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Assessment of sublingual misoprostol as first-line treatment for primary post-partum hemorrhage: Results of a multicenter trial

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Abstract

Aim: The study investigated the effectiveness of sublingual misoprostol when used as primary treatment of primary post-partum hemorrhage (PPH) in a low-income country.

Methods: Maternity care providers in three Nigerian hospitals administrated 800 μm sublingual misoprostol to women experiencing PPH. The outcome variables were estimated blood loss and the need for additional uterotonic drugs after initial treatment with misoprostol. Entry criteria included women in term spontaneous labor, while exclusion criteria were women with operative delivery and those experiencing PPH not due to atonic uterus.

Results: One hundred and thirty-one women with PPH were treated over 6 months. Estimated blood loss ranged 500–2500 mL. Twenty women (15.3%) required additional uterotonic drugs to control continuing blood loss. There were no maternal deaths, while seven perinatal deaths were recorded.

Conclusion: We conclude that although sublingual misoprostol is effective in reducing blood loss due to PPH, it does not effectively treat all forms of PPH. Additional uterotonics and other ancillary treatments would be required.

Key words: case management, maternal mortality, misoprostol, Nigeria, post-partum hemorrhage.

Introduction

Nigeria has been identified as one of six countries that account for 50% of global estimates of maternal deaths.[1] Several published data[2,3] indicate that primary post-partum hemorrhage (PPH) is the leading cause of maternal mortality in the country. Of the estimated 144 daily maternal deaths in Nigeria, 36 (25%) are attributable to PPH.[4] A report by the Society of Gynecology and Obstetrics of Nigeria (SOGON) based on data obtained from major hospitals[5] indicate that PPH due to atonic uterus is the leading cause of maternal mortality in the country.

Active management of the third stage of labor (AMTSL) is the international best practice for preventing PPH due to atonic uterus.[6,7] The World Health

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Organization (WHO) recommends the administration of i.v. oxytocin as first-line drug and i.v. ergometrine as second-line drug to be used within the context of AMTSL for the prevention and treatment of PPH.[6,7] However, there have been concerns about the relative efficacy and effectiveness of oxytocin and ergometrine in African countries due to their higher cost, the need for parenteral administration and loss of drug efficacy due to poor storage practices.[8] These drawbacks have raised the possibility that an orally active drug may be more effective in managing PPH, especially in contexts where women tend not to deliver in hospital settings.

Misoprostol is an orally active uterotonic drug that has been recommended for the prevention and treatment of PPH.[6,9,10] It is effective and safe, and overcomes many of the barriers associated with the use of oxytocin and ergometrine.[11] Misoprostol has been reported to be more effective than placebo in preventing PPH in community but not in hospital births.[12] It is also effective in the treatment of PPH due to atonic uterus.[13,14] A recent randomized, double-blind controlled trial[15] reported the equivalence of sublingual misoprostol when compared to i.v. oxytocin in stopping excessive bleeding due to uterine atony in women who have previously received prophylactic oxytocin.

In 2006, the Federal Ministry of Health of Nigeria[16] approved misoprostol for the prevention and treatment of PPH. Since then, its use for the management of PPH has been reported in various parts of the country.[17,18] In view of recent results indicating that sublingual misoprostol may be as effective as i.v. oxytocin in treating PPH, we hypothesized that misoprostol given alone as first-line treatment for women experiencing PPH due to uterine atony would be effective in stopping bleeding and preventing maternal deaths. This proposition, if confirmed, would be relevant in communities with limited ability to use oxytocin and ergometrine for treating PPH, and in contexts where women tend to deliver outside health-care institutions. The results would also be useful in identifying approaches for scaling up the use of evidence-based methods for treating PPH in communities unable to consistently utilize oxytocin and/or ergometrine as first- or second-line treatment.

Methods

The study was carried out in three Nigerian teaching hospitals: Lagos State University Teaching Hospital, Jos University Teaching Hospital and Aminu Kano University Teaching Hospital. Formative research was first conducted by examining existing data on maternal mortality and assessing the quality of clinical practices relating to the treatment and prevention of PPH in the hospitals. The report of the formative research,[19] revealed high maternal mortality ratios due to PPH and found that none of the hospitals routinely used misoprostol for the prevention and treatment of PPH. They used AMTSL and parenteral oxytocin and ergometrine for the prevention and treatment of PPH rather inconsistently. It was also not their practice to routinely maintain i.v. fluids for women at the time of delivery.

Thereafter, a protocol for the use of sublingual misoprostol for the treatment of PPH in the hospitals was designed. In the protocol, midwives and clinicians were taught to use 800 mcg sublingual misoprostol in women experiencing PPH due to uterine atony, in accordance with the WHO recommendation.[6,8] PPH was defined according to the standard definition of loss of 500 mL or more of blood from the genital tract within 24 h of delivery. Blood loss was determined based on estimates by the attending midwives, and relied on the observational method normally used for estimating blood loss in maternity centers in Nigeria.[20] This consisted of estimates of blood and clots collected in calibrated delivery pans, and those contained in soaked gauze at the time of delivery. It was not considered necessary to accurately measure blood loss as a WHO scientific committee has not found this to be of value in the follow-up of women with PPH.[6]

Successful treatment was cessation of active bleeding within 20 min of misoprostol use, while failed treatment consisted of continued heavy bleeding exceeding 300 mL after this period. Additional uterotonic drugs recommended for those with failed treatment were i.v. ergometrine and oxytocin, and continuous high-dose oxytocin infusion, while ancillary treatment such as blood transfusion and plasma expanders were to be used as necessary.

Eligibility criteria included women in labor at term with singleton pregnancies, who did not have induction or labor augmentation with oxytocic drugs and who gave informed consent. Exclusion criteria were women transferred in labor from other hospitals, those undergoing operative delivery and those experiencing PPH, not due to uterine atony. Uterine atony was confirmed by the presence of a flaccid, non-contracting uterus on abdominal palpation. Careful vaginal examination was conducted in all women to exclude vaginal or cervical tear and retained products of conception as possible causes of PPH.

Misoprostol tablets were procured and made available to the participating hospitals, while protocols for management of PPH with sublingual misoprostol were placed at strategic locations in the maternity units to be used as reference guides or reminders. To monitor the use of the protocol and the outcome of management of PPH, simple monitoring forms for documenting the clinical records of patients were provided. The completed forms elicited information on the sociodemographic characteristics of the women (age, parity, occupation), the clinical diagnosis at admission, the method of delivery, the types and doses of medications given, the need for additional treatment, the duration of hospitalization, and the maternal and fetal outcome.

In calculating sample size, a clinically significant effect of 10% increase in successful treatment of PPH or more over 12 months was of interest. With a reported PPH prevalence rate of 3.0% in Nigeria,[5] and assuming a 60% increase in successful treatment, with a significance of 0.05 and a power of 0.8, a sample size of 130 patients was required. Approval for the study was obtained from the individual hospitals, while ethical approval was provided by the ethical review boards of the Women's Health and Action Research Center (no. WHARC/ERB/2009/03/07).

Data analysis

Data entry was performed with Epi-Info software (Centers for Disease Control) and analyzed with SPSS Pc+ (SPSS). The data obtained from the three hospitals was combined and analyzed for treatment outcomes. The outcome variables were estimated blood loss and the need for additional treatment with other uterotonic drugs following initial treatment with sublingual misoprostol.

Results

Data obtained from the three hospitals are presented in Table 1. As shown, 131 women with PPH due to atonic uterus were treated with sublingual misoprostol in the three hospitals. They ranged in age from 18 to 40 years (median, 28). The parity distribution also varied widely, with most of the women being multiparous. Grand multiparous women (parity, ≥5) comprised over 25% of the sample. Kano and Jos had a higher proportion of grand multiparous women as compared to Lagos.

The estimated blood loss ranged 500–2500 mL (median, 1950 mL). Blood loss was greater in Jos and Kano than in Lagos, but the differences were not statistically significant. The estimated blood loss included the blood lost by the women before they were given sublingual misoprostol. Forty-three women (32.8%) were transfused with 1–4 units of blood (results not shown), while all required i.v. infusion of saline and other plasma expanders. Of the 131 women, 20 (15.3%) required additional treatment with i.v. oxytocin and ergometrine after initial administration of sublingual

Table 1 Characteristics of patients with primary post-partum hemorrhage managed with misoprostol and their clinical outcomes

	Kano	Jos	Lagos	Total
No. of patients	37	38	56	131
Age, median (range), years	28 (19–40)	30 (19–40)	30 (18–36)	29 (18–40)
Parity, *n*				
Para 0	2 (5.4%)	11 (28.9%)	16 (28.6%)	29 (22%)
Para 1	5 (13.5%)	2 (5.3%)	16 (28.6%)	23 (17%)
Para 2–4	14 (38%)	11 (28.9%)	21 (37.5%)	46 (36%)
>Para 5	16 (43%)	14 (36.9%)	3 (5.3%)	33 (25%)
No. needing additional treatment	4 (10.8%)	2 (5.3%)	14 (25%)	20 (15.3%)
Estimated blood loss				
Mean	685	616	650	
Range (mL)	550–1000	500–2500	550–1500	500–2500
Duration of hospital stay	8 h to 3 days	24 h to 7 days	1–8 days	8 h to 8 days
Maternal outcomes	All alive	All alive	All alive	All alive
Fetal outcomes	1 NND	4 NND	2 SB	5 NND 2 SB
Drug complications	4 (6.7%), rigors	1 (2.7%), shivering	0.0	4 (6.7%), rigors; 1, shivering (2.7%)

NND, neonatal deaths; SB, stillbirths.

misoprostol. As shown in Table 1, more women in Lagos required additional uterotonic treatment than in Jos and Kano.

The maternal and fetal outcomes are presented in the bottom panel of Table 1. No maternal deaths occurred in the three project sites. By contrast, five neonatal deaths and two fresh stillbirths occurred, with more perinatal deaths occurring in Jos as compared to Lagos and Kano. The stillbirths were preterm, low birthweight babies, while all five neonatal deaths were babies experiencing severe neonatal asphyxia at birth. As shown in Table 1, the documented drug side-effects of misoprostol were few and consisted only of rigors and shivering.

Discussion

The objective of this study was to determine whether primary PPH can be treated effectively with sublingual misoprostol as first-line drug, especially in countries with high rates of non-institutional deliveries, where the recommended first- and second-line drugs (oxytocin and ergometrine) cannot be effectively used. The results show that 15.3% of the women treated with misoprostol required additional treatment with either oxytocin, ergometrine or both, while 32.8% of the women required blood transfusion. Although the number of women requiring additional treatment after initial treatment with sublingual misoprostol appears high, this may be due to early recourse by providers to traditional regimens, not wanting to jeopardize the chances for the individual women. This probably explains the higher proportion of women requiring additional uterotonic treatment in Lagos despite the lower proportion of grand multiparous women and the lower overall blood loss in the state as compared to the other two study sites.

The results of this study suggest the need for caution in recommending the use of misoprostol as first-line drug for the treatment of PPH in lower levels of care. First, the fact that many women needed i.v. plasma expanders and blood means that traditional birth attendants and primary health-care workers with limited access to blood and blood products cannot all use this method of treatment. Second, although there were no maternal deaths in this cohort of women, the high rate of associated perinatal mortality indicates that there may be concomitant medical complications that providers need to deal with in women presenting with PPH. Many of these could be evolving severe complications or multiple organ damage that may not be amenable to treatment at lower levels of care. Third, follow-up care for both babies and mothers would be required after women survive severe episodes of PPH in order to reduce associated puerperal and neonatal morbidity and mortality. Thus, while primary treatment with misoprostol may be the only option in some lower level facilities, we strongly recommend that women so treated should be promptly referred to secondary or tertiary care centers that have facilities for follow-up treatment and care. The best approach would be to teach primary health-care workers to administrate misoprostol to women experiencing PPH, and then to require them to promptly refer such women to higher levels of care, whether or not they experience continued bleeding.

The results of this study suggest that misoprostol is safe to use at all levels of care for the primary treatment of PPH. Our results suggest a high safety margin, with few side-effects in women taking high doses of misoprostol for the treatment of PPH. However, the study has some limitations which suggest the need for caution in interpreting the findings. First, the lack of randomization reduced the ability to measure the degree to which sublingual misoprostol reduced blood loss and prevented mortality in women experiencing PPH. However, randomization was not considered ethical since sublingual misoprostol has previously been shown to be as effective as i.v. oxytocin in reducing blood loss in women experiencing PPH.[15] Second, it can be argued that an assessment of the effectiveness of misoprostol in the context of lower levels of clinical care would be better appraised by studies conducted at those levels. However, while the outcomes of such assessments are still unknown, we believe that studies conducted at higher levels of care that can mitigate potential problems would be the first step. Later assessments can then be appraised in communities and in lower level centers where actual deliveries take place.

While sublingual misoprostol has been found to be clinically equivalent to oxytocin in treatment PPH due to atonic uterus,[15] this appears to be the first study to investigate the effects of sublingual misoprostol when used for primary treatment of PPH in resource-poor countries. However, oral misoprostol with slower onset of action has previously been shown to be effective in decreasing blood loss and reducing maternal mortality when used for the prevention of PPH in resource-poor countries.[21] We conclude that sublingual misoprostol is effective as a first-line drug for the treatment of PPH, especially when used in contexts where additional uterotonic agents and ancillary treatments

are available. However, in lower level facilities where additional treatment regimens may not be available, the use of sublingual misoprostol for the primary treatment of PPH should be followed by prompt referral of patients to secondary and tertiary level facilities.

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Disclosure

The authors report no declarations of interest.

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