Oral Administration of Misoprostol Reduces Postpartum Haemorrhage in Urban Slums of Bangladesh

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Acronyms

CHW	Community Health Worker
DC	Delivery Center
Manoshi	*Ma, Nabojatok O Shishu*
MMW	*Manoshi* Midwife
PPH	Postpartum haemorrhage
SK	*Shasthya Kormi*
SS	*Shasthya Shebika*
TBA	Traditional Birth Attendant
UBA	Urban Birth Attendant

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Abstract

To avert deaths from postpartum haemorrhage (PPH), *Manoshi* initiated community health workers (CHW) administered oral misoprostol (400μg) to women following childbirth either at delivery centers or home in slums of Dhaka and under Gazipur City Corporation in 2009. To study whether the supervised use of misoprostol would reduce primary PPH following childbirth including its feasibility and community acceptability. A non-randomized control trial was undertaken among 3,900 women in urban slums of Dhaka and Gazipur City Corporation during January-August 2011. Oral misoprostol was prophylactically given to the treatment group following childbirth, while the control group did not receive it. The misoprostol significantly reduced incidence of primary PPH in the intervention group (4.5%) compared to the control group (7.5%). The median blood loss of PPH cases was 868 ml in the treatment and 928 ml in control group. It reduced the rate of bleeding-related emergency transfer, additional medical interventions compared to control group. However, no significant difference was found in blood transfusion between the two groups. We found one-third of the women were aware about misoprostol in intervention while none were aware in the control. The median risk for developing PPH was lesser in the intervention and prolonged third stage of labour found significantly higher in the control group. Misoprostol was found to be widely accepted in the community and feasible to offer parturient by CHWs within 5 minutes following childbirth in intervention group. Prophylactic use of misoprostol administered by CHWs is feasible and effective in reducing the incidence of primary PPH in the parturient of slums of Bangladesh. Besides, community-based education on misoprostol and iron intake throughout pregnancy to reduce the need for blood transfusion should be ensured.

Executive summary

Background

Globally postpartum haemorrhage (PPH) accounts for nearly one-quarter of all maternal deaths while in Bangladesh it is 31%. To avert death from PPH in urban slums of Bangladesh, *Manoshi* intervention started providing 400 µg misoprostol by community health workers (CHW) to women who gave childbirth either at the delivery centres (DC) or at home in Dhaka and Gazipur City Corporation area since 2009.

Objective

This study investigated whether supervised use of oral misoprostol (400 µg) would reduce primary postpartum haemorrhage in urban slums of Bangladesh. It also explored the community acceptability and feasibility of oral misoprostol.

Methods

A non-randomized control trial was undertaken among the women who were in labour in 356 urban slums of Dhaka and Gazipur City Corporation areas during January-August 2011. Women presented with labour pain and planned to have childbirth either at DC or at home were eligible for our study. We assumed 50% reduction from national rate (5%) of postpartum haemorrhage in Bangladesh using 400 µg of oral misoprostol to 2.5%. For additional *Manoshi* interventions which were expected to provide further reduction in PPH from 2.5% to 1.25%. Using power of 80% and significance level 5% and 5% unavailability or non-response rate the calculated sample size was 2,000 for each group. This sampling strategy was changed due to some constraints during field operations, such as using oxytocin for augmenting labour diminished chances of getting eligible women in the control. Considering financial and time limitations, our re-calculated sample size was 3,900 with similar power, level of significance and the proportion of unavailability. In intervention group 2,600 parturient received misoprostol following childbirth, and 1,300 women in control group did not receive misoprostol.

We selected eligible women from the *Shasthya Kormi* (SK) registers in intervention and household survey list in the control. Around 7,328 women were observed with informed consent who were in active labour, afterward excluded some for using intravenous uterotonics for labour induction, having history of prior cesarean section, referring delivery complications such as obstructed labour. A total of 3,900 successful observation of childbirth completed, but 59 parturient were excluded for non-response and incomplete participation in the study, and 31 participants were excluded for not consuming misoprostol.

Observation procedure

We used pre-measured delivery mat and sanitary pads to measure blood loss in PPH. Trained urban birth attendants (UBA)/traditional birth attendants (TBA)/family member placed clean delivery mat under the parturient buttock soon after delivery. CHWs were instructed for immediate referral in case of persistent blood loss and if the mat became fully soaked by blood. Women kept on mat and observed till the placenta was delivered than cleaned her and provided the sanitary pad to use for next 23 hours. Forty-five enumerators observed the management of third stage of labour, recorded the time of every event, and adverse effects of misoprostol.

Outcome measures

The primary outcome measure was primary PPH (blood loss ≥500 ml within 24 h of delivery) amongst the intervention and control group. We considered primary PPH (508 ml) counting one fully soaked mat (448±58 ml) and one fully soaked sanitary pad (60±2 ml) within 24 hours postpartum. Likewise, within the defined period we considered one full-soaked mat (448 ml) and nine full soaked sanitary pads (540 ml) to define severe PPH (1048 ml). Visual estimation of spilled blood loss on floor, plastic, linens was also estimated. For instances, we counted 2.5 fully soaked sanitary pads when the estimated blood loss was approximately 250 ml. Secondary outcome measures included proportion of women needed additional uterotonics to reduce blood loss, required blood transfusion, longer third stage of labour (≥30 minutes), and manual removal of placenta.

Findings and discussion

Our community-based study trialed in urban slums of Bangladesh shows that the 400 µg of oral misoprostol reduced the incidence of primary PPH in the intervention group (4.5%) compared to the control group (7.5%). Furthermore, this uterotonic found associated with significant reduction in the severe primary postpartum haemorrhage and the median blood loss in treatment group.

The median blood loss of PPH cases was 868 ml in the treatment group which was significantly lower compared to the 928 ml in control group. Despite low blood loss, similar trend was observed in blood transfusion requirement in intervention compared to the control. Possible explanations include the fact that more women were clinically anaemic and lower rate of long-term iron consumption in intervention group suggested excessive acute blood loss which required urgent blood transfusion. Although anemia warrant iron but other condition like chronic infection or vitamin A and B_{12} deficiency contribute occurring iron deficiency anaemia as well. However, this study did not reveal the reasons of anaemia anyway.

This study has added evidence of rendering oral misoprostol following delivery by CHWs is safe and useful in preventing postpartum haemorrhage in urban slums of Bangladesh. In addition, it did not have any undesirable adverse effect. To evade

worsening parturient in life-threatening condition like PPH it appears appropriate rendering misoprostol by CHWs as much as feasible. Our study illustrated that prophylactic therapy of 400 µg misoprostol reduced the rate of bleeding related emergency transfer, need for additional medical interventions and further explorations compared to the control, which might be squeezed the burden of childbirth related expenses.

A number of independent associated factors were found to be responsible for the primary PPH. However, median counts of risk for developing PPH found less in the intervention group compared to the control group. Additionally, odds of prolonging the third stage of labour (>30 minutes) found to be significantly higher in the control group. Complications such as retained placenta, experiencing antepartum haemorrhage, fetal malposition found to be potential independent associated factor to develop PPH during spontaneous vaginal delivery.

Inject able uterotonics such as oxytocin always been the drug of choice for preventing PPH in a medical/hospital setting but it is not practicable in resource poor community setting. This study was conducted in response to insufficient verification for efficacy of 400 µg oral misoprostol in reducing PPH in urban community context. Our results supplemented evidence that 400 µg oral misoprostol under supervision of CHWs is safe and effective for marginalized women giving birth in facility limited urban slums for preventing PPH and reducing blood loss in these community. CHWs covered 85% of the parturient in intervention group by offering misoprostol within 5 minutes following childbirth and also provide support on the feasibility. The medicine was also found to be widely accepted in the community as well. Women were agreed to buy, desired to consume, and recommend misoprostol to other parturient in future.

Despite receiving health education on maternal danger signs, referrals and management, we found half of them were aware about PPH and only one-third was concerned regarding uterotonic use in intervention group. Majority of them had a perception that misoprostol was placenta delivery enhancer. It may be because parturient used to receive consented prophylactic misoprostol at delivery centre just after delivery as a guideline of *Manoshi* intervention without having prior knowledge. Emphasizing on providing community-based education regarding the advantages of misoprostol to women and their family members can promote sustainable use of this uterotonic at low-resource settings.

Conclusion and recommendations

This study suggested that using prophylactic dose of 400 µg misoprostol offered by CHWs is feasible and effective in reducing incidence of primary PPH and the median blood loss in PPH in slums of Dhaka and Gazipur City of Bangladesh. Further, it was found to be widely accepted by community as the uterotonic poses least adverse effect. However, the percentage of clinical anaemia found more in intervention and blood transfusion requirement was similar as control. Awareness concerning the effectiveness of misoprostol found to be low in intervention and no knowledge in

control group. These findings suggest that greater emphasis should be given in improving antenatal care, which ensure iron intake throughout pregnancy and strengthen community-based education regarding the advantages of misoprostol. These can promote sustainable use of this uterotonic at low-resource settings which reduce the economic burden due PPH related referral as well as maternal death.

1. Introduction

Haemorrhage is the leading cause of maternal death worldwide accounting for nearly one-quarter of all maternal death (Kalim *et al.* 2009, Derman *et al.* 2006, Maughan *et al.* 2006, MNH Indonesia, 2004, Gulmezoglu *et al.* 2001). World Health Organization (WHO) defines primary postpartum haemorrhage (PPH) as blood loss from genital tract of 500 ml or more in the first 24 hours after delivery of the baby (Carroli *et al.* 2008, Maughan *et al.* 2006, Walraven *et al.* 2005). The global prevalence of PPH is approximately 6% of all deliveries (Carroli *et al.* 2008), whereas in low income countries the prevalence varies from 8.6 to 18.7% (Dolea *et al.* 2000, Derman *et al.* 2006), which found to have a case fatality rate of 2.2% (Etuk *et al.* 1997). In low income setting, PPH accounting for 30% of maternal death (Dolea *et al.* 2000, Derman *et al.* 2006), while in Bangladesh it is 31 % (NIPORT, Measure Evaluation, UNC-CH, USA, ICDDR,B 2011). Bangladesh Maternal Mortality and Health Care Survey (BMMHCS) 2010 indicates that 6.5% of the women experienced excessive bleeding during postpartum period and postpartum death (73%) is a real concern in Bangladesh (NIPORT, Measure Evaluation, UNC-CH, USA, ICDDR,B 2011).

Leading cause of postpartum bleeding is uterine atony, most often preventable (Selo-Ojeme *et al* 1997, Derman *et al.* 2006) by active management of third stage labour. This can be achieved by administration of uterotonics following childbirth, early cord clamping and cutting, initiation of immediate breast feeding, and controlled cord traction on the umbilical cord while awaiting placental separation and delivery (Maughan *et al.* 2006, Walraven *et al.* 2005). The use of injectable uterotonic (oxytocin) is more effective in preventing PPH but is associated with side-effects, such as nausea, vomiting, and diarrhoea (Zuberi *et al.* 2008, Walraven *et al.* 2005). In addition, the ergot alkaloids cannot be used in 10-15% of women who have gestational hypertension (Shanghvi *et al.* 2009). Further, oxytocin and ergot preparation require a skilled provider to inject in hospital setting, availability of sterile syringes, refrigeration and protection against light to preserve its effectiveness and stability (Shanghvi *et al.* 2009, Walraven *et al.* 2005, Gulmezoglu *et al.* 2001).

Misoprostol, a synthetic prostaglandin E1 analogue is an alternative uterotonic drug, can be given to women who give birth in low-resource community setting (Shanghvi *et al.* 2009, Derman *et al.* 2006). In comparison to other prostaglandin analogues, misoprostol has the advantages of being inexpensive, can be taken orally, widely available, does not need refrigeration, and stable at room temperature (Tang *et al.* 2007, Shanghvi *et al.* 2009, Derman *et al.* 2006, Bugalho *et al.* 2001). Furthermore, misoprostol, when orally administered, completely absorbed from gastrointestinal tract very rapidly and undergoes quick first-pass metabolism. Research shows that following a single dose of 400 µg oral misoprostol peaks the level at plasma between 12.5 and 60 minutes (mean ± SD 34 minutes) and declines rapidly by 120 minute (Tang *et al.* 2007, Khan *et al* 2004, Zieman *et al.* 1997). Several investigations have proven that oral misoprostol is safe and effective in preventing acute PPH in rural

community or hospital setting (Shanghvi *et al.* 2009, Derman *et al.* 2006, El-Refaey *et al.* 2000).

The International Confederation of Midwives (ICM) and the International Federation of Gynaecology and Obstetrics (FIGO) declare that, in community or home setting where no oxytocin and skilled providers are accessible, misoprostol may be the only technology to control PPH (ICM and FIGO 2007). Considering the issue described, like other countries, Bangladesh added misoprostol in essential drug list in 2008 (Maternal Health Supplies in Bangladesh 2011).

In 2007, BRAC has initiated an intensive maternal, neonatal and child health (MNCH) or *Manoshi (Ma, Nobojatok O Shishu)*) programme for the urban poor, which has established delivery centers for clean and safe delivery in the slums within municipal areas. In Dhaka, there are 253 delivery centers in five main regions of slums sub-divided into 35 branches. Each DC covers a population of 10,000-15,000. A cadre of community health workers (CHW) including urban birth attendants (UBA), *Shasthya sebikas* (SS) and *Shasthya kormis* (SK) offer intensive maternity care through doorway and facility approach. Their functions include identifying expectant women; provide health and nutritional education, family planning, antenatal, safe delivery and postnatal check-up in the community. Clean and safe delivery services are provided by UBAs and *Manoshi* midwives (MMW) free of cost through easily accessible delivery centres. UBAs receive 6 day training on birthing care, clean delivery, basic management and referral of obstetric complications. In order to prevent PPH, *Manoshi* intervention started providing single dose of 400 µg (two tablets) misoprostol to all women following spontaneous vaginal delivery under strict supervision of CHWs since 2009 (Manoshi 2008-2009). This study investigated whether the supervised use of oral misoprostol (400 µg) would reduce primary PPH in urban slums of Dhaka, Bangladesh. This study also investigated the community acceptability and feasibility of oral misoprostol among women in urban slums.

The specific objectives were:

1. To observe whether 400 µg of misoprostol reduces the primary PPH in spontaneous vaginal delivery
2. To determine the side-effects faced by the misoprostol users, and
3. To investigate the feasibility and acceptability of misoprostol by the urban slum community.

2. Methods

Study design and setting

A non-randomized control trial was undertaken in 112 delivery centres of 356 urban slums of Dhaka and Gazipur municipal areas during January-August 2011 among the women presented with labour pain. We randomly selected 13 branches named Gulshan, Mogbazar, Madartake, Khilgaon, Badda, Kamrangir Char, Mohammadpur, Uttarkhan, Dakkhin Khan, Jagannathpur, Tongi (Gazipur), and Morkun (Gazipur). Geneva camps of Dhaka uddan, Beribadh, Nikunja, Gazipur area were included as control areas. In urban slums, around 50% of the deliveries occurred at home mostly attended by UBAs. Socio-demographically, women in these slums are predominantly Muslim, currently married (99%) and unemployed (83%). The housing, ventilation, water and sanitation, garbage cleaning and drainage, health and education of children are very poor as well as exposed to violent behaviour. The household population are mostly young (<30 years) and population pyramid is very wide, showing that more than a quarter of the population is under five years of age. Educational attainment in terms of ever attending school is 66% (Nurul *et al.*2010). Intervention groups were exposed to meticulous maternity care which includes antenatal, delivery and postnatal care by CHWs. Besides, women were also receiving the essential health care including health and nutrition education, water and sanitation, education, immunization, vitamin A supplementation, family planning, and microfinance intervention of BRAC. The control group received all intervention of BRAC except maternal care.

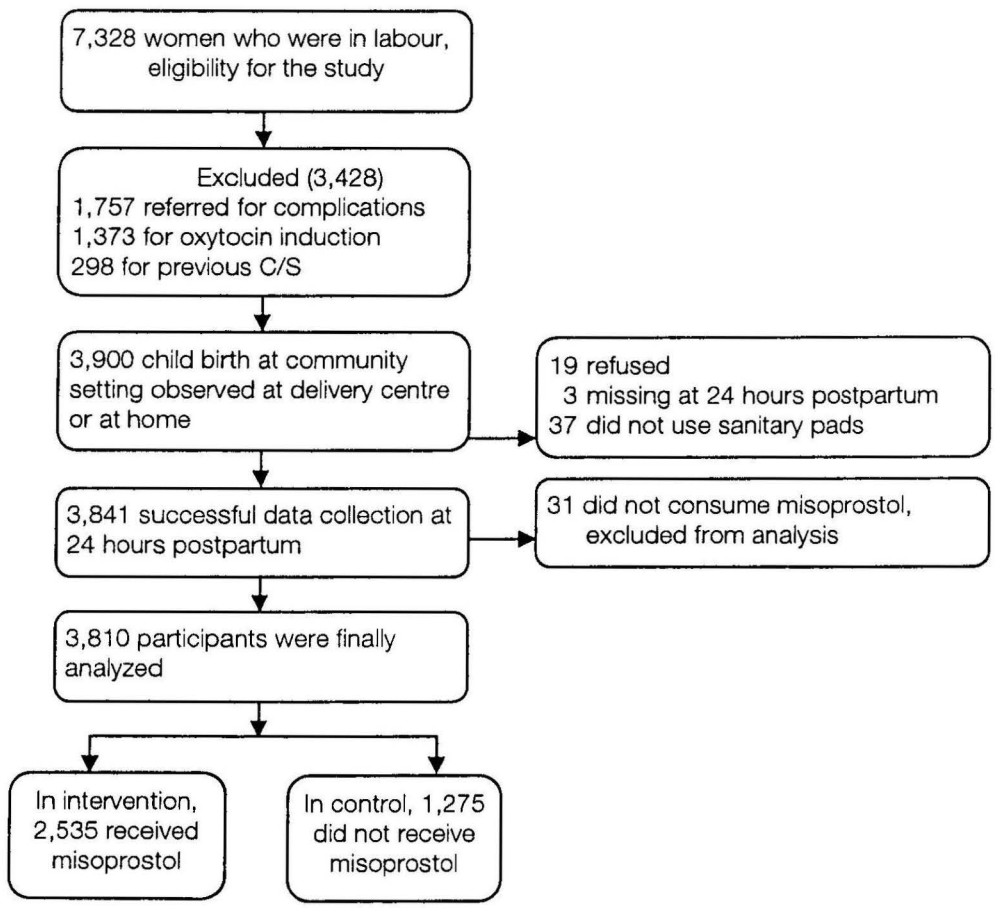
Sample size

Based on previous study (Derman *et al.* 2006), we assumed that there would be a 50% reduction in the national rate (5%) of PPH in Bangladesh to 2.5% with the use of 400 µg of oral misoprostol. As the participants were receiving additional *Manoshi* interventions which were expected to provide further reduction in PPH from 2.5% to 1.25%. Using power of 80%, significance level 5%, and 5% unavailability or non-response rate, the calculated sample size was 2,000 for each group. This sampling strategy had to be changed due to some constraints during field operations, such as using oxytocin for augmenting labour diminished chances of getting eligible women in the control. Considering financial and time limitations, our re-calculated sample size was 3,900 with similar power, level of significance and the proportion of unavailability. Thus, 2,600 women receiving misoprostol following childbirth at delivery centre were considered as intervention group, while 1,300 women who did not receive misoprostol were estimated as control.

Selection of participants

Women presented with labour pain and planned to have childbirth either at DC or at home were eligible for our study and were observed till natural childbirth after obtaining informed consent. We selected expectant women from the SK registers for intervention. We made a household survey for pregnant women and selected participants for control group. Around 7,328 parturient were initially observed but we excluded women who used intravenous uterotonics for labour induction, had previous history of cesarean section, and had delivery complications such as obstructed labour. A total of 3,900 successful observation of childbirth completed but 59 parturient were excluded for non-response and incomplete participation in the study and 31 participants were excluded for not consuming misoprostol.

Figure 1. Trial profile



Training and quality control

Forty-five educated female enumerators and eight monitors received a 10-day intensive training on the study objectives, protocols and observation of using mat and collection of used pads, identification of PPH, communication skill, and maintenance of confidentiality and privacy in research. Furthermore, the interviewers received rigorous training on measuring blood loss by using mat and how to identify excessive bleeding. A structured questionnaire was developed and pre-tested in a slum not located in the catchment areas of DCs. The appropriateness of language, sequencing of questions, and time required to complete the questionnaire were assessed. Three layered monitoring systems ensured the quality of data. A field supervisor along with rotating monitors, a field manager, and a medical doctor supervised the data collection.

Tools used for measuring blood

Local unique approach in Tanzania described by Prata *et al* (2005), traditional birth attendants (TBA) used pre-determined measured 2-Kanga (cloth that used as a skirt, shawl, head wrap or to carry a baby) for identifying, treating and referring PPH cases. Clinical estimation of blood loss is notoriously inaccurate (Bose *et al*. 2006, Duthie 1991). The incidence of PPH was either under-estimated in the visual estimation by 89% (Prasertcharoensuk *et al* 2000) or over-estimated the blood loss by 20% (Razvi 1996, Schorn 2010); discrepancy amplified as the quantity of blood loss increased (Schorn 2010, Glover 2003). Based on the experience of previous study (Quaiyum *et al*. 2009), we used a pre-measured delivery mat (can retain 448.0±58.2 ml blood) and sanitary pad (can absorb 60.2±2.1 ml of blood) to measure blood loss in 24 hours postpartum. The amount of approximately one glass full (250 ml) blood loss was noted and 2.5 fully soaked sanitary pads counted in the questionnaire. Measuring blood loss in a standardized way in community setting rather than clinical estimation, as used in many previous trials of the third stage of labour, enabled us assessing nearly accurate.

Data collection procedure

At the beginning of the study the field enumerators distributed mat, sanitary pads, and poly bags to all selected DCs. In the control areas, field enumerators provided logistics to listed expectant women. Field enumerators made first home visit to those pregnant women and their families during eight months of pregnancy and gave their contact number to be informed about labour pain. We instructed urban birth attendants/local TBAs/family members regarding the use of the mat and how to preserve mat, used pads for 24 hours postpartum. Second visit was paid during childbirth to assess haemorrhage either at DC or at home. Third visit was at 24 hours postpartum; enumerator observed and counted the number of fully soaked pad collected in an airtight poly bag. Finally data were collected using structured questionnaire. In case of PPH, referred for medical intervention, data were collected after returning to their home.

Procedure of measuring the amount of blood loss and observation

Trained UBA/TBA/family member placed delivery mat under the parturient's buttock soon after delivery to identify excessive blood loss. Women kept on mat and observed till the placenta was delivered than cleaned her and provided the sanitary pad to use for next 23 hours. Enumerators observed active management of third stage of labour in terms of early cord clamping and cutting, uterine massage, giving 400 µg misoprostol, and controlled cord traction. Furthermore, they documented the time of childbirth, misoprostol taken by participants, time of introducing mat under respondents' buttock, and placenta delivery. Shivering, nausea, and vomiting were assessed by direct observation or indirect questioning 'Do you have any complaints?' Axillary (under arm) temperature was measured by standard thermometer in intervention group. Bleeding was assessed both by CHWs and enumerators at DCs while in control group observations were done only by field enumerators. CHWs and family members were instructed for immediate referral in case of persistent blood loss and if the mat became fully soaked by blood.

Independent variables

Socio-demographic: Respondents' age was calculated in years and educational attainment was calculated in years of schooling. Economic status was ranked by wealth index which included condition of their housing, cooking, water and sanitation status, and individual possession of wealth.

Reproductive and obstetric indicators: Reproductive indicators consists of respondents' age at marriage and first conception, parity, and previous history of PPH. Obstetric indicators of index pregnancy included antenatal care, experience of violence, and antenatal complications. Delivery indicators included duration of active labour pain (prolong labour considered once labour pain exceeded 12 hours), foetal malposition and movements, intranatal and postnatal bleeding, retained placenta, oral administration of misoprostol following childbirth.

Knowledge on PPH, treatment-seeking options and misoprostol

Feasibility of misoprostol administration: We recorded the time of misoprostol intake and coverage of women to measure the feasibility. Nasreen *et al.* (2011) considered 5 minutes for the earliest commencing time of uterotonics following childbirth in rural Bangladesh and measured the coverage till 30 minutes with 5 minutes interval. Accordingly, we took that time limit as a cut-off to measure feasibility of rendering misoprostol by CHWs in our study.

Community acceptability was assessed by three questions. Whether women were ready to purchase misoprostol ? Would they consume misoprostol in next issue? And would they recommend the uterotonic to other women?

Dependent variable

The primary outcome measure was primary PPH (blood loss ≥500 ml within 24 h of delivery) amongst the intervention and control group. We defined PPH (508ml) in our study when a delivery mat (448ml) and a sanitary pad (60ml) fully absorbed by blood in 24 hours postpartum. Likewise, within the defined period we considered one fully-soaked mat (448 ml) and nine fully soaked sanitary pads (540 ml) to define severe PPH (1,048 ml). Visual estimation of spilled blood loss on floor, plastic, linens was also estimated. For instances, we counted 2.5 fully soaked sanitary pads when the estimated blood loss was approximately 250 ml. Secondary outcome measures included proportion of women needed additional uterotonics to reduce blood loss, required blood transfusion, longer third stage of labour (≥30 minutes), and manual removal of placenta.

Data analysis

Data were analyzed using SPSS version 17. Results were summarized using frequency distributions and cross tabulations. Chi-square or Fisher's exact tests were compared with binary outcomes between the two groups. P values were obtained using two-sided test to compare baseline characteristics. Comparison of age, parity, years of schooling and duration of third stage of labour between intervention and controls were done through t-test and Mann-Whitney. We calculated incidence of primary PPH in women who received misoprostol compared to the control. Median risk was counted from a scale developed for risk for developing PPH during childbirth, ranged from 0-7. Unadjusted logistic regression was carried out to obtain odds ratio (OR) of independent associated factors of PPH.

Ethical consideration

We got approval (ethics reference no. 18) of the Ethical Review Committee of James P. Grant School of Public Health under BRAC University. We took informed consent from the participants.

3. Results

The results show the background characteristics, reproductive and obstetric history of study population, followed by the key findings on antenatal and delivery practices, antenatal complications during index pregnancy, incidence of postpartum haemorrhage, side-effects and community acceptability of misoprostol and reduction of PPH by misoprostol tablets (400 µg).

Background characteristics of the study population

The respondents were predominantly Muslim and housewives. Women in the intervention group was one year younger than the mean age of 23 years, and greater proportion had reading and writing skill compared to control. On average, the respondents of both groups had four years of educational attainment. The respondents in the control group were comparatively well-off (Table 1).

Table 1. Socio-demographic profile of respondents

	Intervention	Control	p value
Age (years)			
<20	25.0	22.8	
20–35	73.1	74.3	
>35	2.0	2.9	
Mean age (±SD)	23.3 ±5.0	23.8 ± 5.3	0.002
Religion			
Islam	98.8	98.3	0.443
Others	1.2	1.7	
Can read & write	58.7	53.3	0.002
Educational status			
No schooling	29.2	34.7	
Primary	39.7	37.2	
Secondary and above	31.4	28.2	
Mean year of schooling ±SD)	4.2 ±4.3	3.8 ±3.6	0.003
Occupation			
Housewives	87.9	85.6	
Garments worker	6.2	7.8	
Maid	1.9	3.1	
Others (Day labour/service/tailor/tiny business)	4.0	3.4	
Wealth ranking			
Poor	31.5	35.5	0.001
Middle income	36.1	30.2	
Non-poor	32.4	34.4	
N= 3810	2535	1275	

Background characteristics of the husbands

Literacy in terms of reading and writing skill of husbands shows no differences. The years of school attainment of husbands between the groups shows no difference. Men's contribution in income generation made through day labours, followed by drivers or van rickshaw pullers, small traders, service and garments workers (Table 2).

Table 2. Husbands' profile

	Intervention	Control	p value
Husbands literacy			
Can read and write	64.6	62.1	0.143
Educational status of husbands			
No schooling	31.8	34.0	
Primary	27.7	25.0	
Secondary and above	40.5	41.0	
Mean years of schooling (SD)	8.1±17.3	7.5±15.7	0.225
Husbands occupation			
Daily wage earner	22.7	25.2	
Driver/rickshaw/van puller	21.9	17.4	
Small business	19.3	23.7	
Service (Office assistant/security guard/ watch man/cleaner)	19.4	12.4	
Garments worker	12.9	18.2	
Others	3.9	3.0	
N= 3810	2535	1275	

Reproductive, obstetric and medical profile of the women

Their average age of marriage was 16 years. They conceived their first child before the age of 18 years. The similar trend of reproductive life was observed in both groups. Despite having on average two children in both groups, number of children born was found to be higher in the control groups. We found from the respondents' medical history that about 4-5% of women experienced excessive bleeding during their last maternal period (antenatal/intranatal/postnatal). (Table 3)

Table 3. Reproductive, obstetrics and medical history of women

Characteristics	Intervention	Control	p-value
Age at marriage (years)			
<18	86.3	88.0	0.114
≥18	13.7	12.0	
Mean age at marriage (±SD)	16.0± 2.4	15.8± 2.4	0.002
Age at first conception			
<20	79.8	79.9	0.966
≥20	20.2	20.1	
Mean age at first conception (±SD)	17.6±2.6	17.4± 2.6	0.032
Number of children ever born			
1	40.5	35.4	
2-3	45.8	48.4	
≥ 4	13.7	16.2	
Mean (±SD) number of children ever born	2.1±1.3	2.3±1.4	0.032
Mean (±SD) number of conception	2.3±1.43	2.4±1.52	0.001
Previous history of excessive bleeding during antenatal/intranatal/postnatal period	5.5	4.3	
N= 3810	2535	1275	

Antenatal and delivery practices in index pregnancy

Antenatal profile of index pregnancy

In intervention group, around two-third of the women received four or more antenatal visits which was twofold higher compared to the control group. Although the women in intervention group commonly received an average five antenatal consultations, we found more (p=0.000) women were clinically anaemic just before the childbirth compared to the control. Regardless of better status in consuming iron compared to the control, only around 8% of women in intervention group were continuing iron intake for six months or more. Greater proportions of antenatal complications were reported in intervention group. However, in control group, more women carried out heavy work and became victim of physical violence during their expectant state (Table 4).

Table 5 shows that the pattern of antenatal complications were found to be similar in both groups excluding some, such as headache, high blood pressure, and high fever which were more reported in intervention group, while fetal mal-position was found to be higher in control group.

Table 4. Practices during antenatal period of index pregnancy

Characteristics	Intervention n=2535	Control n=1275	p-value
Received ≥4 ANC visits	69.4	59.9	0.000
Mean number of ANC visits (±SD)	5.0±3.8	3.2±2.0	0.000
Record of iron intake in ANC			
Consumed < 1 month	46.5	74.2	
1-2.9 months	16.7	10.5	
3-5.9 months	28.9	12.9	
≥ 6 months	7.9	2.4	
Carried out heavy works during pregnancy	56.8	64.1	0.000
Reported antenatal complications/medical problems	68.8	62.4	0.000
Experienced physical violence	14.8	18.5	0.003
Clinically positive anaemia before delivery	21.3	15.7	0.000

Table 5. Reported complications during pregnancy

	Intervention	Control	P value
Swelling of hands/feet	24.1	23.7	0.809
Headache	23.4	19.1	0.003
Blurry vision	19.3	19.8	0.697
High fever	12.7	9.4	0.003
High blood pressure	2.6	1.1	0.002
Rupture membrane	3.3	2.0	0.031
Ante-partum haemorrhage	2.6	2.6	0.915
Foetal mal-posision	1.9	3.1	0.021
Less fetal movement	1.8	2.3	0.323
N	2535	1275	

Practices during delivery

Findings documented that all deliveries were assisted by trained birth attendants in intervention group while the control group were attended by untrained TBAs. Third stage of labour was significantly better managed in intervention group in terms of receiving uterotonics after delivery, cord cutting and tying, and persistent traction on cord. In addition almost every woman practiced early initiation of breastfeeding in intervention group. In contrast, malpractices during manipulating placental delivery such as introducing hair ball into mouth, vigorous pressure on abdomen by heel found to be radically higher in control group (Table 6).

Table 6. Practices during and after childbirth

Characteristics	Intervention n=2535	Control n=1275	p-value
Birth attendants			
Trained TBA/UBA	97.0	22.8	
Health assistants/MMW	3.0	0.2	
TBA/relatives/neighbour	0.0	75.3	
unattended	0.0	1.7	
Management of third stage of labour			
Oral administration of misoprostol	100	0.0	0.000
Cord cutting and tying	98.9	96.9	0.000
Controlled cord traction	90.7	58.7	0.000
Uterine massage	53.8	27.8	0.000
Other initiatives just after delivery			
Provided Vitamin A to mother after delivery	97.8	0.0	0.000
Initiation of breast feeding after delivery	95.9	82.0	0.000
Malpractices			
Hair ball introduce into mouth	0.8	77.8	0.000
Pressing over abdomen to increase intraabdominal pressure by heel	0.0	9.5	0.000

Birth outcomes of the index delivery were more or less similar between the groups (Table 7). The rate of stillborn baby was significantly higher in the control group. However, the rate of intrauterine deaths and neonatal deaths were found to be similar between the groups.

Table 7. Birth outcome of index delivery

	Intervention % (n)	Control % (n)	P value
Birth outcome			
Live birth	99.2 (2515)	98.4 (1254)	0.001
Still birth	0.2 (6)	1.3 (16)	
IUD	0.4 (9)	0.2 (3)	
Neonatal death	0.2 (5)	0.2 (2)	
N	2535	1275	

Perceived knowledge on postpartum haemorrhage and treatment options

Perception of postpartum haemorrhage (PPH)

In response to danger signs during maternal period, around 50% of the respondents in both groups have mentioned that excessive bleeding was one of the threats that might occur during or after delivery. Findings reveal that women in both groups had

similar perception on the reasons of PPH. Women explicitly mentioned that tear in genital region (27-28%), retained placenta (27-32%), performing heavy household activities after childbirth (11-27%), and under-nourishment (26-28%) were the major causes of PPH. One-fifth of the women in control group stated evil air as an important cause of PPH followed by prolonging birthing process (17%) or baby trapped at birth canal (14%). Very few (1%) respondents said that PPH usually occurred to expel the polluted blood following childbirth and from diseased uterus (Multiple responses considered and table not shown).

Care-seeking alertness

In response to treatment options in the incident of PPH, majority (63%) respondents of treatment group stated that they would seek care from professionals or from health facilities, while 31% preferred to report to CHWs. While in the control group, 93% of the women preferred to visit hospitals directly at the first occurrence. A few in both the groups desired to see village doctors and other informal health providers and 1% did not have any choice (table not shown).

Primary PPH identification, management and risk factors

Misoprostol reduced primary postpartum haemorrhage (PPH)

Amongst 3,810 spontaneous vaginal deliveries, 2,535 parturient received misoprostol following childbirth in treatment group and 1,275 did not receive any uterotonic in the control group. Primary PPH occurred in 217 (5.6 %) women in the study. We observed 114 cases of primary PPH in intervention group who received misoprostol, and 96 cases of primary PPH in the control group who did not receive misoprostol (Fig 2).

Figure 2. PPH cases according to use of misoprostol and study sites

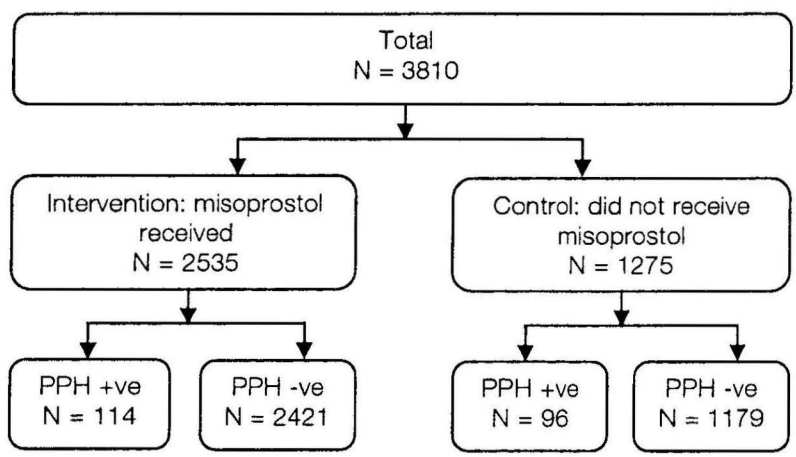


Table 8 illustrates that incidence of primary PPH was 4.5% in intervention group and 7.5%. in the control group. The madian blood loss was 868 ml and 928 ml for treatment and control group, respectively. Parturient who received misoprostol were less likely to experience prolonged third stage of labour and transfer to higher facility for emergency management (2.5% vs 5.2%) and fewer required additional intervention such as medication, intravenous uterotonics, and manual removal of placenta. However, no significant differences between the groups were found in case of blood transfusion.

Table 8. Primary and secondary outcome of misoprostol consumption by treatment group

	Intervention % (n)	Control % (n)	p
Primary outcome			
Incidence of primary PPH (≥500ml)	4.5 (114)	7.5 (96)	0.000
Incidence of sever PPH (≥1000ml) in 24 hours	1.0 (26)	2.3 (29)	0.004
Secondary outcome			
Third stage more than 30 minutes	3.1 (78)	5.3 (67)	0.001
Emergency transfer needed	2.5 (64)	5.2 (72)	0.000
Required additional intervention			
Required medication	2.4 (60)	4.7 (60)	0.000
Use of intravenous uterotonics	1.8 (45)	4.2 (53)	0.000
Blood transfusion needed	1.2 (30)	0.6 (8)	0.121
Manual removal of placenta	1.8 (45)	5.2 (66)	0.000
N=3810	2535	1275	

Active management of third stage of labour and required time for placental delivery

Observation explored that 89% of parturient received active management at third stage of labour (time period since childbirth to delivery of placenta) in intervention. Of them, almost every woman consumed misoprostol (98%) after delivery under direct supervision of CHWs; soon after the childbirth the umbilical cord was properly clamped and cut (99%). In most instances (91%), the cord was held with mild traction (table not shown).

Analysis did not show any significant difference in the time required for placental delivery (Table 9). Placenta was expelled in eight minutes after childbirth. Findings reveal that half of the study population experienced PPH once the placenta was delivered.

Table 9. Average time required for placenta delivery and period of occurring PPH

Characteristics	Intervention n=2535	Control n=1275	p-value
Median time (minutes) to deliver placenta	8	8	0.052
Mean time of placenta delivery±SD	13.1±31.7	14.4±36.4	0.231
Period when PPH took place			
During delivery	3.0	5.8	
Just after delivery before placental delivery	45.5	38.4	
After delivery of the placenta	51.5	55.8	

Risk counts for PPH

Table 10 shows that women in control group had greater risk of developing PPH. On an average, women in control group had three risk factors with range of 0-7.

Table 10. Median risk count for PPH

	Intervention	Control	P
Mean	2.2	2.9	0.001
Median	2	3	
Range	0-6	0-7	

Maternal risk factors of developing PPH are strongly associated with ante-partum haemorrhage, fetal mal-position, longer third stage of labour, anaemia, and forceful placenta delivery (Table 11).

Table 11. Independent odds of developing PPH

Risk factors	SE	P	Odds ratio (CI)
Obstetric history			
Still birth	.329	0.011	2.298 (1.206-4.376)
Parity > 4	.176	0.010	1.570 (1.113-2.216)
Previous episodes of PPH	.234	0.000	2.418 (1.528-3.825)
Antenatal events			
Experienced physical violence	.166	0.001	1.762 (1.273-2.439)
Had physical relationship during pregnancy	.176	0.022	1.495 (1.060-2.110)
Pregnancy complications			
Experienced ante-partum haemorrhage	.217	0.000	13.299 (8.688-20.357)
Fetal mal-position	.237	0.000	11.065 (6.953-17.611)
Premature rupture of membrane	.326	0.039	1.962 (1.035-3.717)
Forced delivery of placenta	.157	0.000	4.695 (3.450-6.389)
Clinically anaemic before delivery	.144	0.000	5.347 (4.031-7.091)
Headache with blurry vision	.178	0.001	1.805 (1.273-2.558)
Third stage of labour >30 min	.187	0.000	14.043 (9.727-20.275)

Once the PPH cases were identified in intervention group, most of them were referred by *Manoshi* CHWs for professional management. They received care mostly from public health facilities followed by private or NGO health facilities. In contrast, one-fifth of the women in the control group were treated at facilities as a substantial

proportion received treatment at their own dwelling. In most cases, drug sellers or village doctors were found to be the key person to provide treatment at home. However, around 17% of the cases in intervention group received treatment at home (Table 12).

Table 12. Referrals and/or skilled care received for PPH

Referred for better management	Intervention	Control
Manoshi – CHWs	97.1	0.0
TBA/TTBA/village doctors	0.0	80.6
Relatives	2.9	19.4
Place of treatment		
Public facilities	60.7	19.7
NGO/private clinics	22.6	15.5
Treated at home	16.7	64.8
Health providers		
MBBS doctor	84.8	32.4
Medicine seller/ village doctor	10.7	56.4
MMW/SK	3.0	0.0
Nurse/paramedics	1.5	5.6
Other informal health providers (TTBA/TBA)	0.0	5.6
N	78	67

Knowledge about misoprostol, side-effects, community acceptability and feasibility

Conception relating to misoprostol

Awareness of PPH was found to be around 37% and one-third (31%) of the women in intervention group have heard about misoprostol. Among them, nine out of ten women stated that misoprostol should be administered immediately after delivery. Knowledge concerning the usefulness of taking the uterotonic, 39% mentioned that misoprostol was supposed to faster the delivery of placenta. Consequently, other responses included that misoprostol had certain properties of preventing excessive bleeding following childbirth (35%), helping uterine involution (5%), relieving abdominal pain/fever/weakness (5%), and assisting in increasing breast milk/blood calcium/haemoglobin/energy (4%). However, 12% said that they did not know how the medicine worked. On the contrary, roughly none (99%) in the control group was aware about this uterotonics (table not shown).

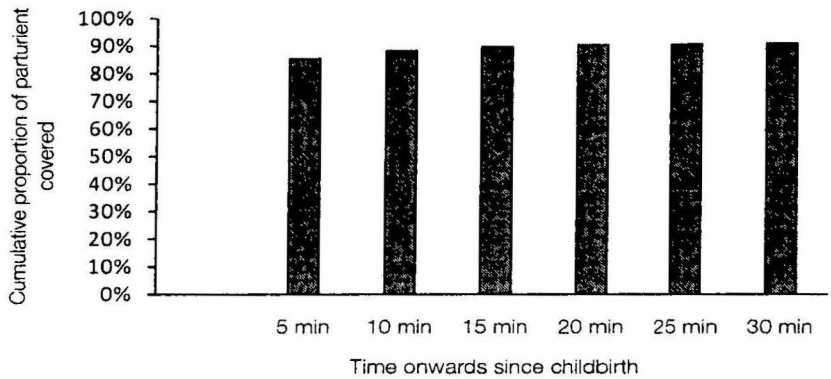
Misoprostol offered by CHWs in intervention

Following the childbirth, woman in intervention group received uterotonics from the urban birth attendants (83%) followed by *Shasthya sebika* (14%), *Shasthya kormi* (2%) and *Manoshi* mid-wives (1%). They were the key persons to supervise and ensure consumption of misoprostol shortly after delivery; within the median of two minutes. Under close supervision of CHWs, a substantial proportion (90%) of the respondents ingested misoprostol before the delivery of placenta (table not shown).

Feasibility

We observed the time pattern of ingesting oral misoprostol after childbirth. The time was clustered into six groups who received misoprostol. Figure 3 shows that a substantial proportion (85%) of parturient was covered within 5 minutes after delivery. Subsequent elapsing every five minutes consistently increased the percentage of misoprostol coverage and it covered up to nine out of ten women within 30 minutes of childbirth.

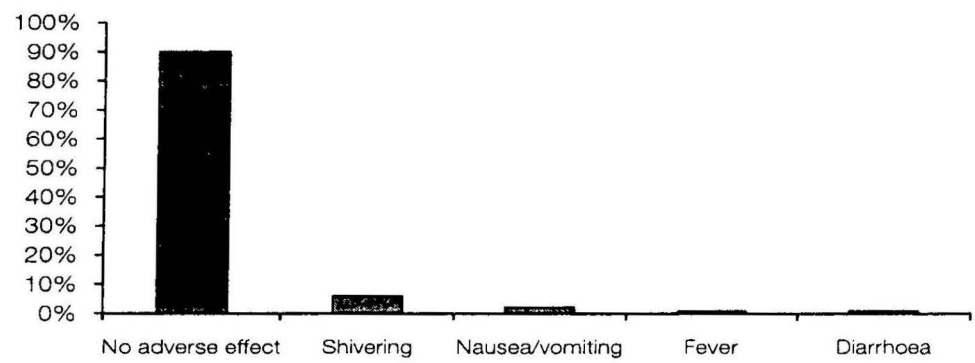
Figure 3. Feasibility of the misoprostol use in community setting



Adverse effects of misoprostol

The dose of 400 µg (two tablets) used in our study resulted minimum adverse effects. One-tenth of the respondents experienced transient side-effects after consuming the medicine (Fig. 4). Considering the safety issue, parturient were observed after providing uterotonics to predicting side-effects. We found transient chills or mild chills/shivering (6%) was the single adverse effect women had experienced. Very insignificant proportion of them faced nausea, elevated body temperature and diarrhoea.

Figure 4. Types of side-effects faced by misoprostol consumers



Community acceptability of misoprostol

Around 89% of the woman explicitly mentioned that they would be eager to recommend their neighbour women to use misoprostol during childbirth, while 88% wanted to use it in their next issue. If required, 87% of them agreed to purchase it (Table not shown).

Motivating reasons for accepting uterotonics

The major grounds for accepting misoprostol at community level included perceived drug efficacy; they (37%) considered this uterotonic as placental delivery accelerator. Around 31% said that they would use it for CHWs' motivation and similar proportion would like to have misoprostol as it remits abdominal pain or weakness. One-fifth of the respondents said that it prevented or reduced excessive bleeding after child delivery. However, very few (2%) had a conception that misoprostol reduced dizziness/shivering/vomiting, increased blood calcium, healthy for fetus or heals neonatal umbilicus. Nonetheless, unacceptability accounted 11% for the reason of unawareness and very few said ineffective.

4. Discussion

Our study shows that 400 µg of oral misoprostol reduced the incidence of primary PPH more in the intervention group (4.5%) in urban slums of Bangladesh compared to control group (7.5%). Furthermore, this uterotonic is associated with significant reduction in the severe primary PPH and the median blood loss in treatment group. Evidence from other studies varied in reporting its effectiveness. Although WHO multicentre randomized trial (Gulmezoglu *et al.* 2001) comparing misoprostol with other traditional uterotonics as well as trials in Gambia (Walraven *et al.* 2005), Turkey (Caliskan *et al.* 2003), and London (El-Refaey *et al.* 2000) reported similar or non-significant trend in reduction of PPH. On the other hand, quite a set of trials have shown that misoprostol was successful in preventing PPH both in community and hospital settings (Nasreen *et al.* 2011, Sanghvi *et al.* 2010, Derman *et al.* 2006, Chandhiok *et al.* 2006, Hofmeyr *et al.* 2004).

The median blood loss of PPH cases was 868 ml in the treatment group which was significantly lower compared to the 928 ml in control group. The blood loss in PPH ranged from 999 ml, 1,000 ml and 1,055 ml were reported in other studies in Nigeria, France and Nepal, respectively (Ijaiya *et al.* 2003, Ducloy-Bouthors *et al.* 2011, Dongol *et al* 2010). Despite low blood loss, similar trend was observed in blood transfusion requirement in intervention compared to the control. Possible explanations include the fact that more women were clinically anaemic and lower rate of long-term iron consumption in intervention group suggested excessive acute blood loss which required urgent blood transfusion. In Bangladesh, 50% of the pregnant women suffer from iron deficiency anaemia. Even iron supplementation is enough in low-income setting as pregnant women undergo chronic infections which end up with vitamin A, vitamin B_{12} and folic acid deficiency. These hampered the improvement of amaemic status of marginalized women in Bangladesh (Hyder *et al.* 2004). As any spout of bleeding in case of anaemic patient is considered as PPH, it can be less than 500 ml of blood loss (Derman *et al* 2006, Zeiman *et al.* 1997). However, this study did not reveal the reasons of anaemia anyway.

This study has added the evidence of rendering oral misoprostol following delivery by CHWs are safe and effective in preventing PPH in urban slums of Bangladesh. Despite living nearer to a health facility, more than two-thirds of the childbirth were attended by TBAs at home in urban slums of Bangladesh without having emergency preparedness (Fronczak *et al.* 2007). At the moment of life-threatening condition like PPH, delay in receiving emergency management may happen due to multiple factors such as decision-making, distance or transportation (Nahar *et al* 2011, Schorn 2010, Sanghvi 2010). Within flash of a moment, women experiencing PPH can deteriorate even in short delay in commencing treatment requiring uterotonincs, blood, intravenous fluids and impending major surgery (Sanghvi 2010). It appears appropriate to avert PPH, distribution of misoprostol to CHWs educating with

rationale of use and time of offering, as much as feasible. Our study illustrated that prophylactic therapy of 400 µg misoprostol reduced the rate of bleeding related emergency transfer, need for additional medical interventions and further explorations compared to the control. Researchers of other low-income setting also approved that use of misoprostol in community-based approach, especially beneficial in health professional scarce locales (Nasreen *et al* 2011, Derman *et al* 2006, Prata *et al.* 2005).

The risk counts of PPH were less in the intervention group compared to control group. Additionally, prolonged third stage of labour (>30 minutes) was found significantly higher in the control group. We found prolonged third stage of labour, experiencing ante-partum haemorrhage, fetal mal-position as potential independent risk factors which had more than 10 fold higher probability of developing PPH during spontaneous vaginal delivery. Maughan *et al.* (2006) and Selo-Ojeme *et al.* (1997) consistently established similar findings.

In intervention group receiving 400 µg of misoprostol was regarded as useful without having any undesirable adverse reaction. We observed that one out of 20 parturient experienced transient chills/shivering, while using 600 µg of oral misporostol. Gulmezoglu *et al.* (2001) and Sanghvi *et al.* (2010) found that 19% and 28% of the women experienced chills/shivering, respectively. Other trials resulted in nausea/vomiting ranged from 1-11% and pyrexia (>38/40^0 C) from 7-8.5% using the maximaum dose of misoprostol (Sanghvi 2010, Hofmeyr 2004, Gulmezoglu *et al.* 2001, Zuberi *et al.* 2008, Tang *et al* 2007). In contrast, we found these side-effects from 1-2 % in our study. It seems using 400 µg misoprostol is as effective as 600 µg with having insignificant adverse effect.

Injectable uterotonics such as oxytocin always been the drug of choice for preventing PPH in a medical/hospital setting but it is not practicable in resource poor community settings. Prior study in rural Bangladesh also provided the proof of effective prevention of PPH by low dose misoprostol distributed by lay CHWs (Nasreen *et al* 2011). In response to insufficient verification for efficacy of 400 µg of oral misoprostol in reducing PPH in urban community context this study was conducted. Our results supplemented evidence that 400 µg of oral misoprostol administered under supervision of CHWs is safe and effective for marginalized women giving birth in facility limited urban slums for preventing PPH and reducing blood loss. CHWs covered 85% parturient in intervention group by offering misoprostol within 5 minutes following childbirth and also provided support on the feasibility. The medicine was found widely accepted in the community as well. Women were willing to buy if necessary, wish to consume in future and recommend to other pregnant women.

Despite receiving health education on maternal danger signs, referrals and management, we found half of the respondents were aware about PPH and one-third in intervention group was concerned regarding uterotonic use. Majority of them had a perception that misoprostol was a placenta delivery enhancer. It may be due to the fact that parturient used to receive consented prophylactic misoprostol at delivery centre just after delivery as a guideline of *Manoshi* intervention without having prior

knowledge. Emphasizing on providing community-based education regarding the advantages of misoprostol to women and their family members can promote sustainable use of this uterotonic at low-resource settings.

Limitations

Our method had limited opportunity to measure every drop of blood for normal delivery as we did not use any measuring scale. We simply measured the blood loss in case of PPH by pre-measured mat and sanitary pads. During the observation of sever PPH we could not retain the blood loss on mat/sanitary pads which spilled during transportation and medical/surgical intervention in operation theatre. To minimize the problem of visual estimation we anticipated approximately 250 ml spilled blood would be equal to 2.5 fully soaked sanitary pads. Field enumerators could not observe deliveries at night; in that case observations were done by UBAs/MMWs or family members. Checklists were filled in by them which include time of childbirth and placenta delivery, time of recording of oral misoprostol intake and side-effects of misoprostol. We re-interviewed women and family members to collect those information in earliest convenience to diminish biasness of CHWs in intervention during recording time.

5. Conclusion and recommendations

This study suggested that using prophylactic dose of 400 μg of misoprostol offered by CHWs is feasible and effective in reducing the incidence of primary PPH and the median blood loss due to PPH in urban slums in Dhaka and Gazipur. Further, misoprostol was found to be widely accepted by community as the uterotonic poses least adverse effect. However, we found greater proportion of clinically anaemic women in intervention group and blood transfusion requirement was same as control. Awareness concerning the effectiveness of misoprostol was found to be low in intervention group and no knowledge in control group. These findings suggest that greater emphasis should be given in improving antenatal care, ensuring iron intake throughout pregnancy, and strengthen community-based education regarding the advantages of misoprostol. These can promote sustainable use of this uterotonic at low-resource settings which reduce the economic burden due to PPH-related referral as well as maternal death.

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