ORIGINAL RESEARCH ARTICLE

Community-Based Availability of Misoprostol: Is It Safe?

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ABSTRACT

This paper evaluates the safety and acceptability of long-term community-based use of misoprostol for management of postpartum hemorrhage (PPH) in home-births, by comparing deliveries with and without misoprostol use in communities of Kigoma, Tanzania. We administered a standardized survey instrument to women who delivered between August 2004 and May 2007. 940 women completed questionnaires, corresponding to 950 deliveries. Findings showed that the majority of TBAs administered misoprostol at the correct time (76%). Receipt of three or five tablets was most commonly reported (47% and 43% respectively). Misoprostol users were significantly more likely to experience shivering, high temperature, nausea, and vomiting after delivery; adjustment for gynecological history and delivery characteristics revealed no significant differences in experience of symptoms. Misoprostol was highly acceptable to all women surveyed. Misoprostol at the community level is a safe intervention *(Afr J Reprod Health 2009; 13[2]:117-128).*

RÉSUMÉ

Disponibilité de misoprostol dans la communauté : Est-il sans danger? Cet article évalue la sauveté et l'acceptabilité de l'emploi à long terme de misoprostol dans la communauté pour le traitement de l'hémorragie du post partum (HPP) dans les naissances à domicile, en comparant les accouchements avec et sans l'utilisation de misoprostol dans les communautés de Kigoma, Tanzamie. Nous avons administré un instrument d'enquête standardisé aux femmes qui ont accouché entre le mois d'août 2004 et mai 2007. 940 femmes ont rempli des questionnaires, ce qui correspondait à 950 accouchements. Les résultats ont montré que la majorité des sages-femmes traditionnelles (SFTs) ont administre misoprostol comme il faut (76%). Elles ont indiqué en général avoir reçu trois ou cinq comprimés (47% et 43% respectivement). Les utilisateurs de misoprostol avaient la possibilité de subir le frissonnement, la haute température, la nausée et le vomissement après l'accouchement ; l'ajustement pour l'histoire gynécologique et les caractéristiques de l'accouchement n'ont pas révélé des différences significatives quant aux symptômes. Misoprostol a été bien acceptable à toutes les femmes enquêtées. Misoprostol au niveau de la communauté est une intervention sans danger *(Afr J Reprod Health 2009; 13[2]:117-128).*

KEYWORDS: Misoprostol; Postpartum hemorrhage; Traditional birth attendants; Community-based; safety; Acceptability

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Introduction

Sub-Saharan Africa accounts for approximately half of all maternal deaths each year, and in Tanzania alone 13,000 women die annually due to pregnancy and delivery related causes.[1] In Africa, more than a third of all maternal deaths are attributed to hemorrhage.[2] Despite effective methods for treatment of postpartum hemorrhage (PPH)—notably the uterotonic oxytocin—mothers' deaths are continuing unabated in resource-poor areas, and in parts of sub-Saharan Africa maternal mortality has stagnated as rates of skilled attendance at birth have declined.[3] Recent WHO recommendations approve the use of either oxytocin or misoprostol alone by a health worker trained in its use for PPH prevention in the absence of active management.[4] Moreover, several controlled trials have demonstrated that misoprostol is safe and effective for the prevention of PPH at the community level, either self-administered, or by a trained auxiliary nurse or traditional birth attendant (TBA).[5-8]

Misoprostol tablets are ideally suited for PPH treatment at home-births and in resource-poor settings because of their ease of use, effectiveness, and safety. Several published studies show that misoprostol is safe for the control of PPH.[6, 9, 10] Experts agree that without skilled attendance, misoprostol may be the only technology available to manage PPH at home-births.[11, 12] Yet despite the published literature, researchers continue to cite a paucity of data on the safety of misoprostol in the community.[13] The debate centers on its use and distribution by lay providers despite examples from health programs utilizing community-based distribution of drugs in prevention of malaria and mother-to-child transmission of HIV.[14-17] Furthermore the standard argument against widespread use of misoprostol cites literature comparing it to oxytocin—typically used only in a hospital setting.

Background

In 2003-2004 we studied household-management of PPH with misoprostol in Kigoma, Tanzania. (Figure 1) Using intervention and non-intervention specified non-adjacent geographical areas, intervention TBAs were instructed to rectally administer five tablets of misoprostol (1000 µg; Zizhu Pharmaceutical, Beijing) to all women delivering vaginally with subsequent blood loss of 500ml or more determined by the *kanga* method.[18] TBAs were instructed to refer women to a health facility 20-30 minutes after misoprostol administration if no significant change in blood loss occurred or if her condition worsened (rapid respiration, fever, sweating or weakness), regardless of blood loss status. TBAs in non-intervention areas were trained to record blood loss of 500ml and to refer women. Since the study's completion in July 2004, TBAs in the intervention area have continued to use misoprostol outside of a study-controlled environment. Additionally, the Tanzanian Food and Drug Authority approved the registration of misoprostol for prevention and treatment of PPH in 2007.[19]

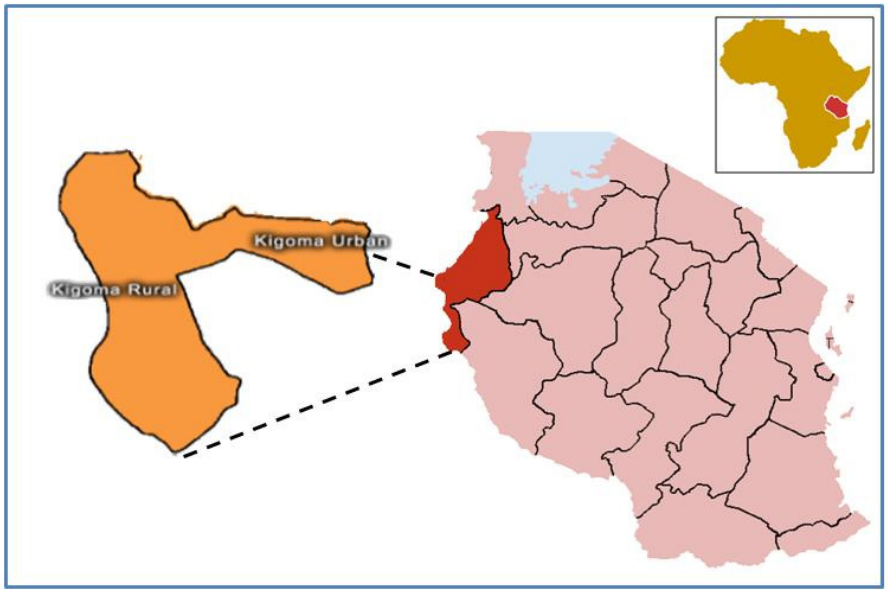


Figure 1: Map of study areas

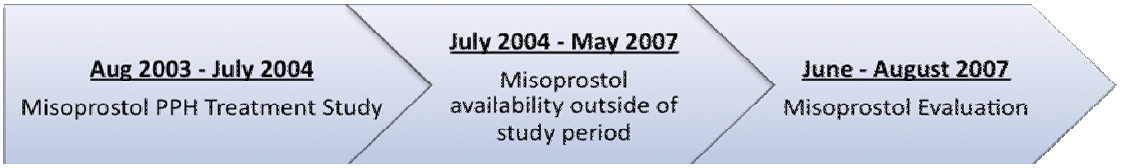


Figure 2: Timeline of Events

In June 2007 we conducted an evaluation of the long-term availability of misoprostol for household management of PPH. (Figure 2) In this paper we assess the safety and acceptability of misoprostol for management of PPH in home-births, by comparing deliveries with and without use of misoprostol.

Methods

Data Collection & Instruments

Of the 30 TBAs involved previously, 23 were still active and agreed to participate in the study. We recruited and trained two supervisors and ten interviewers from Maweni Regional Hospital. Over two months, the field team administered a standardized household survey to women having delivered between August 2004 and May 2007 identified to the interviewer by study TBAs in the same intervention and non-intervention areas as in the 2003-4 study.

The survey instrument was developed in English, translated into Kiswahili and administered orally upon receiving informed consent. The survey included questions about PPH exposure and

comprehension, ANC and delivery information, referral, medication at delivery, and acceptability of misoprostol. Additionally, we conducted a qualitative assessment focusing on individual and community experiences with PPH and misoprostol through in-depth interviews with mothers, TBAs, and health care providers and focus groups discussions with community leaders, TBAs from both intervention and non-intervention areas, and nurses from Maweni Regional Hospital. The Committee for the Protection of Human Subjects, University of California, Berkeley and the Tanzanian Internal Review Board approved the study.

All surveys were reviewed daily for completion, entered into a database with personal identifiers omitted, and analyzed using STATA /IC version 10.0 (*Calverton, MD, USA*).

Safety indicators include: correct timing and dosage of misoprostol; symptoms experienced after childbirth; need of referral interventions; and frequency of serious adverse events (i.e. ruptured uterus, death). Acceptability was measured by participant's willingness to use misoprostol if PPH occurred in a future pregnancy; willingness to recommend misoprostol to friends or family; and willingness to purchase misoprostol in the future. A woman's self-report of the number of *kangas* used to absorb blood after delivery was used to determine perceived blood loss and categorize PPH, using two *kangas* as the threshold for perceived PPH (blood loss of 500ml or more). A woman was classified with severe PPH if she reported soaking four or more *kangas* (perceived bleeding 1000ml or more).

Statistical Analyses

Frequency tables were constructed for participants' characteristics and all variables of interest. We compared deliveries where misoprostol was used with deliveries without misoprostol from both intervention and non-intervention villages. A two-tailed Student t-test was performed to compare means and proportions. Significance was established at p-value <0.05. Logistic regression odds ratios, both crude and adjusted, are presented for experience of symptoms after delivery. Generalized estimating equations were utilized in the multiple logistic regression analyses to account for correlation among respondents recruited by the same TBA.

Results

TBAs reported approximately 3519 deliveries during the study period. Of the 948 women TBAs approached for inclusion in the study, not one declined participation. In total, 940 women completed questionnaires, corresponding to 950 deliveries. Ten women had two deliveries during the study period and completed two surveys each. Misoprostol was used in 164 deliveries (Figure 3).

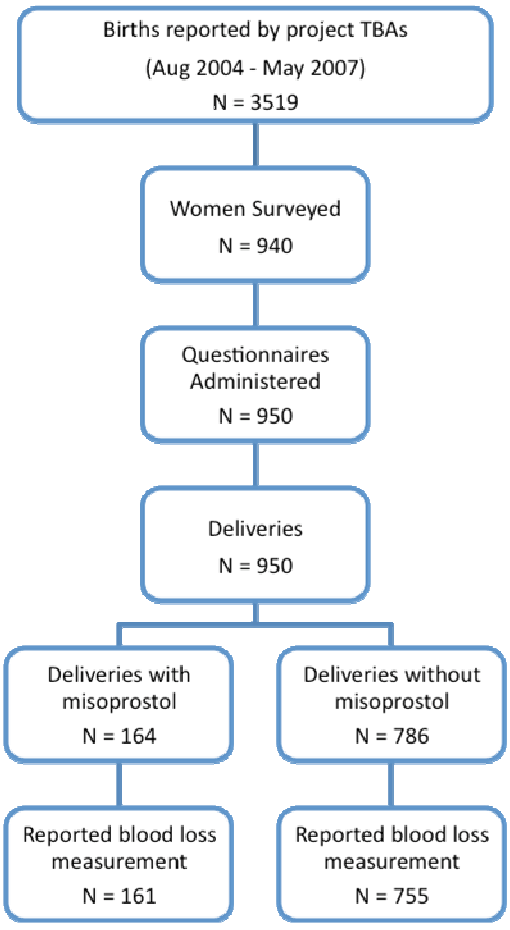


Figure 3: Data collection

Participant's characteristics

Table 1 shows participants' history and delivery characteristics. Parity in our study population averaged 3.8 children per woman. A significantly higher proportion of deliveries without misoprostol were to primiparous women (15% versus 10% of deliveries with misoprostol). Significantly more misoprostol-users had a previous history of PPH (51%) compared to non-users (16%). ANC attendance was nearly universal for this population (99%), averaging 3.9 visits. Among all participants, the majority of births were home-births (93%), and most women delivered with a TBA (83%). Among deliveries without misoprostol, women also delivered alone (n=23) or with the assistance of a friend or relative (n=58). Not surprisingly, there was a significantly greater proportion of women reported soaking two or more *kangas* among deliveries with misoprostol [n=152 (94%)] than deliveries without the drug [n=247 (31%)].

Safety

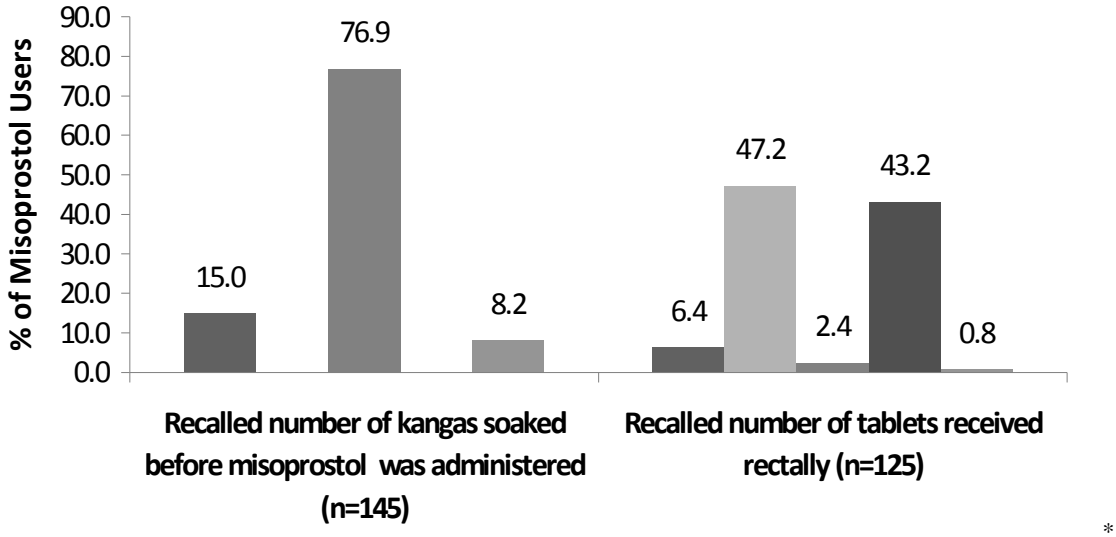
Of the deliveries where the woman remembered the number of *kangas* she soaked before receiving misoprostol, the majority (76%, n=113) received the drug at the appropriate time. TBAs administered misoprostol before the PPH threshold of two *kangas* in 15% of deliveries according to women's recall. These deliveries did not differ significantly in labor characteristics or the woman's gynecological history from those where misoprostol was administered at the correct time. However, a significantly higher proportion of these women (41%) had experienced PPH in a previous delivery than in all deliveries (22%) (p=0.03, data not shown). In twelve deliveries (8%) the women recalled the TBA administering misoprostol after the PPH threshold, nine of whom soaked four *kangas* before the TBA administered misoprostol.

Table 1: Characteristics of the study population

	Study Population (n=940) n (%)	Deliveries with misoprostol (n=164) n (%)	Deliveries without misoprostol (n=786) n (%)	P-value
Parity				
1	135 (14.4)	16 (9.8)	119 (15.1)	0.07
2-4	498 (53.0)	90 (54.9)	415 (52.8)	0.63
5-14	307 (32.7)	58 (35.4)	252 (31.1)	0.41
Mean Parity	3.8 ± 2.2	3.8 ± 1.8	3.8 ± 2.3	0.78
Previous history of PPH				
Yes	205 (21.8)	83 (50.6)	129 (16.4)	<0.01
No	735 (78.2)	81 (49.4)	657 (83.6)	<0.01
Number of ANC visits				
Attended at least one visit	934 (99.4)	162 (98.8)	782 (99.5)	0.30
Mean number of visits	3.9 ± 1.3	3.9 ± 1.2	3.8 ± 1.3	0.47
Place of delivery				
Home	871 (92.7)	156 (95.1)	720 (91.6)	0.12
Facility	66 (7.0)	6 (3.7)	64 (8.1)	0.05
En route	3 (0.3)	2 (1.2)	2 (0.3)	0.08
Assistance during delivery				
Alone	23 (2.5)	0	23 (2.9)	0.03
Relative/ Friend	58 (6.2)	0	58 (7.4)	<0.01
TBA	779 (82.9)	153 (93.8)	631 (80.3)	<0.01
Skilled Provider a	80 (8.5)	11 (6.7)	74 (9.4)	0.27
Perceived bleeding				
2 or more soaked *kangas* b	395 (42.0)	152 (92.7)	247 (31.4)	<0.01
4 or more soaked *kangas* c	82 (8.7)	30 (18.3)	53 (6.7)	<0.01
Cannot remember number of soaked *kangas*	13 (1.4)	3 (1.8)	11 (1.4)	0.68

a Doctor, Nurse-Midwife, Medical Officer, or Nurse Assistant
b PPH (blood loss >500ml)
c Severe PPH (blood loss >100ml)

Among deliveries where women recalled the misoprostol dose they received, three or five tablets were most commonly reported (47% and 43% respectively). (Figure 4) In 43% of deliveries with misoprostol women received the correct dose of misoprostol (five tablets). TBAs reportedly under-dosed rather than over-dosed: only one woman received more than five tablets, stating that she received six.



*

17 women could not remember the number of kangas *they soiled before misoprostol was administered.*
39 could not remember the number of tablets they received.

Figure 4: *Recalled Use of Misoprostol*

There were fewer overall referrals and bleeding-related referrals among deliveries with misoprostol. Only four of the seven referrals in the misoprostol group were bleeding-related compared to 29 out of 40 referrals among deliveries without misoprostol. (Table 2) Of bleeding-related referrals, 17 required interventions: two deliveries where misoprostol was used and 15 deliveries without misoprostol. The interventions received by women referred for excessive bleeding were mainly injection (presumed to be either oxytocin or ergometrine) and IV fluids; one woman who did not use misoprostol received manual removal of placenta.

Symptoms of delivery were experienced by both misoprostol-users and non-users alike, with misoprostol use associated with significantly higher unadjusted odds of experiencing shivering [OR 2.7 (1.9—3.8)], high temperature [OR 2.7 (1.8—4.1)], nausea [OR 3.0 (1.9—4.6)], and vomiting [OR 4.0 (2.3, 6.9). (Table 3) When adjusting for gynecological history, perceived PPH, and TBA effects there were no

Table 2: Distribution of referrals among study deliveries

	Deliveries with misoprostol (n=164) n (%)	Deliveries without misoprostol (n=785) n (%)	P-value
Total Referrals	7 (4.3)	40 (5.1)	0.66
Bleeding-related referrals [a]	4 (57.1)	29 (72.5)	0.42
Other referrals	3 (42.9)	11 (27.5)	0.42

[a] Excessive bleeding and/or retained placenta

Table 3: Distribution and odds ratios of reported symptoms among study deliveries

	Deliveries with misoprostol (n=164) n (%)	Deliveries without misoprostol (n=786) n (%)	Crude Odds ratio (95% CI)	Adjusted Odds Ratio [a] (95% CI)
Experience of symptoms				
None	67 (41.6)	521 (66.3)	reference	
Any	94 (58.4)	265 (33.7)	2.7† (1.9, 3.8)	1.2 (0.7, 2.3)
Shivering	85 (52.8)	208 (26.5)	3.1†(2.2, 4.3)	1.3 (0.7, 2.6)
High Temperature	43 (26.7)	92 (11.7)	2.7†(1.8, 4.1)	1.2 (0.4, 3.4)
Loose stool	3 (1.9)	22 (2.8)	0.6 (0.2, 2.2)	0.8 (0.3, 2.2)
Nausea	37 (23.0)	70 (8.9)	3.0† (1.9, 4.6)	2.0 (0.7, 5.7)
Vomiting	25 (15.5)	34 (4.3)	4.0† (2.3, 6.9)	1.8 (0.5, 6.4)
Shivering + high temperature	38 (23.2)	65 (8.3)	3.3† (2.1, 5.2)	1.5 (0.4, 4.9)
Any 3 or more symptoms	30 (31.6)	38 (14.3)	2.8† (1.6, 4.8)	1.8 (0.5, 6.0)

[a] Adjusting for parity, experience of PPH during a previous pregnancy, ANC attendance, and perceived PPH (soaking 2 or more *kangas*)

significant differences in experience of any symptoms between deliveries with and without misoprostol. Of note, when adjusting only for perceived PPH during the current delivery, only the odds of experiencing of nausea [OR 1.7(1.1, 2.8)] and vomiting [OR 2.1 (1.2, 3.8)] remained significantly higher in deliveries with misoprostol (data not shown).

Many misoprostol-users reported experiencing multiple symptoms, commonly shivering and fever. Symptoms were transient, lasting less than one hour in the majority of deliveries (Table 4). High temperature was the only symptom with a considerable number of women reporting the duration lasting more than two hours [n=7 (17%)]; however, reported duration of high temperature for more than two hours was significantly more common in deliveries without misoprostol (n=36, 42%, p=0.01, data not shown). No misoprostol-users were referred to a health facility due to symptoms associated with use of the drug. Among misoprostol-users, 42% (n=67) did not experience any symptoms compared to two-thirds of non-users (n=521). There were no serious adverse events such as maternal death or ruptured uterus reported during the study period due to availability of misoprostol in the community.

Table 4: Duration of symptoms among study deliveries*

	Deliveries with misoprostol (n=164) n (%)	Deliveries without misoprostol (n=786) n (%)	P-value
Shivering	n = 86	n = 199	
Less than one hour	70 (81.4)	158 (79.4)	0.70
High Temperature	n = 41	n = 86	
Less than one hour	32 (78.1)	39 (45.4)	<0.01
Nausea	n = 34	n = 62	
Less than one hour	30 (88.2)	43 (69.4)	0.04
Vomiting	n = 25	n = 33	
Less than one hour	23 (92.0)	25 (75.8)	0.11
Loose stool	n=3	n= 22	
Mean number of times	2.7 $\pm$ 1.2	3.3 $\pm$ 1.4	0.44

**Of those that remembered time*

Table 5: Distribution for acceptability of misoprostol among study deliveries

	Deliveries with misoprostol (n=164) n (%)	Deliveries without misoprostol (n=786) n (%)	P-Value
Would use misoprostol if experienced PPH in next pregnancy	163 (99.4)	651 (82.8)	<0.01
Would recommend misoprostol to a friend	163 (99.4)	597 (76.0)	<0.01
Willing to purchase misoprostol	152 (92.7)	667 (84.9)	0.01

Acceptability

In our study population, misoprostol for PPH treatment is perceived as highly acceptable. All but one woman who took misoprostol reported they would take misoprostol again if they experienced PPH in a future pregnancy (99%) and would recommend misoprostol to a friend (99%). (Table 5) In both groups, most women were willing to purchase misoprostol, with almost one out of five women willing to pay as much as 1.15 USD for misoprostol. [n=138 (18%)]. (Data not shown) Misoprostol use was associated with significantly higher likelihood of all acceptability measures.

Discussion

Our results indicate misoprostol is a safe and effective means to control PPH at the

community level and, in the absence of continued monitoring and training, TBAs continued to diagnose excessive bleeding and safely administer misoprostol in home births. Early detection of excessive blood loss and a birth attendant's proactive response is crucial to addresses a pivotal delay that contributes to maternal mortality. [20, 21] In our sample, 164 women took misoprostol, of whom 152 were diagnosed with perceived PPH by the *kanga* method. Although not defined as PPH in our study, an additional nine women reported the TBA administered misoprostol after soaking one *kanga*, indicating the TBA identified a potentially dangerous situation and responded accordingly. This evaluation suggests that the *kanga* continues to be a feasible and highly acceptable means to detect blood loss in these communities.

A general limitation of this study is its retrospective design and the reliance on women's recall. By restricting the survey to the most recent pregnancy, or presumably a memorable delivery where complications ensued, we aimed to minimize potential recall bias.

Of interest in our study is the reportedly high number of women who stated they received only three tablets of misoprostol, instead of the recommended five. Whether this is recall bias or reflection of realities of stock shortages on the ground, it is unclear. Additionally misoprostol was increasingly becoming available for PPH prevention in the clinic at this time. We hypothesize the message of the dosage for prevention may have leaked into the community. Future programmatic efforts to introduce misoprostol in the community should clarify the intended indications of the drug and appropriate dosages and routes.

While misoprostol-use was associated with an increased odds of experiencing symptoms, among users symptoms were transient, often lasting less than an hour and were managed in the home. In this context, symptoms may be preferable to the alternatives of death or severe morbidity. Moreover, despite known associated symptoms, misoprostol is highly acceptable in these communities and even more so among misoprostol-users who were significantly more likely to use misoprostol again in the event of PPH in a future pregnancy, recommend misoprostol to a friend, and, perhaps even more convincingly, be willing to purchase the tablets. While significantly more women who took misoprostol were willing to purchase the drug, there was no statistically significant difference in the amount women were willing to pay between users and non-users of misoprostol, indicating the drug's perceived therapeutic value, regardless of previous use of misoprostol.

While not statistically significant, misoprostol-use was associated with fewer bleeding-related referrals. This does not suggest that the availability of misoprostol discourages referrals of complications. TBAs continue to refer women to the nearest health facility. In both groups, TBAs made the majority of referrals or women self-referred. Although seven misoprostol-users were referred, only four were bleeding-related.

Eleven women in our sample received misoprostol by a skilled

attendant in a facility (n=6) or at home (n=5). Depending upon availability of conventional uterotonics and trained staff, misoprostol is either a first-line or back-up uterotonic. Alternative treatments for PPH treatment are necessary, given that conventional uterotonics can fail, supported by the positive findings of other uncontrolled trials assessing the effectiveness of 1000µg misoprostol rectally in patients unresponsive to oxytocin.[9, 22] In a low-resource setting where staff shortages, inadequate storage of oxytocin, and distance to the nearest facility pose serious obstacles to timely emergency obstetric care, the reduced need for referral and additional interventions upon arrival is indeed a boon for safe motherhood, as has been suggested.[23]

Conclusion

This is the only study known to the authors that evaluated the long-term use of misoprostol at the community level. Furthermore the original study on which it was based is the largest community-based trial in the published literature assessing the safety of household management of PPH with misoprostol. Given the safety of the tablets, acceptability of its use, and public health implications for such a simple and affordable technology, we recommend the expanded use of misoprostol for the control of PPH at the community level.

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