

Impact of combined intramuscular hyoscine and vaginal misoprostol on the median number of misoprostol insertion and time to achieve full cervical ripening in post-date pregnancies in federal medical center Owerri, Nigeria

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Abstract

Background: Failed induction of labour is a challenge to both the Obstetrician and patients and remains a common cause of primary caesarean section. Misoprostol, a prostaglandin E1 analogue has been frequently used for cervical ripening and induction of labour with variable outcomes and Hyoscine N-Butyl bromide, which is a smooth muscle relaxant, has been studied widely for its use in labour. The combined effect of both drugs for cervical ripening and labour induction may have a better outcome in labour.

Objectives: To compare the impact of combined intramuscular hyoscine and vaginal misoprostol as opposed to vaginal misoprostol alone on the median number of misoprostol insertion and time to achieve full cervical ripening in post-date pregnancies in Federal Medical Center Owerri, Nigeria.

Study Design: A randomised double blinded clinical trial involving post-date pregnant women who received combined intramuscular hyoscine and vaginal misoprostol and those who received vaginal misoprostol only for cervical ripening and induction of labour.

Methodology: A total of 130 postdated pregnant women who satisfied the inclusion criteria were recruited for the study by systematic sampling. These were equal number of 65 participants each as case and control. They were matched for gestational age and social status. The case group received both vaginal misoprostol and intramuscular hyosine while the control received vaginal misoprostol alone for cervical ripening and induction of labour. The results were analysed using SPSS version 21 with appropriate tables and figures generated.

Results: The mean induction-delivery interval was (18.74±3.00 hours) in women who were given vaginal misoprostol + placebo and (16.6 ±3.00 hours) in those who received both vaginal misoprostol and intramuscular hyoscine. The median number of misoprostol inserted in the placebo group was 2 (2,3) while for hyoscine group it was 3(2,3). The

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mode of delivery between the hyoscine group and the control group did not show any statistically significant difference ($P=0.152$).

Conclusion: The combined intramuscular hyoscine and vaginal misoprostol for cervical ripening and induction of labour as opposed to vaginal misoprostol alone reduces the median number of misoprostol insertion as well as the time to achieve full cervical ripening.

Recommendations: The use of combined intramuscular hyoscine and vaginal misoprostol for cervical ripening and induction of labour should be routinely implemented and also the use of hyoscine pessaries with vaginal misoprostol can be studied to see if there would be a different outcome.

Keywords: Intramuscular; Hyoscine; Vaginal misoprostol; Cervical ripening; Insertion; Impact; Combined; Post-date pregnancies

1. Introduction

Over 20% of women undergo induction of labour, yet there is no conviction on which induction method achieves the shortest labour¹. The use of combined agents to decrease the labour length is an understudied, novel approach to shortening the time to delivery.¹ Many methods are currently been used for cervical ripening and they include mechanical methods like laminaria tent, and intracervical Foley's balloon catheter,^{2,3} however pharmacological agents like oxytocin and prostaglandins are increasingly being studied and are the most commonly used. Although oxytocin is a safe and effective initiator of uterine contractions, its success depends on prelabour cervical status⁴.

The prospective trial known as 'FOR MOMI' trial evaluated time to delivery interval with four routinely used methods of induction: misoprostol alone; concurrent misoprostol and cervical Foley catheter; cervical Foley catheter alone; and concurrent oxytocin and cervical Foley catheter.⁵ The researchers hypothesized that time to delivery would be shorter when combined methods are used than with misoprostol or Foley alone, and that there would be no increase in caesarean delivery, maternal or neonatal morbidity⁵.

Misoprostol is a synthetic 15-deoxy 16-hydroxy, 16-methyl analogue of the naturally occurring prostaglandin E1 that was originally manufactured for prevention and treatment of peptic ulcer diseases.⁶ Several studies have found that misoprostol is effective as an agent for cervical ripening and induction of labour. It is inexpensive, easy to store, and stable at room temperature.⁷ Misoprostol however can be challenging to use because most preparations in the market come in tablets of 200mcg. So, in order to get a 25mcg or 50mcg dose the tablets have to be divided into smaller pieces which may not accurately contain the desired dose of misoprostol required.

Although no trials have been conducted to compare the use of wetted misoprostol tablets and the dry tablets; however, some researchers have indirectly shown that the bioavailability of misoprostol when inserted vaginally appears to be greatly increased when the tablet is wetted. This is useful in the reduction of the adverse effects resulting from multiple insertion.⁸

Hyoscine N-Butyl bromide acts by inhibiting cholinergic transmission in the pelvic parasympathetic ganglia and antagonizing muscarinic receptors of smooth muscles in the abdomen and pelvic organs, thus relieving spasm thus aiding cervical dilatation.⁹ Some researchers have studied the effect of combining vaginal misoprostol with Hyoscine on shortening the time for induction of abortion, while some others have studied the effect of hyoscine on the first stage of labour, and its effect on cervical dilatation.^{10,11} Hyoscine has also been used to prime the cervix prior to intrauterine procedures,¹² however there are no studies of its use in cervical ripening and induction of labour.

A study by Javadi et al observed a statistically significant difference in the mean duration of abortion induction when they compared a combination of misoprostol and hyoscine versus misoprostol alone. ($653.38\text{min} \pm 80.386\text{min}$ vs $726.29\text{min} \pm 64.56\text{min}$) respectively.¹⁰

Studies on the impact of combined intramuscular hyoscine and vaginal misoprostol on the median number of misoprostol insertion and time to achieve full cervical ripening in post-date pregnancies in Nigeria are minimal. This represents a knowledge gap which this study will provide answer to. This study aims to compare the impact of combined intramuscular hyoscine and vaginal misoprostol as opposed to vaginal misoprostol alone on the median number of misoprostol insertion and time to achieve full cervical ripening in post-date pregnancies in Federal Medical Center Owerri, Nigeria.

Methodology

1.1. Study Area

The study was conducted in the department of Obstetrics and Gynaecology of the Federal Medical Centre, Owerri, Imo State, South-East Nigeria. Imo State has a population of 4.6 million people of which 26.8% are women of reproductive age group¹³. Owerri is the capital city and has a population of 470,000 people¹³. Federal Medical Centre Owerri is a Tertiary Health Facility that trains Resident Doctors in all medical and surgical specialties and also provides health care to the people in the city of Owerri as well as nearby semi-urban settlements and neighbouring towns. It receives clients from other States in Nigeria such as Abia and River States as well. The labour ward has 12 beds and about 1800 deliveries are undertaken annually.

1.2. Study Population

The study population were post-date pregnant women who were sure of their last menstrual period or had an early gestational ultrasound scan who presented to the labour ward for cervical ripening and induction of labour.

1.3. Inclusion Criteria

Primigravida, singleton pregnancy, post-date pregnant women with no contraindications to vaginal delivery, no previous history of cervical injury, Bishops score ≤ 5 and cephalic presentation.

1.4. Study Design

The study was a randomised double blinded clinical trial involving two groups namely; post-date pregnant women who received 25 micrograms of vaginal misoprostol 6 hourly till a maximum of 4 doses and a stat dose of intramuscular hyoscine butyl bromide (20 mg) and post-date pregnant women who received 25 micrograms of vaginal misoprostol 6 hourly till a maximum of 4 doses as well as a stat dose of intramuscular water for injection as placebo.

1.5. Study Tool

The study tool was data collection sheets.

1.6. Sample Size

The sample size was 130 comprising 65 eligible participants who received 25 micrograms of vaginal misoprostol 6 hourly till a maximum of 4 doses and a stat dose of intramuscular hyoscine butyl bromide (20mg) and 65 eligible participants who received 25 micrograms of vaginal misoprostol 6 hourly till a maximum of 4 doses as well as a stat dose of intramuscular water for injection as placebo. It was determined by a previously validated formula for randomised clinical trial¹⁴.

1.7. Sampling Technique

The sampling method was systematic sampling. First, post-date pregnant women were screened to determine those who satisfied the inclusion criteria. Second, the eligible participants were randomized using a computer-generated random number. The materials were placed in Sequentially Numbered Opaque Sealed Envelopes. Half of the envelopes (65) contained 4 doses of 25microgram misoprostol tablets, one ampoule of Hyoscine buytl bromide, and one 2 ml syringe in each of them, while the other half contained 4 doses of 25microgram misoprostol, one ampoule of injection water and one 2ml syringe.

1.8. Patients Recruitment

Having obtained informed consent to participate in the study from eligible participants their weights and heights were measured using the stadiometer and the Body mass index derived from the formula $\text{Weight(kg)}/\text{Height(m)}^2$. They were assigned a sequential study number. The researcher and the research assistants then allocated treatment based on the corresponding number. The participants either received 25 μg intravaginal misoprostol which was repeated every 6hours as indicated and Intramuscular hyoscine 20mg stat or 25 μg intravaginal misoprostol to be repeated 6hourly as indicated as well as a stat dose of 1ml intramuscular water for injection. The initial Bishop's score was recorded and patients were examined every 4 to 6 hours to check for any improvement in the Bishops score and the need for further insertions of misoprostol. When the cervix was adjudged to be ripe, an artificial rupture of membranes was done and the labour was monitored with the aid of a partograph till delivery. Augmentation of labour instituted when it was absolutely needed.

Recruitments were done by the researcher with assistance from the first research assistant. The research assistants were two junior resident doctors who were trained about the study protocol (such as the contents of the information sheet, consent form, data collection sheet and also sample collection) daily for one week before commencement of the study. The second research assistant did not know the participants' details. His only duty was to administer medical thus the researcher and the participants did not know whether the participants are receiving hyoscine or placebo.

1.9. Data Collection

Following informed consent from the post-date pregnant women who met the inclusion criteria, a detailed history was obtained including socio demographic characteristics such as; patient initials, hospital number, research number, age, address, occupation and highest educational attainment and a physical examination was conducted such as; anthropometric measurements (weight, height, body mass index and blood pressure).

In the presence of a chaperone, a pelvic examination was carried out to assess the pre-induction cervical inducibility score and it was recorded. This was reassessed 4 hourly or as indicated till delivery. The examination was conducted as follows: The patients were placed in the dorsal position on the examination couch, and with the researcher adorning sterile gloves; the vulva was wiped with dilute chlorhexidine solution from front to back. The middle finger of the examining hand was used to gently depress the posterior fourchette, then the index and middle finger were introduced gently into the vagina to the posterior fornix. The cervix was identified and the position determined. The consistency of the cervix was then noted and the cervical length estimated. The examining fingers were moved laterally to palpate the ischial spines and the station estimated. The middle finger was then gently inserted through the cervix to the internal os and the cervical dilatation was estimated. The presence of amniotic membrane was also ascertained. A clinical pelvimetry was done by attempting to touch the sacral promontory, then the fingers ran along the curve of the sacrum to check its concavity, the ischial spines were also palpated laterally and the subpubic angle was checked. The examining finger was withdrawn gently and examined for any discharge. The patient was assisted to lie in the left lateral position after the examination. The information obtained were documented in the data collection sheets.

1.10. Data Analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 21.0. Statistical analysis was performed with Chi-square for categorical variables, student's *t*-test for normally distributed continuous variables, Mann-Whitney U for continuous variables that are not normally distributed. In all statistical analyses, $p < 0.05$ (95% confidence interval) was considered significant. Results were presented using tables and figures.

2.11 Limitation of the study

Hyoscine comes in ampoules of 1ml and it was difficult getting a similar 1ml ampoule of water for injection to serve as a placebo as most of the available water for injection come in 10mls ampoules, however the bias was reduced by using opaque sealed envelopes to store the materials.

The indication for induction of labour in this study was only postdatism hence, the findings are not generalized to patients who have other indications for labour induction.

2. Results

The study was conducted over a period of 6 months (July 2017 to December 2017). A total of 130 participants were recruited into the study and none dropped out of the study. A total of 65 women had their cervix ripened with misoprostol and a placebo (sterile water for injection) while the other 65 women were given misoprostol and a stat dose of Hyoscine N-butyl bromide.

Table 1 Mean Age of Respondents

Group	Mean \pm SD (hours)	t-test	p value
Case	28.45 \pm 3.21	1.709	0.090
Control	27.55 \pm 2.95		

Table 1 showed a mean age of 28.45 \pm 3.21 in the case group and 27.55 \pm 2.95 in the control group which was not statistically significant.

Table 2 The sociodemographic characteristics of the cases and the control

Characteristics	CASES N (%)	CONTROL N (%)
Level of education		
Secondary	18(27.7)	15(27.7)
Tertiary	47(72.3)	50(76.9)
Patients Occupation		
Professional	24 (36.9)	27 (41.5)
Trader	22 (33.8)	17 (26.2)
Student	11 (16.9)	17 (26.2)
Unemployed	8 (12.0)	4 (6.2)
Husbands occupation		
Professional	42 (64.6)	2(0.5)
Trader	23 (35.4)	30 (46.2)
Tribe		
Igbo	62 (95.4)	64 (98.5)
Yoruba	1 (1.5)	1 (1.5)
Hausa	1 (1.5)	0 (0)
Ebira	1 (1.5)	0 (0)
Booking Status		
Booked	63 (96.9)	63 (96.9)
Unbooked	2 (3.1)	2 (3.1)

Table 2 showed that out of the 65 participants who received Hyoscine, 47 (72.3%) had tertiary education while 18 (27.7%) had secondary level of education while in the control group, 50 (76.9%) had tertiary education while 15 (23.1%) had only secondary education. The occupational status of the case group was as follows; 24 (36.9%) were professionals, 22 (33.8%) Traders, 11(16.9%) and 8 (12.0%) were unemployed, while in the control group, 27(41.5%) were professionals, 17(26.2%) were traders, 17 (26.2%) students and 4(6.2%) were unemployed.

Majority of the participants in the case group were of the Igbo tribe 62(95.4%) while Yoruba, Hausa and Ebira tribes had one participant each giving a percentage of 1.5% respectively. A similar trend was seen in the control group, where 64 (98.5%) were Igbos and one Yoruba parturient (1.5%).

Booked participants constituted 63 (96.9%) each in both the case and control group, and formed the bulk of the participants, while there were only 2(3.1%) participants in either group who were unbooked.

Table 3 Pre-induction Bishop Score

Group	Median (IQR)	Mann-Whitney U	p value
Case	4(3,4)	2105.5	0.972
Control	4(3,4)		

Table 3 showed that the median cervical inducibility score of both study groups was 4 with an interquartile range of (3,4). Mann-Whitney U test was 2015.5 with a P value of (0.92) which did not show any statistically significant difference in the pre-induction cervical inducibility scores of both the cases and control.

Table 4 Median number of misoprostol inserted

Group	Median (IQR)	Mann-Whitney U	p value
Case	2(2,3)	1460.00	< 0.0001
Control	3(2,3)		

Table 4 showed that Mann-whitney U test was used to determine any difference in the number of misoprostol insertions between the two groups. The median number of misoprostol inserted in the placebo group was 2 (2,3) while for hyoscine group it was 3(2,3). The median number of misoprostol inserted differed significantly between the two groups, with the placebo group having more misoprostol insertions.

Table 5 Need for labour augmentation

Group	Labour Augmented?		\bar{X}^2	p value
	Yes	No		
Case	18	47	11.38	0.001*
Control	37	28		

Table 5 showed that augmentation of labour was done for 18 women amongst the cases while 37 women had their labour augmented among the control group. A P value of 0.001 was got using chi square and it showed a statistically significant difference between the two groups

Table 6 Time to achieve full cervical ripening

Group	Median (IQR)	Mann-Whitney U	p value
Case	8(6,10)	1098.5	< 0.0001*
Control	10(8,12)		

Table 6 showed that there was a statistically significant difference in the interval from commencement of cervical ripening to achieving full cervical ripening between the two groups.

Table 7 Mean induction-delivery interval

Group	Mean±SD (hours)	t test	p value	95% CI
Case	16.06±3.00	5.050	< 0.0001*	1.61 - 3.68
Control	18.74±3.00			

Table 7 showed the mean induction delivery interval between the parturients who were given vaginal misoprostol + placebo (18.74±3.00 hours) and those who received both vaginal misoprostol and intramuscular hyoscine butyl bromide (16.6 ±3.00 hours) The mean Induction-Delivery Interval was significantly higher in the placebo group than in the hyoscine group which was statistically significant.

Table 8 showed that there was a statistically significant difference between the cases and control with respect to augmentation of labour. Labour augmentation was more in the placebo group as opposed to the case group. There was no statistically significant difference in the mode of delivery between the two groups. The mean birth weights of the neonates also showed no statistically significant difference between the two groups. The 5th Minute APGAR Scores for the Babies in both groups were between 9 – 10 (i.e. good APGAR scores) and were not statistically significant.

Table 8 Labour and delivery outcomes

	Cases	Control	\bar{X}^2	T test	P value
Labour augmented?					
YES	18	37	11.38		0.001*
NO	47	28			
Mode of delivery					
Vaginal	58	51	2.783		0.152
Abdominal	7	14			
Birth weight of babies					
Mean \pm SD	3.29 \pm 0.41	3.35 \pm .043		0.777	0.438

3. Discussion

This study found out that there was no significant difference in the socio-demographic characteristics of the participants however, the vast majority of the participants in both study groups were from the Igbo tribe of Nigeria. This finding was in-keeping with the fact that the study was conducted in a tribe in Nigeria called Igbo.

The mean induction to delivery interval measured in hours was 16.6 \pm 3.00 in women who received both vaginal misoprostol and intramuscular hyoscine butyl bromide while the control group who received vaginal misoprostol and a placebo had a value of 18.74 \pm 3.00. This showed a statistically significant difference in the induction delivery interval, with the hyoscine group having a significantly shorter duration of labour than the control group. A similar pattern was also seen when the interval from commencement of cervical ripening to a cervical dilatation of 4cm was measured as the interval was also significantly shorter in the hyoscine group than the placebo group, 8 hours (6,10) median (IQR) and 10 hours (8,12) median (IQR) respectively. These findings were in agreement with results of the study by Javadi et al., who compared the effect of adding hyoscine to vaginal misoprostol on shortening the time of abortion induction. The mean duration of abortion induction using Misoprostol with Hyoscine represented statistically significant decrease compared with Misoprostol and placebo (653.38 \pm 80.386 min, with 726.29 \pm 64.56 min).¹⁰ Another study that compared the effect of hyoscine butyl-bromide on the duration of active phase of labor showed that the observed mean duration of the active phase of labor was significantly shorter in the Hyoscine butyl-bromide group (365.11 \pm 37.32 min, range = 280-490) than in the Placebo group (388.46 \pm 51.65 min, range = 280-525)¹⁵.

However, a Nigerian study on the effect of Hyoscine Butyl Bromide on the course of labour gave a contrasting result as there was no significant difference in the mean duration of active labour to second stage between the hyoscine and placebo arms (312.5 versus 305.3 minutes, respectively, P = 0.788)¹⁶. This may be explained by the fact that in their study, the women presented with spontaneous onset of labour and were all multigravida.

The dose of misoprostol tablets required to achieve a favourable cervix was also measured in this study and it was found that the median number of 25microgram misoprostol inserted differed significantly between the two groups, with the placebo group having more misoprostol insertions. The median number of 25microgram misoprostol inserted for the misoprostol+hyoscine group was 2 with and inter quartile range of 2,3 while that of the placebo group was 3 with an inter quartile range of 2,3. The study by Adeniyi et al showed a similar pattern, as the mean number of 25 microgram misoprostol needed to achieve a full cervical ripening was 1.8 \pm 1.1 however there was no concurrent use of hyoscine butyl bromide which might have given a different picture.¹⁴

The mode of delivery between the hyoscine group and the control group did not show any statistically significant difference. Several other studies showed a similar pattern as seen in Adeniyi et al where there was no statistically significant difference in the mode of delivery following misoprostol use for cervical ripening and induction of labour.¹⁴ Girija and Manjunath also reported a similar finding, with no statistically significant difference in the caesarean section and vaginal delivery rates¹⁷.

Other secondary outcomes like the need for labour augmentation were also analyzed in this study, and the difference was found to be statistically significant, as more participants in the control group needed augmentation of labour

compared with the experimental group. This is in consonance with the study by Adeniyi et al where the need for augmentation of labour was also significant¹⁴.

The birth weights of the neonates were analysed using the students T test and no difference was found in the birth weights from both the experimental and control groups. Barau D. et al also showed no statistically significant difference between the birthweights of neonates seen in both groups¹⁶.

The 5th minute APGAR score in the study ranged between 9 and 10 in both groups and none of the neonates required admission into the special care baby unit suggesting that there was no significant effect of hyoscine on any of the major organ systems of the neonates and this finding is comparable to similar studies.^{15,15,16}

4. Conclusion

The combined intramuscular hyoscine and vaginal misoprostol for cervical ripening and induction of labour as opposed to vaginal misoprostol alone reduces the median number of misoprostol insertion as well as the time to achieve full cervical ripening.

Recommendations

Further studies can be carried out on women with indications for cervical ripening and induction of labour other than post-date pregnancy.

Use of hyoscine pessaries with vaginal misoprostol can also be studied to see if there would be a different outcome.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

An institutional approval for this study was obtained from the Ethical Review Committee of Federal Medical Center, Owerri.

Statement of informed consent

Informed written consent was obtained from each participant after adequate counselling and the data obtained from the study were treated with confidentiality and used solely for the purpose of the study.

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