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Sublingual Misoprostol Versus Oxytocin Titration For Induction Of Labour In Parturients With Spontaneous Rupture Of Foetal Membranes At Term: A Randomized Controlled Trial.

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Abstract
Background: *Induction of labour for term premature rupture of fetal membranes (PROM) is associated with greater maternal satisfaction and lower risk of maternal infection compared with expectant management. The ideal method of induction of labour for term PROM is a subject of controversy. Intravenous oxytocin titration has a prime position as a choice agent for induction of labour following term PROM as it has been shown to be efficacious for such purpose. Recent evidence has shown that misoprostol is associated with better outcomes and merits evaluation in our environment.*
Objective*: This study compared the efficacy of sublingual misoprostol and oxytocin for induction of labour in parturients with term PROM.*
Methods*: This was a double blind randomized controlled trial on the efficacy of sublingual misoprostol versus oxytocin titration in women with term in two hospitals at Abakaliki. Two hundred and forty Participants recruited were divided into two groups of 120 participants each. Group A received 25 mcg of sublingual misoprostol and titration of 500 ml of Ringer's lactate solution as placebo with 5ml of sterile water injected into it while group B underwent immediate induction of labour with titration of 5 units of oxytocin in a 500 ml of Ringer's lactate solution and received one tablet of 100mg Vitamin C as placebo. The mean induction delivery interval and the efficacy and side effects of the drug on the mother and baby were noted. Data were collated, tabulated and analyzed using the statistical package for social sciences (SPSS) software (version 22, Chicago II, USA). P value of <0.05 was considered statistically significant.*
Results: *The mean age of the participants were comparable for the groups; 29.9 years ± 4.60 and 30.2 ± 3.67 for misoprostol and Oxytocin groups respectively. The mean time to achieve 3 contractions was 2.40 hours ± 1.53 and 3.30 hours ± 2.21 respectively for the misoprostol and oxytocin groups. This was not significant. However, the mean time taken to achieve active phase parameters and to achieve full cervical dilatation were 2.83 ± 1.70/4.83 ± 2.88 and 4.82 ± 2.37/7.66 ± 3.83 for misoprostol and oxytocin respectively. These were statistically significant (p=0.00001) The difference between the mean induction delivery interval for both arms was significant (p= 0.00001). Ten percent of those that had misoprostol had caesarean intervention as compared with 33.3% ofm thos that had oxytocin. This was also statistically significant (p=0.013). First minute Apgar score <7 was noted in 15 neonates in the misoprostol arm and 29 in the oxytocin arm. At the 5th minute, 15 neonates in the Oxytocin arm still had Apgar score <7 and none in the misoprostol arm. Fifteen neonates in the oxytocin arm required admission in the newborn intensive care unit but none in the misoprostol arm. This was statistically significant. There were no neonatal deaths, uterine rupture tachysystole nor hyperstimulation in both arms. However, 14 and 10 of the parturients in the misoprostol arm had shivering and nausea/vomiting respectively. This was also significant.*
Conclusion: *Sublingual misoprostol shortened the induction delivery interval and reduced the Caesarean section rate with better safety profile in these parturients compared to Oxytocin. Misoprostol was however associated with mild side effects such as shivering and nausea/vomiting.*
Key words: *Term PROM, misoprostol, oxytocin, labour outcomes*

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I. Introduction

Premature rupture of membranes (PROM) occurs when fetal membranes spontaneously rupture with leakage of amniotic fluid before the onset of labour.[1,2,3] When this occurs at term, it is known as term premature rupture of fetal membranes (Term PROM).[1,3] The incidence of PROM is approximately 3-10% of all pregnancies with term PROM accounting for approximately 80% of cases.[4]

While the management of PROM at term has remained one of the most controversial topics in Obstetrics,[4] findings of the International Term PROM trial suggest that immediate induction results in greater maternal satisfaction and lower risk of maternal infection compared with expectant management.[5] Intravenous oxytocin titration has a prime position as a choice agent for induction of labour following term PROM as it has been shown to be efficacious for such purpose.[5] However, as its effects mainly results in uterine contraction concerns have been raised on its efficacy in the presence of an unfavorable cervix.[3,5] The use of prostaglandin preparations with or without oxytocin infusion is a widely recognized and accepted method of labour induction, It is shown to reduce induction-delivery time and reduce the risk of failed induction.[1,6] There are various prostaglandins that have been used in labour induction.[7] Misoprostol is a synthetic prostaglandin E_1 analogue originally intended for prevention of gastric ulcers. It is cheap, stable at room temperature and is effective in cervical ripening and initiating uterine contractions. It can be administered through various routes and has a rapid onset of action; this makes it a desirable option for induction of labour.[8] The sublingual route of misoprostol compared to the other routes has been shown to have the highest peak concentration, shortest time to peak concentration and greatest bioavailability.[8] In addition, the sublingual route avoids the increase in the risk of chorioamnionitis inherent in the vaginal route.

While several authors have compared the efficacy and safety of misoprostol versus oxytocin for induction of labour in term PROM,[4-6,9,] only few studies have used the sublingual route.[4,5] A previous study in the centre, compared intravaginal misoprostol to Foley's catheter with oxytocin for cervical ripening and induction of labour.[10] This study therefore seeks to compare the efficacy and safety of sublingual misoprostol versus oxytocin titration for labour induction at term PROM while adopting standard protocols.

Rupture of foetal membranes is regarded as part of the physiological process of labour. Premature rupture of foetal membranes (PROM) is defined as rupture of fetal membranes before the onset of labour irrespective of the gestational age.[6,11] Depending on the gestational age that it occurs, it could be term or preterm PROM. Fetal membranes rupture that occurs at or beyond 37 weeks of gestation is defined as term PROM (TPROM).[2,11] The incidence of PROM has remained constant through the years and has been reported to be between 3-18%.[12] The incidence of PROM varies widely between institutions. In Nigeria an incidence of 1.94% was reported among 11,241 deliveries. The incidence ranged from 1.9 to 3.9%.[3,13] A study in Mumbai India reported the incidence 12%.[14]

Risk factors for development of premature rupture of membranes include previous history of PROM, incompetent cervix, bacterial infection including chorioamnionitis and cervico-vaginitis. Other risk factors include polyhydramnios, multiple pregnancy, amniocentesis, trauma, prior cervical surgery like conization, low socio-economic status, malnutrition, antepartum haemorrhage and connective tissue disorders like Ehlers-Danlos syndrome.[15,16] It has also been postulated that some antioxidant deficiencies like vitamin C and E are associated with the development of PROM. Vitamin C has been argued to help in collagen synthesis, thereby preventing PROM.[17]

Term PROM is associated with maternal and perinatal complications including chorioamnionitis, puerperal sepsis, postpartum hemorrhage and in cases of overwhelming sepsis, death. Perinatal complications include foetal tachycardia, birth asphyxia, neonatal sepsis, neonatal jaundice, increased neonatal intensive care admission, cerebral palsy and perinatal death. Endale T et al, found that of 185 women with term PROM, 11.4% developed puerperal sepsis, 6.0% and 7% had wound infection and haemorrhage respectively while 1.6% died.[18] Among the 185 neonates, 47% had first minute Apgar scores below normal, 3.8% neonates were stillborn and 11.9% suffered early neonatal death.[18]

In a one-year hospital based prospective study of 100 women with term PROM, Revathi V et al, found that chorioamnionitis complicated 4% of the cases, puerperal fever 22%, abruption placenta 2% and wound infection (both abdominal and episiotomy) in 14% of the cases. Eighty-two neonates were delivered with Apgar scores less than 5 at birth and 18 with Apgar scores greater than 5 at birth. Common causes of perinatal morbidity included birth asphyxia 2%, hyperbilirubinaemia 2%, septicaemia 10%, meningitis 1%, and pneumonia 5%.[18]

Misoprostol is a synthetic prostaglandin E_1 analogue that was used for treatment of peptic ulcer disease because of its gastric acid anti-secretory and various mucosal protective properties.[8] Misoprostol has been found beneficial in Obstetrics and Gynaecology because of its uterotonic activity.[19] Though the tablets of misoprostol

were developed to be used orally, studies have extensively investigated other routes such as; vaginal, rectal, sublingual, and buccal routes. Misoprostol after absorption is rapidly de-esterified to misoprostol acid, the biologically active molecule. Misoprostol is a safe and well tolerated drug especially in low dose regimen. Diarrhoea is the major adverse reaction that has been consistently reported. Other side effects include nausea, vomiting, headache, shivering, fever and chills. However, these side effects are dose dependent. Use of misoprostol has also been associated with tachysystole, hyperstimulation and uterine rupture.[8]

On the other hand, the onset of action of oxytocin is immediate, with a half-life of 3-9 minutes when given intravenously. Duration of action is approximately one hour. Oxytocin is metabolized by the enzymes in the gastrointestinal tract, so it is not active orally and must be administered by intramuscular or intravenous route.[20] The route of excretion is through the biliary system and the kidneys. Side effects include, decrease blood pressure, water retention, impaired uterine blood flow, anaphylaxis, nausea and vomiting, arrhythmias, tachycardia, seizures and uterine rupture.[20]

studies that employed the sublingual route adopted different dosing of misoprostol and oxytocin which were different from practice in my centre, there was also no documentation of time of SROM to time of commencement of induction of labour and these may contribute to the varying findings noted.[4,5,10,21] This study therefore seeks to compare the efficacy and safety of sublingual misoprostol versus oxytocin titration while adopting standard protocols as this has not been done in our centre.

II. Materials And Method

This was a double-blind superiority randomized placebo-controlled study comparing the efficacy and safety of sublingual misoprostol and oxytocin titration in women with spontaneous rupture of foetal membranes at term at the two hospitals in Abakaliki, Ebonyi state. The state is located in the South Eastern Nigeria with 13 local government areas. Abakaliki is the state capital and is the only urban settlement in the state which also has one semi urban community; the rest are rural settlements. The state has a population of 2.1million people based on the 2006 national population census and occupies a land mass of 5932 kilometers square. The vegetation characteristic of the area is the tropical rain forest with an average annual rainfall of 1600mm. Two main seasons - wet and dry characterize the area, with the former happening between April and October while the latter takes place from November to March. Igbos are the predominant ethnic group in the state. Majority of them engage in subsistent farming, petty trading and civil service as their occupation. Literacy level generally is low while poverty is prevalent among this population who are also predominantly Christians. Maternal health indices are poor and ignorance are still prevalent, especially among the rural dwellers. They also have poor health seeking behaviour which stem from poverty and ignorance. The current maternal mortality ratio in Abakaliki is1359 per 100,000 live births according to Ezegwui et al[22].

The teaching hospital serves as a major referral center for Ebonyi, Benue and Cross River states. Patients are usually referred from general hospitals, government owned health centers, private hospitals and from other departments in the hospital. The department of Obstetrics and Gynaecology runs antenatal clinics and delivery services managed by consultants and resident doctors with trained Nurses and Midwives. A Preliminary unpublished data shows that the hospital had 2395 deliveries in the last one year (September 1, 2018 to August 31, 2019), out of which 895 were Caesarean sections, giving a Caesarean section rate of 37.4%.

Mile 4 hospital is a missionary hospital in the state capital. The Obstetrics and Gynaecology department of the hospital is run by two consultant Obstetricians and Gynaecologists, with senior and junior residents posted from the teaching hospital. The department also manages high risk pregnant women according to standardized protocols. The hospital has average delivery of 3773 per annum with a caesarean section rate of 21.3% from unpublished data. In the same period as mentioned earlier, 205 women had term PROM at the Teaching Hospital, giving an average occurrence of 17 patients per month while 231 women at the Mile 4 Hospital were admitted and managed for term PROM in the same period, giving an average occurrence of 19 patients per month.

Participants for this study were drawn from the population of women admitted for induction of labour on account of spontaneous rupture of foetal membranes at term at the two Hospitals, who met the inclusion criteria after obtaining an informed consent. The study lasted for a period of 9 months, so as to meet up with the proposed sample size. The research assistants were Trained on the research protocols in details. The objectives, how to recruit eligible patients, how to fill the pro forma, the outcome measures, and monitoring of the mother, foetus and neonate after delivery. Weekly group meetings were also held as soon as the research commenced for the purpose of feedback and reappraisal.

Inclusion criteria were those that signed informed consent, parturients with singleton pregnancy term PROM, not having contractions and with Bishop score of 5 or less with no contraindication for vaginal delivery. The exclusion criteria were those that refused consent, pre term PROM, contra-indications for vaginal delivery, Grand-multiparous patients, asthma, intrauterine foetal death, non-reassuring foetal heart tracing, previous uterine scar, contraindication to use of prostaglandin, Patients having contractions and Bishop score >5.

Sample Size Determination

The minimum sample size was determined using the formula for calculating sample size for a difference in mean of randomized controlled study[22]

Sample size = $\frac{2SD^2 (Z_{\alpha/2} + Z_{\beta})^2}{d^2}$

Where:

SD: standard deviation of the treatment group 3.7 hours[12]= 222 minutes

$Z_{\alpha/2}$: Standard normal deviate at 5% type 1 error= 1.96

Z_{β}: 80% power = 0.84

d: Mean difference in the induction delivery interval for the misoprostol and oxytocin group = 17-15 hours = 2 hours or 120 minutes)[12]

Therefore:

Sample size per group = $\frac{2 (222)^2 \times (1.96 + 0.84)^2}{(120)^2}$

M (size per group) = $\frac{2 \times 49284 \times 7.84}{14400}$

M (size per group) = $\frac{772773.12}{14400}$

Size per group = 53.67 = 54

10% of the minimum sample size per group (54x0.1=5.4 ≈ 6) would be added to correct for attrition hence the final sample size would be 60 for each arm. We recruited 120 participants per arm.**DRUG**

Procurement, Storage And Destruction

The entire drugs that was used for this study was procured from a reputable pharmacy store in town. The batch number, date of manufacture and expiry dates and the NAFDAC registration numbers were noted for both the misoprostol and the oxytocin. Cold chain was maintained for the oxytocin throughout the study. At the end of the study, following un-blinding, all the used drugs and placebo vials were properly disposed of in the hospital's incinerator.

The participants were randomized by means of a computer generated random-number using the software Research Randomizer®. Using this software, one hundred and twenty numbers were randomly generated from a pool of two hundred and forty random numbers and these numbers were assigned to group A (sublingual misoprostol group) while the remaining one hundred and twenty numbers were automatically assigned to group B (the oxytocin titration group).

Group A received 25µg misoprostol (Cytotec ®;) sublingually every 4 hours following decision to induce labour in PROM at term; they received 500ml of Ringer's lactate into which 5ml of sterile water was added as placebo. Group B received 500ml Ringers lactate with 5 IU oxytocin titration, (Rotex®) and tablet of Vitamin C (Juhel®) as placebo. Concealment was done in sequentially numbered opaque sealed envelopes (SNOSE). The randomization was done by a statistician, while the concealment was done by a hospital pharmacist without revealing the outcome to the researcher. All the envelopes were kept in a locker that was made accessible to all the members of the research team.

Participants that met the inclusion criteria having signed the informed consent form were given sequential study numbers and the corresponding numbered opaque sealed envelope was then allocated to the patient.

Induction Of Labour With Oxytocin

A diagnosis of PROM was made from detailed history and astute clinical examination. Those who did not have contra-indication to vaginal delivery were admitted into the labour ward for induction of labour. Patients with PROM billed for induction of labour with oxytocin titration had pre-induction work up done which included hemoglobin concentration estimation, grouping and cross matching of blood. The Anesthesiologist and Neonatologist were also informed about the admission, in case of the need for Caesarean section and/or possible neonatal resuscitation after delivery. The pre-induction Bishop score was determined by the senior Registrar among the research assistants. This was done by assessing the position of the cervix, cervical os dilatation, consistency of the cervix, cervical length and station of the presenting part. The dose of oxytocin used for induction of labour was 5 IU, in 500ml of Ringer's lactate solution. The infusion was started at 10 drops per minute (5mIU per minute) using the British Standard Blood Giving Set. The dose was then titrated against the uterine contractions by increasing the rate by 10 drops every 30 minutes. Titration was continued until uterine contractions were established at a frequency of 3 in 10 minutes, each lasting between 40 and 60 seconds, or the maximum rate of 60 drops per minute (30mIU per minute) was reached. The Oxytocin dose was reduced whenever 6 or more contractions occurred in 10 minutes or one single contraction lasted more than 60 seconds.

If contractions were inadequate with 5 units of Oxytocin, the dose was increased to 10 units in 500 ml of Ringer's lactate and similarly used. The progress of labour was monitored with a modified partograph with the alert line drawn from zero cervical dilatation and the action line drawn 4 hours to the right and parallel to the alert line at a slope of one centimeter per hour.

The patients in this group also received a tablet of vitamin C similar to the misoprostol as placebo every 4 hourly for 24 hours

Induction With Misoprostol

Following the diagnosis of PROM, the clients admitted into the labour ward and randomized into the misoprostol group for induction of labour had pre-induction work up as was done for the oxytocin group. Twenty-five microgram of misoprostol was inserted under the tongue 4 hourly for a maximum of 4 doses. Every patient in this group also received plain Ringers lactate with 5ml of sterile water added and titrated as in the previous group. The pre-induction Bishop score was also assessed and documented by the Senior Registrars within the research group. Patients in either group who did not achieve established labour was counselled and offered emergency Caesarean section due to failed induction of labour.

Vaginal Delivery

This was conducted with the patient in supine position and the knees drawn up. The parturients were not encouraged to push until the onset of the second phase of the second stage of labour. A careful vaginal examination was done to assess the presenting part and position of the fetus. The delivery of the head and body was controlled by the Accoucheur.

Third Stage

This was actively managed. 10IU of Oxytocin was given intramuscularly within one minute of delivery of the baby to give room for exclusion of undiagnosed twin. The placenta was then delivered by controlled cord traction without awaiting the signs of placental separation according to the new WHO protocol recommended for management of third stage of labour. Following delivery, the patients were placed on high dose oxytocin infusion (40 units in 500ml of Ringers lactate) for at least two hours after delivery and monitored in the lying-in ward before transfer to the post-natal ward.

Outcome Measures

Primary outcome measure is the mean induction delivery interval for both groups. Secondary outcome measures include: the rate of successful vaginal delivery within 24 hours of induction of labour, the rate of caesarean section in both groups and the maternal and neonatal side effect profile in both groups. Tachysystole was said to have occurred when there were more than 5 contractions in 10 minutes, hypertonus as contraction(s) lasting longer than 90 seconds while hyperstimulation was described as the occurrence of foetal heart irregularities in the presence of tachysystole and/or hypertonus.

Statistical Analysis

Data were collated, tabulated and then statistically analyzed using statistical Package for Social Science (IBM SPSS) software (version 20, Chicago II, USA). Continuous variables were presented as mean and standard deviation (Mean ± 2SD), while categorical variables were presented as numbers and percentages. Chi-square test (X^2)/ Fishers exact were used for comparison between groups for qualitative variables while student t-test was used for comparison between groups for quantitative variables. A difference with a P value <0.05 was considered statistically significant.

Ethical Considerations

Ethical clearance was obtained from the Health Research and Ethics committee of the Hospitals. informed consent was obtained from each participant before recruitment into the study. The study objectives, procedure and full implications of participation were discussed with the participants before consent was obtained. The participants were made to understand that declining to participate in the study or withdrawal from the study had no consequences to obtaining care and they can withdraw any time they do not want to continue. All information including history, physical examination findings and results obtained from the participants were kept strictly confidential and used only for the purpose of the research. The cost of the medications and all financial costs were borne by the researchers.

III. Results

Two hundred and fifty-five patients were assessed for eligibility into the study; fifteen patients were excluded while 240 were included. A total of 240 patients were randomized into the study, out of which 120 were

allocated to the Oxytocin group and 120 to the misoprostol group. Analysis of data was done with the intention to treat concept.

Table I below shows the socio-demographic parameters of the two arms with data for age, parity, highest level of education and occupation (p=0.995, 0.094, 0.276 and 0.888 respectively). The mean age of participants were 30.20 years ± 3.67 and 29.9 years ± 4.60 for the Oxytocin and misoprostol arms respectively.

Table 2 shows the comparison of various baseline parameters for both arms of the study. The gestational age, duration of membrane rupture, admission haematocrit and Bishop's score were comparable in both groups (p=0.325, 0.676, 0.08 and 0.581 respectively). The mean gestational ages for the participants in the groups were 39.20 ± 1.20 and 39.40 weeks ± 0.77 respectively for the Oxytocin group and misoprostol group.

TABLE I: COMPARISON OF SOCIO–DEMOGRAPHIC DATA OF PARTICIPANTS

PARAMETERS	**OXYTOCIN (n= 120)**	**MISOPROSTOL (n= 120)**	**P-VALUE**
AGE			
15-19	5	6	0.995
20-24	16	14	
25-29	40	44	
30-34	28	22	
35-39	28	30	
40-44	3	4	
OCCUPATION	**OXYTOCIN (n=120)**	**MISOPROSTOL (n=120)**	**P-VALUE**
Civil servant	49	60	0.888
Trader	10	16	
Farmer	15	8	
House wife	46	36	
HIGHEST LEVEL OF EDUCATION	**OXYTOCIN (n=120)**	**MISOPROSTOL (n=120)**	**P-VALUE**
No formal	0	4	0.276
Primary	0	0	
Secondary	53	51	
Tertiary	67	65	

TABLE 2: COMPARISON OF BASELINE PARAMETERS

PARAMETERS	**OXYTOCIN N=120**		**MISOPROSTOL N =120**	**P-VALUE**
Mean gestational age [weeks] ± SD	39.2 ±1.20		39.4 ± 0.77	0.71
Mean time of rupture of membranes [hours] ± SD	9.74±1.10		9.80 ±1.31	0.496
Mean admission hematocrit [%]	34.45 ± 3.90		33.29 ± 2.70	0.08
Mean Bishop score at onset of induction of labour ± S.D	4.38 ± 0.8		4.44 ± 0.50	0.581
Parity	1.79 ± 2.19		1.74 ± 1.81	0.625

Table 3A shows the comparison of some outcome measures for both arms of the study. The mean duration of time to achieve three contractions was 2.40 hours ± 1.53 for the Oxytocin group and 3.03 hours ± 2.21 for the misoprostol group. The difference was not statistically significant (p=0.083). The mean duration of time to achieve active phase parameters were 4.83 hours ± 2.88 and 2.83 hours ± 1.70 respectively for the oxytocin and misoprostol groups. This was statistically significant (p= 0.00001). The mean time taken to achieve full cervical dilatation was 7.66 hours ± 3.83 and 4.82 hours ± 2.37 for the oxytocin and misoprostol groups respectively. This difference was also statistically significant (p= 0.00001). The mean induction delivery interval for both groups were 7.88 hours ± 3.27 and 5.48 hours ± 2.34 for Oxytocin and misoprostol respectively. This was statistically significant (p=0.00001). The post-partum hematocrit was comparable in both groups; 31.99% ± 3.55 in the oxytocin group and 31.7% ± 2.47 in the misoprostol group (p=0.657).

Table 3B: shows the comparison of maternal/neonatal outcome variables. The mode of delivery was not comparable for the two arms of the study, while 75 (62.5%) participants in the oxytocin arm achieved spontaneous vaginal delivery, 100 (83.3%) in misoprostol did likewise, 40 (33.3%) in the oxytocin group had emergency Caesarean section while 12 (10%) participants in the misoprostol arm had emergency Caesarean section. Participants who had instrumental delivery were 5 (4.2%) in the oxytocin arm and 8(6.7%) in the misoprostol arm. This difference was statistically significant (p= 0.013). Over all, vaginal delivery rate in the oxytocin arm was 66.6% in the oxytocin arm and 90% in the misoprostol arm while Caesarean section rate in the oxytocin arm was 33.3% (p=0.013). The Apgar scores for the two groups at the first and the fifth minutes were not comparable.

Neonates who were asphyxiated at the 5th minute Apgar score were 15 (12.5%) in the Oxytocin arm while none was asphyxiated in the misoprostol arm. All neonates who were asphyxiated at the 5th minute required neonatal intensive care admission (NICU). The difference noted in the APGAR scores at the 1st, 5th minutes and NICU admission were statistically significant between the groups (P=0.030; RR- 1.933 95% CI- 1.044-3.418, P= 0.00002; RR 2.08 95% CI- 1.70-2.53, P= 0.0002; RR 2.08 95% CI- 1.70-2.53 respectively). There were no neonatal deaths in both groups.

Table IV shows comparison of maternal side effects for the two arms. There were no cases of headache, diarrhoea, tachysystole, hypertonus or uterine hyperstimulation in both groups. However, 14 (11.6%) participants in the misoprostol arm had shivering and 10 (8.3%) had nausea and vomiting while no participant in the Oxytocin arm experienced any of the mentioned side effects. These were statistically significant (p=0.00008 and 0.0007 respectively).

TABLE 3A: COMPARISON OF SOME OUTCOME MEASURES

PARAMETERS	OXYTOCIN N=120		MISOPROSTOL N =120	P-VALUE
Mean time to achieve three contractions [hours] ± SD	2.40 ± 1.53		3.03 ± 2.21	0.083
Mean time to achieve active phase of labour [hours] ± SD	4.83 ± 2.88		2.83 ±1.70	0.00001
Mean time to full cervical dilatation [hours]	7.66 ± 3.83		4.82 ± 2.37	0.00001
Mean induction delivery interval [hours]	7.88 ± 3.27		5.48 ± 2.34	0.00001
Mean postpartum hematocrit [%]	31.9 ± 3.55		31.7 ± 2.47	0.657

TABLE 3B: COMPARISON OF SOME MATERNAL/NEONATAL OUTCOME MEASURES

PARAMETERS	OXYTOCIN N=120 (%)		MISOPROSTOL N=120 (%)	P-VALUE	RR (95% CI)
Mode of delivery					
Spontaneous vaginal	75 (62.5)		100 (83.3)		
Caesarean section	40 (33.3)		12 (10)	0.013	N/A
Instrumental delivery	5 (4.2)		8 (6.7)		
APGAR Score (1st minute)					
<7	29 (24.2)		15 (12.5)	0.030	1.933 (1.04-3.42)
≥7	91 (75.8)		105 (87.5)		
APGAR Score (5th minute)					
<7	15 (12.5)		0 (0)	0.00002	2.08 (1.70-2.53)
≥7	105 (87.5)		120 (100)		
NICU Admission	15 (12.5)		0 (0)	0.00002	2.08 (1.70-2.53)
Neonatal death	0 (0)		0 (0)	1	1

TABLE 4: COMPARISON OF MATERNAL SIDE EFFECTS

	OXYTOCIN N=120	MISOPROSTOL N=120	P-VALUE	RR (95% CI)
Headache	0 (0)	0 (0)	1	1
Nausea/Vomiting	0 (0)	10 (10)	0.0007	0.89(0.67-0.98)
Diarrhoea	0 (0)	0 (0)	1 1	1.63(1.013.5)
Shivering	0 (0)	14 (11.6)	0.00008	1
Tachysystole	0 (0)	0 (0)	1	1
Hypertonus	0 (0)	0 (0)	1	1
Uterine hperstimulation	0 (0)	0 (0)	1	

IV. Discussion

The management of term premature rupture of membrane has remained a controversial topic in Obstetrics, with Obstetricians torn between immediate induction of labour and expectant management. With the findings of the International term PROM trial which suggests greater maternal satisfaction and lower risk of infection for immediate induction of labour compared with expectant management[5], most Obstetrician now lean towards offering immediate induction of labour to patients with term PROM. A method of induction of labour which results in a satisfactory outcome for both mother and baby is therefore desirable. Intravenous oxytocin titration has a prime position as a choice agent for induction of labour following PROM. It has been shown to be efficacious for this purpose[5]. However, as oxytocin induces mainly uterine contractions, there are concerns with commencement of induction of labour with oxytocin titration in the presence of an unfavourable cervix[3,5]. Hence, the need to determine as in this study if there is a difference in outcome when a cervical ripening agent such as misoprostol is used for induction of labour.

The comparisons of the maternal socio-demographic variables in the two arms of the study showed similarities in the mean age, occupation, parity and highest educational level. Any difference noted was not statistically significant giving credence to the randomization process. The baseline variables of participants at presentation when compared for the two arms of the study were also similar and not statistically significant. These baseline variables include gestational age, Bishop score before commencement of induction of labour, duration of rupture of membranes and admission hematocrit at the time of diagnosis of term PROM and randomization into the study. Some of these variables mentioned can affect directly or indirectly the progress and duration of labour in the setting of term PROM. This also gives credence to results of the study as they were unlikely to be confounded by these baseline variables.

The mean time taken to achieve three contractions in the two groups were comparable. The difference noted was not statistically significant. Parturients in both arm of the study achieved three contractions within three hours of commencement of induction of labour on the average. Achieving three contractions early is a good prognostic factor in induction of labour.

The mean time taken to achieve active phase parameters was shorter for the parturients in the misoprostol group compared to the oxytocin group. This difference was statistically significant. Misoprostol is a pros2taglandin E1 analogue and acts to soften the cervix while also inducing uterine contractions in the process. With its primary action on the cervix, it is expected that parturients in the misoprostol group would achieve active phase parameters faster that the oxytocin group, oxytocin having its primary action on the myometrium of the uterus. This was different from the findings of Pouralil et al observed a shorter time interval between induction of labour and achieving active phase parameters in favour of the oxytocin group in their study21. The authors of this study did not describe their method of randomization and blinding which can introduce bias in all aspects of the research. This cannot be ruled out as a factor in the results obtained. They however had two groups of pregnant women with term PROM who received 25 micrograms of misoprostol and low dose oxytocin titration respectively as in the index study. The time taken to achieve full cervical dilatation was also observed to be shorter for participants in the misoprostol arm compared to the oxytocin arm. This difference was statistically significant. The progress of labour is measured by cervical dilatation and descent of the presenting part. Misoprostol induces both uterine contraction and cervical changes which are important factors in cervical dilatation and descent of the presenting part. This may explain the difference noted in both arms of the study. This finding agrees with the findings from Pouralil et al, Ameen et al, Suhan et al and Ezechi et al[10,11,21] who all found a shortened duration of induction to full cervical dilatation for the misoprostol arm compared to the Oxytocin arm. This similarity may be explained by the action of misoprostol on the cervix compared with oxytocin that primarily acts on the myometrium.

The induction delivery interval was shorter in the misoprostol arm compared with the oxytocin arm and this difference was statistically significant. This finding is not surprising as participants in the misoprostol arm also achieved full cervical dilation faster in this study as stated above. This finding was similar to the findings by Pouralil et al, Ameen et al, Suhan et al and Ezechi et al[10,11,21,23] who all found a shorter interval from induction to delivery in parturients who received misoprostol. Misoprostol enhances cervical dilatation and in effect labour progress. These studies also used similar protocols as in this study. These may have accounted for the similarities noted.

Majority of the patients in the misoprostol arm achieved vaginal delivery compared with those in the oxytocin arm (83.3% vs 52.5%). This difference was statistically significant. It can be deduced from the foregoing that administration of misoprostol reduced the odds for Caesarean delivery compared with oxytocin. Patients with PROM who received misoprostol were more likely to deliver vaginally. Caesarean section rates were statistically significant when comparison was made between the groups (33% vs 10% in the oxytocin and misoprostol groups respectively). The indications for C/S in the two arms were mainly due to suspected foetal distress and poor progress of labour. Augmentation of labour with Oxytocin titration was done for 15 participants in the misoprostol arm.

0ut of the 240 babies born in both groups, 15 suffered neonatal asphyxia in the Oxytocin arm while none suffered asphyxia using the 5th minute Apgar score. These neonates also required neonatal intensive care admission. The difference noted in these two outcomes were statistically significant. This difference noted may be attributed to the longer duration of labour noted in the Oxytocin arm which was statistically significant compared to the misoprostol arm. These foetuses were exposed for a longer duration to the effects of uterine contraction and other possible factors that follow a longer duration of labour. Induction of labour can be allowed for up to a period of 16 hours provided there are no signs of fetal or maternal compromise. Over all, parturients in the misoprostol arm delivered on average, within 5 hours of commencement of induction of labour. There were no neonatal deaths in both groups. The finding from the 5th minute Apgar score was similar with those from the study done by Pouralil et al[21] who also found that the 5th minute Apgar score was significantly better in the misoprostol arm compared to the Oxytocin arm. However, they noted no statistically significant difference in the groups for the need for NICU admission. This difference in outcome may be accounted for by the finding of no statistically significant difference in the need for resuscitation of the asphyxiated babies in their study, compared

to the index study where all asphyxiated babies required further observation in the NICU after the initial resuscitation. Suhas et al, Ameen et al also reported similarities in the groups as regards 5th minute Apgar score, need for resuscitation and NICU admission[11,12].

In this study, tachysystole, hypertonus or uterine hyperstimulation were not noted in any of the groups. However, a significant number in the misoprostol arm had shivering and nausea/diarrhoea compared with the Oxytocin group. Shivering and nausea and vomiting are well known side effects of misoprostol especially when administered sublingually, with bioavailability of the drug approaching that of intravenous administration of drugs. These findings differed from those of Ameen et al[12] in which they reported a threefold increase in the incidence of tachysystole (more than five contractions in 10 minutes without foetal heart irregularity) among the participants, though the difference was not statistically significant. There was also no significant difference in the incidence of hypertonus and uterine hyperstimulation among the participants in their study. Suhas et al[11] also found an increased incidence of tachysystole in their participants who received misoprostol. This difference was noted to be statistically significant. The differences noted may be attributed to differences in the route of administration of misoprostol and protocol for induction of labour observed in these studies, compared to the index study. Pouralil et al also noted a higher incidence of tachysystole in the misoprostol arm compared to the oxytocin arm[15].

V. Conclusion

This study demonstrated that administration of 25µg of sublingual misoprostol had a good fetomaternal safety profile, can shorten the induction delivery interval and significantly reduce the Caesarean section rate in women with term PROM undergoing induction of labour at the Alex Ekwueme Federal University Teaching Hospital, compared to Oxytocin. Its use however was associated with mild side effects such as shivering and nausea/vomiting.

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Conflict Of Interest
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