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■ Original Research Article

Is Combined Low Dose Misoprostol and Oxytocin More Effective Than Oxytocin Alone in Active Management of Third Stage of Labour? - A Randomized Controlled Trial

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Abstract

Background: Despite established evidence that active management of third stage of labour (AMTSL) reduces the frequency of primary postpartum haemorrhage (PPH), it remains a major direct cause of maternal mortality in low-income countries of the world. This study was to compare the efficacy of combined low-dose sublingual misoprostol and oxytocin, with standard oxytocin alone in the AMTSL. **Methods:** Randomization of 180 parturients to receive either 200ug misoprostol sublingually plus 10 IU intramuscular oxytocin as group A or 10 IU intramuscular oxytocin alone as group B. The mean blood loss, incidence of PPH, need for additional uterotonic, duration of third stage of labour, post-delivery pulse rate (PR), need for blood transfusion and side effects of the drugs were analyzed using chi-square and t-test. **Results:** A total of 180 parturients equally divided into groups A and B. The mean blood loss in group A was 213.44 ± 191.17mls compared to 292.11 ± 242.80mls in group B with a p-value of 0.017. The incidence of PPH in Group A and Group B were 9% versus 13% respectively, *p-value* = 0.343. The differences in other outcomes measured between both groups were not statistically significant except the need for additional oxytocic which was more in group B. **Conclusion:** The addition of low-dose misoprostol to the standard intramuscular dose of oxytocin in AMTSL significantly reduced the mean blood loss as well as the need for additional oxytotic though no significant difference in the incidence of PPH.

Keywords: PPH, AMTSL, misoprostol, Oxytocin and Blood loss.

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INTRODUCTION

Globally, postpartum haemorrhage (PPH) remains the commonest direct cause of maternal mortality contributing about 62% of all forms of obstetric haemorrhage.[1,2]Active management of third stage of labour (AMTSL) involves interventions to facilitate delivery of placenta and enhance uterine contraction, thereby preventing PPH.[3] These interventions include administration of intramuscular oxytocin 10IU within one minute of baby's birth, controlled cord traction to deliver the placenta and uterine massage.[2,3] All three procedures have been found to counter uterine atony which is responsible for about 70% of primary PPH.[3] Postpartum heamorrhage remains the largest direct cause of maternal mortality globally and about eighty-six percent of global maternal death occurred in Sub-Saharah Africa and Southern Asia where most of the low-income countries of the world are located.[1]

World Health Organization (WHO) recommended intramuscular 10IU oxytocin in the third stage of labour as part of the interventions.[4] However, despite established evidence that active management of third stage of labour reduces the frequency of postpartum haemorrhage, it still remains major direct cause of maternal morbidity and mortality in low-income countries of the world.[1,2] To meet the desired maternal health targets of the sustainable development goals, specifically SDG 3:1; reduce the global maternal mortality ratio to less than 70/100,000 live births by

2030, there is a need to focus attention on prevention of maternal death in the low-income countries. This is because majority of global maternal deaths are from those nations.[3,5]

Therefore, The International Federation of Gynaecology and Obstetrics (FIGO), in its active contribution to global effort to reduce maternal death, released supplement article in 2022 on recommendations for prevention and treatment of postpartum haemorrhage.[5] In one of the recommendations for prevention, it was stated that combination of uterotonic drugs such as misoprostol plus oxytocin may be a more effective strategy for prevention of postpartum haemorrhage compared to current standard of oxytocin alone.[5] However, this comes at expense of a higher risk of adverse effects such as shivering and fever associated with misoprostol use.

Ergometrine is an uterotonic that could also be combined with oxytocin. However, the former is sunlight and heat sensitive thus requiring require cold-chain storage which could make maintenance of its potency difficult if there is no constant power supply.[6] Carbetocin is heat-stable but its wide use can be too expensive for the low-income countries.[7] Misoprostol is heat-stable, low cost, readily available and its mechanism of action is different from that of oxytocin and, therefore, their synergistic effect has been reported.[8] In general, the synergistic effect of the two agents would allow the use of low dosage of any of the agent and therefore limit the side effects while improving efficacy.[9] Hence, this study is designed to compared the efficacy of use of combined low dose sublingual misoprostol and oxytocin, with standard oxytocin alone in active management of third stage of labour to prevent PPH.

MATERIALS AND METHODS

This study was a randomized controlled trial conducted at the Department of Obstetrics and Gynaecology, University of Medical Sciences Teaching Hospital, Ondo State, Southwestern, Nigeria. The study protocol was approved by the hospital ethics committee and the ethical approval number was NHREC/TR/UNIMED-HREC-Ondo St/22/06/21. The parturients admitted to our Labour ward for vaginal delivery were the target population for the scope of this study and exclusion criteria were caesarean delivery, preeclampsia/eclampsia, anaemia, multiple gestation, co- existing coagulation disorder and haemoglobinopathies which were confounders. Parturients that refused to participate were also excluded in line with ethical considerations.

The minimum sample size for this study was determined using the formula for comparative study for two population proportions with a statistical power of 80%, level of significance of 0.05 and 95% confidence interval. The minimum sample size in each group was 80 with the use of an estimated proportion for PPH from a previous related study.[10] Taking into consideration the attrition rate, the sample size was increased to 90 for each group, putting the total sample size at 180 participants. The duration of study was 5 months from 1st of November, 2023 to 31st of March, 2024.

To ensure equal chance of participation among participants and eliminate selection bias, randomization was 1:1 using random number generated table by computer-based programme (www.randomization.com). The allocation of participants into groups was concealed to reduce bias. One hundred and eighty sequentially numbered, sealed opaque envelopes each enclosing a paper with a letter A or B were used. Each participant picked one envelope from the set after consenting to participate in the study while on admission in labour ward. The envelope was then only opened by the attending midwife when the delivery was imminent. The letter in the envelope either A or B determined where the participant belonged. Group A had 10IU oxytocin intramuscularly and 200mcg misoprostol sublingually while group B was given only 10IU oxytocin intramuscularly for the active management of third stage of labour.

The drug was administered within one minute of delivery of the baby before clamping and cutting of the cord and the management of the third stage of labor was conducted as recommended in the WHO guidelines.[3] Blood loss was measured using a calibrated drape for blood collection, which was placed under the buttocks before delivery; the calibrated blood collection drape was however opened only after delivery of the baby, clamping and cutting of the cord and prior expected drainage of amniotic fluid. Blood was collected for 1 hour and drape removed thereafter. However, careful surveillance of the parturient for further bleeding was instituted till 24 hours after delivery. The placement of perineal pads by all participants was ensured which were assessed at 3 hours, 6 hours, 12 hours and 24 hours following delivery.

Additional oxytocics were used when subsequent blood loss was adjudged excessive or atonic uterus noted. The blood collected in the calibrated drape was measured and noted. Dry weight of all pads that were used during the third stage were measured and noted. Blood-soaked pads were weighed and the dry weight of

the pads was subtracted in grams. Assuming an equivalence of 1 g to 1 ml, this volume was added to the volume of blood from the calibrated drape to determine total blood loss for each participant.

The primary outcomes measured were mean blood loss and primary postpartum haemorrhage (PPH) incidence. Secondary outcomes measured were post-delivery pulse rate (PR), the need for blood transfusion and side effects of the drugs. The data were collected using prepared proforma. The socio-demographic and obstetric data were recorded. Side effects (vomiting, shivering, headache and fever), the need for additional oxytocics, the duration of the third stage of labour, the need for blood transfusion and the post-delivery pulse rate were noted on the proforma for each participant. The PPH was defined by World Health Organization as blood loss greater than or equal to 500mls after vaginal delivery.

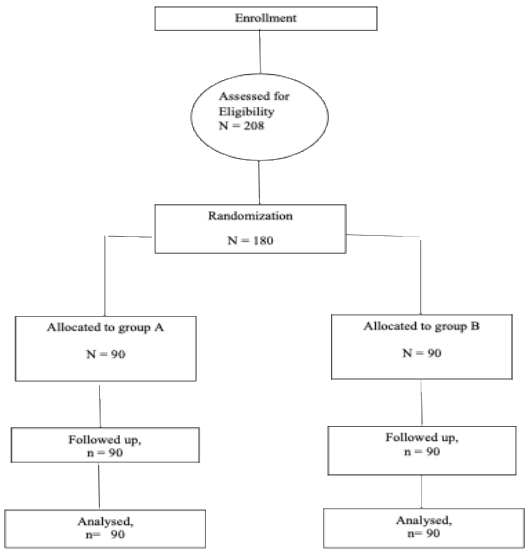

Figure 1: CONSORT Flow Diagram Depicting Participant Enrollment.

The data generated was analyzed using the Statistical Package for Social Science (SPSS) for Windows software version 25. Frequency tables was made and the results tested for statistical significance. Results were presented as mean ± standard deviation, t-test being used to determine the differences between the means of the two groups. For comparing categorical data, Chi square test was used as at when appropriate. The level of statistical significance was set at p- value < 0.05. Ethical clearance was obtained from the institution's ethical committee before commencement of the study and informed consent obtained from the parturients on admission to the labour ward for vaginal delivery.

RESULTS

In this study, the mean blood loss in group A was 213.44 ± 191.17mls compared to 292.11 ± 242.80mls in group B. The difference was statistically significant with p-value = 0.017 (Table 2). There was no significant difference in the incidence of PPH between group A and Group B, 9% versus 13% respectively, p = 0.343 (Table 3).

Table 1: Demographic Characteristics and Gestational Age of the Participants

Variables	Group A N=90 (%)	Group B N= 90 (%)	Statistics
Age			
Less than 20	2 (2.2)	1 (1.1)	X2 = 0.484
20 – 34	64 (71.1)	63 (70.0)	df = 2
≥ 35	24 (26.7)	26(28.9)	p = 0.785
Educational level			
Primary	12 (13.3)	10 (11.1)	X2 = 0.327
Secondary	46 (51.1)	45 (50.0)	df = 2
Tertiary	32 (35.6)	35(38.9)	p = 0.849
Marital Status			X2 = 0.690
Married	86 (95.6)	88 (97.8)	df = 1
Singled	4 (4.4)	2 (2.2)	p = 0.406
Gestational Age			
Preterm	9 (10.0)	5 (5.6)	X2 = 2.381
Term	69 (76.7)	77 (85.5)	df = 2
Postdate	12 (13.3)	8 (8.9)	p = 0.304

The need for blood transfusion in both groups were comparable without significant difference (p-value = 0.700), so also the post-delivery pulse rate with p-value = 0.242. The need for additional uterotonic was significantly reduced in group A compared to group B, 16% versus 33% respectively, p = 0.006. The mean duration of third stage of labour in group A and B were 8.24 ± 6.13minutes and 8.32 ± 6.71minutes respectively without significant difference, p = 0.935. There were no statistically significant differences in the risk factors for PPH between the two groups as revealed in Table 4.

The side effects assessed in this study were nausea, shivering, fever and headache which are shown in the table 5 below. The participants that

experienced side effects were very few in both groups and their percentages are shown in the table. There was no significant difference in the number of the participants that experienced those side effects in both groups when compared statistically. Table 1 shows demographic variables and baseline characteristic that are comparable between the two groups with no statistically significant difference.

Table 2: Comparison of Mean Blood loss, Duration of 3rd Stage of Labor and Post- delivery Pulse Rates of Participants between the Two Groups

Characteristics	Mean ± SD	Mean difference (95% CI)	Student's t-test (p-value)
Blood Loss			
Group A	213.44 ± 191.17	78.67 (14.39 – 142.95)	2.42 (0.017)
Group B	292.11 ± 242.80		
Duration of 3rd Stage of Labor		0.78 (-1.97 – 1.81)	0.81 (0.935)
Group A	8.24 ± 6.13		
Group B	8.32 ± 6.71		
Post – delivery PR		10.84 (-29.10 – 7.39)	1.174 (0.242)
Group A	93.22 ± 16.40		
Group B	104.07 ± 86.10		

Table 3. Comparison of Incidence of PPH, Blood Transfusion and Need for Additional Oxytocics between the Two Groups.

Characteristics	Group A N=90 (%)	Group B N=90 (%)	Statistics
PPH			$X^2 = 0.900$
Yes	8 (8.9)	12 (13.3)	df = 1
No	82 (91.1)	78 (86.7)	$p = 0.343$
Blood Transfusion			$X^2 = 0.149$
Yes	3 (3.3)	4 (4.4)	df = 1
No	87 (96.7)	86 (95.6)	$p = 0.700$
Need for Additional Oxytocics			$X^2 = 7.701$
Yes	14 (15.6)	30 (33.3)	df = 1
No	76 (84.4)	60 (66.7)	$p = 0.006$

Table 4: Identified Risk Factors for PPH among the Participants in both Groups

Variables	Group A N=90 (%)	Group B N=90 (%)	Statistics
Parity			$X^2 = 1.006$
≥ 5	0 (0)	1 (1.1)	df = 1
≤ 5	90 (100)	89 (98.9)	$p = 0.316$
Pre-delivery PCV			$X^2 = 0.097$
Less than 30%	6 (6.7)	5 (5.6)	df = 1
30% and above	84 (93.3)	85 (94.4)	$p = 0.756$
Pre-delivery BP			$X^2 = 0.769$
Normal BP	80 (88.9)	76 (84.4)	df = 1
Elevated BP	10 (11.1)	14 (15.6)	$p = 0.380$
Birth weight			$X^2 = 0.655$
Less than 3.8kg	84 (93.3)	81 (90.0)	df = 1
3.8kg and above	6 (6.7)	9 (10.0)	$p = 0.418$
Genital tract laceration			$X^2 = 1.496$
Yes	39 (43.3)	31 (34.4)	df = 2
No	51 (56.7)	59 (65.6)	$p = 0.221$

Table 5. Comparison of Side Effect Profile between the Two Groups

Characteristics	Group A N=90 (%)	Group B N=90 (%)	Statistics
Nausea			$X^2 = 1.20$
Yes	2 (2.2)	3 (3.3)	df = 2
No	88 (97.8)	87 (96.7)	$p = 0.549$
Shivering			$X^2 = 0.424$
Yes	6 (6.7)	4 (4.4)	df = 1
No	84 (93.3)	86 (95.6)	$p = 0.515$
Fever			$X^2 = 1.239$
Yes	9 (10.0)	5 (5.6)	df = 1
No	81 (90.0)	85 (94.4)	$p = 0.266$
Headache			$X^2 = 0.117$
Yes	4 (4.4)	5 (5.6)	df = 1
No	86 (95.6)	85 (94.4)	$p = 0.732$

DISCUSSION

The results of this prospective randomized comparative clinical trial showed that the use of low-dose misoprostol 200ug in combination with 10IU oxytocin in the active management of the third stage of labour significantly reduced blood loss compared to the use of 10IU oxytocin alone. The incidence of postpartum haemorrhage, though lower with the combined use of sublingual low-dose misoprostol and oxytocin compared with oxytocin alone, did not reach statistical significance. These findings were in agreement with a

similar study by Hofmayr and colleagues who used a higher dose of misoprostol.[9, 11]The sample size of their study was higher and their method of blood loss measurement was different. While calibrated drapes were used in this study for direct blood loss measurement, they collected blood with plastic bedpans and transferred it into measuring jar for measurement. However, their use of a higher misoprostol dose resulted in a higher incidence of shivering and fever in their misoprostol-oxytocin group compared to the oxytocin-alone group. Our study, using a lower misoprostol dose, reported no significant difference in the side effects experienced by participants in both groups. Our study demonstrated that low-dose misoprostol is as effective as higher doses used in other studies.[11, 12]

The mean duration of the third stage of labour was not statistically different in both groups studied. Our results are in agreement with findings from previous studies carried out in Nigeria.[9, 11, 12] The need for additional oxytocic, when the uterus was adjudged to be relaxed and for treatment of postpartum haemorrhage, was significantly higher in the oxytocin-alone group when compared with the misoprostol-oxytocin group. This finding is contrary to those from the studies by Owa et al[10] and Afolabi et al.[13] They compared two groups using misoprostol alone with another that used oxytocin alone. In the study by Afolabi et al, 400mcg misoprostol was given orally while in study by Owa et al, 200mcg misoprostol was given sublingually. They found that the need for additional oxytocic use was not significantly different in their two groups, though Owa et al recorded lower requirement of additional oxytocic in oxytocin group but not statistically significant. The significant difference in the need for additional oxytocic in our study may be explained by the possible synergistic effect in the low-dose misoprostol-oxytocic combination. More so, in this study, additional oxytocin was administered not only when postpartum haemorrhage was diagnosed but also when the uterus was assessed to be poorly contracted, unlike in their studies.

The rate of blood transfusion was not significantly different between the two groups, though it was lower in the oxytocin-misoprostol group, Also the mean post-delivery pulse rates of the participants in both groups were essentially comparable, showing no significant difference. These findings were in agreement with those from the related study of F. Morfaw et al, [14] though their study was retrospective and used a higher dose of misoprostol. The potential confounding factors for postpartum haemorrhage such as the presence of genital tract laceration during delivery, fetal weight, gestational age at delivery, maternal blood pressure, pre-delivery packed cell volume and parity were compared between the two groups. None of the factors reached the level of statistical significance. This result portrays good randomization of the eligible candidates into the study. Furthermore, there was no significant difference between the demographic characteristics of the participants in both groups. Postpartum haemorrhage remains a major cause of maternal mortality especially in developing countries like ours, therefore, its prevention is pertinent to reduction of maternal morbidity and death.

CONCLUSION

We conclude from the results of this study that the combined use of low-dose misoprostol and oxytocin in the active management of the third stage of labour led to a significant reduction of blood loss when compared with the use of oxytocin alone. Also, the need for additional oxytocin use was significantly reduced. The rate of postpartum haemorrhage was not significantly different between the two groups studied.
The limitation of this study was that the participants were not blinded, however, to minimize bias, trained research assistants that collected data for outcome measures and the statistician were blinded to the intervention.

Recommendation

Looking at the challenges of maintaining the cold chain for proper oxytocin storage for optimum efficacy in our environment and the heat stable property of misoprostol and the synergistic effect of misoprostol when used with oxytocin as an adjunct, it will be good to consider the use of lower dose misoprostol with oxytocin in the active management of third stage of labour for prevention of postpartum haemorrhage. Moreover, a recommendation of larger study or meta-analysis looking into lower dose misoprostol as an adjunct to oxytocin in active management of third stage of labour is made.

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Conflicts of Interest: There are no conflicts of interest.

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