

A double-blind randomized controlled clinical trial of oral misoprostol versus ergometrine in the prevention of primary postpartum hemorrhage

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ABSTRACT

Objective: The study was designed to investigate the effectiveness of orally administered misoprostol versus intravenous ergometrine (stored at tropical temperatures) in the prevention of primary postpartum hemorrhage (PPH) among parturients undergoing vaginal delivery in a teaching hospital.

Study Design: A double-blind randomized controlled clinical trial was conducted at the University of Benin Teaching Hospital. One hundred and fifty parturients were offered 400 µg misoprostol and an intravenous placebo for the management of the third stage of labor while another 150 parturients received oral placebo and 0.5 mg intravenous ergometrine.

Results: There was no significant difference in the incidence of PPH (blood loss > 500 ml) between the two groups: 8 (5.3%) for the misoprostol group compared with 7 (4.7%) for the ergometrine group ($P = 0.79$, relative risk (RR) = 1.07, confidence interval (CI): 0.66–1.74). The incidence of severe PPH (blood loss > 1000 ml) was similar between the two groups: 2 (1.3%) in the misoprostol group compared with 1 (0.7%) in the ergometrine group. Similarly, the indices of postpartum blood loss (hematocrit change, need for blood transfusion, and surgical intervention) were comparable between the two groups. A subgroup analysis of high-risk parturients revealed comparable indices. The misoprostol group, however, had a significantly higher risk of shivering in the early postpartum period ($P = 0.00$, RR = 2.01, CI: 1.69–2.38).

Conclusions: The results suggest that oral misoprostol has comparable efficacy to intravenous ergometrine at tropical conditions in the prevention of PPH. However, in view of its easier mode of administration, oral misoprostol may be preferable in rural situations in Africa.

Key words: Ergometrine; misoprostol; postpartum hemorrhage.

Introduction

Postpartum hemorrhage (PPH) is a major cause of maternal mortality and morbidity in developing countries, accounting for between 10 and 50 percent of maternal deaths.^[1-3] Primary PPH is estimated to account for approximately 28% of pregnancy-related deaths on a worldwide basis^[1] and hence projected to account for over 125,000 deaths annually in developing countries.^[2] In over 50% of cases, this is often due to uterine atony.^[4,5]

A hospital-based study in Nigeria reported PPH as the single most important cause of maternal mortality.^[6] Similarly, a study in the Gambia showed that PPH accounted for

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33% of maternal deaths and was the leading cause of death.^[7] Although there is good evidence that prophylaxis with oxytocic drugs in the third stage of labor is effective in preventing PPH resulting from uterine atony, its use in developing countries, especially in tropical environments, poses certain peculiar challenges.^[8]

The most daunting of this may perhaps be the finding that routinely administered uterotonic lose as much as a third of its potency when stored in a tropical environment for only one month.^[9] Arguably, this may be a contributing factor in maternal mortality resulting from PPH in many tropical countries. This has informed the need for the development of more stable uterotonic with a longer shelf life in tropical climatic conditions.^[10]

While the need for the development of a more stable uterotonic remains a priority at all levels of care in the tropics, the need for an orally active uterotonic is particularly important in peripheral units of care.^[8] These facilities are least served by blood banking facilities, personnel, manpower, and the most basic of facilities including syringes and needles. Thus, for the effective prevention of PPH, the use of an orally active uterotonic administered with the minimal requirement will undoubtedly prove indispensable.

One drug that has been shown to have the above properties is misoprostol,^[8,11,12] an orally active, inexpensive prostaglandin analog. Earlier observational studies have shown a reduction in the incidence of PPH following its use, or when compared with a placebo.^[11,12] These studies have been carried out predominantly in developed countries, where the risk and significance of postpartum blood loss may not be similar to that of developing countries. In any case, there is a need for further studies the principle of which is to determine the relative efficacy of orally administered misoprostol and currently administered uterotonic agents stored in tropical conditions. The findings from such a study will inform the use or non-use of oral misoprostol in the prevention of primary PPH especially in tropical conditions.

Objectives

1. To investigate the efficacy of orally administered misoprostol versus parenteral ergometrine in the prevention of primary PPH
2. To investigate the need for additional oxytocic treatment or blood transfusion in both treatment arms
3. To determine whether any particular subgroup of parturient at risk of PPH (using previously identified risk criteria for PPH) would benefit more or less than others in the respective treatment groups

4. To make recommendations on effective methods for preventing PPH in the tropics.

Materials and Methods

Sample size

The primary null hypothesis is that there is no difference between the use of ergometrine and misoprostol in the prevention of primary PPH. The sample size of 286 in both treatment arms was calculated to give an 80% chance of detecting a reduction in blood loss >500 ml of 15% to 4.5%. These ranges of values were determined from previous studies on actively managed labor reporting an incidence in the range of 2.5% to 14.8%.^[13-17] Ethical Approval was obtained from the University of Benin Teaching Hospital Ethics Committee dated 4th January 1999.

Recruitment of cases

The study was a hospital-based double-blind randomized controlled clinical trial, at the University of Benin Teaching Hospital, Benin City, Nigeria. All women undergoing vaginal delivery beyond 28 weeks of pregnancy were enrolled in the study. Women were not eligible for enrollment if they had significantly elevated blood pressure at the antenatal clinic or in the course of labor (diastolic blood pressure > 100 mmHg) or if cesarean section was already planned, or if they were not willing or able to give informed consent.

Women were approached on admission to the labor ward for consent and to determine if they were eligible for participation in the trial. The women in labor were randomized into two groups using computer-generated random numbers. Eligible women were requested to randomly select from a pool of random numbers. Each number was matched with similarly numbered sealed treatment packs containing prepackaged mixtures. Each treatment pack contained four powdered tablets and a syringe and needle containing 2 ml of sterile solution. The packs were identical in shape, color, and weight. Each woman was administered the intravenous injection at the delivery of the anterior shoulder (or after delivery if breech and multiple pregnancies) and four powdered tablets orally with 50 ml of water after delivery. Thus, the trial was double-blinded using double placebos. The content of each syringe was to be discarded and reconstituted if it was not used within 48 hours, to maintain sterility of the parenteral injections. No pack lasted beyond this time frame.

Management of labor

During the second stage of labor, when there was reasonable certainty that vaginal delivery would occur, the packs were opened at the patient's bedside and all preparations

completed to administer the oral tablets and parenteral injection. If for any reason the contents of the pack were returned, the content was to be discarded and the oral drugs re-circulated in the pool. This task was assigned to a different individual from the principal investigator. No pack was however returned during the study period. The identity of the packs was revealed only on completion of the project.

Each woman enrolled in the study, received misoprostol 400 ug or ergometrine 0.5 mg. The misoprostol group received four powdered tablets each of 100 ug misoprostol and a placebo injection while the ergometrine group received 2 ml of 0.5 mg ergometrine intravenously and oral placebo. The third stage of labor was managed actively as currently practiced in the department. The active management consists of the use of a uterotonic agent, clamping, and cutting of the umbilical cord immediately after delivery of the infant and suprapubic pressure with controlled cord traction on palpation of uterine contraction without awaiting signs of placenta separation.

The attending midwife estimated blood loss. Blood was collected in a bedpan at delivery and continued for at least 2 hours after delivery in the labor ward. This was the minimum time a patient is observed in the labor ward after delivery before transfer to the ward if there are no complications. The estimated blood loss was the sum of the measured blood loss and visual estimation of the soaked pads and beddings. Perineal trauma (episiotomy, first or second-degree tear) was sutured promptly if present. The women were carefully observed for features of excessive blood loss, if signs were present, an active intervention was commenced with intravenous ergometrine 0.5 mg and if bleeding persisted 20IU oxytocin infused in 500 ml of 0.9% saline infusion. Further therapeutic measures were taken as deemed appropriate. A detailed recording of all events especially in the third stage of labor as well as possible adverse effects were also done. The attending physician completed the data sheets.

Data analysis

The completed data sheets were collected by the principal investigator but only collated and analyzed at the completion of the study. Though provision for an interim analysis was made in the design of the project, this was not required. All data were entered into a database (Epi-Info 6: Centre for Disease Control and Prevention, Atlanta) before breaking the randomization code for analysis. The results are reported on an intention to treat basis. Comparisons were by the Chi-square test or Fisher's exact test with calculated relative risk (RR) and 95% confidence intervals (CIs) for

non-continuous variables and by the Mann–Whitney test for continuous variables.

The Ethical Research Committee of the University of Benin Teaching Hospital, Benin City, Nigeria approved the study.

Results

The trial involved 300 women: 150 received 400 mg of misoprostol orally and a parenteral placebo while the other 150 received parenteral ergometrine 0.5 mg and oral placebo. Table 1 shows the baseline characteristics and obstetrics history of parturients included in the trial. Both groups were comparable at entry into the trial. Table 2 provides data on intrapartum and immediate postpartum clinical sequelae in both trial groups. The two groups were comparable based on type of labor, duration of labor, intrapartum use of oxytocin, type of delivery, and genital injuries.

Table 1: Baseline Characteristics

	Misoprostol (n=150)	Ergometrine (n=150)	P
Age	30.1 (5.1)	30.0 (4.8)	0.84
Height (cm)	163.4 (7.2)	164.4 (7.2)	0.29
Weight (kg)	70.8 (11.9)	71.9 (11.9)	0.42
BMI	26.4 (4.1)	26.7 (4.0)	0.52
SBP (mmHg)	126.2 (12.5)	123.7 (14.1)	0.10
DBP (mmHg)	78.1 (8.9)	77.7 (8.8)	0.69
Gestational age	38.7 (1.9)	37.6 (6.0)	0.24
Nullipara	42 (28.0)	41 (27.3)	0.90
Para 1-3	84 (56.0)	90 (60)	0.48
Para ≥4	24 (16.0)	19 (12.7)	0.41
Hematocrit	32.8 (3.3)	32.8 (3.3)	0.95

BMI: Body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2: Events in Labor

	Misoprostol (n=150)	Ergometrine (n=150)	P
Type of Labor			
Spontaneous	97 (64.7)	104 (69.3)	0.39
Augmented	26 (17.3)	26 (17.3)	1.00
Induced	27 (18.0)	20 (13.3)	0.26
Duration of first stage (min)	357.0 (270.3)	305.0 (237.9)	0.07
Mean dose of oxytocin (miu)	10.4 (19.0)	6.4 (13.4)	0.21
Duration of oxytocin use (min)	125.1 (224.9)	84.4 (169.1)	0.25
Duration of second stage (min)	10.1 (15.7)	12.5 (24.8)	0.50
Type of delivery			
SVD	145 (96.7)	139 (92.7)	0.12
Ass Breech	2 (1.3)	6 (4.0)	0.14
Ventouse	1 (0.7)	4 (2.7)	0.18
Forceps	2 (1.3)	1 (0.7)	0.56
Birth weight	3.1 (0.3)	3.0 (0.3)	0.38
Episiotomy	61 (40.7)	52 (34.6)	0.28
Perineal tear	27 (18.0)	37 (24.6)	0.16
Cervical tear	3 (2.0)	2 (1.3)	0.65

SVD: Spontaneous vaginal delivery

Table 3: Third Stage and Its Management

	Misoprostol (n=150)	Ergometrine (n=150)	RR (95% CI)	P
Manual placenta removal	6 (4.0)	4 (2.7)	1.21 (0.72:2.03)	0.52
Duration of third stage (mins)	3.9 (10.3)	4.4 (12.4)	-	0.13
Blood loss >500 mls	8 (5.3)	7 (4.7)	1.07 (0.66:1.74)	0.79
Blood loss >1000 mls	2 (1.3)	1 (0.7)	1.34 (0.60:3.00)	0.56
Blood transfusion	-	-	-	-
Ergometrine for PPH	26 (17.3)	21 (14.0)	1.13 (0.85:1.50)	0.43
Oxytocin for PPH	32 (21.3)	24 (16.0)	1.18 (0.91:1.53)	0.24
ERPC for products	5 (3.3)	4 (2.7)	1.11 (0.61:2.02)	0.74
Abdominal surgical intervention	-	-	-	-
High risk group	n=83	n=74	RR (95%CI)	P
Manual placenta removal	4 (4.8)	2 (2.7)	1.27 (0.71:2.29)	0.49
Duration of third stage (mins)	2.5 (2.4)	3.0 (1.9)	-	0.14
Blood loss >500 mls	5 (6.0)	4 (5.4)	1.11 (0.61:2.02)	0.74
Blood loss >1000 mls	-	-	-	-
Ergometrine for PPH	16 (19.3)	13 (17.6)	1.12 (0.79:1.58)	0.56
Oxytocin for PPH	21 (25.3)	20 (27.0)	1.03 (0.74:1.42)	0.87
ERPC for products	-	-	-	-

ERPC: Evacuation of Retained Products of Conception; PPH: Postpartum hemorrhage

Table 3 describes the effect of the trial treatments on the third stage of labor. The incidence of PPH (blood loss >500 ml) was 8 (5.3%) in the misoprostol arm compared with 7 (4.7%) in the ergometrine treatment arm. This difference was not statistically significant ($P = 0.79$, $RR = 1.07$, $CI: 0.66-1.74$). The incidence of severe PPH (blood loss >1000 ml) was 2 (1.3%) in the misoprostol group and 1 (0.7%) in the ergometrine group. Similarly, the proportions of women requiring manual removal of the placenta or an additional uterotonic agent were similar in both groups. The table also provides a subgroup analysis of women with one or more identified risk factors for PPH based on previous studies. At-risk women based on these criteria included primiparity, grand multiparity, uterine fibroid, multiple pregnancies, induction/oxytocin use in labor and women with a history of previous PPH. In this subgroup analysis, the incidence of PPH (blood loss >500 ml) was 3.3% in the misoprostol group and 2.7% in the ergometrine group. The difference was not statistically significant. There was no case of severe PPH (blood loss >1000 ml) and the need for ergometrine or further oxytocin was comparable in the two groups.

Table 4 shows the changes in hematocrit levels between postpartum (2 days after delivery) and prepartum values. A subgroup analysis of high-risk women is also presented. A drop in hematocrit of more than 0.10 was 1.4% in the misoprostol group and 0.7% in the ergometrine group. Though there appeared to be a trend towards lower hematocrit levels in the misoprostol group the difference was not statistically significant.

Postpartum side effects experienced by the two groups are presented in Table 5. The side effects were those reported by parturient before discharge or on clinical observation. Women in the misoprostol group reported a significantly higher incidence of shivering. In general, a comparatively lower incidence of postpartum complications was reported in the ergometrine group.

Discussion

The results of this study suggest that oral misoprostol is of similar efficacy in minimizing blood loss in women in the third stage of labor as compared with parenteral ergometrine. The findings of this study are comparable with reported studies of misoprostol and standard uterotonic agents in third stage management.^[18-20]

To complement the clinical observation of PPH, which is often underestimated, change in hematocrit was used to evaluate the two groups. A change in laboratory criteria as hematocrit or hemoglobin concentration is a more objective, and the American College of Obstetricians and Gynecologists suggest that the definition of PPH may be based on the change in laboratory findings in the postpartum period.^[21] Using this outcome measure, however, both treatment modalities were again of similar efficacy.

A major finding from this study was the observation that parturients at high risk for PPH did not suffer higher adverse morbidity following the use of oral misoprostol and parenteral ergometrine. The incidences of PPH and hematocrit change were similar between the two groups

Table 4: Change in Hematocrit*

	Misoprostol (n=140)	Ergometrine (n=142)	RR (95%CI)	P
>0.01	24 (17.1)	37 (26.1)	0.75 (0.54:1.05)	0.07
0	47 (33.6)	51 (35.9)	0.95 (0.74:1.22)	0.68
≥-0.03	44 (31.4)	34 (23.9)	1.20 (0.94:1.53)	0.16
≥-0.05	16 (11.4)	9 (6.3)	1.33 (0.96:1.83)	0.13
≥-0.10	7 (5.0)	10 (7.0)	0.82 (0.46:1.47)	0.47
<-0.10	2 (1.4)	1 (0.7)	1.35 (0.60:3.03)	0.55
High-risk group	n=80	n=67	RR (95%CI)	P
>0.01	11 (13.8)	11 (16.4)	0.91 (0.58:1.42)	0.65
0	29 (48.8)	34 (50.7)	0.77 (0.56:1.06)	0.10
≥-0.03	20 (25.0)	15 (22.4)	1.07 (0.76:1.49)	0.71
≥-0.05	6 (7.5)	1 (1.5)	1.62 (1.15:2.28)	0.09
≥-0.10	4 (5.0)	5 (7.5)	0.81 (0.38:1.70)	0.54
<-0.10	0 (0.0)	1 (1.5)	-	0.27

*Difference between postpartum and prepartum hematocrit values

Table 5: Postpartum Complications

	Misoprostol (n=150)	Ergometrine (n=150)	RR (95% CI)	P
Nausea	5 (3.3)	2 (1.3)	1.26 (0.73:2.18)	0.47
Vomiting	2 (1.3)	5 (3.3)	0.57 (0.17:1.83)	0.25
Diarrhea	2 (1.3)	0 (0.0)	2.01 (1.80:2.26)	0.16
Shivering	24 (16.0)	2 (1.3)	2.01 (1.69:2.38)	0.00
Headaches	4 (2.6)	2 (1.3)	1.34 (0.75:2.39)	0.41
Vertigo	3 (2.0)	0 (0.0)	2.02 (1.80:2.27)	0.08
Temp >38C	4 (2.6)	2 (1.3)	1.34 (0.75:2.39)	0.41
Secondary PPH	0 (0.0)	0 (0.0)		

PPH: Postpartum hemorrhage

and appeared comparable to the general population on an overview. Previous studies comparing oral misoprostol and standard treatment modalities have often excluded this group of parturients from randomization. The populations studied were often those perceived to be at low risk. Thus, a comparable outcome in this subgroup is an important evidence for the efficacy and use of oral misoprostol in third stage management. It may also serve as a guide for future study design on the subject.

Shivering was significantly higher in the misoprostol group. This finding has been reported by earlier studies. However, such reports have largely been restricted to studies using high dose misoprostol for third stage management.^[18,20] It is postulated that this may be the effect of prostaglandinE1 on central thermoregulatory centers.^[22] Some other studies have also reported pyrexia as a significant complication, though this was not borne from this study.

This study has two major limitations. In the first instance, the sample size used in the survey did not evaluate the equivalence between the two groups. To achieve this, a much larger sample size will be required. This could be achieved

either in the form of a meta-analysis of previous studies or a multicenter collaborative study. The use of clinically estimated blood loss and its shortcomings has been noted earlier. However, the possible effect of this has been greatly minimized by the concomitant use of the hematocrit change and this like the clinical estimation of blood loss, has not shown significant differences in the two groups.

The lack of an orally active stable uterotonic agent is a major impediment to the prevention of PPH in developing countries. The results of this trial suggest that oral misoprostol is as effective as ergometrine in the prevention of atonic uterus. It may, however, have more non-live threatening effects in particular shivering.

In conclusion, based on this study, oral misoprostol may be recommended for the prevention of PPH, the outcome being of similar efficacy to standard management. The same may also be applicable to high-risk parturients for PPH in labor. The side effects appeared minimal and are far outweighed by the potential benefits from its use. There is, however, a need for larger studies or a meta-analysis to demonstrate equivalence between the two groups.

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Conflicts of interest

There are no conflicts of interest.

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