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A randomized controlled study comparing oral misoprostol with intramuscular oxytocin in active management of third stage of labour

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Objective
The study aimed to compare the effectiveness and side effects of 600 μg of oral Misoprostol with 10 international units (IU) intramuscular oxytocin in managing the third stage of labor.

Methods
This open-label, randomized controlled trial included 260 low-risk women in the second stage of labor with anticipated vaginal delivery. They were randomly assigned, to receive either 600 μg of misoprostol orally or 10 IU of oxytocin intramuscularly. The primary outcomes were blood loss during delivery and incidence of postpartum hemorrhage, evaluated using intention-to-treat analysis. Significance was set at $P \leq 0.05$.

Results
Baseline characteristics were similar in both groups ($P>0.05$). The misoprostol group had a significantly lower blood loss than that of the oxytocin group (306.57±176.44 mL vs. 349.37±135.50 mL; relative difference, -12.251 [95% confidence intervals [CI], -22.528 to -1.575]; $P=0.012$). Incidence of postpartum hemorrhage was similar in both the groups (relative risk [RR], 0.952 [95% CI, 0.543 to 0.671]; $P=0.865$). Additional oxytocic therapy requirement was also comparable (RR, 1.143 [95% CI, 0.671 to 1.947]; $P=0.623$). Nausea, shivering, and mean increase in temperature were significantly more common in the misoprostol group than in the oxytocin-parturient group.

Conclusion
In this study, 600 μg oral misoprostol was superior to intramuscular 10 IU oxytocin in reducing blood loss at birth, and equally effective in preventing postpartum hemorrhage. However, misoprostol exhibited more side effects compared to that of oxytocin.

Keywords: Postpartum haemorrhage; Misoprostol; Oxytocin; Nigeria

Introduction

From time immemorial postpartum hemorrhage (PPH) has been a major cause of maternal morbidity and mortality in most countries around the world [1,2]. The world's most beautiful tomb located in India, the Taj Mahal, stands as a testament to this tragedy, as it was built by Shah Jahan in memory of his beloved wife, Empress Mumtaz, who died of PPH in 1630 [3]. In low- and middle-income countries, a mother succumbs to PPH every 6 minutes [4], contributing

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to over 130,000 maternal deaths annually worldwide, with a third occurring in Africa and Asia [5]. Approximately 10.5% of births experience PPH.

Preventing primary PPH will help achieve the first target of goal-3 of the Sustainable Development Goals, which is to reduce the global maternal mortality ratio to less than 70 per 100,000 live births by 2030 [6].

An evidence-based intervention for the prevention of atonic uterus, the leading cause of primary PPH, is the active management of the third stage of labor (AMTSL). Studies have shown that AMTSL reduces maternal blood loss and lower the risk of PPH by approximately 60%. Consequently, AMTSL has been recommended for all hospital deliveries [1,3,7,8].

An integral component of AMTSL involves the prophylactic administration of a uterotonic agent after the baby's delivery, but before the delivery of the placenta, with oxytocin being the first choice uterotonic agent [8,9]. However, several studies have challenged oxytocin's preference over misoprostol based on factors such as effectiveness, heat lability/stability, concentration of active pharmacological ingredients, and ease of administration. Consequently, the choice of uterotonic agent remains contentious, necessitating further studies, reviews, and modifications as needed. Therefore, this study aimed to compare the effectiveness and side effects of misoprostol and oxytocin in the AMTSL.

Materials and methods

This open-label, randomized controlled trial comprised two parallel groups, and aimed to compare the effectiveness and side effects of oral misoprostol and intramuscular oxytocin in the AMTSL between October 2017 and March 2018.

The study population included booked parturients in the active phase of labor, with gestational ages between 37 weeks and 42 weeks and no known risk factors for PPH. Exclusion encompassed participants with hemoglobin concentration ≤10 gm/dL, hemoglobinopathies in pregnancy, chronic medical conditions (e.g., cardiac disease, asthma), hyperthermia of >37.2°C, risk factors for PPH (e.g., high parity, multiple pregnancy, uterine fibroid, adenomyosis, polyhydramnios, PPH history, and previous uterine scar), and those who did not provide consent.

The sample size was determined using data from a previous study [10], and a formula for calculating sample size in clinical trials comparing two groups with a quantitative endpoint [11]. The total sample size consisted of 130 participants in each arm of the study.

Randomization was performed using computer-generated numbers with a blocked restrictive allocation ratio of 1:1 (group B, 130 misoprostol; or group A, 130 oxytocin). A flowchart of the study participants is provided in Supplementary Fig. 1. The allocation sequence was concealed in a sealed envelope, each containing instructions to administer either 600 μg oral misoprostol or intramuscular 10 international units (IU) oxytocin in the AMTSL based on the group assignment.

All eligible patients were informed and counseled about the study in the antenatal clinic starting from 36 weeks of gestation. Recruitment of consenting and eligible patients was carried out upon admission to the labor ward at term, followed by randomization. The researcher or assistant recorded the participants' demographic information and temperature in the information datasheet. Baseline maternal vital signs including pulse rate, respiratory rate, and blood pressure were noted. A venous blood sample was collected from each parturient for estimation of hemoglobin concentration in g/dL, blood grouping, and cross-matching. Labor was monitored, and in the second stage of labor, when vaginal delivery was imminent, consenting women were randomly assigned to either of the two groups of AMTSL by opening a computer-generated numbered envelope. A 1 mL dose (10 IU) of intramuscular oxytocin (Syntocinon, Novartis Pharmaceuticals Ltd., London, UK) stored in the refrigerator was loaded in a syringe, or three tablets (600 μg) of misoprostol (Cytotec, Pfizer Ltd., Kent, UK) were selected according to the patient's group allocation for the management of the third stage of labor.

Within 1 minute after the delivery of the infant, the parturient was administered either 1 mL of oxytocin (10 IU) intramuscularly or three tablets (600 μg) of misoprostol orally with 30 mL of clean bottled water. The cord was double-clamped and cut in between, followed by the delivery of placenta after the first uterine contraction using controlled cord traction. Uterine massage was performed every 15 minutes for 1 hour in all cases.

An additional dose of oxytocin (20 IU in 500 mL of 0.9% saline at 30 drops/minutes) was administered when the uterus was not well contracted after 30 minutes of oxytocic ad-

ministration, or when there was excessive blood loss greater than 500 mL, as assessed using the gravimetric method by the outcome assessor or by the parturient who had oral misoprostol and vomited within 30 minutes of delivery. Patients who underwent episiotomy had a prompt repair to minimize blood loss.

The duration of the third stage of labor in minutes was determined by starting a stopwatch immediately after oxytocin was administered for the delivery of the placenta. Blood loss at delivery was assessed by the researcher or assistants using the gravimetric method. This involved immediate assessment after the baby was delivered. The delivery bed was cleaned and dried of liquor, urine, or meconium; a pre-weighed Nightingale delivery pad was spread underneath the parturient's buttock. Pre-weighed dry gauzes were used to mop up spilled blood on the floor, delivery couch, and other surfaces. Following delivery of the placenta and repair of the episiotomy or perineal tear, the weight of the pre-weighed Nightingale delivery pads and gauzes was subtracted from the weight of the blood-soaked Nightingale delivery pads and gauzes to estimate blood loss. Blood loss estimation was continued in both groups until 1 hour postpartum, by which time the active bleeding subsided, and a perineal pad was applied to the patient's vulva. Estimation was done such that a 1 g difference in weight was equivalent to 1 mL of lost blood [12]. An Ozeri Pronto digital weighing scale (Ozeri Ltd, Hong Kong, China) (model number ASIN B004164SRA) capable of weighing between 1 kg and 5 kg was used.

Maternal pulse rate, blood pressure, and temperature were recorded immediately after delivery and repeated 30 minutes and 60 minutes post-delivery. From the time of oxytocic administration until 1 hour post-delivery, patients were asked about the occurrence of side effects of oxytocic agents, such as nausea, vomiting, diarrhea, and shivering, and their responses were recorded on the information data sheet alongside demographic and postpartum data. Side effects were also noted if they were reported by the woman or observed by the midwife, nurse, researcher, or research assistants. The vital signs of the patients were subsequently monitored every 4 hours as per routine protocol in the postnatal ward, during which the above side effects were reviewed. A second blood sample for hemoglobin concentration was obtained 24 hours postpartum before the patient was discharged, marking the end of the follow-up.

The primary outcome measures included blood loss after delivery and the proportion of participants with PPH (>500 mL). Secondary outcome measures comprised the duration of the third stage of labor, changes in maternal hemoglobin concentration on admission to the labor ward to that at 24 hours post-delivery, the need for the use of additional oxytocic, the occurrence of adverse effects including nausea, vomiting, diarrhea, shivering, and temperature rise, and retained placenta.

Data were tabulated and analyzed using Statistical Package for Social Sciences version 21 (SPSS Inc., Chicago, IL, USA). The effectiveness of the uterotonic agents was assessed based on the amount of blood loss after delivery and the occurrence of PPH. Baseline and demographic characteristics and categorical variables were compared between groups using the *t*-test and chi-square test respectively. Yate's correction was applied in cases where >20% of the expected count was <5. Relative risk (RR), relative difference (RD), and 95% confidence intervals (CIs) were calculated and presented as appropriate. Statistical significance was set at $P<0.05$.

Results

The basic characteristics of the two groups, including age, gestational age, tribe, occupation, and pre-delivery hemoglobin concentration were similar ($P>0.05$) (Table 1).

The misoprostol group exhibited significantly lower blood loss after delivery than the oxytocin group (306.57±176.44 mL vs. 349.37±135.50 mL; RD, -12.251 [95% CI, -22.528 to -1.575]; $P=0.012$). There was no difference in the proportion of participants experiencing PPH between the misoprostol and oxytocin groups (RR, 0.952 [95% CI, 0.543 to 0.671]; $P=0.865$). The mean change in maternal hemoglobin concentration from admission to 24-hour postpartum was similar between the two groups (RD, -40 [95% CI, -69.105 to -0.819]; $P=0.066$). There was no significant difference in the mean duration of the third stage of labor between the misoprostol and oxytocin groups (RD, -7.229 [95% CI, -26.857 to 15.062]; $P=0.503$). The need for additional oxygen was similar between the two groups (RR, 1.143 [95% CI, 0.671 to 1.947]; $P=0.623$). However, nausea, shivering, and the mean rise in temperature were significantly higher in the misoprostol group than in the oxytocin-parturient group, whereas the occurrences of vomiting and diarrhea were similar ($P<0.05$). Notably, no cases of retained placenta were recorded in either group ($P=1.000$). The details are presented in Table 2.

Table 1. Baseline characteristics

Characteristic	Misoprostol group (n=130)	Oxytocin group (n=130)	χ^2	*P*-value
Age (yr)	25.79±2.91	25.76±3.06	0.083[a]	0.934
Gestational age (weeks)	38.93±1.18	38.88±1.35	0.294[a]	0.793
Tribe				
Nupe	108 (83.1)	108 (83.1)	6.431[b]	0.169
Yoruba	9 (6.9)	14 (10.8)		
Hausa	4 (3.1)	0 (0.0)		
Igbo	0 (0.0)	4 (3.1)		
Others	9 (6.9)	4 (3.1)		
Level of occupation				
Unemployed	56 (43.1)	61 (46.9)	7.785	0.100
Artisan	21 (16.2)	25 (19.2)		
Trader/farmer	15 (11.5)	23 (17.7)		
Civil servant	27 (20.8)	17 (13.1)		
Others	11 (8.5)	4 (3.1)		
Pre-delivery Haemoglobin concentration (g/dL)	10.75±0.88	10.79±0.81	-0.368	0.713
Episiotomy	21 (16.2)	25 (19.2)	0.423	0.516
Perineal laceration	0 (0.0)	0 (0.0)	0.001	1.000
Instrumental vaginal delivery	0 (0.0)	0 (0.0)	0.001	1.000

Values are presented as mean±standard deviation or number (%).

[a]Student *t*-test.

[b]Yates correction.

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Table 2. Outcome measures

Outcome variable	Misoprostol group B	Oxytocin group A	Relative difference (95% CI)	Relative risk (95% CI)	*P*-value
A. primary outcome measure					
Blood loss after delivery (mL)	306.57±176.44	349.37±135.50	-12.251 (-22.528 to -1.575)		0.012[a]
PPH (>500 mL)	20 (15.4)	21 (16.2)		0.952 (0.543 to 0.671)	0.865
B. secondary outcome measures					
Change in maternal admission and 24 hours postpaturm haemoglobin concentration (g/dL)	0.18±0.40	0.30±0.68	-40 (-69.105 to -0.819)		0.066
Duration of third stage of labour (minutes)	3.85±3.36	4.15±4.02	-7.229 (-26.857 to 15.062)		0.503
Need for the use of additional oxytocic	24 (18.5)	21 (16.2)		1.143 (0.671 to 1.947)	0.623
Side effects					
Nausea	9 (6.9)	0 (0.0)		19.000 (1.117 to 323.104)	0.0,417[a]
Vomiting	4 (3.1)	0 (0.0)		9.000 (0.489 to 165.499)	0.139
Shivering	40 (30.8)	0 (0.0)		81.000 (5.033 to 1,303.529)	0.002[a]
Diarrhea	2 (1.5)	0 (0.0)		5.000 (0.242 to 103.150)	0.297
Rise in temperature (℃)	0.87±0.53	0.26±0.35	234.615 (157.034 to 330.994)		<0.001[a]
Retained placenta	0 (0.0)	0 (0.0)		1.000 (0.020 to 50.024)	1.000

Values are presented as mean±standard deviation or number (%).
CI, confidence interval; PPH, postpartum hemorrhage.
[a]Significant *P*<0.05.

Discussion

This open-label randomized controlled study demonstrates significantly lower blood loss after delivery when 600 μg oral misoprostol is administered compared to the World Health Organization recommended uterotonic agent of choice, 10 IU intramuscular oxytocin, is administered in AMTSL among no- or low-risk participants. This finding aligns with the results of other studies [13]. Musa et al. [10] also reported lower blood loss after birth in the misoprostol group in a double-blind randomized controlled trial, although the difference was not statistically significant. However, in contrast to our findings, studies by Pangeni et al. [14] and Abd Allah et al. [15] did not show a significant difference in mean blood loss after delivery between the two drugs. Conversely, Mishra et al. [16] found a significantly higher blood loss and PPH incidence in the misoprostol group than in the oxytocin group. The varying results recorded among studies could be due to differences in the methodology including the type of blinding used, the sample size, and the quality of the uterotonic agents employed [17,18]. Studies indicate a significant quality challenge for both oxytocin and misoprostol across low- and middle-income countries, especially in Africa and Asia, which could be due to problems at the manufacturing, storage, distribution, and/or hospital levels. Approximately 39.7% of oxytocin and 38.7% of misoprostol failed the quality tests because of insufficient amounts of active ingredients or counterfeit drugs [18].

This study observed no significant difference between misoprostol and oxytocin regarding the duration of the third stage of labor, drop in postpartum hemoglobin concentration, and the need for the use of an additional oxytocic agent, a finding supported by other studies [14,15,19]. Contrary to these findings, Uthman et al. [13] found a significantly lower reduction in hemoglobin concentration level in the misoprostol group compared to that in the oxytocin group, attributable to significantly lower blood loss after birth [14].

The incidences of shivering and pyrexia were significantly higher in the misoprostol group than in the oxytocin-treated group, consistent with findings from previous studies [10,14,20]. These side effects could be attributed to misoprostol, a prostaglandin E_1 analog, acting on the thermoregulatory center of the hypothalamus and may not solely be considered as postnatal fever [10]. Additionally, diarrhea was significantly more common in the misoprostol group than in the oxytocin group in other studies [20]. However, these side effects are self-limiting and transient.

The limitations of this study include the small sample size, unblinded design, and susceptibility to observer bias, which was overcome by strict compliance to the study protocol by the assessors.

In this study, 600 μg oral misoprostol proved more effective in reducing blood loss at birth compared to intramuscular 10 IU oxytocin, while showing similar efficacy to oxytocin in preventing PPH. However, misoprostol exhibited more side effects, particularly shivering and pyrexia, than oxytocin.

Conflicts of interest

The authors declared no conflicts of interest.

Ethical approval

This study was approved by the Federal Medical Center Bida Health Research Ethics Committee of Nigeria (MCB/HCS/HREC/APPR/VOL.1/10/17).

Patient consent

Written informed consent was obtained from all the participants.

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