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From research to action: Oral Misoprostol for preventing postpartum haemorrhage during home delivery in rural Bangladesh

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Abstract

While Bangladesh has experienced a remarkable 40% decline in maternal mortality over the past ten years, it remains a major health problem. Postpartum haemorrhage (PPH) is one of the most prevalent preventable causes of maternal mortality in the country, accountable for over a quarter of the deaths. In Bangladesh, over 70% of the births take place outside health centres, mostly in poor rural areas. This leads to lack of access to conventional injectable uterotonics(i.e. oxytocin) during the third stage of labour to prevent or treat PPH. The purpose of this paper is to discuss the use of oral misoprostol as an intervention to prevent PPH in rural Bangladesh during home births that take place without trained birth attendants. A review of the existing literature in electronic database, shows robust evidence from Randomised Controlled Trials (RCTs)on the effectiveness of oral misoprostol in preventing PPH. Misoprostol has proved significantly effective (RR 0.58, CI 0.38–0.87) in reducing PPH incidence and to go have a very good safety profile. Furthermore, field trials and operational studies have already proven the feasibility, acceptance and safety of scaling up the use of misoprostol in rural Bangladesh. Therefore, we recommend oral misoprostol to be included in the National Maternal Health Strategy as an intervention to control PPH during home birth in rural Bangladesh.

Keywords: Misoprostol, Postpartum haemorrhage, Uterotonics, Home birth, Rural Bangladesh.

Introduction

According to the recent estimates of the World Health Organisation (WHO), almost 99% of maternal mortality is concentrated in developing countries,[1,2] and every day, more than 800 mothers die of preventable causes,[2] mostly during or after a home birth, without the presence of a skilled birth attendant and prophylaxis.[3] Post-partum haemorrhage (PPH), is one of the major causes of maternal mortality globally,[3] accounting for almost one third of all maternal deaths, and arguably one of the most preventable.[4]

Bangladesh has shown an impressive 40% decline in maternal mortality rate (MMR) between 2001 and 2010.[5] However, the rate is currently stagnant, at 194 per 100,000 live birth.[5,6] So targeted focused approaches are needed to further reduce MMR to 143 per 100,000 live birth by 2015 (the MDG-5 target for Bangladesh).[6] Every year, 12,000 women die in Bangladesh due to pregnancy related causes, and over one quarter (28%) of all these deaths are attributable to post partum haemorrhage (PPH).[5]

PPH, defined by the WHO as the loss of ≥500 ml blood within 24 hours of delivery,[7-9] is easily preventable and manageable through the active management of the third stage of labour.[10] The use of oxytocin as an injectable uterotonic is the standard mechanism; however, oxytocin

Practice Points

- Postpartum haemorrhage (PPH) is one of the most prevalent preventable causes of maternal mortality in Bangladesh.
- There is robust evidence that misoprostol is highly effective in reducing PPH incidence and to go have a very good safety profile.
- Introduction of oral misoprostol for the prevention of PPH will be a very cost-effective intervention in the Bangladeshi rural context, where most deliveries take place at home, supervised by untrained traditional birth attendants.
- Misoprostol is heat stable compared to traditional uterotonics and therefore suitable for the tropical environment of Bangladesh. It has a longer shelf life, is cheaper and doesn't require a high skill level to administer.
- Field trials and operational studies have already proven the feasibility, acceptance and safety of scaling up the use of misoprostol in rural Bangladesh.

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is not heat stable, and in resource poor settings, during home delivery by untrained birth attendants, its use is not feasible.[10] In rural Bangladesh, where over two-thirds of deliveries take place at home, accompanied by traditional birth attendants with little or no training,[11] a community-based, low-cost intervention is required to control PPH and associated death.

The purpose of this policy discussion paper is to aid the Ministry of Health's decision-making process in evaluating the feasibility of using oral misoprostol to prevent and treat PPH during home delivery in a rural Bangladeshi setting, in absence of injectable uterotonics like oxytocin.

Materials and Methods

Electronic databases were searched from the starting date of the database to 30 April 2014. Two independent searches were conducted: the first search was limited to systematic reviews, whereas the second search included randomised controlled trials and any other studies reporting effectiveness, acceptability and safety. The search strategy took into account the participants (low resource countries) and the intervention (oral misoprostol).

The Cochrane Library, PubMed, and POPLINE were searched. The search strategy was guided by a recent systematic review recommended by an expert at the London School of Hygiene and Tropical Medicine.[12] Medical subject headings (MESH) for the search included 'Parturition' and 'Delivery, Obstetric' and keywords were: 'labour' or 'labor', 'clean delivery', 'safe delivery', 'birth*', 'childbirth*', 'intrapartum', 'peripartum', 'perinatal', 'postpartum', 'postnatal', 'obstetric*', 'misoprostol', and 'haemorrhage' or 'hemorrhage'.

Additional studies were identified through reference lists of retrieved articles and recommendations sent to the researchers by th experts in maternal and child health. The search was limited to human subjects only.

Review of the existing evidence base

Over the past 20 years, the role of misoprostol, despite being known to have life-saving capabilities, has been surrounded by controversy because of its ability for induce abortion.[12] However, over the past 10 years, an increasing amount of research has been conducted, exploring its beneficial effects, one of which is its use as a cheap uterotonic to prevent and treat PPH.[12] Initially, some hospital-based studies didn't find enough evidence in favour of the effectiveness of misoprostol use to prevent PPH.[12] A lot of the existing studies compared the effectiveness of misoprostol against that of oxytocin,[13] which was found to be more effective and widely acceptable as the best preventive and treatment measure, especially in an institutional setting.[12] However, it was not clear whether the use of misoprostol would be effective in resource-poor rural settings, where oxytocin is absent, and most of the birth take place outside the hospital with the help of traditional birth attendants.[12] Hence the introduction of an alternative intervention has great potential for benefitting the population.[12]

A recent systematic review published in the British Journal of Obstetrics and Gynaecology, by Hundley *et al*.,[12] estimated the effectiveness of oral misoprostol in reducing PPH as well as its safety in home delivery. The authors focused the review on developing countries (which reflects the country context in Bangladesh), and only included studies comparing misoprostol with either a placebo or no intervention, in a home delivery setting. Thus, this study is particularly relevant to consider here. Although the search strategy was fairly comprehensive, and the paper included a wide range of studies, limiting the search to electronically published journal articles means the review might have missed papers that were printed only. Furthermore, the search was limited to the English language; as such, the authors might have missed articles published in different languages. Ultimately, the authors reviewed ten papers, drawing on six different studies, including two double blind RCTs[13,14] and one quasi-experimental trial from Bangladesh.[10]

Effectiveness

The systematic review, mentioned in the earlier section, found the use of misoprostol to be effective in reducing the incidence of PPH.[12] All six studies included in the review showed some degree of effectiveness, and the pooled estimates of relative risk (RR) was 0.58 (95% CI 0.38–0.87). But the overall grade was very low, so the authors calculated a separate pooled estimate of RR for the RCTs, which was RR 0.65 (95% CI 0.46–0.91), with a very high grade.[12] Derman *et al*.,[13] found oral misoprostol to be significantly associated with reduction of acute PPH (losing ≥500 ml blood, postpartum), acute severe PPH (losing ≥1000 ml blood, postpartum) and mean postpartum blood loss.[7]

In a slightly older, separate systematic review in the WHO Bulletin, misoprostol was found to be effective against a placebo in terms of reducing postpartum blood loss of ≥1000 ml.[15]

Safety

Studies measuring the recommended dose and timing of drug administration found that misoprostol is generally administered at the correct time and in the proper doses. For example, a very large operational research study (a non-randomised controlled community trial, not part of the systematic review) undertaken by Quaiyum *et al*., in Bangladesh, found that 99.8% women had the drug at the correct time and 96.4% had correctly consumed the recommended dose.[7]

Five studies included in the Hundley *et al*.[12] review measured the presence of shivering and fever, and all of them reported increase in shivering in the misoprostol group. But the association was not very strong (pooled RR 2.18 (95% CI 1.00–4.72), with a very low grade of evidence. Further there was contradictory evidence lot of heterogeneity, on pyrexia within the selected studies. One small-scale quasi-experimental study assessing the feasibility, acceptability, and effectiveness of the use of

misoprostol in rural Bangladesh found that almost 38% of the participants from the intervention group reported at least one side effect, whether shivering, fever, nausea or vomiting.[9] However, a different picture emerged from the aforementioned operational study by Quaiyum *et al*.[7] The researchers didn't receive any reports of adverse effect from any of the 46,500 women who received misoprostol during the study period.[7] Furthermore, the side-effects mentioned in the previously referred to small-scale quasi-experimental study, were largely temporary (usually lasting 15-30 min), and out of 558 women who reported any side-effects, only 10 of them reported a need for any additional treatment or care.[9]

Cost-effectiveness

Introduction of oral misoprostol for the prevention of PPH will be a very cost-effective intervention in the Bangladeshi rural context, where most deliveries take place at home, supervised by untrained traditional birth attendants.[9,16,17] In one modelling exercise, it was shown that misoprostol can save over USD 11,500 per 10,000 live births in cost of referral, hospital fees, blood transfusion and IV treatment by preventing PPH.[9,17] Moreover, there will also be direct savings, as the production, storage and distribution cost of misoprostol is comparatively cheaper than conventional uterotonics (e.g. oxytocin). However, misoprostol should only be used where there is no universal 'safe motherhood' coverage, and should not be used to replace standard injectable uterotonics, which is already proven effective and safe.[15]

Acceptability

In Bangladesh, various studies have shown that oral misoprostol is highly acceptable among users.[7,10] For example, while the operational study by Quaiyum *et al*.,[7] found that the acceptance of misoprostol is low among the women who didn't have enough information about its potential effect on PPH and has not used the drug; 98% of the women who have actually used misoprostol, considered it to be useful.

Potential public health impact

Misoprostol is heat stable, and therefore suitable for the tropical environment of Bangladesh compared to traditional uterotonics.[8,10,15] Moreover, it has a longer shelf life, is cheaper and doesn't require a high skill level to administer.[8,10,15] All these benefits make it an ideal intervention to help millions of poor women delivering at home without access to institutional medical support. The WHO has recently recommended the use of misoprostol during the third stage of labour, because of its enormous benefit as an effective uterotonic, and potential for scale up all over the world where conventional uterotonics are not available.[10,15] In a joint statement, both the International Confederation of Midwives (ICM) and the International Federation of Gynaecology and Obstetrics (FIGO) have highlighted oral misoprostol as the only available technology to control PPH in home birth.[10,18,19]

Alternative polices to achieve the objective(s)

As highlighted above, another alternative is the use of Uniject oxytocin.[20] While this innovative solution can potentially be seen as an alternative policy option to control PPH, its use will pose some very difficult operational challenges. It would be comparatively more expensive than misoprostol, would require a cold chain, as oxytocin is heat unstable, and would also require highly trained health workers to administer the injection.[20] Furthermore, currently there is no registered and commercially available Uniject oxytocin in the country. Finally, its effective use in low resource settings is effective has not yet been proven.[19]

Another alternative policy to reduce PPH is improving the access to health facilities and/or availability of trained birth attendants. However, for a developing country like Bangladesh, with limited resources, it will take a long time to upgrade the health system and train enough manpower to provide all the population with access to medically trained professionals. As such, the use of oral misoprostol makes sense in the meantime.

Operational feasibility

The use of oral misoprostol to control PPH during home delivery in rural Bangladesh can be scaled up rapidly at low cost in comparison to the other interventions considered above. Besides, multiple large scale studies have already tested the operational feasibility of this intervention in Bangladesh.[7-10]

Misoprostol is already registered and commercially available in the Bangladeshi market from at least three major drug companies.[7] Being locally produced, it will be comparatively cheaper than if the drug had to be imported. In addition, key government agencies including the Ministry of Health and Family Welfare (MOFW) have committed to incorporate the use of misoprostol into the National Health Policy,[7] which appoints to the existence of a favourable environment to change the policy and scale up the intervention.

Table 1 outlines the key implementation considerations and suggested strategies for misoprostol use to control PPH.

Conclusion and recommendations

A review of the evidence shows that oral misoprostol was found to be very effective in the preventing of PPH. Although less effective than oxytocin, it is a much more feasible policy option in resource-poor settings with tropical climates like Bangladesh. Overall, the evidence is robust and there is no controversy around the fact that, in the absence of oxytocin, oral misoprostol can be used as a very effective uterotonic to prevent PPH in a context where most births take place at home and rural areas where healthcare facilities are limited or non-existantant. Furthermore, field trials and operational studies have already proven the feasibility, acceptance and safety of scaling up the use of misoprostol in rural Bangladesh. Therefore, it is recommended to include oral misoprostol in the National Maternal Health Strategy as an intervention to control PPH during home birth in rural Bangladesh to reduce the maternal mortality rate.

Table 1: Implementation/policy considerations and suggested strategies for misoprostol use

Areas of consideration	Potential challenges of implementation	Suggested Strategies
Misuse and safety	Misuse of misoprostol, especially wrong doses and timing, can lead to unwanted abortion, while high doses before delivery can lead to uterine rupture.[15]	Appropriate clinical guidelines to be developed, based on the most recent and credible evidence regarding the correct doses and timing of drug administration. Raising awareness regarding correct use of the drug, as well both potential benefits and risks among women receiving and TBAs distributing misoprostol at the community level.
Logistics and transportation	Poor communication with river islands and hill tracts – might be a challenge in reaching potential beneficiaries.	Learning from the national immunisation programme can be used to devise a strategy to reach populations in hard to reach areas
Financial implication	Because of the huge population in Bangladesh, misoprostol needs to be procured in huge quantity. Training of vast number of TBAs and community health workers would also be needed.	Resources need to be mobilised from both the government and NGO sectors. Donor support can be sought. Engagement of the private sector (e.g. through private public partnerships) could be another innovation way of solving financial issues.[21] Drugs can be procured in bulk quantity, which would give better negotiation power.
Institutional arrangements	TBAs are not part of Bangladesh's existing health system	Existing health policy can be reviewed to include TBAs as part of the health system.
Quality control of drugs	Manufacturers can supply lower quality drugs. Drugs can be distributed at community level beyond their shelf life	Central monitoring of the manufacturing plants would be required to ensure production quality Well-designed distribution and storage plan need to be formulated.
Monitoring, evaluation and learning	Lack of evidence on the smallest efficacious doses of misoprostol in reducing PPH incidence.[15]	Commission research to gather evidence on the smallest effective dose of misoprostol. The programme should be monitored to track the changes after implementation, using the existing health system monitoring tools.

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