

# Rectal Misoprostol Versus Oxytocin in the Management of the Third Stage of Labour

Steven M. Parsons, MD, FRCSC,<sup>1</sup> Robert L. Walley, MD, FRCSC, FRCOG,<sup>2</sup>  
Joan M. G. Crane, MD, FRCSC,<sup>1</sup> Kay Matthews, RN, MN,<sup>3</sup> Donna Hutchens, BN<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Memorial University of Newfoundland, St. John's NL

<sup>2</sup>Executive Director, MaterCare International, St. John's NL

<sup>3</sup>Consultant Nurse Midwife, MaterCare International, St. John's NL

## Abstract

**Objective:** To compare the effect of rectal misoprostol with intramuscular oxytocin in the routine management of the third stage in a rural developing country.

**Methods:** A randomized controlled trial was performed at two district hospitals in Ghana, West Africa. Four hundred fifty women in advanced labour were enrolled. The only exclusion criterion was a known medical contraindication to prostaglandin administration. Women were randomized to receive rectal misoprostol 800 µg or intramuscular oxytocin 10 IU with delivery of the anterior shoulder. The main outcome measure was change in hemoglobin concentration from before to after delivery. Secondary outcomes included the need for additional uterotonics, estimated blood loss, transfusion, and medication side effects.

**Results:** Demographic characteristics were similar in each treatment group. There was no significant difference between treatment groups in change in hemoglobin (misoprostol 1.19 g/dL and oxytocin 1.16 g/dL; relative difference 2.6%; 95% confidence intervals [CI]–16.8% to 19.4%;  $P = 0.80$ ). The only significant secondary outcome was shivering, which was more common in the misoprostol group (misoprostol 7.5% vs. oxytocin 0.9%; relative risk 8.0; 95% CI 1.86–34.36;  $P = 0.001$ ).

**Conclusion:** Rectal misoprostol 800 µg is as effective as 10 IU intramuscular oxytocin in minimizing blood loss in the third stage of labour. Rectal misoprostol has a lower incidence of side effects than the equivalent oral dose. This confirms the utility of misoprostol as a safe and effective uterotonic for use in the rural and remote areas of developing nations where other pharmacologic agents may be less feasible.

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

Competing Interests: None declared.

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## Résumé

**Objectif :** Comparer l'effet du misoprostol administré par voie rectale à celui de l'oxytocine administrée par voie intramusculaire, dans le cadre de la prise en charge courante du troisième stade du travail au sein d'un pays rural en développement.

**Méthodes :** Un essai comparatif randomisé a été mené au sein de deux hôpitaux de district au Ghana, en Afrique de l'Ouest. Quarante-cinq femmes en travail avancé y ont été admises. La présence d'une contre-indication médicale connue à l'administration de prostaglandines constituait le seul critère d'exclusion. Les femmes ont été affectées, au hasard, à un groupe devant recevoir 800 µg de misoprostol par voie rectale ou à un groupe devant recevoir 10 UI d'oxytocine par voie intramusculaire, au moment de l'extraction de l'épaule antérieure. Le principal critère d'évaluation était la différence entre la concentration de l'hémoglobine mesurée avant l'accouchement et celle qui est mesurée après l'accouchement. Parmi les critères d'évaluation secondaires, on trouvait la nécessité d'administrer des utérotoniques additionnels, la perte sanguine estimée, le recours à la transfusion et les effets indésirables de la médication.

**Résultats :** Les deux groupes de traitement présentaient des caractéristiques démographiques semblables. Aucune différence significative n'a été constatée entre les groupes de traitement en ce qui concerne les changements constatés au niveau de l'hémoglobine (misoprostol : 1,19 g/dL et oxytocine : 1,16 g/dL; différence relative : 2,6 %; intervalle de confiance [IC] à 95 %, 16,8 % – 19,4 %;  $P = 0,80$ ). Le seul critère d'évaluation secondaire significatif était le grelottement, lequel s'est avéré plus courant au sein du groupe « misoprostol » (misoprostol : 7,5 %, par comparaison avec 0,9 % pour l'oxytocine; risque relatif : 8,0; IC à 95 %, 1,86 – 34,36;  $P = 0,001$ ).

**Conclusion :** L'administration de 800 µg de misoprostol par voie rectale est aussi efficace que l'administration de 10 UI d'oxytocine par voie intramusculaire, en ce qui concerne la minimisation de la perte sanguine au cours du troisième stade du travail. Le misoprostol administré par voie rectale compte une incidence d'effets indésirables moins élevée que celle qui est associée à l'administration d'une dose équivalente par voie orale. Cela confirme l'utilité du misoprostol à titre d'utérotonique sûr et efficace pour une utilisation au sein des régions rurales et éloignées des pays en développement où l'emploi d'autres agents pharmacologiques pourrait s'avérer difficile.

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## INTRODUCTION

The rate of maternal mortality varies worldwide, but rates are lower in developed (Western) countries.<sup>1-3</sup> Simple interventions in the community such as adequate food and shelter, clean drinking water, immunization programs, and public health education have led to improved survival for the population as a whole.<sup>2</sup> These interventions have also decreased maternal morbidity and mortality. One of the commonest causes of maternal mortality in the developing world is obstetric hemorrhage, particularly postpartum hemorrhage.<sup>1-3</sup> The incidence of fatal PPH has been reduced in the Western world, largely because of active management of the third stage, which involves controlled cord traction, uterine fundal massage, and administration of a pharmacologic uterotonic.<sup>4</sup> For example, average rates of maternal mortality in many developed regions of the world are 20/100 000, whereas rates in developing regions can be as high as 920/100 000 (Sub-Saharan Africa).<sup>2</sup>

The standard pharmacologic uterotonic agent has traditionally been oxytocin or a combination of oxytocin and ergometrine maleate (Syntometrine). Use of these agents routinely during the third stage of labour has demonstrated a 40% average decrease in PPH, with a number needed to treat of 22 women to prevent one PPH, when compared with placebo or physiologic management.<sup>4</sup> With this evidence, a working group of the WHO has recommended that active management of the third stage of labour, including the use of parenteral oxytocin, be carried out at the most peripheral or lowest level of the maternal health care system possible.<sup>5</sup> The use of misoprostol, indicated for the treatment of NSAID-induced peptic ulcer disease,<sup>6</sup> has been studied for this and many obstetrical and gynaecological indications including cervical ripening for induction of labour.<sup>7-12</sup> Misoprostol has also been used for the medical management of first trimester spontaneous abortions and for first or second trimester termination of pregnancy, alone or in combination with another abortifacient (mifepristone or methotrexate).<sup>13-18</sup> Studies of the use of

misoprostol for prevention or treatment of PPH have shown mixed results, but the studies differ in the dose administered, chosen route of delivery, and outcomes measured.<sup>19-37</sup> This fact was highlighted in a meta-analysis of the use of misoprostol in the management of the third stage of labour.<sup>36</sup> The meta-analysis compared studies using misoprostol doses of 200 to 600 µg, mostly by the oral route although some studies used rectal administration. The comparison groups typically received 5–10 IU oxytocin parenterally, but some studies were placebo-controlled. The largest study within the meta-analysis, a multicentred randomized controlled trial of misoprostol 600 µg orally versus oxytocin 10 IU parenterally and involving 18 249 women, was performed on behalf of the WHO.<sup>37</sup> The conclusion of this trial and of the subsequent meta-analysis by the same authors was that misoprostol should not replace oxytocin as the pharmacologic uterotonic of choice in areas where oxytocin is the established standard.

The toxicology profile of misoprostol makes testing of a wider range of dosages feasible, with lethal levels in animal models reached only at doses of 100 times the usual therapeutic range in humans.<sup>38</sup> The usual experience with misoprostol is a side effect profile consisting mainly of gastrointestinal side effects and changes in thermoregulation with increased temperature and shivering.<sup>39-41</sup> Previous studies have shown a different pharmacokinetic profile for misoprostol when the first-pass metabolism of the gastrointestinal tract is avoided.<sup>38-40</sup> These studies have shown a lower peak concentration of misoprostol acid (the active metabolite of misoprostol), but a slower elimination and longer duration of action.

The objective of the current study was to evaluate the effectiveness and side effects of rectal misoprostol and intramuscular oxytocin in the routine management of the third stage of labour. We chose a higher dose of misoprostol (800 µg) than most previous investigators, with the exception of two small studies of rectal misoprostol for primary treatment of PPH.<sup>27,31</sup> The conclusion that misoprostol should not replace oxytocin in centres where oxytocin is routinely available may ultimately be valid, but we must be aware of the additional considerations with use of oxytocin, including the need for refrigerated storage, use of syringe and needle for parenteral administration, and limited shelf life. In our study hospitals in Ghana, oxytocin was usually available; however, the same is not true of many public hospitals in developing countries, and oxytocin is usually not available to the traditional birth attendant who performs most of the deliveries in the villages. We know that many women in developing countries never come to a hospital for labour and delivery.<sup>3</sup> We must strive to make the system better for these women by having available a uterotonic agent that is

## ABBREVIATIONS

CI	confidence interval
CS	Caesarean section
EBL	estimated blood loss
Hb	hemoglobin
NSAID	non-steroidal anti-inflammatory drug(s)
PPH	postpartum hemorrhage
WHO	World Health Organization

**Table 1. Demographic characteristics and risk factors for postpartum hemorrhage**

	Misoprostol 800 µg PR	Oxytocin 10 IU IM
Maternal age in years	25.7 (6.6)	25.8 (7.1)
Gravida	2 [1,4 ]	2 [1,4 ]
Para	1 [0,3 ]	1 [0,3 ]
Gestation in weeks	37.1 (2.0)	36.9 (2.5)
Birth weight in grams	2961 (574)	2950 (538)
Laceration	17/208 (8.2%)	23/208 (11.1%)
Episiotomy	37/220 (16.8%)	45/214 (21.0%)
Pre-delivery hemoglobin in grams/dL	11.4 (1.7)	11.4 (1.7)
<i>PPH Risk Factors</i>		
Grand multiparity (> para 5)	17/224 (7.6%)	14/225 (6.2%)
Current multiple gestation	6/222 (2.7%)	8/225 (3.6%)
Previous PPH	4/224 (1.8%)	3/224 (1.3%)
Precipitous labour (< 3 hours)	4/224 (1.8%)	3/224 (1.3%)
Coagulation abnormalities	0/224	0/224
Chorioamnionitis	0/224	1/225 (0.4%)
Polyhydramnios	0/224	0/225
Previous CS	4/224 (1.8%)	9/225 (4.0%)
Oxytocin induction or augmentation	11/223 (2.2%)	3/225 (1.3%)
At least one risk factor for PPH	35/224 (15.6%)	38/225 (16.9%)

Values are given as mean (standard deviation), median [quartiles].

easy and simple to administer, cheap to obtain, and safe to use by individuals with little or no formal medical training.

## **METHODS**

The methods used in this study are similar to those used in a study we performed of oral misoprostol in the management of the third stage of labour.<sup>42</sup> Women were recruited between April and December 2002 at two district hospitals in the Brong Ahafo Region of Ghana, West Africa. At Holy Family Hospital in Techiman, there are approximately 3000 births annually, while at St. Theresa's Hospital in Nkoranza there is an average of 800 deliveries per year. Most of the women come from local villages, referred by midwives at the polyclinics or traditional birth attendants in the villages. Nurse midwives staff the labour wards with backup from the generalist physician (medical officer).

This research was approved by the Human Investigation Committee of the Faculty of Medicine, Memorial University of Newfoundland, and the local health authority in Sunyani, Ghana. Patients learned of the study from the nurse midwives when they presented either for routine prenatal care or to the labour and delivery ward. Informed consent was obtained from the woman in her own language, using a standardized form after admission to the labour ward. When it was clear that a vaginal delivery was very

likely, a patient was offered entry to the trial with a conditional randomization. The next sequentially numbered, opaque, sealed envelope containing a standard data sheet with a random assignment to either the control group (intramuscular oxytocin) or the treatment group (rectal misoprostol) was opened. A separate box held individually packaged treatments containing 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, one package of water based lubricant and two medium sized latex-free gloves for the treatment group. After informed 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 known contraindication to prostaglandin administration (hypersensitivity or medical conditions, including asthma or epilepsy). Women at perceived high risk for PPH were not excluded, but the factors that increased the risk were recorded on the data sheet. They were as follows: grand multiparity (greater than para 5), multiple gestation, previous PPH, precipitous labour (less than three hours), coagulation abnormality, chorioamnionitis, polyhydramnios, previous Caesarean section, and oxytocin induction or

**Table 2. Primary and secondary outcome measures indicative of blood loss**

	Misoprostol 800 µg PR	Oxytocin 10 IU IM	Relative risk or difference (95% CI)
Change in Hb in g/dL	1.19 (1.3)	1.16 (1.1)	2.6% (-16.8, 19.4%)
Postpartum Hb in g/dL	10.3 (1.7)	10.2 (1.7)	0.9% (-2.1, 4.1%)
Length 3rd stage in minutes	6.9 (6.1)	6.2 (4.6)	11.3% (-5.0, 27.6%)
Average EBL in mL	163.5 (106.7)	186.5 (230.1)	-12.3% (-30.2, 5.5%)
EBL > 500 mL	3/217 (1.4%)	6/224 (2.7%)	0.58 (0.25, 3.86)
EBL > 1000 mL	0/217	1/224 (0.4%)	0.52 (0.05, 5.65)
Additional uterotonic	9/223 (4.0%)	19/224 (8.5%)	0.48 (0.22, 1.03)
Clinical diagnosis of PPH	3/224 (1.3%)	8/226 (3.5%)	0.38 (0.10, 1.41)
Blood transfusion	1/217 (0.9%)	5/221 (2.3%)	0.20 (0.02, 1.73)
Maternal mortality	0/224	1/226 (0.4%)	0.50 (0.05, 5.52)

Values are given as mean (standard deviation)

\*To calculate a RR for EBL > 1000 mL and maternal mortality, 1 was added to each group to avoid an undefined (division by zero) result.

augmentation of labour. Women with intrauterine fetal death or stillbirth were allowed to participate if it was felt that the pregnancy had otherwise reached a viable gestational age, which was greater than 28 completed weeks at these hospitals.

The treatment was administered at delivery of the anterior shoulder, or as soon as feasible after delivery (i.e., within one to two minutes). A subjective estimate of blood loss was recorded. If a woman had significant blood loss, the usual hospital protocol would be initiated at the discretion of the attending physician. This protocol included use of intravenous oxytocin, attention to lacerations, removal of retained placental tissue, and blood transfusion as required. If a patient had agreed to participate in the trial but failed to achieve vaginal delivery, her randomization envelope was simply returned to the box to be used for the next patient in the trial.

After delivery, women were monitored for additional blood loss and the occurrence of shivering by objective or subjective report. Temperature was monitored routinely and noted in the data sheet when greater than 37.5°C. At approximately 12 hours postpartum, a second blood sample was drawn to determine postpartum hemoglobin concentration. Because it was standard practice at these hospitals to discharge patients within 24 hours of a normal vaginal delivery, measuring hemoglobin levels at 24 hours postpartum was not feasible.

### Sample Size Calculation

Sample size was calculated 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 delivery to after delivery. A standard deviation of 0.3 g/dL was calculated from the sample. A difference of > 0.1 g/dL between the groups was felt to be clinically significant, based on a survey of obstetricians at our centre. Using  $\alpha = 0.05$  and  $\beta = 0.10$ , we found the minimum required sample size to be 191 women per group. We produced 450 randomized packages to allow for lost supplies and inadequately completed data sheets.

### Statistical Analysis

Data were analysed on an intent-to-treat basis by parametric and nonparametric tests, using Statistix Version 7.1 (Analytical Software, Tallahassee FL). Primary outcome and continuous variable secondary outcomes were tested using a two-sided student *t* test. The primary outcome was considered statistically significant at an  $\alpha$ -level of 5% ( $P < 0.05$ ). *P* values were reported for the secondary outcomes. The dichotomous secondary outcomes were analysed using chi-squared or Fisher exact tests, where appropriate, and *P* values are reported accordingly.

### RESULTS

A total of 450 women were enrolled and randomized to receive either rectal misoprostol (224) or intramuscular oxytocin (226) during the study period. Four hundred forty women (220 in the misoprostol group; 220 in the oxytocin group) had both pre-delivery and postpartum hemoglobin concentration assays recorded for analysis (Figure). There was no significant difference between the groups regarding baseline characteristics or risk factors for postpartum hemorrhage (Table 1). In the oxytocin group, 16.9% of women,

**Table 3. Medication side effects**

	Misoprostol 800 µg rectally	Oxytocin 10 IU intramuscularly	Relative risk (95% CI)
Nausea	1/212 (0.5%)	4/216 (1.9%)	0.26 (0.03, 2.26)
Vomiting	1/214 (0.5%)	2/213 (0.9%)	0.50 (0.05, 5.45)
Shivering	16/213 (7.5%)	2/213 (0.9%)	8.0 (1.86, 34.36)
Temperature > 37.5 °C	8/200 (4.0%)	4/209 (1.9%)	2.09 (0.64, 6.83)
Hypertension	2/202 (0.9%)	0/203 (0%)	3.02 (0.32, 28.73)

\*To calculate a RR for hypertension, 1 was added to both groups to avoid an undefined (division by zero) result.

and in the misoprostol group, 15.6% of women had at least one risk factor for PPH.

There was no significant difference between the groups for change in hemoglobin concentration. The mean ( $\pm$  standard deviation) decrease in hemoglobin concentration was 1.19 (1.33) g/dL for the misoprostol group and 1.16 (1.08) g/dL for the oxytocin group (risk difference 2.6%; 95% CI -16.8–19.4;  $P = 0.80$ ). Secondary outcome measures did not show a significant difference between the groups (Table 2), specifically in estimated blood loss (EBL > 500 mL or EBL > 1000 mL), postpartum hemoglobin, length of third stage, clinical diagnosis of PPH, or need for blood transfusion. There was one maternal death in the oxytocin group, secondary to a postpartum hemorrhage. Unfortunately we do not have further information regarding this case as the hospital chart was not available for further review. No other woman required an operative intervention (such as manual removal of placenta, dilatation and curettage, laparotomy, or hysterectomy) or had estimated blood loss greater than 1000 mL. There was a trend towards decreased use of additional uterotonic in the misoprostol group compared with the oxytocin group with a relative risk of 0.48 (95% CI 0.22–1.03;  $P = 0.052$ ).

The groups were similar in the incidence of nausea, vomiting, temperature greater than 37.5 °C, and increased blood pressure (Table 3). There were significantly more women with shivering (7.5% vs. 0.9%; relative risk 8.0; 95% CI 1.86–34.36;  $P = 0.001$ ) in the misoprostol group.

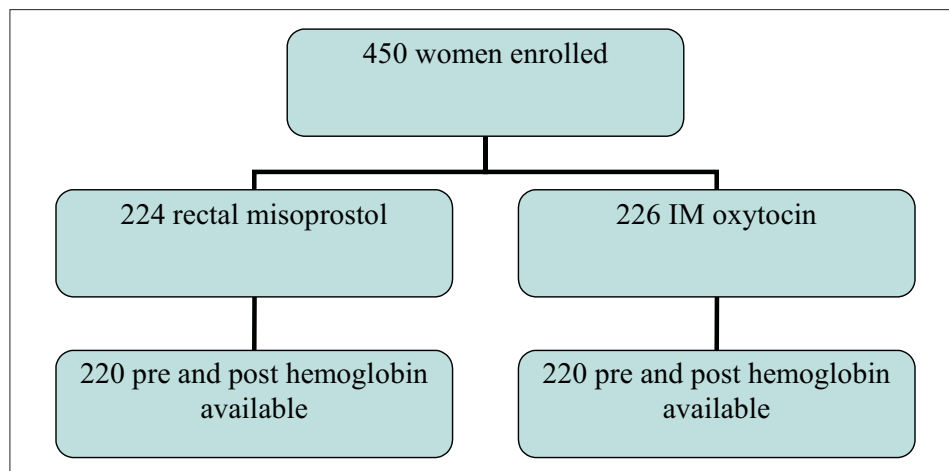
## DISCUSSION

This study has confirmed the utility of rectal misoprostol for routine management of the third stage of labour, as determined by change in hemoglobin concentration from before to 12 hours after delivery. The present investigation is unique in its rural location in a developing country, the level of involvement of the nurse midwives, and the higher than usual dose of rectally administered misoprostol. We

included high-risk patients in the study, the only exclusion criterion being a known medical contraindication to prostaglandin administration. These were important aspects of the study, because the women who are dying of obstetric hemorrhage live in these rural villages, are cared for primarily by nurse midwives or traditional birth attendants, and obviously cannot change their own risk factor profile.

Investigators for the WHO concluded that 600 µg of oral misoprostol is 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).<sup>37</sup> This large multicentred study has now become the standard for comparisons in the literature evaluating use of misoprostol in the third stage of labour. Although the primary outcome (measured blood loss greater than 1000 mL) seems to be a valid endpoint, it is nevertheless an arbitrary figure and may be unimportant in any particular clinical scenario. Interventions to halt further blood loss (e.g., laparotomy, evaluation under anaesthesia, selective arterial embolization) or blood product transfusion are more indicative of the severity of the hemorrhage than measured blood loss in any clinical situation. In fact, in the WHO trial, the need for blood transfusion was actually higher in the oxytocin group and approached significance, with a  $P$ -value of 0.06. There were other concerns about the WHO study, including statistical heterogeneity amongst individual centres for the primary outcome of blood loss, and the failure to record the route of oxytocin administration (intravenous or intramuscular). The WHO group indicated that they used the highest dose of misoprostol that is considered effective (600 µg) without an unacceptable level of side effects. Considering the observed level of side effects, they suggest that higher doses of misoprostol should not be tested. In the dose-finding trial carried out prior to this study, WHO investigators observed a rate of shivering of up to 28% using a 600 µg oral misoprostol dose.<sup>38</sup> In our study of rectally administered misoprostol

Flow diagram of study enrolment



using a dose of 800 µg, the observed incidence of shivering was only 7.5%, although this was significantly higher than the 0.9% observed in the oxytocin group. Higher doses and alternative routes of misoprostol administration were not evaluated in the dose-finding trial, which in retrospect is unfortunate. The current study demonstrates a very favourable side-effect profile for rectally administered misoprostol. These rates of side effects are similar to those associated with 600 µg rectal misoprostol cited in a meta-analysis published in the Cochrane Library (any shivering 11.9%, fever  $\geq 38^\circ\text{C}$  4.0%).<sup>35</sup>

The WHO authors performed a meta-analysis of 16 studies comparing the effects of oral or rectal misoprostol with the effects of oxytocin or placebo in the third stage of labour.<sup>36</sup> They concluded that many of the individual studies lacked the power to determine whether misoprostol was truly as effective as parenteral oxytocin. They argued that the findings of no difference may have been merely due to a lack of statistical power to show the difference, and that only the WHO multicentred trial had a sample size large enough to determine the answer. However, the meta-analysis included only three trials of rectal misoprostol, and these used a lower dose (400 µg) of misoprostol than the current study.

In a recent study of 1620 women giving birth in a rural setting in India, oral misoprostol given after delivery was more effective than placebo in reducing the rate of PPH and mean postpartum blood loss, but side effects of shivering and fever were more frequent with misoprostol than with placebo (shivering 52.2% vs. 17.3%, fever 4.2% vs. 1.1%, respectively).<sup>33</sup> A study by our group of 800 µg oral misoprostol compared with intramuscular oxytocin found

higher rates of shivering and fever with misoprostol than oxytocin (shivering 80.7% vs. 3.6%, fever 11.4% vs. 0%, respectively).<sup>42</sup> The low incidence of side effects with the 800 µg dose of rectal misoprostol in the current study (nausea 0.5%, vomiting 0.5%, shivering 7.5%, and fever 4.0%) is encouraging and suggests that rectal administration may be superior to oral for limiting gastrointestinal and thermoregulatory side effects while maintaining uterotonic properties.

There are several shortcomings in the current study. As in our study of oral misoprostol in Ghana,<sup>42</sup> the standard deviation in hemoglobin concentration observed in the current study was higher than estimated in the sample size calculation, thereby reducing our ability to identify significant differences in the outcomes of interest. Also blood loss was not measured objectively because there were too few staff members at the study centres to carry this out.

## **CONCLUSION**

Misoprostol 800 µg given rectally is effective in minimizing blood loss when utilized as the pharmacologic agent in active management of the third stage of labour, as measured by change in hemoglobin concentration from before to 12 hours after delivery. This dose and route of administration are well tolerated, and the usual side effects of shivering and increased temperature were noted only infrequently. This is further evidence for the utility of misoprostol as an effective uterotonic and provides a simple therapeutic option for health care providers in developing nations to use in the battle against obstetric hemorrhage.

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