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SPECIAL ARTICLE

Cost-effectiveness of misoprostol to control postpartum hemorrhage in low-resource settings

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Abstract

Objective: To test the cost-effectiveness of training traditional birth attendants (TBAs) to recognize postpartum hemorrhage (PPH) and administer a rectal dose of misoprostol in areas with low access to modern delivery facilities. **Method:** A cost-effectiveness analysis, modeling two hypothetical cohorts of 10,000 women each giving birth with TBAs: one under standard treatment (TBA referral to hospital after blood loss ≥ 500 ml), and one attended by TBAs trained to recognize PPH and to administer 1000 μg of misoprostol at blood loss ≥ 500 ml. **Result:** The misoprostol strategy could prevent 1647 cases of severe PPH (range: 810–2920) and save \$115,335 in costs of referral, IV therapy and transfusions (range: \$13,991–\$1,563,593) per 10,000 births. By preventing severe disease and saving money, it dominates the standard approach. **Conclusion:** Training TBAs to administer misoprostol to treat PPH has the potential to both save money and improve the health of mothers in low-resource settings.

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1. Background

Postpartum hemorrhage (PPH) is the largest single cause of maternal death worldwide. Though PPH is largely preventable and manageable in developed country settings, it is often fatal in areas where mothers have little access to high-quality obstetrical services and blood transfusions [1].

In a large proportion of pregnancies in developing countries, traditional birth attendants (TBAs) are the only available source of care. Over 60% of women in sub-Saharan Africa and 80% in rural West Africa deliver without professionally trained attendants [2]. Traditional birth attendants (TBAs) are informally trained providers of care during pregnancy, childbirth and the postnatal period that are independent of the health system [3]. Some recent studies suggest formal training of TBAs can successfully lower maternal and neonatal mortality [4]. Other studies have found little or no health improvements after TBA training [5].

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Many have focused on the ultimate need to increase the proportion of deliveries attended by formally trained providers over the long run. However, the high number of TBA-attended deliveries and formidable obstacles to increasing deliveries attended by formally trained providers underscores the importance of finding feasible ways to optimize TBA performance here and now.

Misoprostol has gained much attention over the past few years as an easy-to-use, inexpensive, thermostable, non-injection alternative to oxytocin for the treatment of PPH [6–8]. It causes uterine contractions, and has found applications in labor induction [9] and in controlling PPH [8, 10–12]. Furthermore, this prostaglandin agonist can be rapidly absorbed through oral, rectal, or vaginal administration. In hospital settings where other parenteral drugs such as oxytocin are available, misoprostol may offer no clinical advantages [7]. However, in areas where millions of women deliver outside of the hospital setting, misoprostol's high efficacy, thermostability, safety, ease of administration, and low cost makes it a promising agent in the hands of trained TBAs.

A 2005 intervention trial with 849 participants in Kigoma, Tanzania taught TBAs to recognize and rectally administer 5 tablets of misoprostol (1000 µg; Zizhu Pharmaceutical, Beijing) when PPH occurred [13]. The intervention group instructed the TBAs to refer women to the nearest health facility 20 to 30 min after administration of misoprostol if no significant change in blood loss was observed and/or if the patient presented important signs of deterioration. The Kigoma study proved both the safety and efficacy of training TBAs to use misoprostol to prevent further bleeding and PPH complications.

This paper tests the cost-effectiveness of the misoprostol strategy by modeling a misoprostol intervention for hypothetical cohorts of 10,000 women laboring with TBAs in sub-Saharan Africa, drawing parameters for costs and effects from the medical literature.

2. Methods

A cost-effectiveness analysis was conducted from the medical sector perspective by comparing a strategy of training TBAs to administer misoprostol for control of PPH to the standard approach of referring women with PPH to local hospitals. The outcome of interest was the prevention of severe PPH, defined as blood loss >750 ml. Though the standard definition of PPH is blood loss >1000 ml, this model is based on the Kigoma trial, which used the soaking of three or more kangas, or standard-sized cloths which absorb approximately 250 ml of blood each, to define severe PPH.

The direct costs of treatment were calculated over a one-year horizon that would be incurred in two hypothetical cohorts of 10,000 women in labor attended by TBAs. Women in the intervention cohort were attended by TBAs who had been trained to recognize PPH (blood loss ≥500 ml), and give 1000 µg of misoprostol rectally when PPH occurred. Those in the non-intervention area were given standard treatment, defined as referral to the nearest facility if PPH occurred. The assumption was made that TBAs in the non-intervention group would be able to recognize PPH by the number of blood-soaked birth cloths of a standard size, and that in both groups transportation to the nearest facility would be available at a cost. Direct costs were estimated based on year 2005 costs in US dollars, except where noted in Table 1. From the medical sector perspective, costs of lost productivity and intangible costs were ignored.

Table 1 Parameters

	Baseline	Low	High	Source
<i>Costs</i>				
Number of TBAs needed to treat 10,000 deliveries	83	25	331	[20,21,13]
Opportunity cost of TBA training time	\$25.44	\$6.48	\$30.16	[14] [a]
Cost of 5-day training per TBA; teachers and materials	\$10.05	\$3.09	\$17.01	[22,23]
Cost of 1000 µg misoprostol	\$2.75	\$1.65	\$2.75	[8,15]
Cost per hospital bed-day	\$27.60	\$7.39	\$47.80	[24]
Length of hospital stay (days)	2	1	10	
Cost of transportation to hospital	\$5.31	\$2.65	\$44.25	Prata Field Data [13] [b]
Cost of IV fluids+ infusion line	\$4.48	\$2.12	\$6.83	Prata Field Data [13,25]
Cost of blood transfusion	\$63.87	\$60.68	\$67.06	[25,26]
<i>Incidence of postpartum hemorrhage</i>				
Postpartum hemorrhage > 500 ml	31.0%	21.7%	40.4%	[13,18] [c]
<i>Outcomes under misoprostol</i>				
Severe PPH (blood loss ≥ 750 ml)	1.8%	0.9%	5.0%	[11,13,17] [d]
IV Fluid needed per severe PPH	12.5%	10.0%	15.0%	[13]
Blood transfusion needed per severe PPH	12.5%	10.0%	15.0%	[13]
<i>Outcomes under standard care</i>				
Severe PPH (blood loss ≥ 750 ml)	18.2%	9%	34.2%	[13,18] [e]
IV Fluid needed per severe PPH	34.7%	27.8%	41.7%	[13]
Blood transfusion needed per severe PPH	22.2%	17.8%	26.7%	[13]

^aYear 2000 dollars.

^bAll prices converted from Tanzanian Shillings (TSH) to USD using 2005 rates. Baseline = 6000 TSH (peri-urban to urban); Low = 3000 TSH (within urban area); High = 50,000 TSH (rural to urban transport).

^cLow is the average of control and intervention arms in Prata et al.; High is from Strand et al.; Baseline is the average of Strand and Prata.

^d5% estimated from Walraven's finding that 2.5% of women bleed > 1000 ml with 200 µg misoprostol.

^e34.2% estimated from Strand's natural history of 40.4% of women bleeding > 1000 ml.

2.1. Costs

Costs of misoprostol treatment, TBA training, hospital referrals, hospitalization, IV fluids, and blood transfusions, were derived from the literature and from field data. The cost models were:

Eq. (1): Cost model for misoprostol arm

$$C = \text{TBA training costs} + \text{TBA time costs} + \text{Drug costs} \\ + \text{Costs of side effects} + \text{Costs of transport} \\ + \text{Cost of hospitalization} + \text{Costs of treatment for PPH} \quad (1)$$

Eq. (2): Cost model for standard care arm

$$C = \text{Costs of transport} + \text{Cost of hospitalization} \\ + \text{Costs of treatment for PPH.} \quad (2)$$

To determine appropriate remuneration for TBAs attending 5 days of training, lost time costs were estimated using salary estimates for level one skilled labor converted using the purchasing power parity (PPP) index. To estimate a range of costs appropriate to the sub-Saharan region, the average salary for the AfroD region was converted using Uganda PPP for the baseline; the average for AfroE converted using Ghana PPP for the high estimate; and country-specific estimates for Tanzania as the low end [14].

Acquisition costs for 1000 µg of misoprostol (five 200 µg tablets) range from \$1.65–\$2.75 [8,15]. Misoprostol is currently being manufactured generically in China, Taiwan, India, Egypt, Colombia, and Brazil [16]. In practice, misoprostol is not currently included in some national formularies, so it was necessary to make an assumption that misoprostol will become available.

Side effects from misoprostol include high temperature, sweating, shivering and vomiting, and diarrhea. Most symptoms last only a few minutes when misoprostol is administered rectally to treat PPH [13]. Severe side effects are rare. In a South African trial, 3/244 women (1.88%) had temperatures ≥ 40 °C after 1000 µg misoprostol [11], and in the Gambia, 2/79 women (2.53%) receiving 200 µg misoprostol had temperatures ≥ 39 °C, though none had temperatures ≥ 40 °C [17]. Because side effects requiring additional medical treatment are so rare and self-limited, the costs for medical treatment of side effects were estimated to be essentially zero.

Hospital transport costs were based on field data from Kigoma, converted from Tanzanian Shillings (TSH) to US dollars (USD) using 2005 rates, and assumed for the entire region. A range of costs was used to cover transport both within urban areas and from rural to urban centers. Field data were also used for the costs of IV fluids and infusion lines, and averaged with WHO data.

See Table 1 for a full listing of the parameters for the model and their sources from medical literature.

2.2. Effects

Incidence of PPH for both cohorts was projected using a range of estimates from trials in Tanzania and Angola [13,18]. In the non-intervention cohort, the number of cases of PPH that progressed to severe PPH was estimated using the same data, and costs associated with treating severe PPH were calculated.

Data on the effectiveness of misoprostol for controlling PPH were taken from the Kigoma study and a 2004 study in the Gambia [11]. Effectiveness rates from these trials were applied to the women projected to have PPH in the intervention cohort, who would theoretically receive 1000 µg of misoprostol. The number of women with PPH who would progress to severe PPH was calculated based on the effectiveness of misoprostol at preventing PPH in these trials.

2.3. Cost-effectiveness

The costs for each arm were totaled using Eqs. (1) and (2), above. Incremental cost was calculated as the difference between the cost of providing the misoprostol intervention to 10,000 women laboring with TBAs and the cost associated with providing standard care to 10,000 women laboring with TBAs. The incremental costs and incremental outcomes of each strategy were used to calculate the incremental cost-effectiveness ratio.

2.4. Sensitivity analysis

Some uncertainty remains in the overall prevalence of PPH and severe PPH. Wide ranges for the incidence of PPH and severe PPH were used, based on data from the Kigoma trial [13] and Angola [18].

There is also uncertainty over the effectiveness of misoprostol to prevent severe PPH. Though there have been several trials of

Table 2 Cost-effectiveness of misoprostol and standard care applied to 10,000 births

	Severe PPH (>750 ml)	Severe PPHs averted	Costs per 10,000 births	Change in cost	Incremental cost-effectiveness ratio
<i>Baseline</i>					
Standard care	1823	0	\$138,982.15		N/A
Misoprostol	176	1647	\$23,646.61	−\$115,335.54	Dominates
<i>Low end</i>					
Standard care	900	0	\$19,274.80	0	N/A
Misoprostol	90	810	\$5,283.83	−\$13,990.97	Dominates
<i>High end</i>					
Standard care	3420	0	\$1,856,986.47	0	N/A
Misoprostol	500	2920	\$293,393.85	−\$1,563,592.62	Dominates

misoprostol to treat PPH, the dosages and routes of administration have varied widely. For the most accurate data on rectal administration of 1000 µg misoprostol to treat PPH, Kigoma data were used for the baseline estimate of misoprostol effectiveness, and the range was extended to cover findings from trials that used 1000 µg misoprostol via other routes [11,17]. All parameters were based on field data from Kigoma and/or peer-reviewed medical literature. Univariate and multivariate sensitivity analyses were run based on the ranges in Table 1.

3. Results

With TBA training and use of misoprostol in a cohort of 10,000 births, a baseline estimate of 1647 cases of severe PPH could be prevented. Multivariate sensitivity analysis produced a range of 810–2920 prevented cases. The misoprostol strategy would also save \$115,336 in transport, hospital fees, IV therapy, and blood transfusions (range of savings: \$13,991–\$1,563,593). Because the misoprostol strategy would prevent severe disease and save money, it dominates the standard approach of TBAs referring women with PPH to hospitals (Table 2).

4. Discussion

The WHO estimates that there are 14 million obstetric hemorrhages every year, and PPH is the single most common cause of maternal death worldwide [19]. This study shows that TBA-administered misoprostol could save money and prevent a substantial burden of severe PPH, thereby saving lives.

Most trials of obstetric applications of misoprostol have been conducted in hospital settings where there are often more attractive pharmaceutical options for managing the third stage of labor. Hospital-based trials of misoprostol generalize poorly to the field settings where many sub-Saharan African women still give birth. There has been only one prospective trial to date of the strategy of training TBAs in PPH recognition and the use of misoprostol.

Further prospective trials of misoprostol administration by TBAs are needed before TBA-administered misoprostol is recommended for widespread use in out of hospital deliveries. If subsequent studies show effectiveness of misoprostol consistent with the wide range tested in this model, the misoprostol strategy could be very promising. Currently only two sub-Saharan African countries have approved misoprostol for obstetric use. The promise of misoprostol as a potentially life-saving tool in the hands of trained TBAs suggests that approval should be reconsidered soon to enable more pilot testing and potential scale up.

These findings suggest that training TBAs to administer misoprostol for the treatment of PPH has the potential to both save millions of dollars in countries with limited health resources, particularly in sub-Saharan Africa, and improve the health of mothers across the developing world.

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