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CLINICAL ARTICLE

Double-blind randomized controlled trial comparing misoprostol and oxytocin for management of the third stage of labor in a Nigerian hospital

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ABSTRACT

Objective: To compare the efficacy of oral misoprostol with that of oxytocin for active management of the third stage of labor (AMTSL). *Methods:* A double-blind randomized control trial was undertaken at a center in Ilorin, Nigeria, between January and June 2013. Every other eligible patient (in the first stage of labor at term, to have a spontaneous vaginal delivery, and no/low risk of postpartum hemorrhage [PPH]) were randomly assigned with computer-generated random numbers to receive oral misoprostol (600 μg) plus placebo injection or oral placebo plus oxytocin injection (1 mL of 10 IU) in the third stage of labor. The primary outcome was amount of blood loss during delivery. *Results:* Mean postpartum blood loss was 325.85 ± 164.72 mL in the 100 patients given misoprostol and 303.95 ± 163.33 mL in the 100 patients given oxytocin ($P = 0.391$). PPH (≥500 mL blood loss) was recorded in 15 (15.0%) patients given misoprostol and 14 (14.0%) given oxytocin ($P = 0.841$). Shivering, pyrexia, and diarrhea were all significantly more common in the misoprostol group ($P < 0.01$ for all). *Conclusion:* The efficacy of oral misoprostol was similar to that of intramuscular oxytocin. Adverse effects associated with misoprostol were transient and self-limiting. Thus, oral misoprostol is efficacious and a good alternative to oxytocin for AMTSL.

Pan African Clinical Trials Registry: PACTR201407000825227.

1. Introduction

Obstetric hemorrhage is a leading cause of maternal mortality, causing 127 000 deaths annually worldwide [1]. Nearly all maternal deaths are due to postpartum hemorrhage (PPH) and are preventable [2]. There are nearly 14 million cases of PPH each year [2]. The contribution of PPH to maternal mortality is disproportionately higher in low-resource countries, particularly in rural settings with limited infrastructure, availability of skilled delivery attendants, and access to uterotonic agents for management of PPH [3,4].

Active management of the third stage of labor (AMTSL) has been shown to prevent PPH. A systematic review [5] established that risk of PPH can be reduced by 60% when AMTSL is implemented. Furthermore, WHO and other international agencies recommend that AMTSL should be offered to all women who deliver with a skilled birth attendant [6,7]. The evaluation of individual components of AMTSL has focused on uterotonic drugs—e.g. ergometrine, oxytocin, syntometrine, and misoprostol—that cause contraction and retraction of the uterus after delivery, thereby minimizing blood loss [8]. However, the use of ergometrine is discouraged because of adverse effects (e.g. increased blood pressure, nausea, and vomiting); oxytocin and misoprostol are considered to be effective and to have acceptable adverse effects [9].

Both a WHO multicenter randomized controlled trial [10] and a Cochrane systematic review [11] on the use of misoprostol for AMTSL showed that there is a higher risk of severe PPH among women taking misoprostol than among those taking oxytocin. By contrast, recent studies [8,12–16] have found no significant difference in the amount of blood loss between misoprostol and oxytocin groups.

Although WHO regards oxytocin as the gold standard for PPH prevention and misoprostol as an alternative in low-resource settings [6,10], further studies comparing misoprostol and oxytocin for AMTSL in different settings with robust methods will add to the existing evidence. The aim of the present study was to compare the efficacy and adverse effects of oral misoprostol with those of oxytocin for AMTSL.

2. Materials and methods

In the present double-blind randomized control trial, women attending the labor ward of the Department of Obstetrics and Gynecology

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of the University of Ilorin Teaching Hospital, Ilorin, Nigeria, were enrolled between January 1 and June 30, 2013. Eligible participants were at term, were advanced in the first stage of labor, were to have a spontaneous vaginal delivery, and had no or low risk of PPH. The exclusion criteria were grand multiparity (≥5 deliveries), multiple pregnancy, uterine fibroids, polyhydramnios, pre-eclampsia or eclampsia, chronic maternal illnesses (e.g. hypertension, cardiac disease, and asthma), and prepartum hemorrhage (e.g. placenta previa and placental abruption). Additionally, patients who had previously had PPH, had received oxytocin and/or misoprostol other than in the third stage of labor, were to undergo a planned instrumental vaginal delivery, had prolonged rupture of membranes, or had anemia (hemoglobin <100 g/L) were excluded. Study approval was obtained from the Ethical Research Committee of the hospital and the National Agency for Food and Drug Administration and Control as per the trial protocol. Informed consent was obtained from all participants.

Eight research assistants were trained by the lead researcher (A.O.M.) for 2 weeks before the study began. The research assistants were second-year registrars, two from each of the four subunits of the department who were in charge of the labor ward during working hours and on-call periods. The training covered patient selection, the randomization process, administration of research medications, the gravimetric method of blood loss estimation and other outcome assessments, vital signs assessment, blood sample collection, and appropriate completion of the information data form.

Sample size calculations established that 100 participants were necessary in both groups to achieve 80% power, with a significance level of 0.05 and a 10% attrition rate. Patient selection was based on a multistage sampling technique. In stage 1, systematic random sampling was used to select every other eligible patient on admission to the labor ward. In stage 2, participants were allocated to receive oral misoprostol plus placebo injection or oral placebo plus oxytocin injection. Allocation was done by blocked (restrictive), double-blind randomization using computer-generated random numbers prepared by an independent statistician. Opaque envelopes containing these random numbers were opened in the third stage of labor. Participants, caregivers, and outcome assessors (researchers or research assistants) were masked to group allocation. Investigators were not masked for data analysis.

Within 1 minute of delivery of the neonate and clamping of the cord, each participant was given an injection and three oral tablets with approximately 50 mL of clean water. Participants assigned to misoprostol received three 200-μg tablets of misoprostol (600 μg in total; Eprostol 200, Lincoln Pharmaceuticals, Ahmedabad, Gurat, India) and 1 mL of placebo by injection (sterile water). Participants assigned to oxytocin received 1 mL of 10 IU oxytocin (Rotexmedica, Trittau, Germany) by injection and three placebo tablets (lactose).

The placenta was delivered by controlled cord traction. Irrespective of the group allocation, an additional dose of oxytocin was given if the uterus was not well contracted after 30 minutes of oxytocic administration, or if there was excessive vaginal bleeding (blood loss ≥500 mL) or vomiting within 30 minutes of delivery.

Blood loss at delivery was assessed by the outcome assessor using the gravimetric method [17]. Blood loss estimation was continued until 1 hour after delivery in both groups.

Maternal blood pressure, pulse, and temperature were recorded immediately after delivery and again after 30 and 60 minutes. Within 1 hour of delivery, the patients were asked about the occurrence of adverse effects such as nausea, vomiting, diarrhea, and shivering. Any adverse effects were noted or observed by the midwife or outcome assessor. Blood samples were taken before delivery and 24 hours after delivery to assess hemoglobin concentration.

The primary outcome measure was the amount of blood loss during delivery. Secondary outcome measures included the change in maternal hemoglobin concentration between admission to the labor ward and 24 hours after delivery, the duration of the third stage of labor, the incidence of a prolonged third stage of labor (>30 minutes), the need for manual removal of placenta, the use of additional oxytocin, and the occurrence of adverse effects (nausea, vomiting, diarrhea, shivering, and temperature ≥38 °C).

The study data were entered into a personal computer and analyzed via SPSS version 18.0 (SPSS Inc, Chicago, IL, USA). Analyses were per protocol: women were included when they had definitely received the allocated intervention and full data were available. Efficacy in each group was determined by the proportion of participants with a blood loss of 500 mL of more and the proportion of those who had additional oxytocic drugs. Statistical significance was determined via the χ^2 test, Student t test, relative risks (RRs) with 95% confidence intervals (CIs), and relative differences with 95% CIs, as appropriate. $P < 0.05$ was taken to be statistically significant.

3. Results

Of the 200 study participants included in analyses, 100 had received oral misoprostol and 100 received intramuscular oxytocin for AMTSL (Fig. 1). Baseline demographic and clinical variables were similar across groups (Table 1).

Table 2 shows the results for the primary outcome. The third stage of labor was longer in the oxytocin group than in the misoprostol group, but the difference was not significant (Table 3). The decrease in hemoglobin concentration was slightly greater in the misoprostol group, but it did not differ significantly (Table 3). There were no cases of manual removal of the placenta in the misoprostol group, and two cases in the oxytocin group ($P = 0.1552$). Regarding adverse effects, diarrhea, shivering, and pyrexia were significantly more common among women in the misoprostol group ($P < 0.01$ for all) (Table 3). Nausea was reported only in the oxytocin group.

4. Discussion

In the present double-blind randomized controlled trial, postpartum blood loss and drop in hemoglobin concentration was higher in the misoprostol group than in the oxytocin group, but the differences were not significant. These results are in keeping with findings from other centers [8,13–15,18], although Uthman et al. [19] reported a significantly lower mean postpartum blood loss with misoprostol than with oxytocin in a study in Maiduguri, northeastern Nigeria. The reason for the variation between studies is unknown, but might be related to pharmacokinetics and geographic differences: the high temperature and probably unfavorable storage conditions in the Maiduguri study might have contributed negatively to the pharmaceutical stability of oxytocin injection and thus its effectiveness.

In the present trial, no differences in the number of cases of PPH and additional oxytocin usage were observed. This finding is in keeping with several other studies [8,12,14,15,20–22]. However, a WHO multicenter randomized trial [10] found a significant difference: 20% of women given misoprostol had a measured blood loss of at least 500 mL, compared with 14% of those given oxytocin (RR 1.44, 95% CI 1.35–1.54; $P < 0.001$). Additionally, 15% of women in the misoprostol group and 11% in the oxytocin group required additional uterotonics (RR 1.40, 95% CI 1.29–1.51; $P < 0.001$) [10].

The present trial reported no cases of retained placenta in the misoprostol group and only two cases in the oxytocin group. Similar findings have been reported in many other studies [8,14,15,18,20,21], with an incidence of retained placenta of less than 2% in both groups.

Shivering, pyrexia, and diarrhea were the most common adverse effects in the present study and were significantly more prevalent among women in the misoprostol group. This is a common finding in many studies that have compared misoprostol with oxytocin [8–10,14,15,18,20–23], although Afolabi et al. [13] reported no rise in temperature between the pre-intervention and post-intervention periods in either group in their study in Ile-Ife, Nigeria. The pathogenesis of shivering