Original Article

# Misoprostol versus oxytocin in preventing postpartum hemorrhage: A randomized controlled trial

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**ABSTRACT**

**Objective:** To compare low dose sublingual misoprostol with the standard 10 IU of intramuscular oxytocin in active management of third stage of labor.

**Materials and Methods:** A total of 104 women with term pregnancy were randomized to receive either 200 μg misoprostol sublingually or 10 IU oxytocin intramuscularly after vaginal delivery. Primary outcome measured was mean blood loss and incidence of primary postpartum hemorrhage (PPH). Secondary outcome measured included duration of third stage of labor, side effects of drugs and need for additional oxytocics to treat life-threatening hemorrhage.

**Results:** A total of 104 women with term pregnancy in two groups of 52 were studied. The mean blood loss with sublingual misoprostol and oxytocin groups was 320.58 ± 244.12 vs. 253.27 ± 171.74 ml; $P = 0.11$. There was no significant differences between the misoprostol and oxytocin groups with regard to the incidence of PPH (19.2% vs. 13.5% respectively; $P = 0.43$). More women in the misoprostol group experienced side effects compared with those in oxytocin group; however, the difference was not statistically significant ($P = 0.26$). The mean duration of third stage of labor was similar and the difference was statistically not significant (6.65 ± 3.47 vs. 6.08 ± 3.07 minutes) ($P = 0.38$), as well as need for additional oxytocics (13.5% vs. 5.8% $P = 0.18$) misoprostol and oxytocin, respectively.

**Conclusion:** Sublingual misoprostol has similar efficacy to standard intramuscular oxytocin in preventing PPH following vaginal birth. Misoprostol at 200 μg with its thermostability may be an effective alternative to intramuscular oxytocin in active management of third stage of labor.

**Key words:** Primary postpartum hemorrhage; misoprostol; uterotonics.

## Introduction

Active management of the third stage of labor (AMTSL) is a strategy for prevention of postpartum hemorrhage (PPH) which consists of interventions designed to facilitate the delivery of the placenta and averting uterine atony. PPH is still the leading cause of maternal mortality despite some decline in the overall mortality, an estimated 303,000 maternal deaths occurred in 2015, a decline of 43% from levels in 1990.[1]

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Uterine atony accounts for greater 70% of the primary PPH.[1] The most ideal uterotonic agent for the active management of third stage of labor has been the subject of research. However, intramuscular 10 IU of oxytocin remains the standard of care by the World Health Organization (WHO) recommendation.[2,3]

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Despite the preference for oxytocin, it is not always feasible to administer oxytocin in economically challenged environment, given its requirement for cool storage.[3] Carbetocin room temperature stable (RTS) is a new development by WHO to address the challenge of cold chain transport and storage with oxytocin; however, it also requires skilled personnel for parenteral administration and sterile equipment like oxytocin.[4] The use of oxytocin and other parenteral uterotonics is often restricted to urban centers. Ease of administration and storage with the background of its effectiveness, favors the use of misoprostol in communities of resource poor settings.[5]

The most recent Cochrane database review of misoprostol for third stage recognized the paucity of published work on lower dose of misoprostol for active management of third stage of labor and suggested the need for further research on low dose misoprostol.[6,7]

This study was a prospective randomized controlled comparison of a low dose 200 μg sublingual misoprostol with the standard 10 IU of intramuscular oxytocin for the active management of third stage of labor. The effect of this low dose regimen on postpartum blood loss and the side effects was compared with the standard treatment of intramuscular oxytocin.

## Materials and Methods

The study was a randomized clinical trial carried out at the Department of Obstetrics and Gynaecology, Federal Medical Centre Owo, Ondo State, Nigeria. The study protocol was approved by the hospital ethical committee. The targeted population was booked women admitted into the labor room anticipating vaginal delivery and who had a singleton pregnancy with cervical dilatation of 6 cm or less and packed cell volume of at least 30%. Women in advanced stage of labor (cervical dilatation >6 cm), known allergies to prostaglandins, oxytocin homologues or excipients, had a serious cardiovascular disorder, serious hepatic or renal disease, or epilepsy were not eligible. All the participants gave a written informed consent.

The sample size was determined using statistical formula for comparing two proportions with accepting a study power of 80%, confidence interval of 95%, study/control of 1:1 and an acceptable dropout rate of 10%. A total of 104 subjects were needed to make the study statistically significant.

Women underwent randomization when vaginal birth was imminent. A block randomization, using computer-generated random numbers, was used to allocate study participants. A total of 104 similar opaque envelopes were used for the study. The envelopes were drawn to know the group into which a subject falls only when delivery is imminent. Women were randomly assigned to receive a single intramuscular injection oxytocin at a dose of 10 IU or 200 μg sublingual misoprostol immediately after the birth of the baby, the drug was administered and the management of the third stage of labor was conducted as recommended in the WHO guidelines.[2] Period taken from delivery of fetus to delivery of placenta was noted. Blood loss was measured using a plastic drape for blood collection (the BRASSS-V Drape), which was placed under the buttocks before delivery; the calibrated blood collection receptacle was however opened only after delivery of the baby, clamping and cutting of the cord and drainage of amniotic fluid. Blood was collected for 1 hour but careful surveillance for further bleeding was put in place till 24 hours after delivery. Additional oxytocics were used when subsequent blood loss was adjudged excessive. The blood collected in the receptacle was visually noted and also transferred to a measuring jar and volume noted. Dry weight of all swabs that were used during the third stage were measured and noted. Blood soaked swabs were weighed and the dry weight of the swabs was subtracted in grams. Assuming an equivalence of 1 g to 1 ml, this volume was added to the volume of blood from the BRASSS-V drape. Participation in the study ended at discharge from the facility, transfer of the woman to a higher care unit or death. Primary outcomes were quantity of blood loss and incidence of PPH. Secondary outcomes included duration of the third stage, need for adjunctive uterotonics to treat life-threatening hemorrhage and side effects of drugs used. Obtained results were subjected to statistical analysis using the SPSS version 20. Descriptive statistics were presented using charts, graphs and tables as appropriate. Quantitative variables were described using measures of central tendencies like mean and median as appropriate. Association between qualitative variables were tested using Chi-square test, while associations between various quantitative variables were determined using the Student's t-test and other tests as found appropriate. The level of significance was set at 5%. Ethical clearance was obtained from the institution's ethical committee before commencement of the study.

## Results

The total number of vaginal deliveries during 3 months study period was 382. A total of 104 women with term pregnancy in two groups of 52 each were studied. Demographic and base line characteristics of the two groups were comparable [Tables 1 and 2]. The mean blood loss with sublingual misoprostol and oxytocin groups was 320.58 ± 244.12 vs. 253.27 ± 171.74 ml; ($P = 0.11$), [Table 3].

The mean duration of third stage of labor was similar and the difference was not statistically significant (6.65 ± 3.47 vs. 6.08 ± 3.07 minutes) ($P = 0.38$), as well as need for additional oxytocics (13.5% vs. 5.8% $P = 0.18$) misoprostol and oxytocin, respectively. There were no differences at the 5% level of significance between groups with regard to the incidence of PPH (19.2% vs. 13.5% respectively; $P = 0.43$), [Table 4]. Among the women who were recruited (safety population), the frequencies of the expected side effects did not differ significantly between the two groups [Table 5]. In misoprostol group, side effects were shivering, fever, nausea and abdominal pains, while the oxytocin group abdominal pains, headaches and shivering.

## Discussion

In this randomized comparative study, we found low dose 200 μg sublingual misoprostol and 10 IU intramuscular oxytocin after vaginal delivery similarly effective in active management of third stage of labor with comparable mean blood loss. Though overall blood loss with oxytocin was less, suggesting better efficacy; the difference was not statistically significant. This finding is in agreement with previous studies carried out in Nigeria by Afolabi *et al*.[5] and Oboro and Tabowei[8] using higher dose of misoprostol. The proportion of subjects in the misoprostol group who experienced PPH was similar to that of oxytocin. The need for additional oxytocics for the treatment of PPH between the two groups was also comparable. This finding agrees with works of Afolabi *et al*.[5] Oboro and Tabowei,[8] and Chaudhuri *et al*.[9] The use of BRASSS-V drapes also ensured a more precise determination of postpartum blood loss and this may have reduced cases that would have been erroneously regarded as cases of PPH.[10]

The side effect profile was similar in the misoprostol group compared with oxytocin group. This is consistent with previous studies. The noted incidence of side effects with misoprostol group were however lower than that of previous studies where higher doses of misoprostol were used.[5,8,11,12]

Availability of parenteral oxytocics for management of third stage of labor remains largely a hospital-based practice confined mostly to urban centers. WHO revealed that only about half of expectant mother in developing countries have their deliveries attended by a skilled birth attendant, and only about 36% deliver in health facility in Nigeria (NDHS 2013). In Nigeria, like other developing countries, most deliveries take place outside the hospital therefore making the use of parenteral oxytocics unlikely and even in the hospital-based deliveries, the challenge of maintaining cold chain for oxytocin is enormous.

## Conclusion

Sublingual misoprostol has similar efficacy to standard intramuscular oxytocin in the active management of third stage of labor. This study also revealed that a 200 μg tablet may be as effective as the previously investigated higher doses. Thus, misoprostol at 200 μg with its thermostability may be an effective alternative to intramuscular oxytocin in active management of third stage of labor.

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Nil.

**Table 1: Maternal baseline characteristics**

| Characteristics | Misoprostol $n=52$ (%) | Oxytocin $n=52$ (%) | $\chi^2$ | $P$ |
|---|---|---|---|---|
| Age (years) | | | | |
| 20-29 | 22 (42.3) | 28 (48.1) | 1.54 | 0.46 |
| 30-39 | 28 (53.8) | 23 (44.2) | | |
| 40 and above | 2 (3.8) | 1 (2.9) | | |
| Marital status | | | | |
| Single | 2 (3.8) | 3 (5.8) | 0.21 | 0.65 |
| Married | 50 (96.2) | 49 (94.2) | | |
| Parity | | | | |
| 0 | 9 (17.3) | 20 (38.5) | 6.37 | 0.174 |
| 1 | 17 (32.7) | 11 (21.2) | | |
| 2 | 20 (38.5) | 17 (32.7) | | |
| 3 | 4 (7.7) | 2 (3.8) | | |
| 4 | 2 (3.8) | 2 (3.8) | | |
| Genotype | | | | |
| AA | 42 (80.8) | 42 (80.8) | 2.22 | 0.33 |
| AS | 10 (19.2) | 8 (15.4) | | |
| AC | 0 (0) | 2 (3.8) | | |
| Blood group | | | | |
| O-positive | 29 (55.8) | 33 (63.5) | 5.39 | 0.37 |
| A-positive | 13 (25) | 6 (11.5) | | |
| B-positive | 8 (15.4) | 10 (19.2) | | |
| O-negative | 2 (3.8) | 1 (1.9) | | |
| B-negative | 0 (0) | 1 (1.9) | | |
| A-negative | 0 (0) | 1 (1.9) | | |

**Table 2: Mean gestational age, blood pressure and packed cell volume**

| Characteristics | Misoprostol (±SD) | Oxytocin (±SD) | $t$ | $P$ |
|---|---|---|---|---|
| Gestational age (weeks) | 39.43 (1.17) | 39.32 (1.17) | 0.45 | 0.66 |
| Mean arterial blood pressure | 83.53 (10.42) | 81.59 (9.57) | 0.98 | 0.33 |
| Intrapartum packed cell volume | 32.92 (2.99) | 32.17 (3.13) | 0.07 | 0.94 |

**Table 3: Mean blood loss and mean duration of third stage of labour**

| Characteristics | Misoprostol $n=52$ (±SD) | Oxytocin $n=52$ (±SD) | Mean difference (95%CI) | $P$ |
|---|---|---|---|---|
| Blood loss (ml) | 320.58 (244.12) | 253.27 (171.74) | 67.30 (14.8,149.4) | 0.11 |
| Duration of third stage (min) | 6.65 (3.47) | 6.08 (3.07) | 0.56 (0.71,1.84) | 0.38 |

**Table 4: Postpartum hemorrhage and need for additional oxytocics**

| Characteristics | Misoprostol *n*=52 (%) | Oxytocin *n*=52 (%) | $\chi^2$ | *P* |
|---|---|---|---|---|
| PPH (≥500 ml) | 10 (19.2) | 7 (13.2) | 0.63 | 0.43 |
| No PPH (<500 ml) | 42 (80.8) | 45 (86.5) | | |
| Additional oxytocics required | 7 (13.5) | 3 (5.8) | 1.77 | 0.18 |
| Additional oxytocics not required | 45 (86.5) | 49 (94.2) | | |

**Table 5: Side effect profile**

| Characteristics | Misoprostol *n*=9 (%) | Oxytocin *n*=5 (%) | $\chi^2$ | *P* |
|---|---|---|---|---|
| Nausea | 1 (11.1) | 0 (0) | 5.29 | 0.26 |
| Shivering | 4 (44.4) | 1 (20) | | |
| Fever | 2 (22.2) | 0 (0) | | |
| Headache | 0 (0) | 1 (20) | | |
| Abdominal pain | 2 (22.2) | 3 (60) | | |

## Conflicts of interest

There are no conflicts of interest.

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