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Sublingual Misoprostol in Active Management of the third Stage: Maternal Outcome

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Abstract

Background: *The use of uterotonic agents in active management of the third stage of labor has been shown to reduce postpartum hemorrhage. Although intramuscular oxytocin remains the uterotonic of choice, others such as intravenous oxytocin, ergometrine, carboprost, and misoprostol can be used. Sublingual misoprostol has been shown to have the greatest bioavailability, achieving the highest plasma concentration in the shortest time when compared to other routes at equal dose.*

Objective: *To evaluate whether the addition of sublingual misoprostol to intramuscular oxytocin in active management of the third stage of labor is beneficial.*

Methodology: *This was a randomized controlled trial that involved all women planned for vaginal delivery who presented in labor. After consenting, these women were randomly assigned and received either 600µg of sublingual misoprostol and 10IU of intramuscular oxytocin or 10IU of intramuscular oxytocin alone. Following delivery of the placenta, blood loss was assessed by the gravimetric method. The data obtained was analyzed and compared between the two groups.*

Results: *Three hundred and six women were randomized in this study, one hundred and fifty-three women into each group. Baseline characteristics and risk factors for postpartum hemorrhage were similar for both groups except for parity, maternal weight, and cervical laceration. When these were subjected to logistic regression, they were not found to significantly predict the occurrence of postpartum hemorrhage.*

Sublingual misoprostol in addition to IM oxytocin significantly reduced postpartum hemorrhage, duration of the third stage, blood transfusion, and need for additional uterotonics as compared to IM oxytocin alone. Fever and shivering occurred more in the misoprostol group, but only shivering was statistically significant. All side effects were transient and self-limiting.

Conclusion: *The addition of sublingual misoprostol to IM oxytocin has statistical significance in reducing primary postpartum hemorrhage, duration of the third stage of labor, blood transfusion, and need for additional oxytocics.*

Introduction

Primary postpartum hemorrhage (PPH) is traditionally defined as bleeding from the genital tract of 500mls or more in the first 24 hours following vaginal delivery or 1000mls or more following caesarean delivery. It remains a leading cause of maternal mortality, particularly in the developing world[1] accounting for about a quarter of all maternal deaths. Its prevention, which has become a key component of safe motherhood, is thus important and a rational strategy. Uterine atony accounts for seventy five percent of PPH, and it is generally prevented by the use of uterotonics in active management of the third stage of labor[2].

The third stage of labor refers to the time between birth of the baby and delivery of the placenta and membranes. The third stage of labor may be managed expectantly or actively. When managed actively, it is considered prolonged if it lasts longer than 30 minutes, and this is associated with a six-fold rise in primary postpartum hemorrhage[3]. In expectant management, uterotonics are not administered and the placenta is delivered by maternal effort, while active management involves the use of uterotonics and delivery of the placenta by controlled cord traction. Active management is recommended by WHO, the International Confederation of Midwives, and the International Federation of Gynecologists and Obstetricians[4] as this has been shown to reduce the incidence of postpartum hemorrhage[2].

The uterus comprises three layers: the endometrium, myometrium, and serosa. The myometrium consists of an interlacing network of muscle fibers, which aside from aiding placental separation when they contract, serve as the main force for securing hemostasis by constriction of blood vessels that run through it to the placental bed following placental separation. This is known as the living ligatures[5].Uterotonics play a role in the management of the third stage of labor by causing contractions of these muscle fibers.

Uterotonics that have been used in the active management of the third stage of labor include oxytocin, ergometrine, carboprost, and misoprostol. Although oxytocin via the intramuscular route is preferred[6], it can also be given through the intravenous route, especially during a caesarean delivery when the patient already has an intravenous access. Misoprostol can be administered through sublingual, oral, vaginal, and rectal routes. Sublingual misoprostol has been shown to have the greatest bioavailability, achieving the highest plasma concentration in the shortest time when compared to other routes at equal dosage[7].

Misoprostol was discovered in 1973 and was developed for the prevention of non-steroidal anti-inflammatory drugs-induced peptic ulcers due to its anti-secretory and mucosal protective properties[8]. Its off-label use in obstetrics and gynecology has, however, overshadowed this. WHO has listed misoprostol as one of its essential drugs and also recommended the use of misoprostol in areas where active management is not being practiced or where no skilled birth attendants are available in preventing primary postpartum hemorrhage[9] partly because it is readily available, cheap, thermostable, and has a long shelf life at room temperature when still in its packet. Also, it can be administered without specialized training.

A study done in Ecuador to determine the relationship between the dose and side effects of sublingual misoprostol showed that at 600µg, drug-related side effects are significantly reduced while maintaining efficacy[10]. In 2007, an expert group was convened in Bellagio, Italy, by WHO to advise on the optimal dosages of misoprostol. This was to ensure that while efficacy was maintained, safety was not compromised. The resulting guidelines were published in a supplement to the international journal of gynecology and obstetrics in the same year the group met. This has formed the basis for

misoprostol dosage in reproductive health and also for the choice of 600µg for this study.

Methods

Study design, settings, and participants

This study was a randomized control clinical trial carried out in the labor ward of a tertiary health facility in Abeokuta, Southwest Nigeria, after ethical approval was obtained from the Hospital's Health Research Ethics Committee. Abeokuta is the capital city of Ogun State, Nigeria, and it has a population of about 500,000 based on 2018 population estimation. As of 2018, the hospital where the study was conducted had a delivery rate of about 2300 births per year.

Patients were recruited between 8th of March 2018 to 30th of August 2018. Included in the study were women with ≤4 deliveries, singleton pregnancy, gestational age of ≥34 weeks, and vertex presentation. Pregnancies with previous primary postpartum hemorrhage, pregnancy-induced hypertension, asthma, cardiac disease, induction of labor, instrumental delivery, antepartum hemorrhage, history of manual removal of placenta in previous pregnancy, and previous caesarean delivery were excluded. Also excluded were women in whom sublingual misoprostol will not be possible, for example if vomiting, and women hypersensitive to oxytocin and misoprostol.

Antenatal clinic attendees were informed about the study during the information and education session at the antenatal clinic. The research was further explained to the women who presented in labor and were expected to deliver vaginally. After taking their consent, these women were then randomized for participation in the trial. The patients were blindly assigned to one of the two groups by choosing a number from a range of numbers. These women received oxytocin and misoprostol if the chosen number was in a set of numbers that had previously been produced online using Stat Trek. If not, will just get oxytocin. Uterotonics were administered within a minute of delivery. The maternal demographic details, labor, and delivery variables were recorded on a data sheet for each woman in either study group.

After delivery of the baby, all fluids, mostly liquor, were immediately removed from the delivery table, and a preweighed, fresh nightingale was laid under the buttocks of the patient. Pre-weighed sanitary pads were also provided and used for mopping when necessary. The third stage of labor was actively managed using the WHO model, which includes: (1) administration of a uterotonic, for this study either IM oxytocin 10IU only or IM oxytocin 10IU with 600µg sublingual misoprostol, within a minute of delivery of the baby; (2) controlled cord traction to deliver the placenta with membranes; and (3) massage of the uterine fundus after the placenta is delivered. The same brand of misoprostol and oxytocin were used throughout the period of study in order to avoid the effect that may be associated with varying strengths of drugs. The observations for duration of third stage of labor were noted in minutes using a stop clock. Placenta and membranes were carefully examined under running water for completeness and any abnormality.

The nightingale drained into a wedge-shaped plastic basin that was placed on a shelf below the delivery table. Blood loss was gathered in the basin for a minimum of 60 minutes, or until the bleeding ceased if it hadn't stopped after that time. All of the blood-soaked nightingales and perineal pads were counted once bleeding stopped and put in the collection basin. The basin and its contents were then weighed on an electronic scale. Assuming that one gram is equal to one milliliter[11], estimated blood loss (EBL) was determined by deducting the initial weight of the basin and perineal pad from the weight obtained after delivery and bleeding had stopped.

Women's hematocrit was determined at admission as well as 24 hours and 48 hours post-delivery. Women that developed hemorrhage in excess of

500 ml were managed as per routine therapeutic method.

Statistical analysis

Information from the proforma was fed into a computerized spreadsheet using IBM SPSS package version 22. Analysis was done using descriptive statistics and inferential statistics. Chi-square was used for categorical variables, while Mann-Whitney U test was used to analyze quantitative variables. One sample t test was used to compare the mean estimated blood loss from this study to that of Fawole et al[12]. Shivering was also compared in a similar fashion using binomial. A p value of < 0.05 was considered statistically significant.

Results

A total of 306 women were recruited into the study. One hundred and fifty-three women each were randomized into the trial and control groups. The trial group had sublingual misoprostol and IM oxytocin, while the control group had IM oxytocin alone. All women received allocated intervention, completed follow-up, and were analyzed accordingly. No data was lost.

The socio-demographic characteristics of the 2 arms of the study are described in Table 1. Regarding maternal age, educational status, and gestational age, there was no statistically significant difference between the two groups, while there was for parity and maternal weight.

Risk factors associated with primary postpartum hemorrhage that were identified in this study are shown in Table 2. In total, 27 (8.8%) women had cervical laceration, 3 (2.9%) in the trial group, and 24 (15.7%) in the control group. This was statistically significant. However, when cervical laceration as well as maternal weight and parity were subjected to logistic regression as shown in Table 3, they were not found to significantly predict the occurrence of postpartum hemorrhage. Back to table 2, in the trial group, 78 (51.0%) women had episiotomy while 51 (33.3%) women had perineal tear as compared to 60 (39.2%) and 63 (41.2%), respectively, in the control group. These were not statistically significant.

Table 4 shows the rate of postpartum hemorrhage, which was defined as blood loss greater than or equal to 500mls, was higher in the control group (12 (7.8%)) when compared to the trial group. This was found to be statistically significant. The pattern of occurrence of PPH in this study helps explain the statistical difference in the transfusion rate of the control and trial groups. In total, nine women had blood transfusions, and they were all in the control group. When the mean fall in packed cell volume (PCV) of the trial group (2.65 ± 1.523%) was compared to that of the control group (3.52 ± 2.811%), it was found to be statistically significant. Contrarily, the mean rise was not. The mean estimated blood loss post-delivery for the trial group was 149.41 ± 64.21mls while it was 205.49 ± 189.68mls for the control group. This was significantly different. Also, the difference in the mean duration of the third stage of labor for the trial (4.04 ± 1.831mins) and control (5.39±5.112mins) groups was statistically significant. All of the women that had additional uterotonic (30 (9.8%)) were in the trial group. Three women had manual removal of the placenta, and also like the last variable, they were all in the control group, but unlike it, the difference from the trial group was not statistically significant.

Table 5 shows side effects observed during the period of the study. Of the total 117 (38.2%) women that had shivering, 105 (68.6%) were in the trial group, and 12 (10.3%) women were in the control group. This was significant statistically. 15 (9.8%) women had fever in the trial group, while 6 (3.9%) had in the control group. All the women that had swollen lips (3 (2%)) were in the control group. Just as in fever, this was not statistically significant.

Table 6 shows the comparison made for estimated blood loss and shivering between this study and that of Fawole et al. to find out if there was any statistical difference using one sample t test and

binomial, respectively. There was a statistically significant difference in mean blood loss and shivering for the trial group but not in the control group. This was done as the two studies are somewhat similar.

Table 1: Socio-demographic and Obstetrics characteristics of study populations according to groups

Characteristics	Total Number (%)	Trial Group (n=153)	Control Group (n=153)	p-value
Maternal Age group (years)	**n (%)**	**n (%)**	**n (%)**	
< 35	231 (75.5)	117 (76.5)	114 (74.5)	
≥ 35	75 (24.5)	36 (23.5)	39 (25.5)	0.690
Parity				
Nulliparous	129 (42.2)	72 (47.1)	57 (37.3)	
Primiparous	81 (26.5)	30 (19.6)	51 (33.3)	0.023
Multiparous	96 (31.4)	51 (33.3)	45 (29.4)	
Educational Status				
Primary	15 (4.9)	6 (3.9)	9 (5.9)	
Secondary	30 (9.8)	18 (11.8)	12 (7.8)	0.16
Undergraduate	9 (2.9)	9 (5.9)	0 (0.0)	
Graduate	231 (75.5)	108 (70.6)	123 (80.4)	
Postgraduate	21 (6.9)	12 (7.8)	9 (5.9)	
Gestational Age (weeks)				
< 37	72 (23.5)	30 (19.6)	42 (27.5)	
37 – 40	144 (47.1)	69 (45.1)	75 (49)	0.054
> 40	90 (29.4)	54 (35.3)	36 (23.5)	
Maternal Weight (Kg)				
< 90	267 (87.3)	144 (94.1)	123 (80.4)	0.01
≥ 90	39 (12.7)	9 (5.9)	30 (19.6)	

Table 2: Risk factors associated with PPH

Characteristics	Total Number (%)	Trial Group (n=153)	Control Group (n=153)	p-value
Cervical laceration	**n (%)**	**n (%)**	**n (%)**	
Yes	27 (8.8)	3 (2.9)	24 (15.7)	
No	279 (91.2)	150 (98.0)	129 (84.3)	0.000
Episiotomy				
Yes	138 (45.1)	78 (51.0)	60 (39.2)	
No	168 (54.9)	75 (49.0)	93(60.8)	0.051
Perineal tear				
Yes	114 (37.3)	51 (33.3)	63 (41.2)	0.156
No	192 (62.7)	102 (66.7)	90 (58.8)	

Table 3

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Parity	-.870	.510	2.909	1	.088	.419	.154	1.139
	maternal weight	.042	.030	2.022	1	.155	1.043	.984	1.106
	cervical laceration(1)	21.410	2328.368	.000	1	.993	1987483589.263	.000	.
	Constant	-23.808	2328.369	.000	1	.992	.000		

a. Variable(s) entered on step 1: parity, maternal weight, cervical laceration.

Table 4: Primary and secondary outcomes.

Characteristics	Total Number	Trial Group	Control Group	p-value
Primary postpartum hemorrhage				
Blood loss ≥500ml	12 (3.9%)	0 (0.0%)	12 (7.8%)	0.001
Packed cell volume				
Mean rise in PCV	4.27 ± 3.263	4.19 ± 2.994	4.36 ± 3.581	0.764
Mean fall in PCV	3.05 ± 2.253	2.65 ± 1.523	3.52 ± 2.811	0.007
EBL				
Mean	177.45 ± 144.13	149.41 ± 64.21	205.49 ± 189.68	0.001
Duration of third stage				
Mean	4.72 ± 3.893	4.04 ± 1.831	5.39±5.112	0.002
Blood transfusion				
Yes	9 (2.9%)	0 (0%)	9 (5.9%)	
No	0 (0%)	153 (100%)	144 (94.1%)	0.007
Additional measures				
Additional oxytocic	30 (9.8%)	0 (0%)	30 (19.6%)	0.000
Manual placenta removal	3 (1.0%)	0 (0%)	3 (2.0%)	0.248
Cervical laceration repair	27 (8.8%)	3 (2.9%)	24 (15.7%)	0.000

a Values are given as number (percentage) or mean ± SD.
b n=153 in each group.

Table 5: Side effects

Side effect	Trial group	Control group	p-value
Shivering	105 (68.6%)	12 (10.3%)	0.000
Fever	15 (9.8%)	6 (3.9%)	0.070
Swollen lips	0 (0.0%)	3 (2.0%)	0.248
Shivering and fever	12 (7.8%)	3 (2.0%)	0.017

a Values are given as number (percentage)
b n=153 in each group.

Table 6: Comparison with study by fawole et al.

Characteristics	This study	fawole et el	p-value
EBL			
Trial group	149.41 ± 64.21	211.8 ± 204.7	0.000
Control group	205.49 ± 189.68	217.5 ± 201.5	0.435
Shivering			
Trial group	105 (68.6%)	172 (26.14%)	0.000
Control group	12 (10.3%)	52 (7.94%)	0.383

a Values are given number (percentage) or as mean ± SD

Discussion

Active management of the third stage of labor (AMTSL) is traditionally performed as it has been shown to reduce the incidence of PPH, the quantity of blood loss, and the use of blood transfusion[2]. However, despite routine use of AMTSL, reports from developed countries indicate a rise in the PPH rate[13]. This increase is especially troubling because severe PPH, even when not fatal, jeopardizes the woman's fertility, exposes her to the risks of transfusion and intensive care, and incurs costs. As a result, this trial was carried out to determine if the addition of misoprostol to oxytocin in active management of the third stage of labor would be effective in reducing the occurrence of postpartum hemorrhage.

The majority of the women enrolled were nulliparous as well as less than 35 years, and this may explain the high rate of episiotomy and perineal tear observed in the study. This will be in agreement with the findings by Kartal et al[14] who showed that the rate of episiotomy tends to increase as the age and parity of women decrease.

Most of the women delivered at an estimated gestational age that fell between thirty-seven and forty weeks. This was not out of place, as most deliveries are expected to occur during this period. The incidence of PPH as found out in this study was 3.9%, which is close to the range (4%–6%) quoted for the incidence[15] of PPH but is in contrast to what was observed in studies carried out by Fawole et al[12] (6.22%) and Adegbola et al[16] (6.6%). All these studies, including the present study, were carried out in the south-western region of Nigeria. The statistical difference in the incidence of PPH between the two arms of this study could explain the difference in incidence of PPH between this study and that of Fawole et al., where although there was a difference in the incidence of PPH between its two groups, it was not statistically significant. Various studies comparing misoprostol to oxytocin have either found it equally[17] or not as[18] effective in preventing PPH when used in AMTSL. This is in contrast to the finding in this study and can be explained by the fact that in this study the route of administration of misoprostol was sublingual or because it was combined with oxytocin or both.

PCV was noticed to increase post-delivery in some of the women. This was not reported in any of the studies reviewed and is probably due to shunting of blood from the uterus and placenta bed to circulation following delivery and administration of oxytocics. The mean rise in PCV for the two groups was not statistically significant, but the mean fall in PCV was. This statistically significant fall was in contrast to what was reported by Kaudel et al[17]. The mean EBL in the trial group of this study was statistically different from the control group, which is in contrast to what was observed in other similar studies[12, 17, 19, 20].

The average duration of the third stage of labor was 4.04 ± 1.831mins and 5.39 ± 5.112mins for the trial and control groups, respectively. The statistically significant reduction in the average duration of the third stage of labor in the trial group may have contributed to the reduction in EBL seen in this group. The finding is not comparable with those of other studies comparing misoprostol with oxytocin[17, 20, 21]. In total, nine women required blood transfusions, and all were in the control group. Again, in contrast to other studies, it was statistically significant[12, 20]. Twenty-four women had repair of cervical laceration in the control group as compared to three, and even though this difference was statistically significant, it does not appear to have significantly impacted the incidence of PPH. Even though all the women that had manual removal of placenta were in the control group, it was not statistically significant. This is comparable to findings by Fawole et al and other studies[20, 22].

All the women, 30 (19.6%), that required additional uterotonic were in the control group, and this was statistically significant. This was better than what was observed in other studies[12, 20, 22, 23] where there was either no difference or the difference was not significant.

Shivering and fever were the most commonly identified side effects of misoprostol in this study, like in previous studies[12, 20, 22, 23]. 105 (68.6%) women had shivering in the trial group compared to 12 (10.3%) women in the control group, and this was statistically significant just like in the quoted studies. The occurrence of fever was not statistically significant, just as in the study carried out by Diallo et al[20]. This was however in contrast to findings by Kaudel et al[17], Musa et al.[22] and Shilpa et al.[23] where there was a statistically significant difference in the occurrence of fever. In 15 (4.9%) women, 12 (7.8%) in the trial group, and 3 (2.0%) in the control group, there was an overlap in the occurrence of shivering and fever. A rare side effect of oxytocin, swollen lips, was seen in 3 (2.0%) of the women randomized to the control group. This was, however, not statistically significant, and none of the comparative studies reviewed reported this. All side effects noticed in this trial were self-limiting, and there was no maternal death.

Statistical tests were done to compare EBL and shivering from this study to that of Fawole et al. in order to find out if there was any statistical difference. This was done using one sample t test and binomial, respectively. The study by Fawole et al. was chosen as it is similar to this study. A major difference being that a dose of 400µg of sublingual misoprostol was used by Fawole et al. as compared to 600µg used in this study. One sample t test showed that there was a statistically significant reduction in EBL in the trial groups but not in the control groups. This means the increment in dose of misoprostol was beneficial. However, there was also a statistically significant increase in the incidence of shivering in the trial groups. Hence, a cost-effectiveness study will therefore be necessary to determine if this benefit is worth it.

Strengths

This was a randomized control trial. Estimation of blood loss was done using the gravimetric method, which is more objective than the visual method that was used in some of the studies to which this study was compared. Finally, with a sample size of 306, the study had a reasonable population to draw conclusions from.

Limitations

There was no masking of both the women and care providers involved in this trial to the intervention status. It is assumed that this may create some level of bias, and as such, a double-blinded design would have been more appropriate. This study was conducted among a selected few. As a result, a large multicenter study is required before determining if the addition of 600µg of sublingual misoprostol to oxytocin in AMTSL is beneficial. Lastly, an objective assessment of both tolerability to the adverse effects of the drugs and patient satisfaction was not made.

Conclusion

This study showed that the addition of 600µg of sublingual misoprostol to IM oxytocin in AMTSL is effective in reducing the incidence of PPH, duration of the third stage of labor, and need for additional oxytocics. Even though self-limiting, there was a concomitant increase in shivering and fever. Hence, a cost-effectiveness study is required to determine if the benefits of adding sublingual misoprostol in AMTSL are worth it.

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Conflicts of Interest

None.

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