

Comparative study of the side effect profiles of sublingual misoprostol and rectal misoprostol used in prevention of postpartum haemorrhage in Enugu, Nigeria

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Abstract-

Background: Misoprostol has uterotonic properties and can be administered rectally or sublingually in prevention/treatment of post-partum haemorrhage. There is a need to investigate the misoprostol side effects associated with the different routes.

Objective: To compare the side effect profile, blood loss and preference of sub lingual misoprostol with rectal misoprostol use in preventing primary post-partum haemorrhage in women with risk factor(s) to PPH.

Methodology: This is a prospective comparative study that involved 200 participants who were randomized to two groups by 1:1 computer-based randomization (group A & group B). Each participant in group A received 600mcg sub lingual misoprostol plus rectal placebo and participants in group B received 600mcg rectal misoprostol plus sub lingual placebo after delivery. The delivery mat already in use and soaked with liquor was removed once delivery was imminent and a new pre-weighed mat replaced under the patients buttocks and also a pre-weighed sanitary pad placed in her vulva to collect all the blood loss, in addition, drug side effect(s), preferred route of misoprostol administration were assessed and findings documented in the proforma. Blood loss throughout a period of 24 hours after delivery was measured by gravimetric method. Weight gain from the sanitary pad/ delivery mat was calculated as 1g = 1ml. The sanitary pad/mat was weighed in triplicate and the mean of the three weights entered into the database. The difference was the amount of blood loss assuming 1g to be equivalent to 1ml of blood.

Result: Greater number of research participants in sub lingual group (58%) had drug side effect compared with rectal group of participants (18%); P-value = 0.001. This was statistically significant, although well tolerated. The sub lingual group exhibited higher shivering (48% versus 12%; $p < 0.001$), vomiting (6.0% versus 0.0%; $p < 0.001$) and fever, (4.0% versus 0.0%; $p < 0.001$) while the rectal route group showed higher cases of diarrhoea (6.6% versus 0.0%; $p < 0.001$). The median 24hour post-partum blood loss was less in sub lingual group compared with rectal group (110ml vs 170ml; $P=0.001$). Almost all the participants in the study (99%) preferred sub lingual route of misoprostol administration even with its higher but well tolerable side effects.

Conclusion: It is concluded that sub-lingual route of misoprostol administration is associated with higher but well tolerated side effects and is also the preferred route for misoprostol administration.

Key words: Side Effects, Misoprostol, Sub-lingual, Rectal, Post-partum haemorrhage

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INTRODUCTION

Post-partum haemorrhage remains the major cause of morbidity and mortality following child birth [1]. Post-partum haemorrhage accounts for about 40 maternal deaths per 100,000 births in sub-Saharan Africa [2] as against rates of 1 in 100,000 births in the United Kingdom. Blood loss in excess of 1000ml is physiologically significant and capable of causing hemodynamic instability [3]. Majority of the deaths occur within 4 hours of delivery which indicates that Primary PPH may be a consequence of the mismanagement of the third stage of labour [4]. It is an obstetric emergency that can largely be prevented. The incidence is increasing worldwide. It affects 1% to 5% of all deliveries with about 14 million women suffering from primary post-partum haemorrhage annually and at least 128,000 of these women bleeding to death [5].

Uterine atony is the leading cause of Post-partum Haemorrhage (PPH), which can be prevented with the use of uterotonics [6-8]. Oxytocin is preferred in hospital-based settings [6-8], however, use of oxytocin has a lot of limitations in low-income countries where births still occur at home with untrained birth attendants who do not have facility for its storage and preservation. [9-13]. Misoprostol has shown to be a good alternative for oxytocin in prevention of PPH but its use has been limited by incidences of adverse effects like gastrointestinal symptoms, shivering, pyrexia, fatigue, and headache [14,15]. It is readily availability, temperature stable, not requiring refrigeration, and has a long shelf-life [16-19]. Misoprostol can be administered rectally, vaginally, or sub lingually [20, 21]. It has shown to be effective in preventing PPH

when administered per rectum as prophylaxis following delivery, but with the short coming of invasion of women's privacy and risk of faecal matter contamination of surgical wound from this route. Different routes of misoprostol administration are perceived differently by women who are often helpless at the time of its administration especially in multi-ethnic society where we belong. There is a need to unravel the more suitable and acceptable route of misoprostol administration. This study compared the adverse effects, blood loss and preference of sub-lingual with rectal misoprostol used in the prevention of PPH in women with risk factors for PPH.

GENERAL OBJECTIVE

To compare the side effect profile, blood loss and preference of sub lingual misoprostol with rectal misoprostol use in preventing primary post-partum haemorrhage in Enugu

SPECIFIC OBJECTIVE

- 1) To determine and compare the number of participants that will develop side effects of misoprostol in the two groups
- 2) To determine and compare the number of participants that will develop primary PPH in the two groups.
- 3) To determine the preferred route of misoprostol administration in the two groups

STUDY DESIGN

This is a randomized Comparative study of the side effect profiles of sub lingual misoprostol and rectal misoprostol used in prevention of post-partum haemorrhage in Enugu, Nigeria.

RESEARCH PARTICIPANTS

The research participants for the study were recruited from pregnant women with identified risk factor(s) for primary post-partum haemorrhage (obstructed labour, grand-multi parity, multiple gestation, polyhydramnios, prolonged labour, caesarean section) who had childbirth in ESUT-TH after getting their written informed consent.

ELIGIBILITY CRITERIA

- Consent to the study
- Willingness to deliver in ESUT-TH
- No obvious co-morbidity like placental preavia and uterine fibroid

EXCLUSION CRITERIA

- Consent refusal
- No willingness to deliver in ESUT-TH
- Allergy to misoprostol
- Obvious co-morbidity

SAMPLE SIZE CALCULATION

The minimum sample size (n) for one arm of the study was determined using the formula [22].

$$n = 2[(a+b)^2 s^2] / (u_1 - u_2)^2$$

Where,

n= sample size of each group

a= 1.96 i.e. Z score for an error of 5% (95% confidence level)

b= 0.80 i.e. Z score for estimated study power of 80%

s= population variance (standard deviation) of the outcome in the control group

$u_1 - u_2$ = minimum difference between means of study and control group.

In a related randomized controlled study that compared the efficacy of sub lingual versus rectal misoprostol in prevention of post-partum haemorrhage [23], it was found that the standard deviation of the mean after use was 163.33

Therefore, $s = 163.3$

Assuming a standard effect of 0.4

$$u_1 - u_2 = 163.33 \times 0.4 = 65.32$$

$$\begin{aligned} \text{Therefore, } n &= 2[(1.96+0.8)^2 163.33^2] / (65.32)^2 \\ &= 2[(2.7)^2 26676.6889] / 4268.270224 \\ &= 2[7.6176 \times 26676.6889] / 4268.270224 \\ &= 406424.69072928 / 4268.270224 \\ &= 95 \end{aligned}$$

Assuming attrition rate of 5% sample size per group

$$\begin{aligned} &= 95 + (0.05 \times 95) \\ &= 95 + 5 = 100 \end{aligned}$$

Therefore, the total sample population for the study = $100 \times 2 = 200$

PROCEDURE

A self administered proforma was used to obtain information on biodata, obstetrics history / risk factors for PPH and preferred route of choice for misoprostol administration.

RANDOMISATION OF RESEACH PARTICIPANTS

Each participant was randomized to two groups by 1:1 computer-based randomization (group A & group B)

Each participant in group A received 600mcg sub lingual misoprostol plus rectal placebo and participants in group B received 600mcg rectal misoprostol plus sub-lingual placebo.

Pharmacy department provided the study drugs and placebo in unidentifiable form to the patients but not to the researcher and research assistant.

SAMPLING TECHNIQUES

Recruitment started in antenatal clinic at 36 weeks gestation. Patient was counselled and her consent obtained. She was then assigned to either group A or B as described above. Following the patient's admission into the labour ward, the research assistants received the prepared drug from the pharmacy and other materials and kept ready at the designated tray and were immediately administered at the delivery of the baby. Following the delivery of the baby, the delivery mat already in use and soaked with liquor was removed and a new pre-weighed mat replaced under the patients buttocks and also a pre-weighed sanitary pad placed in her vulva which collected all the blood loss. The folder of the participant was examined to know the group she belonged; trained doctor and mid-wives (research assistants) took the responsibility of patient allocation of appropriate drug and placebo according to the designed root and randomization table. Both the outcome assessor and patients were blinded to the study medication. Question that bordered on the preferred route of misoprostol administration was administered to each participants and response recorded in the proforma. Active management of third stage of labour was done and patient evaluated for any genital tract laceration. Episiotomy when given was repaired immediately. Patient was observed for 2 hours in the labour ward before her transfer to the postnatal ward where further monitoring was continued till the next 24 hours. While on observation post-partum any side-effect from the drug was assessed and findings documented appropriately in the provided proforma.

ESTIMATION OF BLOOD LOSS

Blood loss throughout a period of 24 hours after delivery was measured by gravimetric method. This involved the use of a mettler PB153 weighing scale to weigh the sanitary pads and delivery mat followed by the application of a known weight (pre-weighed) sanitary pad which was applied to the vulva and delivery mat put under the buttocks which was used to collect all the blood loss and pads and mats re-weighed to estimate blood loss. Afterwards, other pre-weighed vulva pads was used by the patient to collect any other blood loss. These pads were collected from the patient whenever she changes pad and stored in an air-tight transparent polyethylene bag and all weighed after 24hours. Weight gain from the sanitary pad / delivery mat was calculated as 1g = 1ml. The sanitary pad/mat was weighed in triplicate and the mean of the three weights entered into the database. The difference was equivalent to the amount of blood loss assuming 1g to be equivalent to 1ml of blood.

OUTCOME MEASURES

The outcome measures include occurrence of misoprostol side effects, 24 hour post partum blood loss and preferred route of misoprostol administration.

STATISTICAL ANALYSIS

DATA ANALYSIS

Data analysis was done using statistical package for social science version 23.

Level of significance was set at 0.05.

Results

Table 1: Socio-demographic characteristics of the study participants

Variables	Sublingual group (n=100)	Rectal group (n=100)	Test stat	p-value
Mean age (years)	27.52 ± 2.08	28.20 ± 3.94	t= -3.77	<0.21
Marital status			$\chi^2 = 3.09$	0.38
Single	4(4.0%)	6(6.0%)		
Married	90(90.0%)	92(92.0%)		
Widowed/divorced/separated	6(6.0%)	2(2.0%)		
Educational status			$\chi^2 = 0.59$	0.74
Primary	4(4.0%)	6(6.0%)		
Secondary	28(28.0%)	30(30.0%)		
Tertiary	68(68.0%)	64(64.0%)		
Occupation			$\chi^2 = 4.46$	0.11
Employed	40(40.0%)	46(46.0%)		
Unemployed	48(48.0%)	50(50.0%)		
Self-employed	12(12.0%)	4(4.0%)		
Ethnicity			$\chi^2 = 2.98$	0.40

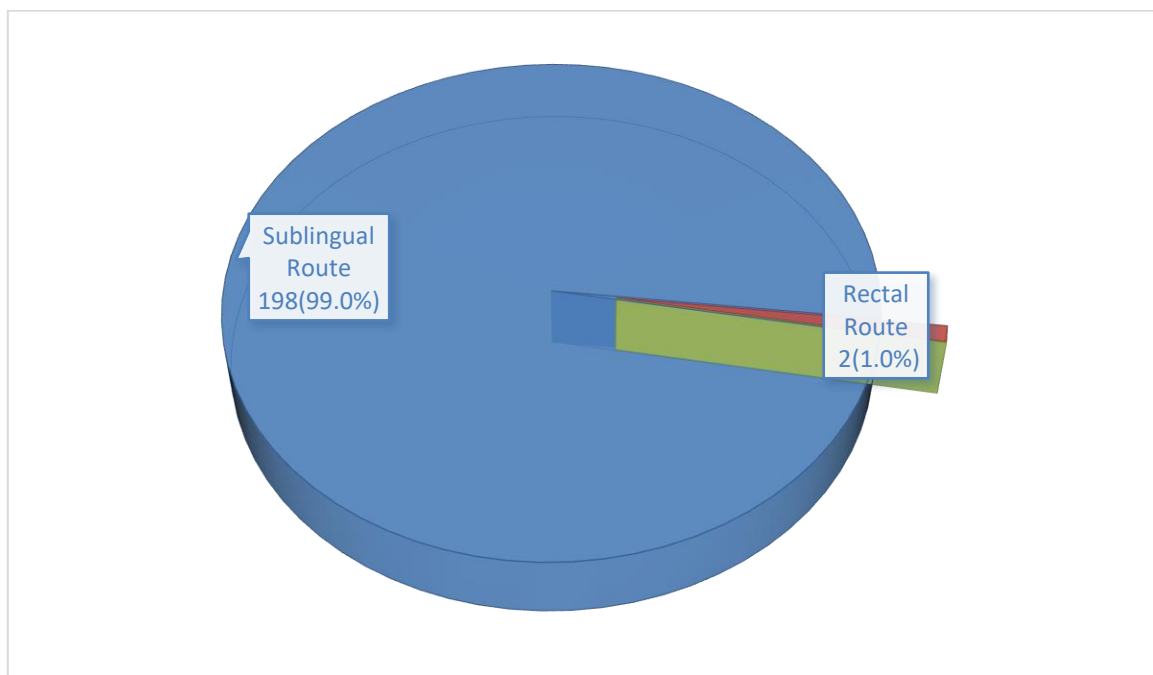
Igbo	90(90.0%)	88(88.0%)		
Hausa	2(2.0%)	4(4.0%)		
Yoruba	6(6.0%)	8(8.0%)		
Others	2(2.0%)	0(0.0%)		
Religion			$\chi^2= 0.42$	0.52
Christianity	96(96.0%)	94(94.0%)		
Islam	4(4.0%)	6(6.0%)		

Table 2: Comparison of the safety (side effects) of the route of misoprostol administration among the participants

Variables	Sub-lingual group (n=100)	Rectal group (n=100)	Test stat	p-value	OR (95% CI)
Presence of side effects			$\chi^2 = 33.96$	<0.001	
Present	58(58.0%)	18(18.0%)			6.3 (3.3 – 12.0)
Absent	42(42.0%)	82(82.0%)			
Type of side effect			$\chi^2 = 22.88$	<0.001	
Diarrhoea	0(0.0%)	6(6.0%)			1.1 (0.0 – 2.7)
Fever	4(4.0%)	0(0.0%)			17.5 (0.9 – 33.2)
Vomiting	6(6.0%)	0(0.0%)			25.2 (1.3 – 45.7)
Shivering	48(48.0%)	12(12.0%)			7.8 (3.7 – 16.3)
None	82(82.0%)	42(42.0%)			Reference

NB: OR = Odd Ratio, CI = Confidence Interval

Figure 1: Preferred route of misoprostol administration



DISCUSSION

The mean age of the research participants in the two groups was 27.9 years. There was no statistical difference in the observed socio-demographic characteristics of the research participants in the two groups. Greater number of research participants in sub-lingual group (58%) had drug side effects compared with rectal group of participants(18%); P-value = 0.001. This was statistically significant, although well tolerated. The sub-lingual group exhibited higher shivering (48% versus 12%; p < 0.001), vomiting (6.0% versus 0.0%; p < 0.001) and fever, (4.0% versus 0.0%; p < 0.001) while the rectal route group showed higher cases of diarrhoea (6.6% versus 0.0%; p < 0.001). The median 24hour post-partum blood loss was less in sub-lingual group compared with rectal group (110ml vs 170ml; P=0.001). The mean post-partum Hb(g) was higher in sub-lingual group, 10.00±1.21vs 9.00± 0.61 P=0.30. Almost all the participants in the study (99%) preferred sub-lingual route of misoprostol administration even with its higher but well tolerable side effects. In a study that compared different routes of misoprostol administration, similar higher side effect profile was the attribute of sub-lingual route of misoprostol administration compared with the other routes [1]. The observations in the current study as it concerns blood loss are in line with similar observation in a

randomized controlled trial of sub-lingual versus rectal route of misoprostol administration in elective Caesarean delivery conducted in Nigeria, where it was noted that sub-lingual route of misoprostol administration was more effective in reducing intra-operative blood loss at elective Caesarean than rectal route of administration¹⁴. Similar finding also characterized another comparative study of different routes of administration of misoprostol in management of third stage of labour where it was found that the amount of blood loss and haemoglobin deficit were least with sub-lingual group, and it was concluded that sub-lingual misoprostol was more effective in reducing blood loss during third stage of labour [23,24]

CONCLUSION

It is concluded that even though the adverse effects of misoprostol were found to be more with sub-lingual administration, sub-lingual route is preferred, with less blood loss and the adverse effects of the drug are well tolerated

RECOMMENDATIONS

It is recommended that sub-lingual route of misoprostol be used due to the observe wide acceptance and efficacy and appropriate patients counselling on the misoprostol side effects to be adopted in cases where misoprostol administration is to be carried out.

Compliance with Ethical Standards

Conflicts of Interest: The authors declare that they have no competing interests.

Funding/Support: There was no external funding for this study.

Ethical considerations: Ethical clearance was obtained from the ethical committee of ESUT Teaching Hospital Parklane. Written informed consent was gotten from the participants after explaining in details the study process.

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