Oxytocin via Uniject (a prefilled single-use injection) versus oral misoprostol for prevention of postpartum haemorrhage at the community level: a cluster-randomised controlled trial

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Summary

Background Access to injectable uterotonics for management of postpartum haemorrhage remains limited in Senegal outside health facilities, and misoprostol and oxytocin delivered via Uniject have been deemed viable alternatives in community settings. We aimed to compare the efficacy of these drugs when delivered by auxiliary midwives at maternity huts.

Methods We did an unmasked cluster-randomised controlled trial at maternity huts in three districts in Senegal. Maternity huts with auxiliary midwives located 3–21 km from the closest referral centre were randomly assigned (1:1; via a computer-generated random allocation overseen by Gynuity Health Projects) to either 600 µg oral misoprostol or 10 IU oxytocin in Uniject (intramuscular), stratified by reported previous year clinic volume (deliveries) and geographical location (inland or coastal). Maternity huts that had been included in a previous study of misoprostol for prevention of postpartum haemorrhage were excluded to prevent contamination. Pregnant women in their third trimester were screened for eligibility either during community outreach or at home-based prenatal visits. Only women delivered by the auxiliary midwives in the maternity huts were eligible for the study. Women with known allergies to prostaglandins or pregnancy complications were excluded. The primary outcome was mean change in haemoglobin concentration measured during the third trimester and after delivery. This study was registered with ClinicalTrials.gov, number NCT01713153.

Findings 28 maternity hut clusters were randomly assigned—14 to the misoprostol group and 14 to the oxytocin group. Between June 6, 2012, and Sept 21, 2013, 1820 women were recruited. 647 women in the misoprostol group and 402 in the oxytocin group received study drug and had recorded pre-delivery and post-delivery haemoglobin concentrations, and overall 1412 women delivered in the study maternity huts. The mean change in haemoglobin concentrations was 3·5 g/L (SD 16·1) in the misoprostol group and 2·7 g/L (SD 17·8) in the oxytocin group. When adjusted for cluster design, the mean difference in haemoglobin decreases between groups was not significant (0·3 g/L, 95% CI −8·26 to 8·92, p=0·71). Both drugs were well tolerated. Shivering was common in the misoprostol group, and nausea in the oxytocin group. Postpartum haemorrhage was diagnosed in one woman allocated to oxytocin, who was referred and transferred to a higher-level facility for additional care, and fully recovered. No other women were transferred.

Interpretation In terms of effects on haemoglobin concentrations, neither oxytocin nor misoprostol was significantly better than the other, and both drugs were safe and efficacious when delivered by auxiliary midwives. The programmatic limitations of oxytocin, including short shelf life outside the cold chain, mean that misoprostol could be more appropriate for community-level prophylaxis of postpartum haemorrhage.

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Introduction

Despite substantial progress since 1990, Senegal's maternal mortality rate of 320 per 100 000 livebirths in 2013 is still almost double its UNDP Millennium Development Goal target of 168 deaths per 100 000 livebirths.[1] Postpartum haemorrhage is the main cause of maternal mortality in Senegal: it accounts for more than 29% of maternal deaths.[2] Only around 50% of deliveries in the country (37% in rural areas) are attended by skilled personnel qualified to prevent or treat obstetric complications.[3] Additionally, lack of available trained personnel in rural areas and transport constraints make standard injectable uterotonics for the prevention and treatment of postpartum haemorrhage difficult to access.[4]

Uterotonics effectively reduce the frequency of postpartum haemorrhage.[5–6] Studies done in well resourced hospital settings show that oxytocin prophylaxis is associated with less postpartum blood loss than is misoprostol prophylaxis.[7,8] However, oxytocin is not always feasible—and might be less effective—in resource-poor settings: cool storage is necessary, and because it is given by injection, sterile equipment and skilled personnel are

Research in context

Evidence before this study

Both misoprostol and oxytocin delivered via Uniject (a prefilled, easy-to-use, single dose of oxytocin) effectively prevent postpartum haemorrhage, and, in 2011, WHO added both to its essential medicines list for this indication. We searched PubMed with the terms "postpartum haemorrhage", "misoprostol", "Uniject", and "oxytocin" for any articles published in English between Jan 1, 2010, and June 30, 2012. We also reviewed materials from organisations working on postpartum haemorrhage to be apprised of any ongoing research. We included randomised controlled studies, pre-intervention and post-intervention trials, and Cochrane reviews of either misoprostol or oxytocin; community level trials; and a review of trials in which the Uniject delivery system was used for other drugs.

Because the largest randomised controlled trials in which misoprostol was assessed were all double-blind and systematically measured blood loss, and because the assessments of oxytocin in Uniject were free of selective outcome reporting, we thought that the risk of bias was low. For all trials, data reported were complete and we found few cases of missing outcomes or loss to follow-up. We found no trials comparing oxytocin in Uniject and misoprostol at the community level.

Added value of this study

This study is the first cluster-randomised community-based trial to compare the efficacy of the two most widely used uterotonics for prevention of postpartum haemorrhage. We showed that misoprostol is not significantly less efficacious than oxytocin in Uniject when used at the community level, and reported some evidence suggesting that it might be better.

Implications of all the available evidence

In view of the programmatic limitations of oxytocin in Uniject reported in this study, the Ministry of Health in Senegal chose to introduce misoprostol for prevention of postpartum haemorrhage at maternity huts nationwide, providing uterotonic coverage where it was previously unavailable. Misoprostol is now recommended as the more pragmatic uterotonic for use at the community level. There is still no good evidence that universal prophylactic coverage with any uterotonic has a positive effect on reduction of maternal mortality.

essential.[9] Misoprostol is a safe and effective alternative,[10] and is recommended for use in settings where injectable uterotonics are neither available nor feasible.[11] Results of community-based studies have shown that misoprostol is associated with significant reductions in blood loss[12,13] and suggest that the drug could improve maternal outcomes when community-level providers are involved.[14]

Oxytocin delivered via Uniject (BIOL, Argentina) has also been investigated for prevention of postpartum haemorrhage.[15–17] This novel, simple, prefilled, single-use delivery system does not necessitate additional sterile equipment and can be used by community-level providers, thus reducing some of the limitations of standard intramuscular or intravenous administration. In community-based assessments, Uniject was safer than, and preferred to, a traditional needle and syringe, and was easily administered by all levels of providers.[15,18]

In 2011, WHO added misoprostol and oxytocin via Uniject to its essential medicines list for prevention of postpartum haemorrhage.[19] Both could help to improve access to uterotonics that are not yet widely available in rural settings in low-income countries. In a multi-site international trial in which oxytocin (given intravenously or intramuscularly) and misoprostol during the third stage of labour were directly compared, postpartum haemorrhage (defined as blood loss ≥500 mL) and severe postpartum haemorrhage (blood loss ≥1000 mL) were more common with misoprostol.[20] However, the community-based programmatic efficacy of these two uterotonic drugs has not been rigorously compared. We did this individually powered, cluster-randomised trial to determine whether oral misoprostol or oxytocin in Uniject is better at preventing postpartum haemorrhage when delivered to women in a rural, community-based setting in Senegal, where the effectiveness of oxytocin might be compromised.[21]

For the **trial protocol** see https://clinicaltrials.gov/ct2/show/NCT01713153

Methods

Study design and participants

Our study was a cluster-randomised controlled trial at 28 village-level maternity huts in three health districts in Senegal (Thiadiaye, Kolda, and Medina Yero Foula). Maternity huts are village-based health structures that are managed by an auxiliary midwife and a community health agent. In Senegal, auxiliary midwives are elected by their communities and generally receive 3–6 months of training on safe and clean delivery. All participating auxiliary midwives received an additional 3 days' theoretical training (including a clean and safe delivery refresher) and 4 days' practical training at the closest secondary level health facility. Services in maternity huts are provided in a space including a consulting area (desk and chairs) and a delivery area (delivery table). Typically, maternity huts have no instruments or medicines. Referral services are contingent on the availability of transportation in each village.

The field implementation of the study was coordinated by ChildFund Senegal. Gynuity Health Projects (new York, NY, USA) was responsible for overall study coordination. The protocol was approved by the National Council on Health Research, National Ethical Committee, Ministry of Health and Prevention, Senegal. Continuous