 7.1 (Analytical Software, Tallahassee, FL). The primary outcome was tested using a 2-sided Student *t* test and was considered statistically significant at an α level of 5% ($P < 0.05$). Continuous variable secondary outcomes were also tested using a 2-sided Student *t* test, but continuous variable outcomes that were not normally distributed were assessed using Wilcoxon rank sum test. Secondary outcomes were considered statistically significant at an α level of 0.1% ($P < 0.001$). This conservative level was used in order to minimize the risk of a type I error. Dichotomous variable secondary outcomes were analyzed using chi-square (Pearson or Fisher exact) and were also considered statistically significant at an α level of 0.1% ($P < 0.001$). Relative risk ratios and risk differences (95% [for the primary outcome] or 99.9% [for the secondary outcomes] confidence intervals [CI]) were also calculated for these outcomes. Lowering the α level decreases the likelihood of a type I error, allowing for multiple testing of these secondary outcomes.

RESULTS

We enrolled a total of 450 women and randomized them to receive either oral misoprostol (225 women) or intramuscular oxytocin (225 women) during the study period. All patients had predelivery and postpartum hemoglobin concentrations recorded for analysis. There was no difference between the groups regarding baseline characteristics or risk factors for postpartum hemorrhage (Table 1). At least one risk factor for postpartum hemorrhage was present in 21.3% of the group receiving misoprostol and in 19.1% of the oxytocin group.

The mean (\pm SD) decrease in hemoglobin concentration was 1.07 (\pm 1.14) g/dL for the misoprostol group and 1.00 (\pm 1.04) g/dL for the oxytocin group, a difference that was not significant (relative difference 7%; 95% CI -13, 27%, $P = 0.54$) (Table 2). Other indicators of blood loss (use of additional uterotonics, estimated blood loss > 500 mL, length of third stage, clinical diagnosis of PPH, or need for blood transfusion) were not significantly different between the groups. There was no maternal mortality in either group, and no woman required an operative intervention (manual removal of placenta, dilatation and curettage, laparotomy, or hysterectomy) or had estimated blood loss greater than 1000 mL.

With respect to medication side effects, the groups were similar in the incidence of nausea, vomiting, and diarrhea

Table 1. Baseline characteristics and risk factors for postpartum hemorrhage

	Misoprostol 800 µg PO n = 225	Oxytocin 10 IU IM n = 225
Mean maternal age (years ± SD)	27.0 ± 6.4	26.7 ± 7.0
Nulliparous (%)	78/225 (34.7)	76/225 (33.8)
Mean gestation (weeks ± SD)	37.4 ± 1.8	37.4 ± 1.7
Mean birth weight (grams ± SD)	3078 ± 532	3007 ± 498
Laceration (%)	21/204 (10.3)	19/204 (9.3)
Episiotomy (%)	40/215 (18.6)	32/219 (14.6)
Mean predelivery Hb (g/dL ± SD)	10.6 ± 1.8	10.5 ± 1.8
PPH Risk Factors		
Grand multiparity (para > 5) (%)	22/224 (9.8)	15/225 (6.7)
Current multiple gestation (%)	16/224 (7.1)	9/224 (4.0)
Previous PPH (%)	2/224 (0.9)	3/224 (1.3)
Precipitous labour (< 3 hours) (%)	1/224 (0.4)	0/224 (0)
Coagulation abnormalities (%)	1/224 (0.4)	0/224 (0)
Chorioamnionitis (%)	2/224 (0.9)	2/223 (0.9)
Polyhydramnios (%)	0/223 (0)	1/223 (0.4)
Previous CS (%)	8/222 (3.6)	6/223 (2.7)
Oxytocin induction/augmentation (%)	11/223 (4.9)	10/223 (4.5)
At least one risk factor for PPH (%)	48/225 (21.3)	43/225 (19.1)

PO: by mouth; IU: international unit; IM: intramuscular; SD: standard deviation; Hb: hemoglobin; PPH: postpartum hemorrhage; CS: Caesarean section.

(Table 3). There were significantly more individuals in the misoprostol group with shivering ($P < 0.0001$) and temperature greater than 37.5°C ($P < 0.0001$).

DISCUSSION

Unlike several of the previous studies of misoprostol in the management of the third stage of labour,¹⁷ this study was conducted in a rural setting in a developing country. The hospital involved is a referral centre for local polyclinics and accepts patients from all the surrounding villages. Midwives and medical officers staff this facility; there are no consultant obstetricians. Any woman presenting for anticipated vaginal delivery was offered enrolment in this study, even those considered to be at increased risk of postpartum hemorrhage. The only exclusion criterion was a contraindication to prostaglandin administration. Several previous studies included only women at low risk of postpartum hemorrhage.¹⁷ These differences were important aspects of the study because many of the women who die of obstetric hemorrhage live in these rural villages, are cared for primarily by nurse midwives or traditional birth attendants, and obviously cannot affect their own risk factor profile.

The conclusion of the WHO trial was that misoprostol should not replace oxytocin in centres where oxytocin is the established norm for prophylaxis of postpartum hemorrhage.¹⁶ The investigators in the WHO trial acknowledged that use of misoprostol may be beneficial at the time of catastrophic bleeding or in situations where oxytocin is not readily available. They found that 600 µg of oral misoprostol was less effective than parenteral oxytocin in minimizing blood loss as defined by the incidence of discrete outcomes: measured blood loss greater than 1000 mL or use of additional uterotonics.¹⁶ Although this study was multicentred and attained a large sample size of more than 18 000 women, the primary outcome was not a continuous measure (e.g., change in hemoglobin concentration), such as we have employed. Blood loss of greater than 1000 mL is an arbitrary figure and may be unimportant in a particular clinical scenario.

Certainly interventions to halt further blood loss (e.g., laparotomy, examination under anaesthesia, selective arterial embolization) or blood product transfusion are more indicative of the severity of the hemorrhage. In fact, in the WHO trial, the need for blood transfusion was actually

Table 2. Primary and secondary outcomes indicating or related to blood loss

	Misoprostol 800 µg PO	Oxytocin 10 IU IM	Relative Risk	Relative Difference	<i>P</i>
Mean change in Hb in g/dL (SD)	1.07 (1.14)	1.00 (1.04)	-	7.0% [-13.2, 27.2%] [†]	NS
Mean postpartum Hb in g/dL (SD)	9.5 (1.7)	9.4 (1.9)	-	1.1% [-4.9, 7.0%]	NS
Additional uterotonic (%)	16/225 (7.1)	21/225(9.3)	0.76 [0.27, 2.17]	-	NS
Mean length of 3rd stage (minutes ± SD)	6.0 ± 5.5	6.3 ± 5.8	-	-4.8% [-32.5, 23.0%]	NS
Median EBL in mL (quartiles)	150 (100,200)	150 (100,200)		0% [-20.1, 20.1%]	NS
EBL > 500 mL (%)	0/225 (0) ⁺	5/225 (2.2)	0.20 [0.01, 7.27]	-	NS
Clinical diagnosis of PPH (%)	4/225 (1.8)	7/225 (3.1)	0.57 [0.07, 4.39]	-	NS
Blood transfusion (%)	1/222 (0.5)	2/221 (0.9)	0.50 [0.01, 27.65]	-	NS

* 95% confidence interval for the primary outcome, change in hemoglobin, all others are 99.9% confidence intervals.

[†] To calculate a relative risk for EBL > 500 mL, 1 was substituted for 0 in the misoprostol group to avoid an undefined (division by zero) result.

Values are given as relative risk or relative difference (95% or 99.9% confidence interval).

PO: by mouth; IU: international unit; IM: intramuscular; Hb: hemoglobin; SD: standard deviation; NS: not significant; EBL: estimated blood loss; PPH: postpartum hemorrhage.

higher in the oxytocin group and approached significance with a *P* value of 0.06.

We chose 800 µg of oral misoprostol as the test dose on the basis of the findings of the WHO group and others that dosages of 400 µg to 600 µg may be of questionable value. This group stated that they used the highest effective dose of misoprostol that could be used without producing an unacceptable level of side effects. They also suggested that given their observed level of side effects, higher doses of misoprostol should not be tested.¹⁶ This conclusion was based on a dose-finding trial where the investigators compared only two doses of misoprostol: 400 µg or 600 µg orally.¹⁸ Higher doses of misoprostol were not evaluated, nor were alternate routes of administration.¹⁹ The main outcomes in the dose-finding trial were pyrexia and shivering. There was no difference in gastrointestinal side effects. For pyrexia (temperature > 38° C within one hour of treatment), the relative risk was higher in both the misoprostol treatment groups when compared with the oxytocin group. Shivering also occurred more frequently in the misoprostol groups and appeared to be dose dependent. For the current study we chose to use 800 µg of misoprostol as the side effects of this medication are transient and self-limited. Given the significance of symptoms such as shivering and fever, we felt that the ratio of risk to potential benefit using this dose was acceptable.

A meta-analysis of 16 studies comparing use of oral or rectal misoprostol with either oxytocin or placebo in the third stage of labour concluded that many of the individual studies lacked the statistical power to determine whether misoprostol was truly as effective as parenteral oxytocin.¹⁷

The authors of this meta-analysis argued that finding no difference in effectiveness may have been due to lack of statistical power to demonstrate a difference, and they concluded that only the WHO trial had a sample size large enough to answer the question. The WHO trial investigators concluded that the effect of parenteral oxytocin was superior to 600 µg of oral misoprostol. In the same discussion, however, the authors noted that trials comparing misoprostol with placebo or no treatment have also failed to show a positive effect, and some even suggest a negative effect. In the context of the meta-analysis, however, some details of the individual studies may be lost. For example, Hofmeyr et al. compared 400 µg oral misoprostol to placebo alone and found an increased rate of measured blood loss greater than 1000 mL in the placebo group compared with the misoprostol group.²⁰ Although the results approached but failed to reach significance, it is important to consider one point. On review of their data, the investigators realized that the observed treatment effect might have been tempered by the optional use of parenteral oxytocin, which had been permitted if clinicians felt that there was greater than average blood loss. On further analysis of their data, it was noted that the placebo group received infusion of additional uterotonic more often than the misoprostol group (2.8% vs. 8.4%, *P* = 0.006), thereby dampening the intended treatment effect of misoprostol.

It is important that the potential limitations of the current study be addressed. We acknowledge that unblinding for some participants was possible because the envelopes for women who were initially randomized but who subsequently underwent Caesarean section were returned and

Table 3. Gastrointestinal and thermoregulatory side effects

	Misoprostol 800 µg PO	Oxytocin 10 IU IM	Relative Risk [99.9% CI]	<i>P</i>
Nausea (%)	2/223 (0.9)	4/222 (1.8)	0.50 [0.03, 8.45]	NS
Vomiting (%)	1/221 (0.5)	4/224 (1.8)	0.25 [0.01, 9.90]	NS
Diarrhea (%)	5/221 (2.3)	0/218 (0) [*]	4.91 [0.14, 177.95]	NS
Shivering (%)	180/223 (80.7)	8/223 (3.6)	22.50 [7.14, 70.87]	< 0.0001
Temperature > 37.5C (%)	24/211 (11.4)	0/218 (0) [*]	24.80 [0.88, 701.63]	< 0.0001
Hypertension (%)	1/208 (0.5)	0/215 (0) [*]	1.03 [0.01, 107.22]	NS

*To calculate a relative risk for diarrhea, temperature, and hypertension, 1 was substituted for 0 in the oxytocin group to avoid an undefined (division by zero) result.

PO: by mouth; IU: international unit; IM: intramuscular; CI: confidence interval; NS: not significant.

used for the next women enrolled. This was estimated to have occurred for only a few women, however, as the envelopes were opened only if a woman was in advanced labour and vaginal delivery was considered to be highly likely. Blood loss was not measured objectively because there were too few staff at this rural centre to carry this out. Finally, the standard deviation in hemoglobin concentration observed in the study was higher than estimated in the sample size calculation, thereby reducing the power to see a significant difference if it existed.

The current study attempted to address the issue of the use of misoprostol by midwives for routine management of the third stage of labour in the rural areas of developing countries. We hoped to move a step closer to providing traditional birth attendants with a safe, easy to administer, inexpensive, and effective treatment to use in the village at the time of postpartum bleeding that is greater than average. It is not an effort to circumvent the normal channels of management of postpartum hemorrhage, merely an effort to buy time until a woman can be safely transported to a centre with facilities and personnel capable of dealing with such a crisis. We used a higher dose of oral misoprostol (800 µg) than has been used in previous studies. Although we did see a higher incidence of the shivering and increased temperature in the experimental group, these symptoms were transient and had no adverse consequences.

CONCLUSION

Misoprostol 800 µg given orally was found to be effective in minimizing blood loss when utilized as the pharmacologic agent in active management of the third stage of labour, as measured by the change in hemoglobin concentration from before delivery to 12 hours after delivery. This is further

evidence of the utility of misoprostol as an effective uterotonic and provides a positive step towards arming the health care providers of developing nations in the battle against obstetric hemorrhage.

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