ORIGINAL ARTICLE

Randomization of two dosing regimens of vaginal misoprostol for cervical ripening and labor induction in a low resource setting

AA Adeniyi, AA Odukogbe[1], A Olayemi[1], O Oladokun[1], AO Adeniji[2], CO Aimakhu[1], C Enakpene[3]

Department of Obstetrics and Gynaecology, Federal Medical Centre, Ido Ekiti, Nigeria, [1]Department of Obstetrics and Gynaecology, University College Hospital, Ibadan, [2]Department of Obstetrics and Gynaecology, Ladoke Akintola University Teaching Hospital, Ogbomoso, Nigeria, [3]Department of Obstetrics and Gynaecology, State University of New York, Downstate Medical Centre, USA

Abstract

Objectives: To compare the effectiveness of two dosing regimens of vaginal misoprostol for cervical ripening and induction of labour.

Materials and Methods: Pregnant women with singleton low risk pregnancy at term scheduled for elective induction of labour were randomized to receive either 25 μg or 50 μg of vaginal misoprostol for pre-labour cervical ripening. All the patients received antenatal care and delivered at the University College Hospital (UCH) from January 1st to May 31st 2006. A total of 128 patients were randomized; 65 patients received 25 μg and 63 patients received 50 μg of vaginal misoprostol.

Results: Significantly higher number of patients in the 50 μg group progressed to active labour as compared with the 25 μg group (95.2% versus 84.6%, $P < 0.05$). The need for oxytocin augmentation of labour was higher among the 25 μg as compared with 50 μg (39.7% versus 16.4%, $P = 0.007$). There was higher proportion of patients in the 50 μg group delivering vaginally within 24 hours as compared with the 25 μg group (98.2% versus 90.0%, $P = 0.063$). However, the mean interval between the first dose of misoprostol and vaginal delivery was not statistically different in the two groups (754 ± 362 minutes and 885 ± 582 minutes, $P = 0.152$). The incidence of caesarean section was similar in the two groups (7.7% versus 11%, $P = 0.580$). Labour complications, such as precipitate labour, tachysystole and abnormal fetal heart rate patterns were greater in the 50 μg group.

Conclusion: Twenty-five microgram of misoprostol appears to be as effective as 50 μg for pre-induction cervical ripening and labour induction. Though 50 μg of vaginal misoprostol resulted in relatively faster delivery and less need for oxytocin augmentation, it was associated with more labour complications as compared with 25 μg of misoprostol.

Key words: Cervical ripening, labour induction, misoprostol

Date of Acceptance: 06-Sep-2013

Introduction

A major factor that influences successful induction of labour is the cervical status. If the cervix is unripe, closed, firm and uneffaced, with Bishop score less than 6, the conventional method of induction of labour by surgical amniotomy becomes technically difficult and intravenous infusion of oxytocin results in prolonged labour with risks of maternal and fetal complications, unsuccessful inductions and unnecessary increased rate of caesarean section.[1,2]

Address for correspondence:
Dr. Adeniyi,
Department of Obstetrics and Gynaecology Federal Medical Centre
P.M. B 201, Ido - Ekiti, Nigeria.
E-mail: olivesclinics@gmail.com

Access this article online	
Quick Response Code:	**Website**: www.njcponline.com
	DOI: ***
	PMID: *******

While many methods have been described for cervical ripening,[3,4] recent efforts have been focused on the pharmacological agents mainly oxytocin and prostaglandins. Although oxytocin is a safe and effective initiator of uterine contractions, its success depends on prelabour cervical status.[5]

Misoprostol is a synthetic 15-deoxy 16-hydroxy, 16-methyl analogue of the naturally occurring prostaglandin E_1 that was originally manufactured for prevention and treatment of peptic ulcers diseases.[6] Several studies have found that misoprostol is effective as an agent for cervical ripening and induction of labour. It is inexpensive, easy to store, and stable at room temperature.[7] Despite many widely reported trials on misoprostol, several practical aspects of its administration are still yet to be well established and these include; the appropriate dosage, the dosing interval, and route of administration, with doses ranging from 25 μg to 100 μg.[8,9] This study was designed to contribute to the ongoing research efforts on the appropriate use of misoprostol in obstetrics. It focused on comparison of two dosing regimens (25 μg versus 50 μg) of misoprostol for pre-labour cervical ripening and induction of labour.

Materials and Methods

The study was a randomized trial on low risk singleton pregnant women, at term scheduled for elective induction of labor who received antenatal care and delivered at the University College Hospital (UCH), Ibadan during the study period. The study protocol was approved by the College of Medicine University of Ibadan and University College Hospital IRB. Adequate information was provided to the patients and they were properly counseled about the risks and benefits of misoprostol. Informed consent was obtained from each participant before inclusion in the study. Inclusion criteria were: (1) Singleton pregnancy at ≥37 weeks gestational age, (2) Bishop's score of ≤5, (3) Cephalic presentation, (4) Reassuring fetal heart rate pattern, (6) Intact fetal membranes. The exclusion criteria were: (1) Mal-presentation; (2) Multiple gestation, (3) Placenta praevia, (4) Estimated fetal weight of > 4000 g, (5) Non-reassuring fetal heart rate, (6) Evidence of cephalo-pelvic disproportion, (7) Any contraindication to receiving prostaglandins e.g. glaucoma and (8) Previous uterine surgery. All pregnancies were well-dated with last menstrual periods and/or first trimester sonogram done to ascertain the appropriate gestational age.

They were then randomized using a computer generated random numbers into either the 25 μg group or the 50 μg group. The patients were assigned by means of table of random number with blocks of four to receive intra-vaginal misoprostol of 25 μg or 50 μg (as prepared by the pharmacy unit of the University College Hospital, Ibadan). Group allocation was predetermined and placed in consecutively numbered and sealed opaque envelopes. Once a patient was deemed eligible and had signed the informed consent to participate in the study, she was assigned a sequential study number. The primary investigator, who was responsible for maintaining the envelopes, was contacted to open the corresponding numbered envelope for the purpose of treatment allocation.

The minimum sample size for each study arm was calculated to be 40 participants. However, a deliberate over sampling of 25% gave a total sample of 50 in each group. This corresponded to a statistical power of 80%, $P = 0.05$ at 95% confidence level. One hundred and twenty-eight (128) participants were enrolled in the study. None of the enrolled patients in the study withdrew. Sixty-five (65) received 25 μg and sixty-three (63) received 50 μg of intra-vaginal misoprostol.

The initial and subsequently Bishop Scores were assessed by the principal investigator. All those who fulfilled the study criteria received either 50 μg or 25 μg of intra-vaginal misoprostol in the posterior fornix every 6 hours for a total of 4 doses for cervical ripening or until satisfactory Bishop scores were established, with the maximum exposure time of 24 hours. The participants were managed in labour by the routine Obstetricians covering the labour and delivery unit and used the standard protocol of care for any intervention in labour.

Management of labour

Oxytocin infusion and active management of labour were commenced in those patients with satisfactory Bishop Score (≥6) who did not enter active labour (defined as the occurrence of at least 3 strong uterine contractions in 10 minutes each lasting 40-60 seconds) after maximum exposure to either dose regimen, or had a spontaneous rupture of membranes without an ensuing adequate uterine contractions. Oxytocin infusion was not started until at least 4 hours after the last dose of misoprostol. By use of a standardized protocol, oxytocin titration was commenced at 4 miu/min and increased at intervals of 30 minutes to achieve adequate uterine contraction pattern of at least 3 contractions in 10 minutes, each lasting for 40-60 seconds.

At active phase of labour, routine intra-partum labour managements were without regard to the dosing regimens. The fetal heart rates were monitored by intermittent auscultation or with hand held Doppler periodically. Primary outcomes were pre-induction Bishop score, duration to achieve cervical ripening or onset of active labour, interval from first insertion of misoprostol to vaginal delivery, need for oxytocin augmentation, route of delivery, and Apgar scores. Secondary outcome measures were occurrence of uterine hypertonia, tachysystole, abnormal fetal heart rate, uterine rupture, and any other direct complications.

Data analysis

Data collected were entered into a computer with a standard proforma of Statistical Package for Social Sciences (SPSS version 11.0). Statistical analysis was performed with Chi-square for categorical variables, student's *t*-test for normally distributed continuous variables, Mann-Whitney U for continuous variables that were not normally distributed. Fisher's exact test with Yates correlation was performed whenever appropriate. All tests were two-tailed (or sided) with a $P = 0.05$ considered as statistically significance.

Results

A total of 128 patients were enrolled in the study; 65 patients received 25 μg and 63 patients received 50 μg of misoprostol. The maternal demographic characteristics were similar in both study groups. Post-date pregnancy was the most common indication in both groups, accounting for 71% and 76.2% for 25 μg and 50 μg groups respectively. The pre-induction cervical assessments by the Bishop score in both groups were comparable [Table 1].

There was significantly higher proportion of patients in the 50 μg group who progressed to active labour as compared with the 25 μg group (95.2% versus 84.6%, $P = 0.049$). The mean interval between the first dose of misoprostol and vaginal delivery is shorter in the 50 μg group (754 ± 362 minutes) than in the 25 μg group (885 ± 582 minutes), but it was not statistically significant ($P = 0.152$). There is no significant difference between the number of doses required to achieve favorable cervicalscore of >6 or active labour between the two groups 1.8 ± 1.1 for 25 μg group and 1.7 ± 0.7 for 50 μg group ($P = 0.689$).

No patients in the either arm of the study group received the maximum dose of misoprostol to achieve a favorable Bishop score or active labour. The need for oxytocin augmentation among those who progressed to labour was higher in the 25 μg group (40.0%) than the 50 μg group (15.9% $P = 0.007$) [Table 2].

The incidence of caesarean section was similar in the two groups 7.7% and 11.0% for 25 μg group and 50 μg group respectively. More patients had caesarean section for poor progress of labour in the 25 μg group than in the 50 μg group while more patients had caesarean section on account of abnormal fetal heart rate in the 50 μg group. However, neither of these differences assumed statistical significance level [Table 2]. The overall rate of successful vaginal delivery and the rate of caesarean delivery were similar between the two groups [Table 2].

Adverse labour outcomes were mainly tachysystole (defined as the occurrence of more than five contractions in ten minutes for two consecutive ten minutes period), precipitate labour (delivery less than three hours after onset of labour), fetal distress and meconium stained liquor. All these were significantly higher in the 50 μg group ($P = 0.038$) [Table 3].

The birth weights of the neonates were similar in the two groups 3143 ± 475gm in 25 μg group and 3237 ± 486 in 50 μg group ($P = 0.291$). The Apgar score of the neonates at one minute and five minutes were not statistically different. The overall fetal outcomes were not statistically different in the two groups.

Table 1: Cervical assessment by bishops score

Bishop score	25 μg (*n*=65)	50 μg (*n*=63)	Significance***
Pre-ripening/ induction score			
1	3 (4.6%)	2 (3.2%)	*P*=0.581
2	6 (9.2%)	5 (7.9%)	*P*=0.347
3	22 (33.9%)	22 (34.9%)	*P*=0.892
4	23 (35.4%)	24 (38.2%)	*P*=0.673
5	10 (15.4%)	10 (16.4%)	*P*=0.671
Mean group bishop score	3.8±1.1	3.4±1.0	*P*=0.871

Data presented as *n* (%) or Mean+SD, ***Mann-Whitney U-test

Table 2: Labour outcome

	25 μg (*n*=65)	50 μg (*n*=63)	Significance
Onset of labor during ripening	55 (84.6%)	60 (95.2%)	*P*=0.049*
Need for oxytocin augmentation	26 (40%)	10 (15.9%)	*P*=0.007*
Mode of delivery			
Vaginal delivery	60 (92.3%)	56 (88.9%)	*P*=0.580*
Caesarean section	5 (7.7%)	7 (11.1%)	*P*=0.382*
Indications for caesarean section			
Failure to progress	3 (4.6%)	2 (3.2%)	*P*=0.682**
Fetal heart rate abnormality	2 (3%)	5 (7.9%)	*P*=0.081**
Mean interval between first insertion and delivery			
<12 hrs	36 (60%)	34 (60.7%)	*P*=0.871***
12-24 hrs	18 (30%)	21 (33.3%)	*P*=0.781***
>24 hrs	6 (10%)	1 (1.8%)	*P*=0.063***
Mean induction-delivery interval			
Mean (minutes)	885±582	754±362	*P*=0.152***
Mean (hours)	14.7±9.7	12.6±6.1	
No of doses (mean)	1.8±1.1	1.7±0.7	*P*=0.689***

*Chi square-test, **Fisher's exact test, ***Student's *t* test

Table 3: Adverse labour outcome

Adverse effect	25 μg (*n*=65)	50 μg (*n*=63)	Significance***
None	55 (84.6%)	40 (63.5%)	*P*=0.578*
Tachysystole	0 (0.0%)	2 (3.2%)	*P*=0.036**
Precipitate labour	3 (4.6%)	5 (7.9%)	*P*=0.041**
Fetal heart rate abnormality	4 (6.2%)	10 (15.9%)	*P*=0.038**
Meconium staining of liquor	0 (0.0%)	6 (9.5%)	*P*=0.035**
Vomiting	2 (3.1%)	0 (0.0%)	*P*=0.007**

*X^2, **Fisher's exact test

Discussion

The result of this study further supports the efficacy of misoprostol as a cervical ripening and labour- inducing agents with 85% and 95% for 25 μg and 50 μg respectively achieving vaginal deliveries. This result is comparable to the report of El-Sharbiny *et al.*,[5] in which 82% and 86% respectively were reported.

The findings of this study shows that labour outcomes such as the need for oxytocin augmentation and duration to achieve active labour agreed with other studies[10-13] in which 50 μg dose demonstrated significant advantage. However, this study could not demonstrate a statistically significant difference in the induction-to-delivery interval between the two groups, although the interval was shorter with 50 μg dose group. A similar finding was reported by Meydanli *et al.*,[6] in which they reported (685 ± 201 min versus 627 ± 177 min; $P = 0.09$) respectively.

A major factor in Meydanli's study was the restriction of indication to post-term pregnancies, to the exclusion of other common indications for induction of labour.[6] Though our study was not limited to post-term pregnancies, the final analysis showed that this was the most common indication, with 73% in our study. This proportion is high when compared to the studies of How *et al.*,[14] and EL-Sharbiny *et al.*,[5] in which post-term pregnancies constituted 20% and 27%, respectively. Both these studies[5,14] reported significantly shorter induction-to-delivery interval for women who received 50 μg of misoprostol.

If the above factor is considered, indeed heterogeneity in the indications for induction of labour in our study might be a factor in the differences observed in the studies of How *et al.*,[14] and EL-Sharbiny *et al.*,[5] Farah *et al.*,[15] also reported no significantly shorter induction-to-delivery interval between 25 μg and 50 μg groups, though with 3 hours dosing interval. The reported values of 895 ± 572 min versus 787 ± 538 min for 25 μg and 50 μg respectively, are similar to our own values.

The finding of similar caesarean section rate (8% versus 11%) between the two groups were comparable to those reported by Sanchez-Ramos *et al.*,[16] (19.1 versus 18.9%), El-Sharbiny[5] (17.2% versus 14.2%) and Saxena *et al.*, (30% versus 30%).[17] The incidence of tachysystole was higher with 50 μg in this study (0.0 versus 3.2%). This complication has been a contentious issue in the safety profile of misoprostol as a cervical-ripening agent[18,19] The incidence rate of 3.2% in this study is lower than 20.8% reported by Sanchez-Ramos *et al.*,[12] and 25% by Has *et al.*,[13] The lower incidence may be due to strict protocol criteria of 6 hours dosing interval and not commencing oxytocin augmentation earlier than 4 hours after the last dose of misoprostol when necessary.[2,20]

The higher rate of fetal heart rate abnormalities (reported as fetal distress) in this study (16% for 50 μg) compared to 4.5% reported by Liu *et al.*,[21] may be partly due to the method of diagnosis of these abnormalities as this study relied solely on Pinnard stethoscope for fetal monitoring as obtained in many low resource settings.[22] This might have increased the possibility of over diagnosis of fetal heart rate abnormalities. This latter point is supported by the fact that there was no significant difference in the Apgar scores in the two groups and none of the babies had Apgar score of less than 7 at 5 minutes.

The proportion of patients with vomiting in this study was unexpectedly higher in the 25 μg group. While vomiting is a known side-effect of misoprostol, it is usually dose related and occurs in higher doses commonly used in medical abortions.[23] The finding in this study probably represent the response of the patients to other medications used in the management of labour mainly ergometrine, especially as both incidents of vomiting occurred in the third stage of labour. It may also represent the wide range of response to misoprostol in different women.[23]

The overall neonatal outcomes: Apgar score, need for resuscitation, admission to special care baby unit and indication for such admissions were similar in the two groups, and comparable to previous studies.[12,13,17,18]

Major limitations of this study include the non-availability of 25 μg and 50 μg tablets in the country at the time the study was conducted. The error that the method of obtaining these doses from the available 100 μg might have introduced to the study could not be quantified. Also the sample size of the study is small such that it has no statistical power to evaluate the safety of misoprostol.

We conclude that 25 μg of intra-vaginal misoprostol is as effective as 50 μg in pre-induction cervical ripening and appears safer; although, there is less need for oxytocin and that more patients achieved delivery within 24 hours with 50 μg dosage. The higher rate of uterine contractile abnormalities with 50 μg dose is of particular concern.[24] More studies are needed to further confirm the result of the study and particularly in relation to the safety profile of misoprostol for cervical ripening and induction of labour especially in low resource settings.

References

1. Bishop EH. Pelvic scoring for elective induction. Obstet Gynaecol 1964;24:266-8.
2. Adeniji OA, Oladokun A, Olayemi O, Adeniji OI, Odukogbe AA, Ogunbode O, *et al.* Pre-induction cervical ripening: Transcervical foley catheter versus. Intravaginal misoprostol. J Obstet Gynaecol 2005;25:134-9.
3. Harman JH Jr, Kim A. Current trends in cervical ripening and labour induction. Am Fam Physician 1999;60:477-84.
4. McFarland BL, Gibson MH, O'Rear J, Harman P. A national survey of

herbal preparation use by nurse-midwives for labor stimulation. Review of the literature and recommendations for practice. J Nurse Midwifery 1999;44:205-16.
5. El-Sherbiny MT, El-Gharieb IH, Gwewly HA. Vaginal misoprostol for induction of labour. 25 vs. 50 microg dose regimen Int J Gynaecol Obstet 2001;72:25-30.
6. Meydanli MM, Caliskan E, Burak F, Narin MA, Atmaca R. Labour induction post-term with 25 micrograms vs. 50 micrograms of intravaginal misoprostol. Int J Gynaecol Obstet 2003;81:249-55.
7. Wing DA, Rahall A, Jone MM, Goodwin TM, Paul RH. Misoprostol: An effective agent for cervical ripening. Am J Obstet Gynaecol 1995;172:1811-6.
8. Diro M, Adra A, Gilles JM, Nassar A, Rodriguez A, Salamat SM, *et al*. A double-blind randomized trial of two dose regimens of misoprostol for cervical ripening and labour induction. J Matern Fetal Med 1999;8:114-8.
9. Wang Z, Li W, Ouyan W. Safety and efficacy of intravaginal misoprostol for cervical ripening in the third trimester of pregnancy. Chinese Journal of Obstet. Gynaecol 1997;32:326-8.
10. Hassam AA. A comparison of oral misoprostol tablets and vaginal prostaglandin E2 pessary for induction of labour at team. J Coll Physicians Surg Pak 2005;15:284-7.
11. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol with vaginally administered misoprostol for cervical ripening and labour induction. Am J Obstet Gynaecol 1999;180:1155-60.
12. Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labour induction: A meta-analysis. Obstet Gynaecol 1997;89:633-42.
13. Has R, Batukan C, Ermis H, Cevher E, Araman A, Kiliç G, *et al*. Comparison of 25 and 50 microgram of vaginally administered misoprostol for pre-induction cervical ripening and labor induction. Gynecol Obstet Invest 2002;53:16-21.
14. How HY, Leaseburge L, Khoury JC, Siddiqi TA, Spinnato JA, Sibai BM. A comparison of various routes and dosages of misoprostol for cervical ripening and induction of labour. Am J Obstet Gynaecol 2001;185:911-5.
15. Farah LA, Sanchez-Ramos L, Rosa C, Del Valle GO, Gaudier FL, Delke I, *et al*. Randomized trial of two doses of the prostaglandin E1 analog misoprostol for labour induction. Am J Obstet Gynaecol 1997;177:364-9.
16. Sanchez-Ramos L, Kaunitz AM, Delke I. Labour induction with 25 mg versus 50 mg intravaginal Misoprostol: A systemic Review. Obstet Gynaecol 2002;99:145-51.
17. Saxena P, Puri M, Bajaj M, Mishra A, Trivedi SS. A randomized clinical trial to compare the efficacy of different doses of intravaginal misoprostol with intracervical dinoprostone for cervical ripening and labor induction. Eur Rev Med Pharmacol Sci 2011;15:759-63.
18. Kolderup L, McLean L, Grullon K, Safford K, Kilpatrick SJ. Misoprostol is more efficacious for labour induction than prostaglandin E2, but is it associated with more risk? Am J Obstet Gynaecol 1999;180:1543-50.
19. Hall R, Duarte-Gardea M, Harlass F. Oral versus vaginal misoprostol for labour induction. Obstet Gynaecol 2002;99:1044-8.
20. ACOG citizen petition to FDA. Washington DC; 2000.
21. Liu HS, Chu TY, Chang YK, Yu MH, Chen WH. Intra-cervical misoprostol as an effective method of labour induction at term. Int J Gynaecol Obstet 1999;64:49-53.
22. Kwawukume EY, Ayertey RP. The use of misoprostol for induction of labour in a low-resource setting. Trop J Obstet Gynaecol 2002;19:78-81.
23. Allen R, O'Brien BM. Uses of misoprostol in obstetrics and gynecology. Rev Obstet Gynecol 2009;2:159-68.
24. Hofmeyr GJ, Gulmezoglu AM, Pileggi C. Vaginal misoprostol is effective in inducing labour. Cochrane Database Syst Rev 2010;1:30.

How to cite this article: ???

Source of Support: Nil, **Conflict of Interest:** None declared.