AFRICAN JOURNAL OF MEDICINE and medical sciences

VOLUME 33, NUMBER 2 JUNE 2004

ISSN 1116—4077

Afr. J. Med. med. Sci. (2004) 33, 105-108

Experience with intravaginal misoprostol in the management of intra-uterine fetal death

AO Fawole, AO Adekunle⁺ OS Sotiloye, AO Arowojolu⁺ and EO Otolorin*

*Departments of Obstetrics and Gynaecology, Federal Medical Centre, Abeokuta, ⁺University College Hospital, Ibadan and *JHPIEGO Corporation, Johns Hopkins University, Baltimore, USA*

Summary

This collaborative study between the departments of Obstetrics and Gynaecology of the University College Hospital, Ibadan and Federal Medical Centre, Abeokuta assessed the value of intravaginal misoprostol in the management of intra-uterine fetal death. Fifty-six women at gestational ages between 17 weeks and term admitted for intra-uterine death with no contraindications to misoprostol received 400mcg of misoprostol administered intravaginally 12-hourly, until the establishment of effective uterine contractions.The mean gestational age was 27.9 weeks ± 7.1(SD) and the mean Bishop score was 2.7 ± 2.4(SD). The mean duration of onset of contractions was 5.0 hours ± 8.4 (SD); the mean induction-delivery interval was 17.5 hours ± 6.3(SD). Ninety three percent of the women had expelled within 48 hours. Successful induction was achieved in all women. Prophylactic vacuum aspiration was performed (lower gestation only) in 19.6% of cases. Fever, nausea and vomiting were the commonest side effects (7.1%). Neither gestational age nor the cervical score significantly affected the insertion-contraction or induction-delivery intervals. Intra-vaginal Misoprostol at the dosage administered is safe, effective and reduces staff workload.

Keywords: *Intra-vaginal misoprostol, induction of labour, intra-uterine fetal death*

Résumé

Une étude collaborative entre les départments d'obstétriques et gynéacologique des centres hospitalier de l'Université d'Ibadan et du centre médicale féderale d 'Abéokuta évaluait la valeur du misoprostol intravaginale pour le ménagement de la mort du fetus intra-utrine. Cinquante six femmes sans contracdictions du misoprostol recevaient 400 mg administré intravaginallement tous les 12 heures jusqu' à l'établissement des contarctions utérine effective. L'age moyen de gestation était de 27.9 ±7.1 semaines et le score moyen de Bishop etait 2.7±2.4 (SD). LA duree moyenne d'initiation des contractions était de 5 ± 8.4 heures. L'intervalle moen d'induction de l'accouchement etait de 17.5±6.3 heures. 93 pour cent des femmes était exclu entre 48 heures. L'induction réussie était achevée chez toutes les femmes. L'aspiartion prophylatique d'air était effectuée (faible gestation) chez 19.6% des cas. La fiévre , nausée et vomissement étaient les effects indésirables les plus fréquente(7.1%) Ni l'age de gestation ou le score cervical affectait significativement l'utilité des contractions ou les intervalles d'induction de l accouchement. Le misoprostol intra-vaginal à la dose administré est effective et recommendée. Et aussi réduit le poids du travail des employés.

Correspondence: Dr. A.O. Fawole, Reproductive Health Care Centre, Department of Obstetric and Gynaecology, Federal Medical Centre, PMB 3031, Abeokuta.

Introduction

Intra-uterine fetal death occasionally constitutes a management dilemma when the cervix is unripe and resistant to stimulation. Being more associated with unfavourable cervix than when the fetus is alive, induction of labour for a dead fetus is usually more challenging. Under these circumstances, prostaglandin preparations have been shown to be beneficial [1]. The prostaglandin preparations that have been registered for cervical ripening and labour induction are expensive and unstable, requiring refrigerated storage [2].

Misoprostol, a synthetic prostaglandin E1 analogue has been shown to be an effective stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostanoid receptors [3] and has consequently found applications in the management of obstetric and gynaecologic problems even though it has not been registered for these purposes. It is closely related to other prostaglandins used in obstetric practice such as Dinoprostone (PGE2), Carboprost (15-methylPGF2α), Gemeprost (PGE1) and Sulprostone (PGE2α analogue). Misoprostol is inexpensive, easily stored at room temperature with a shelf life of seven years, has few systemic side effects and rapidly absorbed when administered orally or vaginally [2]. It has been evaluated in medical abortions [4, 5, 6], induction of labour [7] and induction of labour following intra-uterine death [8, 9].

Misoprostol was developed and marketed for the prevention of peptic ulcer disease caused by prostaglandin sythetase inhibitors. Evaluation of its safety profile with respect to obstetric and gynaecologic indications is required to facilitate its registration for these purposes. This study was designed to document experience with intra-vaginal misoprostol in the induction of labour following intra-uterine fetal death.

Materials and methods

This is a descriptive, collaborative research carried out in the Departments of Obstetrics & Gynaecology of the Fed

eral Medical Centre, Abeokuta and the University College Hospital, Ibadan between January 1, 2000 and September 30, 2001. Women with diagnosis of intra-uterine fetal death between 17 weeks of gestation and term and no previous Caesarean section scar were recruited into the study. Prior to the commencement of the trial, all hospitals were informed of the nature of the trial and requested to refer patients for inclusion in the study. Ethical approval was obtained from the Research Ethical Committees of the two study sites. Each patient was counseled about the nature of the trial and an informed consent obtained.

On admission, a full history was taken and physical examination performed. The uterine size was noted, Bishop score evaluated and ultrasound confirmation of fetal death done. The clotting time and haematocrit were also determined. Further investigations were undertaken for specific indications.

All the women were given intra-vaginal Misoprostol 400 mcg (Searle & Co., Chicago) every 12 hours until the establishment of effective uterine contractions (at least 3 contractions in every 10 minutes lasting for 40 seconds). Intravenous access was established but intravenous fluids were not administered unless indicated. The time of the onset of contractions was documented along with the time of delivery/expulsion. The complications of treatment, the need for oxytocin augmentation and evacuation post-expulsion were recorded. The data entry and analysis were done using dBase IV software. Statistical comparisons were done using chi-squared and the student's t-test as appropriate. Some of the results were presented in frequency tables.

Results

Fifty-six women with intra-uterine fetal death at gestational ages between 17 weeks and term who satisfied the study criteria were recruited into the study. Some selected characteristics of the women (age, number of previous vaginal deliveries, number of living children, uterine size, Bishop score and the number of Misoprostol administrations) are shown in Table 1. Contractions started in twenty women (35.7%) within one hour of insertion. Thirty women (53.6%) had contractions between 1 and 12 hours after insertion and contractions started in 6 (10.7%) after 12 hours of Misoprostol insertion. The interval between insertion of Misoprostol and delivery is also shown in Table 1. The mean interval between insertion and the onset of contractions was 5.0 ± 8.4 hours; and the mean interval between insertion and delivery was 17.5 ± 16.3 hours.

Table 2 shows a comparison of the intervals between insertion and the onset of contraction and insertion and delivery. The insertion-contraction and insertion-delivery intervals were shorter when the Bishop score was greater than 5. However, these differences did not reach statistical significance.Most of the women (78.5%) delivered within 24 hours of insertion of Misoprostol. Successful induction was achieved in all cases. Only one patient required oxytocin augmentation. There were no associations between the gestational age and onset of contractions (X^2=2.4; P = 0.7); Bishop score and the onset of contraction (X^2=1.1; P = 0.6); Bishop score and the interval between insertion and delivery (X^2= 4.7; P = 0.3). The Bishop score did not influence the number of Misoprostol insertions (X^2= 1.8; P = 0.6). Eleven women (19.6%) had prophylactic evacuation done post-expulsion. This was mainly for women at lower gestations. The side effects are shown in Table 3. Fever, nausea and vomiting

Table 1: Some selected characteristics of the women and the interval between Misoprostol insertion and delivery.

Characteristic	Mean (± SD)	Range
Age (years)	30.3 (5.0)	20-40
Previous vaginal deliveries	1.4 (1.5)	0-5
Number of living children	1.2 (1.4)	0-6
Uterine size (weeks)	27.9 (7.1)	14-42
Bishop score	2.7 (2.4)	0-9
Total number of Misoprostol administrations	1.6 (1.0)	1-7
Interval (hours)	Frequency (n)	Percentage(%)
<6.0	13	23.2
6.1 – 12.0	11	19.6
12.1–18.0	13	23.2
18.1-24.0	7	12.5
>24.0	12	21.5
Total	56	100.0

Mean = 17.5 ± 16.3 hours

Table 2: Bishop score and insertion-contraction and insertion-delivery intervals

Bishop score	Insertion-contraction interval (hours) n mean (±SD)	Insertion-delivery interval (hours) n mean (±SD)
≤5	50 5.3 (8.8)	50 18.4 (16.9)
>5	6 1.96 (2.4)	6 9.8 (5.9)
	P = 0.4	*P = 0.2*

Table 3: Side effects of treatment

Side effect	Frequency (n)	Percentage (%)
Fever	4	7.1
Nausea	4	7.1
Vomiting	4	7.1
Diarrhoea	2	3.6

were equally common (7.1%). More than half of the patients (55.4%) spent less than 5 days in hospital.

Discussion

The application of Misoprostol in clinical obstetrics and gynaecology is attractive given its enormous economic advantage and ease of administration. Misoprostol has been used extensively (either alone or in combination with Mifepristone) in first trimester abortions [5, 6, 10] and second trimester abortions [4, 11]. These studies have confirmed the effectiveness of Misoprostol as an abortifacient. It has also been evaluated for third trimester cervical ripening and induction of labour [7, 12], active management of the third stage of labour [13] and the treatment of post-partum haemorrhage. A recent review confirmed the effectiveness of low dose (25 mcg four to six hourly) Misoprostol for cervical ripening and induction of labour but raised concern about the increase in fetal heart rate changes associated with uterine hyperstimulation [14].

Systemic side effects associated with Misoprostol include diarrhoea, nausea, vomiting, hyperthermia, shivering and blood pressure elevation (8, 13, 14). The vaginal route is associated with fewer side effects and higher success [9, 15]. Few studies have investigated the role of Misoprostol in the management of intra-uterine fetal death. The present trial confirms the relative ease of administration of intra-vaginal Misoprostol. The demand on the medical staff was minimal. These advantages make Misoprostol ideal for use for this indication in busy resource poor developing country settings. The study also confirms the effectiveness of intra-vaginal Misoprostol in the management of intra-uterine fetal death as previously noted [8, 9]. The dose in this study (400mcg every 12 hours) - which is less than the highest dose of misoprostol (600mcg) regarded as effective without an unacceptable level of side-effects [16] - is higher than the 100mcg every 12 hours employed by Bugalho *et al* [9] but less than 400mcg every 4 hours in the Mariani-Neto *et al* [8] study. The lower dosage may probably account for the absence of side effects reported in the Bugalho *et al* [9] study. The observed side effects in the present study were however self-limiting requiring no treatment. Contrary to the finding of Bugalho *et al* [9], the Bishop score was not significantly associated with the insertion delivery interval in the current study. The explanation may probably lie in the differences in the pattern of the distribution of gestational age. However, gestational age was not significantly associated with insertion-delivery intervals in both studies. This discrepancy deserves further investigations.

This study has confirmed the effectiveness and safety of intra-vaginal Misoprostol at the administered dose. It is cheap and convenient for the patient and the medical team. Misoprostol is suitable for the tropics in having no special storage requirements.

References

1. Keirse, MJNC. Prostaglandins in pre-induction cervical ripening: Meta-analysis of world-wide experience. J Reprod Med 1993; 38 (suppl.): 89-98.
2. Homeyr, GJ. Misoprostol administered vaginally for cervical ripening and labour induction in the third trimester. WHO Reproductive Health Library 1999; Issue 2.
3. Senior, J; Marshall, K; Saneha, R; Clayton, JK. In vitro characterisation of prostanoid receptors on human myometrium at term pregnancy. Br J Pharm 1993; 108: 501-506.
4. Bugalho, A; Bique, C; Almeida, L; Bergstrom, S. Pregnancy interruption by vaginal misoprostol. Gynecol Obstet Invest 1993; 36: 226-229.
5. Bugalho, A; Bique, C; Almeida, L; Bergstrom, S. Application of vaginal misoprostol before cervical dilatation to facilitate first trimester pregnancy interruption. Obstet Gynecol 1994; 83: 729-731.
6. Ngoc, MTN; Winikoff, B; Clark, S; Ellertson, C; Am, KN; Hieu, DT; Elul, B. Safety, efficiency and acceptability of Mifepristone-Misoprostol medical abortion in Vietnam. Int Fam Plan Perspect 1999; 25: 10-14.
7. Merrell, DA; Koch, MAT. Induction of labour with Misoprostol in the second and third trimester of pregnancy. S Afr Med J 1995; 85: 1088-1090.
8. Mariani-Neto, C; Leao, EJ; Barrto, MCP; Kenj, G; Aquino, MMA; Tuffi, VHB. Use of Misoprostol for labour induction in stillbirths. Rev Paul Med 1987; 105: 325-328.
9. Bugalho, A; Bique, C; Machungo, F; Faundes, A. Induction of labour with intra-vaginal Misoprostol in intra-uterine fetal death. Am J Obstet Gynecol 1994; 171: 538-541.
10. Grimes, DA. Medical abortion in early pregnancy: A review of the evidence. Obstet Gynecol 1997; 89: 790-796.
11. Bugalho, A; Bique, C; Pereira, C; Granja, AC; Bergstrom, S. Uterine evacuation by vaginal misoprostol after second trimester pregnancy interruption. Acta Obstet Gynecol Scand 1996; 75: 270-273.
12. Sanchez-Ramos, L; Kaunitz, AM; Del Valle, GO; Delke, I; Schroeder, PA; Briores, DK. Labour induction with the prostaglandin E1 methyl analog Misoprostol vs Oxytocin: a randomised trial. Int J Gynecol Obstet 1993; 43: 229.
13. Gulmezoglu, AM; Villar, J; Ngoc, NTN et al. WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 2001; 358: 689-695.
14. Hofmeyr, GJ; Nikodem, VC; de Jager, M; Drakely, A. Side-effects of oral misoprostol in the third stage of labour: a randomised placebo controlled trial. S Afr Med J 2001; 91: 432-435.

15. El Refaey, H *et al.* Induction of abortion with mifepristone (RU 486) and oral or vaginal misoprostol. N Engl J Med 1995; 332: 983-987.
16. Lumbiganon, P; Hofmeyr, J; Gulmezoglu, AM; Pinol, A; Villar, J. Misoprostol dose-related shivering and pyrexia in the third stage of labour: WHO Collaborative Trial of Misoprostol in the Management of Third Stage of Labour. Br J Obstet Gynaecol 1999; 106: 304-308.

Received: 11 February 2002
Accepted: 23 March 2004