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Safety and efficacy of misoprostol in induction of labour in prelabour rupture of fetal membrane in Nigerian women: a multicenter study

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Abstract

Background: Misoprostol, a prostaglandin E_1 analogue compared to prostaglandin E_2, has the advantage of being inexpensive and stable at room temperature, with its proven efficacy and safety. However studies on the effect of pH on the efficacy of misoprostol have yielded conflicting results. Thus its use in the induction of labour in patients with premature rupture of membrane requires further investigation.

Objective: To evaluate the safety and efficacy of misoprostol in induction of labour in Nigerian women with prelabour rupture of membrane after 34 weeks of gestation.

Materials and Methods: Three hundred and forty six Nigerian women with prelabour rupture of membrane who consented to participate in the trial were randomised into two arms of misoprostol and oxytocin. Labour was managed with WHO partograph. The primary outcome was the caesarean section rate and induction vaginal delivery interval.

Results: The mean induction to vaginal delivery interval was significantly shorter in the misoprostol arm (504 mins) compared to 627 mins in the oxytocin arm (t=3.97; p=0.005). The caesarean section rate of 18.1% among the misoprostol arm was also significantly lower than the 41.4% recorded in the oxytocin arm (p=0.002). Among patients with Bishop score greater than 6 there were no statistically significant differences between the two groups in the outcomes measured.

Conclusion: Misoprostol is not only effective but also safe when compared with titrated oxytocin in Nigerian parturients with prelabour rupture of membrane after 34 weeks.

***Key words**: Misoprostol, Prelabour rupture of membrane, Induction of labour.*

Introduction

Prelabour rupture of fetal membrane (PROM) is a common obstetric condition complicating about 3-18% of all pregnancies (1-3). It is a severe and potentially lethal threat to the mother and fetus (1, 3).There is still no agreement regarding the optimal approach to its management (1-5). While some reports favour early induction of labour based upon the fact that the risk of maternal and neonatal infection increases the longer the duration of rupture of membrane (ROM) (1,2), others have shown that expectant management is safer and more successful in achieving vaginal delivery (4,5). Despite the divergent views the only sure way of reducing infectious morbidity associated with PROM is the institution of an active management protocol of labour induction especially if fetal maturity is not in doubt (3).

Though active management reduces infectious morbidity associated with the conservative management approach to this condition, it is associated with high caesarean section rate especially with the use of titrated oxytocin in the presence of unfavourable cervix (6). Prostaglandin E_2, though effective in labour induction even in the

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presence of unfavourable cervix, its cost and need for special storage in addition to the transportation needs made its use unattractive to obstetricians in many developing countries (7, 8). Misoprostol, a prostaglandin E_1 analogue has the advantage of being inexpensive and stable at room temperature, with its proven efficacy and safety (7, 8). Studies on the effect of pH on the efficacy of misoprostol have yielded conflicting results (7, 9, 10). Thus its use in the induction of labour in patients with PROM requires further investigation since the liquor amnii alters the pH of the vagina (7). Equally, though Misoprostol have been found to be superior to oxytocin in patient with intact membrane, its dosages and regimens need further evaluation (8, 11, 12). In this study we evaluated the safety and efficacy of misoprostol compared to oxytocin in labour induction in the presence of PROM in Nigerian women.

Materials and methods

All consecutive and consenting women meeting the eligibility for inclusion into the study admitted into the obstetric units of three multidisciplinary proprietary hospitals (Havana Specialist Hospital, Rao Specialist Hospital and Felin Hospitals) in Lagos, Nigeria because of prelabour rupture of fetal membrane after 34 weeks with singleton cephalic and live fetus from January 2001 to July 2006 were enrolled into the study after an informed consent. They were randomly assigned to either of vaginal misoprostol induction or titrated intravenous oxytocin induction using a computer generated random numbers.Excluded from the study were cases of prelabour rupture of membrane before 34 weeks, intrauterine fetal death, non-reassuring fetal heart tracing on non stress test, parae 5 and above, previous uterine scar and known contraindication to use of prostaglandin or induction of labour.Approval was obtained from the hospitals ethical committee. Induction of labour was commenced once the diagnosis of PROM was confirmed. Prior to commencement of induction of labour, cervical assessment was performed using the criteria of Bishop. All the patients were commenced on ampicillin/cloxacillin combination and metronidazole on admission and then continued for five days.

Misoprostol arm

100mcg of misoprostol was inserted after the women had emptied their bladder. This dose was repeated 12hourly until contraction ensued or until a maximum total dose of 500mcg was given. The 100mcg dose was prepared by halving 200mcg tablet of misoprostol (Cytotec®, Searle Chicago IL. USA) using a pill cutter. After insertion, the women remained in bed for about 2hours to allow absorption. A sanitary towel was applied to ensure that the inserted tablet did not fall unnoticed.

Titrated intravenous oxytocin arm

Oxytocin (Syntocinon®, Sandoz) in 5% dextrose water intravenous infusion was commenced at 0.5mIU/minute and doubled every 30minutes until 3 contractions in 10 minutes lasting 40- 45 seconds is obtained. It is then maintained at this rate. Labour in both arms was monitored using the WHO partograph (13). Labour complications were managed according to the units' protocol. Hyper-stimulation (more than five contractions in ten minutes or contractions lasting more than 60seconds on two occasions within 3minutes) was managed with hydration with normal saline, analgesics, oxygen and salbutamol inhalation. If this conservative option fails, emergency caesarean section is performed. Labour induction was considered successful if the patients delivered vaginally within 24hours of commencement of induction. Caesarean section rate, induction to vaginal delivery interval, hyper-stimulation rate, fetal distress, puerperal sepsis, duration of hospital stay, neonatal admission and death rate were noted and recorded.

Statistical analysis

The recorded data were analysed with comparison between arms using chi-square with Yates correction, Fischer's exact test and students't tests as appropriate. Intra-group and subgroup analysis were also performed to determine the effect of the state of the cervix on the induction outcome. For this analysis the patients were grouped into two groups of those with Bishop score less than or equal to six and those with Bishop score greater than 6. The odd ratio and 95% confidence interval were obtained where appropriate. A p-value<0.05 was considered significant. Statistical analysis was done using Epi info version 6 and SPSS version10 statistical soft ware.

Results

Three hundred and sixty one women met the inclusion criteria for inclusion into the study. After informed consenting process, fifteen (4.2%) declined to participate preferring expectant management option. The remaining 346 who accepted to participate and signed the informed consent were randomised into either of the two arms. However 4 patients in misoprostol arm who earlier consented, declined later to be induced with misoprostol and opted for oxytocin. They were obliged but excluded from the study. Three patients originally randomised to misoprostol arm (2) and oxytocin arm (1) started having contraction before admission protocols could be concluded and thus were excluded. The maternal sociodemographic characteristics of the women enrolled into the study is shown in Table I.

There was no statistically significant difference between the two arms in all the parameters obtained and compared. The total misoprostol dose required to induce labour ranged from 100mcg (single insertion) in 143 (85.6%) patients to 300mg (three insertions) in 7 (4.2%) patient. Seventeen (10.2%) patients had two insertions. The oxytocin required to achieve adequate uterine contraction ranged from 2mmIU/minute to 64mIU/minute, with majority (61.6%) achieving this at oxytocin dose range between 16 and 32mIU/minute. The maternal and neonatal outcomes measured are shown in Table II. Though the mean time from administration of induction agent to the onset of uterine contraction was significantly shorter in the oxytocin arm (194.5 vs. 116.2 minutes; p=0.02), the induction to vaginal delivery interval was significantly shorter in the misoprostol arm; an average time of 504mins in the misoprostol arm compared to 627mins in oxytocin arm (t=3.97; p=0.005). Seventy-one patients had failed induction in the oxytocin arm (caesarean section rate of 41.3% as against thirty one (caesarean section rate of 18.0%) women in the misoprostol arm. This difference is also statistically significant (p=0.03). A subgroup analysis [using Bishop score (BS) above or less than 6] comparing the outcome of labour induction showed that at BS greater than 6 , there were no statistical significant difference between the two induction methods with respect to caesarean section rate (p=0.91) and induction vaginal delivery interval (0.33). The caesarean section rate was 19.5% in the oxytocin group compared to 17.4% in the misoprostol group. At BS less than or equal to 6, there were statistically significant difference between the two groups. The caesarean section rate and induction vaginal delivery interval were 19.4% and 581minutes respectively in the misoprostol group compared to 57.9% and 845 minutes in the oxytocin group (p= 0.00 for both parameters). Further intra-group analysis showed that while there were no statistically significant difference (p=0.90) in the caesarean section rate between patients in the misoprostol group with BS greater or less than 6 (17% vs. 19.4%). In the oxytocin group there were statistically significant differences (p=0.00) between the caesarean section in the two subgroup. The caesarean section rate was 57.9% in those with BS less than or equal to 6 compared to in those with BS greater than 6 was 19.5%.

Table I. Socio-demographic characteristics of the studied women.

Characteristics	Misoprostol arm n=167	Oxytocin arm n=172	t test	p-value
Mean age (years)	26.4 ± 5.3	26.3 ± 5.1	0.221	0.83
Mean parity	2.0 ± 1.0	2.2 ± 1.1	1.838	0.10
Mean bishop score	4.3 ± 1.0	4.5 ± 1.0	1.000	0.34
Mean gestational age	38.7 ± 2.3	38.8 ± 2.3	1.468	0.16
Mean birth weight	3.50± 0.61	3.46±0.77	0.259	0.80

Table II. Maternal and neonatal outcome in both arms of the study.

Outcome	Misoprostol group (n=167)	Oxytocin group (n=172)	t or x^2 or Fischer exact test	Odd ratio	95% confidence interval	p-value
Induction to established labour interval #	194.5 ± 83.8	116.2 ± 63.8	3.976	-	-	0.002
Induction delivery interval #	504.0 ± 73.8	627.0± 161.4	3.969	-	-	0.005
Caesarean section rate∗	31(18.6%)	71(41.3%)	19.72	0.32	0.19- 0.55	0.03
Hyperstimulation rateϕ	5(3.0%)	2(1.2%)	0.27	1.46	0.90-2.37	0.42
Puerperal sepsis	0(0.0%)	0(0.0%)	-	-	-	-
Average hospital stay (days) #	3.8 ± 1.7	4.2 ± 1.9	1.00	-	-	0.343
Fetal distress∗	17(10.2%)	30(17.4%)	3.16	0.54	0.27-1.06	0.08
Birth Asphyxia∗	5(3.0%)	8(4.7%)	0.32	0.76	0.38-1.52	0.57
Perinatal deathϕ	1(0.6%)	2(1.2%)	0.00	0.68	0.14-3.37	0.30

ϕ =Fischer exact test ∗ =Chi square test # =Students't test.

The indications for caesarean section in both arms are shown in Table III. A large percentage of caesarean section in oxytocin arm was for prolonged labour as against cephalopelvic disproportion in the misoprostol arm. There were no significant difference in the fetal distress rate (p=0.46), perinatal death (p=0.5) and duration of hospital stay (p=0.34) and other neonatal outcome measured. Uterine hyper-stimulation occurred in five (3.0%) subjects in the misoprostol arm compared to two (1.2%) in the oxytocin arm (p=0.42).

Table III. Indication for caesarean section in the study.

Indications	Misoprostol arm (n= 31)	Oxytocin arm (n=71)
Cephalopelvic disproportion	15(48.4%)	20(28.2%)
Prolonged labour	9(20.0%)	37(52.1%)
Fetal distress	4(12.9%)	10(14.1%)
Antepartum haemorrhage	3(9.7%)	4(5.6%)

Chi square test =5.66; p-value=0.13

Discussion

Results of present study confirm that misoprostol induction of labour in the presence of PROM is associated with shorter induction delivery interval and lower caesarean section rate with comparable safety profile. Though the finding of shorter induction to delivery interval is similar to reports of Chang (14), Sanchez-Ramos (15) and Kramer (16), its statistically significant lower caesarean section rate is at variant with previous reports, which reported similar rates (16, 17). The higher caesarean rate among the oxytocin arm may be related to the limited effect of oxytocin on the cervix. This was further confirmed in this study in which there were no difference between misoprostol and oxytocin in patients with Bishop score greater than 6 but a statistically significant difference in those with Bishop score less than or equal to 6. Previous studies have shown that failed induction is a major disadvantage of active management of PROM with oxytocin (4, 5). In this study though the cervical score at commencement of induction were comparable (see Table I), its unfavourability placed the oxytocin arm at disadvantage since misoprostol is a cervical ripening agent. While misoprostol acts at both the cervical level and uterine level, oxytocin effect is principally on the uterus. It was not surprising that majority of the failed induction in the oxytocin arm were due to prolonged labour as against cephalopelvic disproportion in the misoprostol arm. Induction of labour in the presence of unfavourable cervix with oxytocin is like driving a car against a closed gate. Misoprostol will first open the gate before getting behind the wheels. Equally in our centers after 15 hours of adequate uterine contraction without achieving vaginal delivery the induction is deemed to have failed and is thus terminated by caesarean section. The difference between our report and that of others may be equally due to the fact that we commenced induction immediately the diagnosis was confirmed without any waiting period. The method has the advantage of reducing infectious morbidity but at a cost of higher caesarean section rate if oxytocin is used. No case of puerperal sepsis in this patient justifies this active management protocol. We thus recommend when using oxytocin for induction in presence of unfavourable cervix, a conservative approach seems more appropriate with antibiotics coverage; but when using misoprostol, induction could commence immediately PROM occurred with good outcome. Our study also used a different dose regimen than the dosage regimen frequently reported.

We used 100mcg misoprostol every 12 hourly instead of 25-50mcg every 4-6 hourly. The positive outcome of our study using entirely different dosage regimen suggest that more trials needed to be conducted with different dosage regimen in different settings before final decision and consensus is made on it. In a Meta analysis of misoprostol induction of labour in presence of rupture membrane by Lin MG and her colleagues, only 9 studies compared misoprostol and oxytocin (18). This confirms that more studies need to be conducted before a consensus can be made. Li Xiao-mao and his colleagues concluded their Meta analysis by suggesting that the dosages and regimens of misoprostol in term labour induction need further investigation before it can be widely used clinically (11).

A concern among the misoprostol treated patients is the occurrence of hyper-stimulation (8, 11,15,19-21). Our study showed that the incidence of hyper-stimulation is related to dose and dosage interval, with a dose of 100mcg giving 12hourly, we were able to achieve a lower hyper-stimulation rate (3.0%) compared to other dosage regimes that either used a lower dose at more frequent intervals or higher dose (15-17, 19-21) .The frequency of occurrence in misoprostol arm was comparable to oxytocin arm (p=0.42).

In conclusion misoprostol is not only effective but safe when compared with titrated oxytocin in the presence of PROM. The fear of the possible effect of Liquor amnii on the safety and efficacy of misoprostol is unfounded.

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