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ORIGINAL ARTICLE

Randomised Controlled Trial of Sublingual and Rectal Misoprostol in the Prevention of Primary Postpartum Haemorrhage in a Resource-Limited Community

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Abstract

Background/Purpose Misoprostol is beneficial in preventing postpartum haemorrhage (PPH). However, there is no consensus yet as to which route will give the balance of efficacy, safety and patient preference, especially at the recommended dose of 600 mcg. This study compared the efficacy and adverse effects of rectal and sublingual misoprostol for the prevention of PPH.
Methods In a prospective fashion, consenting eligible parturients were randomised into two groups to receive either 600 mcg of misoprostol rectally or sublingually after vaginal delivery. All study participants were followed up till 24 h postpartum. Primary outcomes were blood loss of 500 ml or greater and at least 10% change in peripartum haematocrit levels.
Results Seven (6.7%) and 16 (15.7%) of the sublingual and rectal routes, respectively, had PPH. However, the odds of having PPH after rectal misoprostol were at least twice the odds after the sublingual route ($p=0.041$). Also, the mean blood loss after the first, fourth and 24th hour postpartum were significantly higher after rectal administration. Although significantly more patients had shivering and pyrexia after sublingual misoprostol, it was acceptable to more participants than the rectal route.
Conclusion At the recommended dose, sublingually administered misoprostol ('the sweet of life') is associated with a lower incidence of PPH than the rectal route. Despite its higher incidence of shivering and pyrexia, it was accepted by more women than rectally administered misoprostol.
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Keywords Postpartum haemorrhage · Misoprostol · Rectal · Sublingual · Adverse effects

Introduction

The first target of Sustainable Development Goals 3 is to reduce global maternal mortality ratio to less than 70 per 100,000 live births [1]. The commonest cause of maternal mortality worldwide remains obstetric (especially postpartum) haemorrhage, accounting for nearly one-quarter of all cases, with about two-thirds of women with postpartum haemorrhage (PPH) demonstrating no clinical risk factors [2–5]. Unfortunately, developing nations contribute 99% of the global deaths from PPH, because many women there still deliver in facilities that are ill-equipped to manage PPH [6, 7]. In Nigeria, PPH accounts for the highest number of maternal deaths, cases of 'near-miss' and peripartum hysterectomy [8, 9].

Evidence has shown that managing the third stage of labour actively is the most important preventive strategy for primary PPH, an approach that is based on the use of

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uterotonics, and reduces PPH caused by uterine atony by 60% [10–14]. Although the uterotonic of choice is intramuscular oxytocin, challenges with refrigeration, availability, cost and skill/necessary requirements for its administration have made it less successful in rural settings and low-and-middle-income countries (LMIC), the very population where PPH is commonest [15–17].

Misoprostol has been introduced into the list of uterotonics because of its long shelf-life, stability without refrigeration, low cost, ease of administration even without skilled accouchers and effectiveness in preventing PPH. Although it has a number of side effects such as shivering, pyrexia, nausea, vomiting and diarrhoea, these are dose-related and self-limiting [18].

Interestingly, misoprostol can be administered buccally, orally, sublingually, vaginally and rectally. Rectal misoprostol is widely used in Nigeria as prophylaxis against PPH following spontaneous vaginal delivery and caesarean birth. Sublingual administration of misoprostol could be a better option because of its rapid uptake, prolonged duration of action and the greatest total bioavailability compared with rectal route of administration [15], which has a slower onset of action and may also be irritating to both parturients and accouchers. However, following a randomised controlled trial on misoprostol use in the prevention of PPH, the authors concluded that the route that will give the best balance of efficacy and safety is yet unclear [19]. A well-designed study of both routes will help address this question, especially at the recommended dose of 600 mcg and in this setting where there is a dearth of studies comparing the efficacy of both routes.

Materials and Methods

The study was conducted in the labour ward of Ekiti State University Teaching Hospital (EKSUTH), Ado-Ekiti, Nigeria. The hospital receives referrals from other towns in Ekiti State, parts of Ondo, Osun and Kogi States. Ekiti State is one of the six southwestern states in Nigeria, and it is thus situated entirely within the tropics. It has a total land area of 5887.89 km^2. with a human population of 2,398,957 [20]. Ado-Ekiti, the semi-urban state capital, is largely made up of the indigenous Yoruba, with a mix of immigrant ethnicities like the Ebira, Hausa and Fulani. These form rural communities whose health needs are served by primary and secondary care facilities that use the Teaching Hospital as their referral centre. Thus, the mixture of rural and semi-urban populations in Ado-Ekiti makes it suitable for the study, and the choice of EKSUTH for this study was purposive. The Ethics and Research Committee, EKSUTH gave approval for the study, which was also registered with the Pan African Clinical Trials Registry (Unique Identification Number: PACTR201911500348367).

The study was a randomised controlled trial of women who presented at the labour room of EKSUTH, and had spontaneous vaginal deliveries at term, between 01 January, 2019 to 30 June, 2019. The design and reporting were done in accordance with the CONSORT Statement 2010 [21]. Eligible participants were women with term cephalic-presenting singletons in whom vaginal delivery was anticipated. All recruited patients were adequately counselled and their written informed consent obtained. They were at liberty to decline participation without any negative impact on the quality of care they will receive in the hospital. Women who had caesarean or instrumental delivery, packed cell volume below 24%, antepartum haemorrhage, severe pregnancy-induced hypertension, pre-eclampsia/eclampsia, birth weight $\geq$ 4000 grammes, vaginal/cervical lacerations, concurrent medical disorders (cardiovascular disease, liver disease, sickle cell anaemia, diabetes mellitus, thyroid disorders, coagulation disorders and bronchial asthma), and those that refused to participate were excluded from the study.

Based on the incidence of postpartum haemorrhage obtained from a randomised study involving sublingual misoprostol in a LMIC [22], to achieve a study power of 80%, confidence interval of 95%, level of significance of 5% and an acceptable drop-out rate of 10%, 95 women would be needed in each arm of the study.

Resident doctors and the labour ward staff were informed about, and trained to recruit participants for the study. After obtaining a written informed consent, antenatal history and physical examination were done along with the review of the antenatal records of the index pregnancy. The first trimester ultrasound scan was used to ascertain the estimated gestational age, if the parturient was unsure of her last menstrual period.

Participants were assigned, by means of computer-generated random numbers in blocks of four, to receive 600 mcg (3 tablets of 200 mcg each) of misoprostol (Cytotec, Pfizer Pharmaceuticals Limited, United Kingdom) either via the rectum (arm A) or sublingually (arm B). Group allocation was predetermined and placed in consecutively numbered and sealed opaque envelopes, all kept in a box sequentially. Once a patient deemed eligible was in the second stage of labour, and had given informed consent for study participation, she was assigned a sequential study number. Allocation of patients started from the first sealed opaque envelope until the last pack was completed sequentially. Using this method, equal numbers of subjects were assigned to each treatment arm. The medication was administered at the delivery of the foetus by an independent person who was not involved in randomisation and in measurement of blood loss. Uterine massage, clamping and cutting of the cord with the delivery of the placenta by controlled cord traction were ensured

according to the protocol of the hospital. Performance bias was significantly minimised by ensuring that the labour ward staff could give other uterotonics in line with the hospital's protocol should there be excessive bleeding. This was boldly written on cardboard and pasted on the walls of the labour room. Additional uterotonics were administered in the form of 10iu of oxytocin parenterally, with 20iu oxytocin in 500 ml of normal saline by an intravenous infusion. Once delivery of the foetus occurred, any oxytocin infusion used for labour augmentation was discontinued.

To calculate the blood loss at delivery, two pre-weighed absorbent underlay sheets were employed during labour. The upper sheet, which would contain the liquor, was rolled away before the placenta is delivered. Immediate blood loss postpartum was measured from the second absorbent underlay sheet and pre-weighed pads applied under the buttocks and the perineum, respectively. The pre-weighed perineal pads and absorbent underlay sheets were weighed, applied, changed and re-weighed at 1 h, 4 h and 24 h' postpartum using a digital weighing scale (Seca GmbH and co, Hamburg, Germany), which was calibrated prior to, and in between, use. The total blood loss was calculated from the values obtained over 24 h. The blood loss was estimated as difference of the weight changes in the pre-weighed pads and absorbent underlay sheets before and after delivery, based on the fact that 1 g is equivalent to 1 ml of blood [23, 24]. Packed cell volume (haematocrit) was checked at admission into the delivery suite and prior to discharge from the hospital. Ten per cent or more (≥ 10%) decrease in antepartum value was regarded as postpartum haemorrhage [25]. Body temperature was measured by a digital thermometer from the axilla sixty minutes after administration of the study treatment. Pyrexia was defined as a temperature of at least 38 °C, while the occurrence of fever was obtained on verbal enquiry. Prior to discharge from the hospital, a Likert scale was used to assess the participants' level of satisfaction with the route of administration employed [26].

Data collected were entered into, and analysed, using Statistical Software for the Social Sciences version 21 (SPSS 21, IBM, Chicago). Pearson's Chi-square test (or Fisher's test, where appropriate) was used to determine the association between categorical variables, while student's t test was employed to compare continuous variables. Odds ratios and the corresponding 95% confidence interval were calculated as appropriate, with the level of significance set at p value less than 0.05.

Results

Data analysis was based on 206 participants (in two groups based on the route of administration of the study treatment: 102 participants in the rectal misoprostol arm and 104 women in the sublingual misoprostol arm), because six out of the 212 randomised women were excluded due to incomplete data (Fig. 1). Table 1 showed the socio-demographic characteristics of the women included in the study. Most of the women, 110 (53.4%) were at least 30 years of age, 161 (78.2%) were multipara, and 184 (89.3%) were of the Christian religion. Three (1.5%) of the participants had no formal education, while 6 (2.9%) and 37 (18%) were single and unemployed, respectively. However, the two groups of participants had comparable socio-demographic characteristics.

The clinical and obstetric attributes of the women were displayed in Table 2. Two (1%) of the study population had a history of postpartum haemorrhage, while 155 (75.2%) had normal packed cell volume before delivery. The duration of pregnancy exceeded 40 weeks in 3 (1.5%) of the women, and nine (4.4%) participants spent less than 3 h in the active phase of labour. Again, there were no significant differences between the two groups with respect to their observed clinical and obstetric characteristics.

The incidence of postpartum haemorrhage, using the volume of blood loss after delivery, was 11.2%. The odds of bleeding in excess of 500 ml after delivery in the rectal misoprostol group was at least two times the odds in the sublingual group [OR: 2.578(1.013-6.563), $p = 0.041$]. When the criterion of at least 10% drop in the packed cell volume was used, the incidence of PPH was 13.6%, with the odds being significantly higher with the rectal route than the sublingual route ($p = 0.013$). The mean blood loss after the first, fourth and twenty-fourth hour postpartum were significantly higher in the arm with rectal route than that with the sublingual route ($p = 0.012$, < 0.001 and < 0.001, respectively). Also, the mean percentage change in the packed cell volume before and after delivery was significantly higher in the rectal misoprostol arm than the sublingual group ($p = 0.001$). Significantly more women who had sublingual misoprostol were satisfied with the route of administration and experienced shivering with pyrexia compared with those in the rectal arm ($p = 0.004$, < 0.001 and 0.049, respectively). The two groups of women were comparable with respect to the other secondary outcomes and safety indicators (Table 3).

Discussion

Evidence has continued to emerge from LMIC regarding the efficacy of misoprostol in preventing PPH, after its recommendation by the World Health Organisation as an alternative to oxytocin. The index study, which was conducted in a low-resource setting, found a significantly lower incidence of PPH (using both the amount of blood lost after delivery and at least 10% drop in the haematocrit) after sublingual administration of misoprostol than with the rectal route.

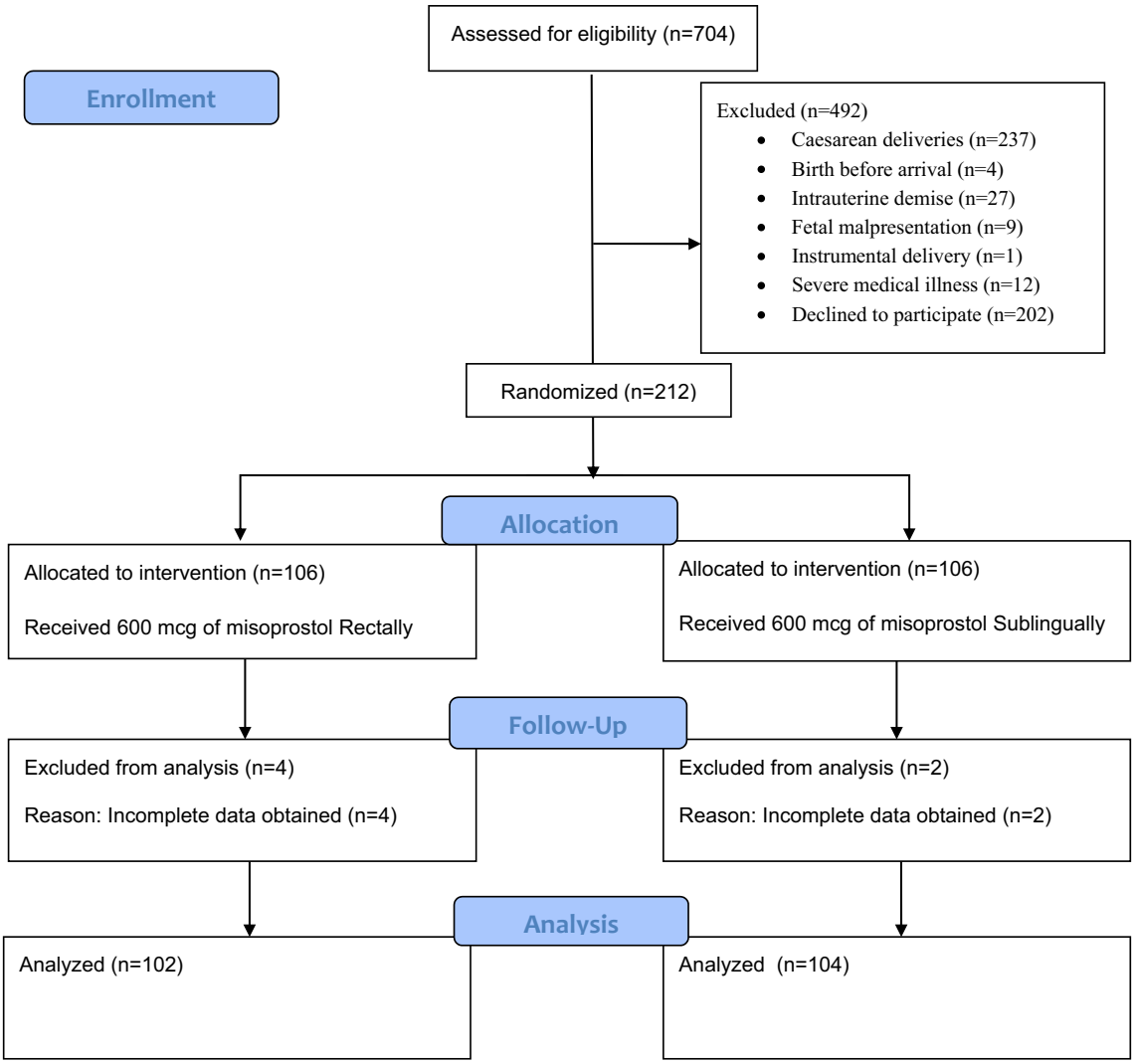

Fig. 1 Flow diagram of the study

The incidence of PPH in this study using misoprostol only as the third-stage uterotonic was 11.2%. Studies with similar objectives have found incidence ranging between 7.4 and 12% [27, 28]. Comparing the different routes of administration in this study, the incidence of PPH in the sublingual group was significantly lower than in the rectal group. While a quasi-randomised study found no difference between them [27], other studies similarly showed that the sublingual route was associated with reduced blood loss [28–31]. Authors have documented low rates of PPH between 5 and 9.7% when misoprostol was administered sublingually, the variations possibly due to the dose of the drug used in their works [15, 18, 27, 32, 33].

Our study showed that the mean blood loss after the first, fourth and twenty-fourth hour, and the mean percentage change in haematocrit values were significantly lower in the sublingual group than the rectal group. This observation could be due to its faster onset of action, prolonged activity, and greater bioavailability in the serum compared with when administered rectally [15, 34]. However, the need for additional uterotonics, need for blood transfusion and occurrence of vaginal bleeding in excess of 1000 ml were comparable when misoprostol was administered via either route.

The commonest side effects of the drug were shivering and pyrexia, and both were significantly more after sublingual administration. Misoprostol has been known

Table 1 Socio-demographic characteristics of the participants versus route of treatment

Characteristics	Route of administration			χ^2	*p* value
	Rectal	Sublingual	Total		
	n (%)	*n* (%)			
Age (years)					
< 30	48 (47.1)	48 (46.1)	96 (46.6)	0.017	0.896
≥ 30	54 (52.9)	56 (53.9)	110 (53.4)		
Mean age ± SD	29.75 ± 4.39	30.63 ± 4.34		− 1.447[a]	0.149
Parity					
Primipara	22 (21.6)	23 (22.1)	45 (21.8)	0.009	0.924
Multipara	80 (78.4)	81 (77.9)	161 (78.2)		
Religion					
Christianity	94 (92.2)	90 (86.5)	184 (89.3)	3.401	0.183
Islam	7 (6.9)	14 (13.5)	21 (10.2)		
Traditional	1 (1)	0 (0)	1 (0.5)		
Employment status					
Unemployed	12 (11.8)	25 (24)	37 (18)	5.511	0.138
Unskilled	23 (22.5)	21 (20.2)	44 (21.4)		
Semi-skilled	51 (50)	42 (40.4)	93 (45.1)		
Skilled/Professional	16 (15.7)	16 (15.4)	32 (15.5)		
Marital status					
Single	5 (4.9)	1 (1)	6 (2.9)	2.828	0.093
Married	97 (95.1)	103 (99)	200 (97.1)		
Education					
No formal	2 (2)	1 (1)	3 (1.5)	1.365	0.714
Primary	1 (1)	3 (2.9)	4 (1.9)		
Secondary	20 (19.6)	19 (18.3)	39 (18.9)		
Tertiary	79 (77.5)	81 (77.9)	160 (77.7)		

[a]Student's *t* test

to mediate pyrexia by crossing the blood–brain barrier, and resetting the hypothalamic temperature-regulator to a higher level. In other to attain this higher temperature level, the body shivers, and increases both its muscular and cardiac activities, and these effects are less pronounced after rectal administration [19, 35]. They are usually self-limiting and rarely worrisome, a fact corroborated by the finding that despite the higher incidence of side effects with sublingual misoprostol, significantly more women expressed satisfaction with the route [7].

Since the routes of drug administration differed, the study was limited by the non-use of placebo controls. However, the authors attempted to minimise this by having different personnel administer the drugs, and estimate the blood loss and other outcome measures. Besides, the method of estimating the blood loss could have been influenced by the presence of faeces, urine and liquor in the underlay sheets. This bias has been mitigated by the use of the same method of evaluating blood loss in both groups.

Table 2 Clinical and obstetric characteristics of the participants

Characteristics	Route of administration			χ^2	*p* value
	Rectal	Sublingual	Total		
	n (%)	*n* (%)			
History of PPH					
Yes	2 (2)	0 (0)	2 (1)	2.059	0.244[a]
No	100 (98)	104 (100)	204 (99)		
Antepartum PCV (%)					
< 33	26 (25.5)	25 (24)	51 (24.8)	0.058	0.809
≥ 33	76 (74.5)	79 (76)	155 (75.2)		
Mean antepartum PCV (%) ± SD					
	34.67 ± 3.99	34.62 ± 3.19		0.102[b]	0.919
Duration of pregnancy (weeks)					
≤ 40	100 (98)	103 (99)	203 (98.5)	0.358	0.549
> 40	2 (2)	1 (1)	3 (1.5)		
Mean duration of pregnancy (weeks) ± SD					
	38.57 ± 1.07	38.79 ± 0.73		− 1.726[b]	0.086
Duration of active phase of labour (hours)					
< 3	3 (2.9)	6 (5.8)	9 (4.4)	1.695	0.429
3–12	97 (95.1)	94 (90.4)	191 (92.7)		
> 12	2 (2)	4 (3.8)	6 (2.9)		
Active management of the third stage of labour					
CCT	102 (100)	103 (99)	205 (99.5)	0.986	1.000[a]
Uterine massage	102 (102)	102 (98.1)	204 (99)	1.981	0.159

CCT controlled cord traction, *PCV* packed cell volume

[a]Fisher's exact test

[b]Student's t test

In conclusion, when combined with other routine components of active management of the third stage of labour, sublingually administered misoprostol was associated with a reduced incidence of PPH and mean blood loss when compared with rectal administration for the prevention of PPH in low-resource settings. Although it is associated with a higher incidence of shivering and pyrexia, parturients could be reassured that these would be mild and self-limiting.

Table 3 Primary and secondary outcome measures by route of administration

Outcome	Categories	Route of administration		OR (95% C.I.)/*t* test	*p* value
		Rectal	Sublingual		
		n (%)	*n* (%)		
Primary	*Blood loss ≥ 500 ml*				
	Yes	16 (15.7)	7 (6.7)	2.578 (1.013–6.563)	0.041*
	No	86 (84.3)	97 (93.3)		
	≥ 10% change in PCV				
	Yes	20 (19.6)	8 (7.7)	2.927 (1.225–6.995)	0.013*
	No	82 (80.4)	96 (92.3)		
Secondary	*Blood loss after delivery (ml) [mean ± SD]*				
	1 h	196.42 ± 75.79	170.39 ± 72.05	2.526[b]	0.012*
	4 h	322.30 ± 112.1	264.51 ± 98.32	3.930[b]	< 0.001*
	24 h	386.50 ± 137.3	314.42 ± 114.5	4.090[b]	< 0.001*
	Pattern of PCV changes pre- and postpartum				
	Pre-PCV	34.67 ± 3.99	34.62 ± 3.19	0.102[b]	0.919
	Post-PCV	32.29 ± 3.57	32.86 ± 3.14	− 1.199[b]	0.232
	% change	6.74 ± 3.67	5.05 ± 3.35	3.458[b]	0.001*
	Need for additional uterotonics				
	Yes	20 (19.6)	11 (10.6)	2.062 (0.933–4.559)	0.070
	Vaginal bleeding ≥ 1000 ml				
	Yes	0 (0)	0 (0)		
	Need for blood transfusion				
	Yes	3 (2.9)	1 (1)	3.121 (0.319–30.51)	0.303
	Acceptance of route of administration				
	Satisfied	74 (72.5)	92 (88.5)	0.345 (0.164–0.724)	0.004*
	Unpleasant effects				
	Shivering	16 (15.7)	61 (58.7)	0.131 (0.068–0.254)	< 0.001*
	Headache	1 (1)	1 (1)	1.020 (0.063–16.53)	1.000[a]
	Diarrhoea	3 (2.9)	2 (1.9)	1.545 (0.253–9.448)	0.681[a]
	Fever	5 (4.9)	13 (12.5)	0.361 (0.124–1.052)	0.054
	Pyrexia	3 (2.9)	10 (9.6)	0.285 (0.076–1.067)	0.049*
	Death	0 (0)	0 (0)		

*Significant at $p < 0.05$

[a]Fisher's exact test

[b]Student's *t* test

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Authors' Contribution All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by BTA and JOA. The first draft of the manuscript was written by JOA, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data Availability The data can be obtained from the trials registry, or from the authors after due permission from the institution.

Compliance with Ethical Standards

Conflict of interest The authors declare that there are no conflicts of interests.

Ethical Statement The study was done in accordance with the 1964 Declaration of Helsinki. All recruited patients were adequately counselled and their written informed consent obtained. They were at liberty to decline participation without any negative impact on the quality of care they will receive in the hospital. The institution's Ethics and Research Committee gave approval for the study, which was designed and reported in line with the CONSORT Statement 2010.

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