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THE CENTRAL AFRICAN JOURNAL OF MEDICINE

ORIGINAL ARTICLES

Induction of labour with titrated oral Misoprostol suspension. A comparative study with vaginal Misoprostol

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Abstract

Objective: To compare the effectiveness of titrated orally and vaginally administered misoprostol for induction of labour.

Study Design: Unmasked randomized controlled trial.

Setting: Department of Obstetrics and Gynaecology University of Zimbabwe, Harare.

Subjects: Pregnant women with singleton foetus in cephalic presentation booked for induction of labour, were randomized to receive titrated orally or vaginally administered misoprostol.

Main Outcome Measures: The main outcomes were the duration of labour and induction to delivery interval. The secondary outcomes were neonatal and maternal complications.

Methods: 134 women were recruited into the study; 69 and 65 were randomized into orally and vaginally administered misoprostol respectively.

Results: The baseline characteristics in the two groups were similar. Women induced with titrated oral misoprostol suspension had a shorter interval from administration of the drug to initiation of uterine contractions (OR = 0.94 .95% CI 0.42 to 2.12) and a longer duration of labour (OR = 0.36; 95% CI 0.16 to 0.79). Labour was augmented with oxytocin in the oral group. The mean drug dose was 28mcg in the oral group.

There was no difference in the mode of delivery between the two groups. Hypertonic uterine contractions were not detected. Ruptured uterus did not occur in the study population. There were more neonatal admissions in the vaginal than the oral group (OR = 1.03 .95% CI 0.29 to 1.39).

Conclusion: Titrated oral misoprostol suspension is as effective and safe as vaginal misoprostol for induction of labour even in poor resource countries where *intrapartum* monitoring is inadequate.

Introduction

Misoprostol (cytotec) a synthetic prostaglandin E_1 analogue has antisecretory and protective properties which promote healing of gastric/duodenal ulcers.[1] It has uterotonic effect on the uterus which has spured its use in the treatment of *post partum* haemorrhage, termination of pregnancy and induction of labour.[2-4]

Induction to delivery interval of midtrimester pregnancy with an intra-uterine death can be as short as 30 minutes inclusive of complete delivery of the placenta.[3]

Although misoprostol is not licenced for induction of labour, its use in poor resource countries has increased in the past 10 years because it is cheap, available, has a long half life and can be stored at room temperature.[5]

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Randomized trials have shown misoprostol to be better or equivalent to prostaglandin E_2 in inducing labour.[6-10] Induction of labour with vaginal misoprostol was associated with shorter duration of labour.[6-10]

In a study at Harare Hospital Zimbabwe, intravaginal misoprostol was the best agent for cervical priming and induction of labour with 63% of women going into labour after a single dose.[6,10] The duration of labour was significantly shorter; there was less use of oxytocin in labour, a shorter induction to delivery interval, and fewer Caesarean sections for failure to progress.[6,10]

Concerns of increased maternal and foetal morbidity have been documented with the use of vaginal misoprostol.[11] Hypertonic uterine contractions; ruptured uterus; tachysystole; fever; chorioamionitis and vaginal pain have been described.[7,11] Ruptured uterus in primiparous women has been documented when 100mμg was used.[12] Other minor side effects in the mother were nausea; vomiting; diarrhea; rashes; dizziness; abdominal pains and flatulence.[1,11] Passage of meconium, low Apgar scores and increased Caesarean section for foetal heart rate abnormalities have been observed in the foetus.[7]

The optimal route and safe dosage of misoprostol is still being studied. Misoprostol tablets can be given intra-vaginally, sublingually, rectally and orally as a suspension.[2,13] Most studies in the literature have used the intravaginal route.[3,5,6] The side effects of vaginal misoprostol are dose related.[12] The current drug formulation of two hundred microgram 200μg tablet available in our country is difficult to break into a measurable dose.[13] The absorption of misoprostol in the vagina is slow and erratic making it difficult to estimate the drug levels before a repeat dose is inserted. A repeat dose creates an accumulation of the drug leading to overdose. Once the drug is dissolved in the vagina it cannot be removed if foetal or maternal complications occur.

When a 200μg misoprostol tablet is dissolved in 200ml of water each 1ml contains 1ug, a known drug dose can be administered. Small incremental doses reduce hyperstimulation making it safer to use in multiparous women.[12] The drug can be stopped immediately when maternal and foetal complications develop.

Pharmacokinetic studies have shown a more rapid time to peak concentration and rapid onset of uterine activity with misoprostol administered orally rather than vaginally[14]. The induction to delivery time and failed vaginal delivery in 24 hours was less with the vaginal than with oral route.[15-17] Vaginal misoprostol when compared to an equivalent oral dose results in sustained uterine activity.[18]

Studies which have compared oral and vaginal misoprostol have used fixed oral dose regiments.[14,19] One multicentre study compared titrated oral misoprostol suspension with vaginal dinoprostone.[13]

This study was carried out in a poor resource country where the effectiveness and safety of oral suspension was compared with vaginally administered misoprostol in induction of labour. It was hypothesized that misoprostol given orally in decreasing doses reduces the risk of uterine hyperstimulation, uterine rupture and foetal heart rate abnormalities.

Materials and Methods

Between January 2005 to June 2008 all suitable pregnant women admitted to Harare Maternity Hospital; Zimbabwe, for induction of labour were recruited into the study. The indications, timing of induction and management of the women were determined by the obstetric team in the labour ward on that day. Singleton pregnancies with a live foetus in a cephalic presentation were included in the study as well as those with an intra-uterine death. The patients signed an informed consent form. Excluded were women with an abnormal foetal heart, cephalopelvic disproportion, previous Caesarean section, multiple pregnancy or known sensitivity to misoprostol. All the women had an assessment of the Bishop score before the drugs were administered.

The study was approved by the hospital ethics committee. Eligible women were randomly allocated to oral or vaginal misoprostol. Investigators were not blinded as the drug was given as an oral suspension or as a tablet inserted into the vagina. Randomisation of the subjects in equal numbers was done using a table of random numbers, allocated into groups recorded onto cards placed in an opaque envelope,
sequentially numbered and placed into a box. The time of administration of the drugs was recorded.

In the women randomised to the oral group, 200mμg tablet was dissolved in 200ml of safe water by stirring until small sediments remained. Each 1ml contained approximately 1μg of Misoprostol. An ordinary marked 20ml syringe was used to draw the suspension. The suspension was given to the patient to swallow in the presence of the midwives. The starting dose for primiparous was 30ml followed by 20 ml every hour until uterine contractions started. Parous women were given 20 ml) to start dose followed by 15ml every hour until uterine contractions started. In a patient where the whole 200ml was given without any contractions, alternative methods of induction or delivery of the baby were initiated.

In the other group, 200μg misoprostol tablet was broken into a quarter tablet (approximately 50μg) was inserted into the posterior vaginal fornix by the attending doctors.

Patients were monitored throughout labour, delivery and *post natally* until discharged. During labour the membranes were ruptured when the cervix was 3cm dilated except in HIV positive where they were ruptured at full cervical dilation.

The management of the patients during labour and *post partum* was done by the team of doctors responsible for the patient including those on call. The interval from administration of misoprostol to the start

of uterine contractions and delivery was recorded. The progress of labour was plotted on a partogram (labour chart.) The foetal heart rate, cervical dilation, descend of the presenting part, passage of meconium, strength and duration of contractions, blood pressure, temperature, and urine output were monitored.

Hypertonic uterine contractions defined as contractions lasting two minutes were specifically looked for. Biochemical tests were performed where it was necessary. Labour was augmented with oxytocin where necessary four hours after stopping oral or vaginal misoprostol. Pethidine was administered by the midwives. Caesarean sections were done where indicated. In all patients, blood loss in the third stage was estimated and recorded.

The main outcome measures of the study were the duration of labour and the induction to delivery interval. Secondary measures in the mother were *post*

partum haemorrhage, vaginal pain and hypertonic uterine contractions. Passage of meconium, admission to neonatal unit, low Apgar score and death of the neonate in the first week were the primary outcomes of the foetus.

To detect for a four hour difference in the mean duration of labour, at a 5% significance level and a power of 90%, the minimum sample size was estimated at 60 per group. We enrolled a total of 134 women, 69 in oral and 65 in the vaginal group.

Results

A total of 134 women were recruited into the study; 69 (51%) were induced with oral suspension and 65 (49%) with vaginal misoprostol.

Table I: Baseline characteristics of women induced with oral Misoprostol and vaginal Misoprostol.

Characterstics	Oral (%)	Vaginal (%)	p value
Number	69 (51)	65 (49)	
Median age (years)	23	24	0.21
Median gestational age (weeks)	38	38	0.56
Median parity	0	1	0.27
Median bishop score	5	5	0.09
Traction catheter used	3	0	0.19
Indication for induction			
Hypertension	22 (32)	21 (32)	
Post term	38 (55)	37 (58)	0.36
Prelabour rupture membranes	8 (11)	4 (5)	
Intra-urine death	1 (1)	3 (5)	
Time of membrane rupture			**Odd Ratio (95% CI)**
Prelabour	7 (10)	4 (7)	0.87 (0.48 - 3.58)
During labour	39 (57)	32 (49)	1.5 (1.2 - 1.8)
At delivery	23 (23)	29 (44)	1.01 (0.36 - 1.07)

There were no differences between the two groups in age, parity, mean gestational age and median bishop score.

The indications for induction in both groups were intra-uterine death, hypertension, post term and prelabour ruptured membranes. Traction catheter was used in 3% of the women in the oral group, none in the vaginal group.

Table II: Labour characteristics of women induced with oral vaginal Misoprostol.

Characterstics	Oral n (%)	Vaginal n (%)	OR (95% CI)
Number	69 (100)	65 (100)	
Doses given to initiate labour : mcg			
20	56 (82)	0	
30	1 (1)	0	
50	3 (4)	62 (95)	1.48 (0.46 - 1.55)
Greater than 50	9 (13)	3 (5)	
Mean number of doses given	5	2	
Mean drug dose mcg	28	50	
Interval between administration of drugs to beginning contraction: hrs			
Less than 10	17 (25)	9 (13)	0.94 (0.42 - 2.12)
10 to 15	43 (63)	38 (58)	1.01 (0.65 - 1.57)
Greater than 15	9 (12)	19 (29)	1.06 (0.5 - 2.3)
Mean duration of labour	10.3	6.8	0.94 (0.4 - 1.3)
Augmentation labour with oxytocin			
Yes	14 (21)	1 (2)	p=0.06

Table II illustrates the labour characteristics of the women in the study; 2µg of oral misoprostol suspension was sufficient to initiate labour in 95% women, mostly parous women. A small proportion, 1% and 4%, required up to 30mcg and 50mug respectively. Thirteen percent required more than 50ug of oral misoprostol, all nulliparous women. A quarter tablet initiated labour in 95% of women in the vaginal group whilst 5% required a second dose. The mean drug dose given in the oral group was 28µg.

Women who were induced with oral misoprostol had a shorter time interval from administration of the drug to the beginning of uterine contraction: 25% in the oral group and 13% in the vaginal group had stated contractions in less than 10 hours. The difference was statistically significant (OR 0.94 ;95% CI 0.42 to 2.12). The mean duration of labour was longer in women administered oral misoprostol than vaginal, 10.3 hours and 6.8 hours respectively. Labour was augmented with oxytocin in 21% of women in the oral and 1% in the vaginal group.

Table III: Outcome of induction of labour using oral and vaginal Misoprostol.

Characteristic	Oral (%)	Vaginal (%)	p value
Number	69 (100)	65 (100)	
Normal vaginal delivery	61 (89)	59 (90)	0.7
Vacuum extraction/Forceps	3 (4)	3 (5)	0.09
Emergency Caesarean section	5 (7)	3 (5)	0.12
Indications for Caesarean section	**5 (100)**	**3 (100)**	
Failure to progress	4 (80)	1 (33)	0.08
Cord prolapse	0	1 (33)	0.02
Cephalopelvic disproportion	0	1 (34)	
Malpresentation	1 (20)	0	0.01
Complications of induction			
None	63 (92)	69 (90)	
Post partum haemorrhage	5 (7)	5 (8)	0.15
Vomiting	1 (1)	1 (1)	0.03

Table III illustrates the outcome of induction of labour using oral and vaginal misoprostol: 89% and 90% of women induced with oral and vaginal misoprostol had successful normal vaginal deliveries respectively.

A small proportion in both groups had vacuum extraction. Caesarean sections were performed in 7% and 5% in the oral and vaginal groups respectively. The differences in the mode of deliveries did not reach statistical significance.

The indications for caesarean sections were failure to progress, cord prolapse, cephalopelvic disproportion and malpresentation. There were no operations performed on account of foetal heart rate abnormalities.

The complications recorded in both groups were vomiting and *post partum* haemorrhage. The difference was not significant. There were no patients who either ruptured their uterus or had hypertonic uterine contractions. No women died during the study.

Table IV: Foetal outcome following induction with oral and vaginal misoprostol.

Characteristics	Oral n (%)	Vaginal n (%)	OR (95% CI)
Number	69 (100)	65 (100)	
Live birth	68 (99)	62 (97)	0.9
Still birth	1 (1)	3 (3)	
Mean birth weight (grams)	2929	2971	p=0.62
Mean Apgar score	8.4	8.2	1.01 (0.9 - 2.6)
Neonatal unit admission			
Yes	11 (17)	15 (28)	
Reasons for admission to neonatal unit	**11 (100)**	**15 (100)**	
Low Apgar score	0	1 (6)	
Meconium passage	6 (55)	8 (54)	1.07 (0.9 - 2.8)
Prolonged labour	1 (9)	0	
Recessing	0	3 (20)	
Prelabour rupture of membranes	4 (36)	3 (20)	1.13 (0.25 - 2.05)

Table IV illustrates the foetal outcome following induction of labour with oral and vaginal misoprostol. Ninety percent of the babies in the oral and 97% in the vaginal group were delivered alive and well. The still born babies in both groups were known intra uterine deaths and were the reason why induction was done. There were no *intrapartum* or first week neonatal deaths in both groups.

The mean birth weight and Apgar scores were similar in both groups, 28% of babies in the vaginal group and 17% in the oral group were admitted into the neonatal unit; all survived. The difference was statistically significant (OR 1.03 ; 95% CI 0.29 to 1.38). Meconium passage; prelabour rupture of membranes; low Apgar score; prolonged labour and chest recession were the main reasons for admission to the neonatal unit.

Discussion

This was an unmasked randomized controlled study in which the midwives knew what was being given to the patient. The drugs were administered as suspension or tablets orally and vaginally respectively and could not be masked. We feel, however, that our study results were not biased by this as data entry was done by midwives not involved in the management of the patients.

We compared oral and vaginal misoprostol for induction of labour because the hospital or the patients could not afford to purchase prostaglandins E_2. One multicentre study compared oral misoprostol with vaginal dinoprostone.[13]

In another study, oral and vaginal misoprostol were compared with prostaglandin gel and pessaries. At our institution, a quarter tablet of misoprostol inserted vaginally has been adopted for induction of labour without any study to support it. Both oral and vaginally administered misoprostol are cheaper than dinoprostone.[1]

Oral administration was easy and accepted by patients whilst discomfort was felt by some patients on vaginal insertion. Latex gloves worn by the doctors made the vaginal route more expensive than the oral.

A starting oral dose of 30mug in primiparous and 20mµg in multiparous women were chosen as 20 to 25mug is thought to be the optimum dose to prime and ripen the cervix and stimulate uterine contractions.[13] Our dosing schedule was different from other researchers who gave the oral drug every two hours until there were adequate contractions occurred.[13] The

mean oral dose was 28mug in our study.

Our study showed that oral titrated misoprostol suspension was associated with a shorter interval from induction to initiating uterine contractions. The duration of labour was longer and primiparous women required augmentation of labour with oxytocin.

Multiparous women required only 20mcg oral misoprostol to initiate labour and labour was much shorter when compared with women of lower parity. Primiparous women, a fifth of the study population required augmentation of labour with oxytocin.

The mode of delivery was similar in the two groups. The Caesarean section rate in the study was much lower than the hospital's monthly average of 20%.[20] Hypertonic uterine contractions were not detected by the midwives, who identified uterine the contractions by palpation of the abdomen. We did not have continous cardiotocography or external manometry which has been used by other researchers. Four percent of patients given misoprostol orally developed uterine hyperstimulation with fetal heart rate changes in a multicenter study.[13] A study done at our institution failed to identify hyperstimulation; this was attributed to poor monitoring of the uterine contractions during labour.[6,8]

The interval from administration of the drug to initiation of uterine contractions was short in both groups. Patients with prelabour rupture of membranes had a shorter duration of labour. This suggests that misoprostol acts faster on an already primed cervix as is the case in women with prelabour rupture of membranes. Oral administration of misoprostol is preferable to vaginal when inducing women with prelabour rupture of membranes as it reduces the risk of introducing infection. The tablet inserted in the vagina can be washed away before it has dissolved in women with prelabour rupture of membranes.

We are of the opinion that the route and dose of misoprostol used in our study reduced the risk of uterine hyperstimulation. The disadvantage of oral misoprostol in this study was the longer duration of labour and the need for augmentation of labour with oxytocin. However, this was compensated by successful vaginal delivery; reduced risk of uterine hyperstimulation; short interval from administration of the drug to initiation of labour and fewer admissions to neonatal unit.

The rate of foetal distress was low in our study although some studies have shown higher rates.[7] There was less meconium passage associated with oral misoprostol attributed to the small titrated doses.

Conclusion

Titrated oral misoprostol is as safe and effective as vaginal misoprostol for induction of labour in poor resource countries where monitoring of labour is minimal. Although the study was done at a tertiary hospital, the protocols in our district hospital labour wards are similar, the drug can be used at district and provincial hospitals.

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