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ABSTRACT

***Background*: Pre-labour rupture of membranes (PROM) at term is a common event whose management varies from centre to centre. The practice at the Kenyatta National Hospital (KNH) for patients with PROM at term is to initiate delivery of the patient soon on admission with intravenous oxytocin, if there are no contraindications to vaginal delivery. However, in PROM at term, if the cervix is not ripe,vaginal administration of prostaglandin pessaries for cervical ripening is not possible when there is active draining of liquor, thus use of intravenous oxytocin may take a very long time or fail all together.**

Oral misoprostol at low doses has been found to be a safe and effective agent for labour induction in numerous studies carried out in the developed world, where there are better resources for monitoring of labour. None of the studies has been carried out in Kenya, a limited resource country. Therefore, there is a need to determine the effectiveness and safety of oral misoprostol solution at the KNH, a limited resource set up.

***Objective*: To determine the effectiveness and safety of 2-hourly 20 mcg oral misoprostol solution compared to the standard intravenous oxytocinin labour induction in mothers with pre-labour rupture of membranes at term at the Kenyatta National Hospital.**

***Design*: An unblinded randomised clinical trial.**

***Setting*: Kenyatta National Hospital Labour Ward Unit.**

***Participants*: Eighty three pregnant women with pre-labour rupture of membranes at term without an indication for Caeserian section were consented and randomised for labour induction with either oral misoprostol at a dose of 20mcg 2-hourly up to a maximum of 4-doses, or with intravenous oxytocin according to the WHO protocol.**

***Main outcome measures*: Induction to delivery interval; maternal complications and early neonatal outcomes.**

***Results*: The overall induction success rates in the misoprostol arm was 81% versus 83% in the oxytocin arm (P=0.447). The mean induction to vaginal delivery interval in the misoprostol arm was 8.4 hours as compared to 9.45 hours in the oxytocin arm (P=0.116). The induction to active labour interval was similar in the two study arms. The mean induction to active labour in the misoprostol arm was 4.02 hours as versus 4.51 hours in the oxytocin arm (P=0.223). Two women who had failed induction with misoprostol were augmented with oxytocin and delivered vaginally. The Caesarean section rates were 19% in the misoprostol arm and 17% in the oxytocin arm (P=0.447), which was not statistically significant. The maternal outcomes were similar in the two study arms. Four women had tachysystole in the misoprostol arm, compared to three**

in the oxytocin arm (P=0.253). In the misoprostol arm two women had hypertonus compared to three in the oxytocin arm (P=0.322).There was one case of hyperstimulation in the misoprostol arm and two in in the oxytocin arm. There were no differences in the foetal/ neonatal outcomes. No baby had an Apgar score of less than seven at one or five minutes. No baby was admitted to the New Born Unit in either of the two arms. There was no case of a still birth in either of the study arms. There was no significant difference in the passage of meconium between the two arms, 39% in the misoprostol arm and 35.7% in the oxytocin arm (P=0.755). The passage of meconium did not impact on the neonatal outcomes.

***Conclusion*: Oral misoprostol solution 20mcg 2-hourly is as safe and effective as the standard intravenous oxytocin for labour induction in women presenting with pre-labour rupture of membranes at term at the Kenyatta National Hospital.**

INTRODUCTION

When pre-labour rupture of membranes (PROM) occurs at term, it can be managed either actively by prompt induction of labour or expectantly. Among different authors prompt induction can mean waiting 2 to 12 hours after membranes rupture, whereas expectant management may refer to no induction, but more commonly means induction from 24 to 96 hours (1).

Intravenous oxytocin has been the standard induction agent in PROM at term (12).

Misoprostol, a synthetic prostaglandin E1 (PGE1) analogue was marketed from 1988 primarily for the prevention and treatment of peptic ulcer disease caused by non-steroidal anti-inflammatory drugs, but was noted to have uterotonic side effects. Further research revealed it to induce myometrial contractions as well as produce cervical ripening.

In the past decade, several studies have been carried out on misoprostol for the induction of labour for various indications including PROM at term (2-6).

The Cochrane Database of Systematic Reviews 2009, gathered data from 56 studies with 11,590 women on the administration of oral misoprostol for labour induction (7). They assessed oral misoprostol compared to placebo, vaginal dinoprostone, intra-cervical dinoprostone, intravenous oxytocin and vaginal misoprostol. The comparison with intravenous oxytocin group: - Eight trials including 1026 women have compared oral misoprostol with intravenous oxytocin. Five studies used 100 mcg (818 women), two studies used 50 mcg (178 women) and one used 20 mcg solution (30 women). The study comparing 20mcg oral misoprostol solution with intravenous oxytocin showed no statistically significant difference in reported outcomes of vaginal delivery not achieved within 24 hours (RR 0.7 95% C.I, 0.3-1.65), or Caesarean delivery rate (RR 0.57, 95% C.I. 0.22-1.50). Meconium staining of the liquor was seen more frequently in the misoprostol group (RR 1.72, 95% CI 1.08 to 2.74), but this was not reflected in significant differences in any adverse foetal or neonatal outcomes. There was no difference in the rate of uterine hyperstimulation syndrome. The data concluded that oral misoprostol is an effective agent for induction of labour with advantages over other agents or routes of induction.

However, most of these studies have been carried out in developed world where there are better resources for monitoring of labour. In the developing countries (including Kenya), resource constraints in the majority of the maternity units leads to less than optimal monitoring of induced labour (i.e, not having one–to-one care). Labour outcomes may thus vary from unit to unit, country to country depending on the availability of resources. Therefore there is a need to determine the effectiveness and safety of oral misoprostol solution at the KNH, a limited resource set up. If the safety of low dose oral misoprostol is realised at the KNH's maternity unit, then benefits such as its low cost, easy storage (does not require refrigeration unlike oxytocin), and ease of administration can be utilised. The results can also be up scaled for use in our resource constrained country.

We report here the results of a randomised clinical trial evaluating efficacy and safety of oral misoprostol solution 20mcg administered 2-hourly, as compared to the standard intravenous oxytocin in labour induction in mothers admitted to Kenyatta National Hospital's (KNH) labour ward with a diagnosis of pre-labour rupture of membranes at term.

Research Question: Is oral 20mcg solution misoprostol administered 2-hourly as effective and as safe as the standard intravenous oxytocin in labour induction in women with pre-labour rupture of membranes at term at the Kenyatta National Hospital?

Hypothesis: Oral misoprostol solution administered at 2-hourly intervals is not as effective and a safe as the standard intravenous oxytocin in labour induction in women with pre-labour rupture of membranes at term at the Kenyatta National Hospital.

The broad objective:To determine the effectiveness and safety of oral misoprostol solution administered 2-hourly as compared to the standard intravenous oxytocin in labour induction in patients with pre-labour rupture of membranes at term at the Kenyatta

National Hospital.

The Specific objectives: to compare the induction to delivery intervals in the two study arms; to compare the prevalence of maternal complications in both labour induction regimens; to compare the early neonatal outcomes in both induction regimens.

Study population: The study population consisted of women presenting to the labour ward of Kenyatta National Hospital (KNH) with pre-labour rupture of membranes of four or more hours at term. They included those who had been on antenatal follow up at the KNH as well as those who have been referred from other clinics.

Study design: This was an unblinded randomised clinical trial designed to compare the effectiveness and safety of oral misoprostol solution administered 2-hourly to the standard intravenous oxytocin in labour induction for pre-labour rupture of membranes at term.

Study procedures: All women presenting to KNH`s labour ward admission desk between August and September 2009, with a history suggestive of PROM, were examined to confirm a diagnosis of PROM, a term gestation and the foetal well-being.

PROM was diagnosed on the based on any or all of the following:
A history of flow of liquor down the legs without being in labour; Active draining of liquor from the cervix with or without Valsalva manouvre; Pooling in the posterior fornix; Litmus test.

The gestational age of 37-completed weeks was based on the following: -
Extrapolation of the last menstrual period; Extrapolation from the date of quickening; Palpation of the fundal height; Extrapolation of ultrasound findings in the first and second trimesters

Foetal well-being was assessed as follows: -
Auscultation of the foetal heart using a fetoscope was done at the initial patient assessment, then repeated again after randomisation before the start of treatment, then every 30 minutes before the onset of active labour, every 30 minutes during active labour, and every five minutes during the second stage of labour. If foetal bradycardia, tachycardia or an irregular foetal heart developed, treatment was stopped and the condition managed by position change, oxygen and intravenous fluids with or without caesarean delivery depending on the stage of labour. Meconium staining of liquor was monitored. If meconium staining developed, treatment was stopped and the condition managed depending on the stage of labour. Cord prolapse was looked out for during vaginal examinations. If present it was to be treated as an emergency.

Randomisation was based on a computer-generated randomisation table. Computer-generated random numbers indicating the study allocation were printed on cards which were put in opaque envelopes and sealed. This was done by a person not directly involved in the study (the investigator and the research assistant midwives were not involved in this process). Consenting participants were assigned to induction method by opening the next sequentially numbered opaque sealed envelope. The envelope was opened by the investigator or the research assistant midwives in the presence of the participant. After opening the envelope, the investigator and the participant became aware of the treatment allocation. Thus, the study was a non-blinded clinical trial.

Once the diagnosis of term PROM had been made and foetal well-being assured, participants were put through an eligibility check list of inclusion and exclusion criteria.

The inclusion criteria included:Gestational age of 37 completed weeks and above, Rupture of membranes for four hours and above without labour, Singleton pregnancy in cephalic presentation, willingness to participate.

The exclusion criteria included: Previous uterine surgery (Caeserian sections, myomectomy), Clinical diagnosis of Chorioamnionitis: (maternal fever[more than 38ºC plus any two of the following: maternal tachycardia, foetal tachycardia, uterine tenderness, offensive vaginal discharge), Unexplained vaginal bleeding, pre-eclampsia, Intrauterine growth retardation, Contraindications to prostaglandins eg asthma. Those in active labour, High parity (more than para 4), Multiple pregnancy, Placenta praevia, Diabetes mellitus, Rhesus isoimmunisation, Meconium stained liguor, Non-reassuring foetal status (meconium stained liquor, foetal tachycardia, foetal bradycardia, late decelerations), Unwillingness to participate.

Those who were eligible for the study were counseled on the nature of the study by the investigator or the research assistant midwives. Those who accepted to participate were recruited and signed the informed consent form.

Their socio-demographic information and obstetric history was obtained. The investigator or the research assistant mid wife then picked a sealed opaque envelope containing a randomly generated computer number, the envelope opened in the participant's presence, and the participant assigned to either the misoprostol or the oxytocin arm as per the envelope. Before starting treatment, the participant was re-examined to check foetal well-being.

Misoprostol solution was obtained by dissolving a 200mcg tablet in 200ml of boiled and cooled tap water to obtain a concentration of 1mcg per ml (8). The 200 ml of misoprostol solution was put in a 300 ml container. This was done by the Chief Pharmacist of the KNH. Calibrated cups were used to measure

20ml (20mcg) of misoprostol solution which was administered to the participants in the misoprostol arm. The solution remains stable up to 24-hours after which it is discarded (9).

Misoprostol solution was administered orally at 20mcg 2-hourly (8), for a maximum 4-doses or until there was established labour. Those not in active labour four hours after the fourth dose of misoprostol were considered failed induction and started on oxytocin. Augmentation with oxytocin was used if labour progressed at less than 1cm per hour after reaching 4cm in the absence of meconium-stained liquor, abnormal foetal heart rate or pathological molding. Oxytocin was administered as per the WHO protocol.

The study participants were put on prophylactic antibiotics as per KNH`s protocol (if PROM at term was more than 18-hours, participants were put on oral erythromycin 500mg 6-hourly). Labour was monitored through the use of a partograph. In both groups Caesarian delivery was done for the standard obstetric indications. The progress of labour and the maternal and foetal outcomes were recorded in the questionnaires.

The outcome measures of the study:

A: Primary outcome measures included: (1)Induction to vaginal delivery, (2) Vaginal delivery achieved, (3) Uterine hyperstimulation with foetal heart rate (FHR) changes, (4) Serious maternal morbidity or death (e.g. uterine rupture, admission to intensive care unit), (5) Serious neonatal morbidity (e.g. seizures, birth asphyxia , neonatal encephalopathy) or perinatal death,

B: Secondary outcome measures included: (1) Oxytocin augmentation. (2) Uterine hyperstimulation without FHR changes; (3) Apgar score less than seven at five minutes; (4) Postpartum haemorrhage; (5) Any other maternal complications.

The sample size (n) calculation: Using the null hypothesis, it is a two tailed (Z1 –α 12) study with a power of 80% ($Z_{1-\beta}$) (11).

$Z_{1-\alpha 12}$ = (2-tailed) =1.96
$Z_{1-\beta}$ = 80%power =0.84
δ_1 = 6.4 (standard deviation of the misoprostol group)
δ_2 = 6.5 (standard deviation of the oxytocin group)
μ_1 = 12 (mean induction time of the misoprostol group)
μ_2 = 8 (mean induction time of the oxytocin group)

$$n = \frac{(Z_{1-\alpha 12}+Z_{1-\beta})^2 \times (\delta_1^2+\delta_2^2)}{(\mu_1-\mu_2)^2}$$

$$n = \frac{(1.96 + 0.84)^2 \times (6.4^2+6.5^2)}{4^2}$$

n =41

The sample size is calculated to be 41 participants for each group.

Ethical Review: The protocol was approved by the Kenyatta National Hospital/University of Nairobi Ethics Review Committee, and registered with the KNH Scientific Committee.

Data management: Data were collected using coded questionnaires. The raw data were verified to check for errors or omissions made while filling out the data entry form. Data were subsequently entered into a computer, processed and analysed using SPSS Statistics for windows, Version 18.0. Students t-test was used to test associations of parametric data; while Pearson`s chi-square test, Fishers exact and Mann-Whitney-U-tests were used for non-parametric statistics. Results were presented in frequency distribution and descriptive statistical tables.

RESULTS

Of the 83 enrolled pregnant women with pre-labour rupture of membranes at term, 41 were randomised to the misoprostol arm while 42 were randomised to the oxytocin arm.

There were no differences in socio-demographic characteristics in the 2-study groups; with a median age of 24 years (interquartile range[IQR] 22-28), a median of 12 years of education (IQR 10-17), and most were housewives (Table 1).

Table 1
Socio-demographic characteristics

Characteristic	Median, IQR, N% Misoprostol N= 41	Or N% Oxytocin N= 42	P
	Misoprostol N= 41	Oxytocin N= 42	P
Age years, Median, interquartile range(IQR)	24(22, 28)	24(22, 28)	
Education years, Median, IQR	12(10,17)	12(10,17)	
Occupation			
Student	4(9.8%)	3(7.1%)	0.584
Housewife	13(31.7%)	14(33.3%)	0.475
Self-employed	12(29.3%)	8(19%)	0.132
Civil-servant	6(14.6%)	8(19%)	0.384
Private	6(14.6%)	9(21.4%)	0.269

The obstetric characteristics of the 2-study populations were similar. The median gestational age was 38 weeks (IQR 38-40), they had a median Bishop's score of 4 (IQR 4-5) and most of the women were nulliparous (Table 2).

Table 2
Obstetric characteristics of the study population (N/%)

Characteristic	Median, IQR, N% Misoprostol (N= 41)	Oxytocin (N= 42)	P
Parity			
0	18(43.9%)	17(42.9%)	0.254
1	17(41.5%)	16(40.2%)	0.37
2	4(9.8%)	6(12.3%)	0.398
3	2(4.9%)	3(4.6%)	0.376
Median gestation weeks, IQR	38(38,40)	38(38,40)	
Median Bishop's score, IQR	4(4,5)	4(4,5)	

The mean duration of PROM in the misoprostol arm was 6.13 hours compared to 8.21 hours in the oxytocin arm, this was not statistically significant (Table 3).

Table 3
Duration of PROM by study group

Duration of PROM (hrs)	Misoprostol N=41	Oxytocin N=42	P
4-8	23	19	0.238
8-12	15 190.379		
Above 12	3	4	0.253
The mean duration of PROM (hrs)	6.13	8.21	0.149

There were no statistically significant differences in the induction to vaginal delivery intervals between the two study arms. The mean induction to vaginal delivery interval in the misoprostol arm was 8.4 hours as

compared to 9.45 hours in the oxytocin arm (P=0.116). The mean induction to active labour in the misoprostol arm was 4.02 hours as compared to 4.51 hours in the oxytocin arm (P=0.223) (Table 4).

Table 4
Summary statistics on duration of induction by study group

Duration (hours)	Misoprostol (N= 41) Mean (1 SD)	Oxytocin (N= 42) Mean (1 SD)	P
Induction to active labour	4.02(1.52)	4.51(1.93)	0.226
Induction to second stage of labour	8.38(2.31)	9.03(3.11)	0.335
Induction to delivery time	8.4(2.35)	9.45(3.04)	0.116

There were eight women with failed induction in the misoprostol arm compared to seven in the oxytocin arm (P= 0.76). There were no significant differences in the modes of delivery in the two arms, with 35 women (85%) in the misoprostol arm delivering vaginally compared to 36 women (83.3%) in the oxytocin arm (P= 0.447). Oxytocin augmentation was given to two (4.9%) of the women in the misoprostol arm. The two women who had failed induction with misoprostol were augmented with oxytocin and delivered vaginally. They were analysed as failed induction in the misoprostol arm. The Caesarean section rates were 19% in the misoprostol arm and 17% in the oxytocin arm (P= 0.447), which was not statistically significant. Three mothers were delivered by Caesarean due to failed induction in the misoprostol group compared to three in the oxytocin group (P= 0.473). There were three Caesarean deliveries in the misoprostol group due to non reassuring foetal status compared to four in the oxytocin arm for the same indication (P= 0.474) (Table 5).

Table 5
Outcome of labour induction by study group

Outcome	Misoprostol N=41) No.(%)	Oxytocin (N=42) No.(%) n	P
Success of induction			
Succeeded	33(80.5)	35(83.3)	0.76
Failed	8(19.5)	7(16.7)	0.65
Mode of delivery			
Vaginal	35(81)	35(83)	0.447
Caesarian section	6(19)	7(17)	0.447

Uterine contraction abnormalities were not statistically significant between the two arms. Four women had tachysystole in the misoprostol arm compared to three in the oxytocin arm (P=0.253). In the misoprostol arm two women had hypertonus compared to three in the oxytocin arm (P=0.322).There was one case of hyperstimulation in the misoprostol arm and two in in the oxytocin arm (P=0.316). There were no cases of uterine rupture, postpartum haemorrhage, retained placenta or maternal death in either of the two arms (Table 6).

Table 6
Maternal complications by study group

Complication	Misoprostol N= 41	Oxytocin N= 42	P
Tachysystole	4	3	0.253
Hypertonus	2	3	0.327
Hyperstimulation syn	1	2	0.316

No baby had an Apgar score of less than seven at ine or five minutes. Eleven neonates had Apgar scores of seven to eight at five minutes in the misoprostol group compared to 9 in the oxytocin group (P=0.286). Thirty neonates had Apgar scores of nine to ten at five minutes in the misoprostol group compared to 33 in the oxytocin group (P=0.229). Hence there were no statistically significant differences in Apgar scores in the two study groups. No baby was admitted to the New Born Unit in either of the two arms. There was no case of a still birth in either of the study arms (Table 7).

Table 7
Neonatal outcomes by study group

Outcome	Misoprostol N= 41	Oxytocin N= 42	P
Infants Apgar score at 1min			
0-6	0	0	
7-8	28	24	0.693
9-10	13	18	0.628
Infants Apgar score at 5 min			
0-6	0	0	
7-8	11	9	0.286
9-10	30	33	0.229
Meconium passed(N/%)			
Yes	16(39)	15(35.7)	0.755
No	25(61)	27(64.3)	0.755
Birth weight (Mean/SD)	3103.9(382)	3184.52(372.12)	0.3330

DISCUSSION

In a randomised, unblinded study of women presenting with pre-labour rupture of membranes at term at the Kenyatta National Hospital, we assessed the safety and effectiveness of induction of labour using oral misoprostol solution administered two-hourly compared to the standard intravenous oxytocin, and found no difference in duration of labour, mode of delivery, maternal or neonatal outcomes. These data indicate that oral misoprostol solution two-hourly, is as safe and effective as intravenous oxytocin for induction of labour among women at term with PROM. Our findings are in agreement with other data, including a systematic Cochrane review (7).

The mean induction to vaginal delivery interval in the misoprostol arm was 8.4 hours as compared to 9.45 hours in the oxytocin arm (P=0.116). This finding is in keeping with other studies done before. In the Cochrane Review 2009, six trials comparing oral misoprostol to oxytocin, involving 758 women with PROM were reviewed (7). Overall there were no statistically significant differences in induction to vaginal delivery interval (P=0.86).

The mode of delivery was similar in the two arms with 81% of the women in the misoprostol arm with vaginal births compared to 83% in the oxytocin arm (P=0.447). Caesarean section deliveries were 17% and 19% in the misoprostol and oxytocin arms respectively (P=0.447).In the Cochrane review (7), there were no statistically significant differences in the modes of delivery between oral misoprostol and oxytocin for labour induction in term PROM in the six trials reviewed. However, the Caesarean section rates were lower ranging from 4.9-13.2 %. This could be attributed to the fact that these studies were carried out in the developed countries where there is intensive electronic monitoring of labour. This study was carried out in a limited resource set up where facilities such as foetal scalp blood sampling for foetal acaedemia are currently not available. This could explain the fact that 7 out of 12 Caesarean deliveries done in this study were due to non-reassuring foetal status.

The maternal outcomes were similar in the two study arms. There were no cases of uterine rupture, postpartum haemorrhage, retained placenta or maternal death in either of the two arms. Uterine contraction abnormalities were not statistically significant between the two arms. There was one case of hyperstimulation in the misoprostol arm and two in in the oxytocin arm (P=0.316). This compares favorably with similar studies in the Cochrane Review (7, P=0.73).

There were no statistically significant differences in the foetal/neonatal outcomes in the two study

arms. No baby had an Apgar score of less than seven at one or five minutes, no baby was admitted to the New Born Unit, and there was no case of a still birth in either of the study arms. There was no significant difference in the passage of meconium between the two arms, 39% in the misoprostol arm and 35.7% in the oxytocin arm (P = 0.755). Similar studies in the Cochrane review (7) have had a similaroutcomes regarding passage of meconium (P=0.098).The passage of meconium did not impact on the neonatal outcomes.

This study comparing oral misoprostol and oxytocin used a low dose of oral misoprostol 20 mcg administered two-hourly. This low dose of misoprostol could account for the lack of any severe adverse event in this study. This dose appears to be safe and effective for labour induction in women with pre-labour rupture of membranes at term.

The strength of this study is that it was a randomised clinical trial, there was no loss to follow-up, and then study participants adhered to treatment. None of the study participants requested a different arm after allocation to a study arm.

The study is limited by the fact that it was an unblinded clinical trial, thus there is a possibility of bias in clinical decision making and in the assessment of outcomes. Another limitation is that there are no commercially available 20 mcg misoprostol tablets. To get 20 mcg used in this study, a 200 mcg misoprostol tablet was dissolved in 200 ml of water to achieve a concentration of 1mcg / ml, thus there is no guarantee that each of the 20 ml of the solution contained 20mcg misoprostol.

In conclusion, oral misoprostol solution administered at 20mcg two-hourly is as effective and as safe as intravenous oxytocin for labour induction in women presenting with pre-labour rupture of membranes at term at the Kenyatta National Hospital.

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