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■ Original Research Article

A Randomized Controlled Trial of Effects of Oral Propranolol on the Duration of Oxytocin Labor Induction Among Nulliparous Women in Abakaliki, Nigeria.

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Abstract

Background: Prolonged labor, despite oxytocin induction, is a common obstetric challenge of nulliparity. Due to paucity of literature, this study was aimed at assessing synergistic role of oral propranolol on improving labor induction towards decreasing maternal morbidity and mortality. **Methodology:** Study design was open labelled superiority randomized controlled trial, among eligible nulliparous women recruited by simple random sampling. Following computer-assisted randomized allocation to study groups, group A received 20mg of oral propranolol 10 minutes before oxytocin induction, while group B were only oxytocin induced, with partograph monitoring for all subjects. Study duration was six months. **Analysis:** SPSS version 25.0 used to enter and analyze data. The main outcome measure was duration of induction in minutes. Associations between continuous variables were analyzed using Fisher's exact test while the chi-square ($\chi 2$) test was used for categorical variables to compare mean. P-value was set at 0.05. **Results:** Duration of labor was normally distributed. Comparing groups A and B, there was no significant difference in mean duration of labor in minutes for total (559.2 vs. 560.9), as well as each of the stages comprising latent phase (243.0 vs. 238.2), active phase (282.8 vs. 330.4) second stage (35.6 vs. 34.7) and third stage (10.0 vs. 12.0) ($p>0.05$). **Conclusion:** Administration of 20mg oral propranolol prior to induction of labour with oxytocin did not accelerate labour progress. So higher doses with or without multiple dosing should be considered in future studies.

Keywords: Propranolol, Labour, Induction, Nullipara

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Introduction

Labour is a physiological process[1-3] and ideally should be spontaneous and progressive.[2-4, 6-9] However, there may be need for induction of labour especially in nulliparous women who are at increased risk of postdatism.[4,5] This procedure is not without its complications.[1,5] Therefore, shortening the duration of labour without compromising the maternal and neonatal wellbeing is the goal of every obstetrician.[1] Induction of labour is indicated in cases of prolonged pregnancies or for other maternal or fetalreasons. [4,10] In 2018, Ikeotuonye et al in Abakaliki, reported 2.76% induction rate with 75.4% success rate[11] while in 2006, Ibekwe and Obuna in Abakaliki noted that poor progress/prolonged labour accounted for 10.7% of the indications for caesarean section. [12]

Labour management involves interventions that aims at safe mother and quality baby that grows into good adulthood rather than watchful waiting.[13] Some pharmacological agents like oxytocin and prostaglandins are used conventionally in obstetrics for induction of labour. However, prolonged labour and its sequale still occur necessitating search for new agents like the use of beta-receptor antagonists like propranolol working in synergy with oxytocin to shorten the duration of labour without compromising maternal and neonatal outcomes.[4,10,14-17] This is because of the role of uterine contractions in the labour process.[4,18,19] Adrenaline secretion is increased during labour because of pain and anxietyassociated with it and this has been noted to dapplethe effectiveness of uterine contraction leading to dysfunctional labour[20]. This effect has been found to be inhibited by propranolol use in labour.[4]

Few studies have demonstrated the effectiveness of propranolol, a non-selective beta-blocker and the oldest beta receptor antagonist with wide therapeutic index[21-25], in potentiating labour progress during induction.[4,10,14-17] This pool of evidence suggests a significant reduction in the duration of labour with none or minimal side effects in patients who receive propranolol in labour. [4,10,14-17]

The role of propranolol in accelerating labour progress during induction of labour has not been evaluated in West Africa, within the limits of our search. More so, epinephrine, which is a tocolytic and secreted more with stress and anxiety of labour, is found more in black than white women.[18,26-29] The introduction of a beta blocker which antagonizes epinephrine effect might eliminate the effect of epinephrine and lead to improved labour outcome[30,31]. The effect of this drug on labour has not been demonstrated among Nigerian nulliparous women. This study is conceived to fill this knowledge gap.

Methodology

This was a clinical superiority open labeled, randomized controlled trial on the effectiveness of oral propranolol in shortening the duration of labour during induction of labour in the department of Obstetrics and Gynaecology of Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA) and Mile 4 Hospital Abakaliki, all in Ebonyi State of Nigeria[32]. The study included only nulliparous women who met the inclusion criteria and consented to the study. Total of 28 nulliparous women were recruited for the study and were randomized using the software Research Randomiser. Patients were recruited[33] into the appropriate arm and labour was monitored with partograph according to departmental protocol for induction of labour[36].

Group A: Received 20 mg of Propranolol orally before the commencement of oxytocin titration.

Group B: Had only oxytocin titration.

The primary outcome measures were the total mean duration of labour and the mean durations of 1st, 2nd and 3rd stages of labour. Secondary outcomes were total mean dosage of oxytocin used in active phase labour, mode of delivery, indications for caesarean section, Maternal outcome (mean pulse rate and blood pressure), fetal outcome (mean fetal heart rate), and Neonatal outcome (mean APGAR scores at 1st and 5th minutes, neonatal intensive care admission).

Data Collection and Analysis

All data sheets were collected at the end of the study. The sheets were separated using the record of

randomization sequence; their data were recordered in the appropriate groups. The generated data were analysed with IBM-SPSS software version 22 (Chicago II, USA) 2015. Absolute and relative frequencies and percentages of categorical variables; mean, range and standard deviation of continuous variables were calculated. Fisher's exact-test was used for comparison between groups for continuous variables while chi-square ($\chi 2$) test was used for categorical variables. P-value of ≤ 0.05 was taken as significant.

Ethical Considerations

Ethical clearance was obtained from the Hospital and Research Committee (HREC) of the Alex Ekwueme Federal University Teaching Hospital and Mile Four Hospital, Abakaliki.

Results

Over the study period, a total of 28 participants who met the inclusion criteria were recruited into the study. The subjects were equally distributed between group A (oxytocin and propranolol) and group B (oxytocin only).

Table I: General Characteristics Among the Groups

VARIABLES	A (N=15) Mean± SD Range	B (N=13) Mean± SD Range	Fisher's exact-test	P-value
Mean Age (years)	25.47±4.55 18-36	26.08±4.941 20-37	0.340	0.736
Mean GA (weeks)	39.8±1.095 38-41	39.5±0.58 36^{+3}-41^{+6}	0.986	0.333
Mean BW (kg)	2.93±0.547 2-4	3.27±0.578 2-4	1.594	0.123
Mean HT (cm)	159.2±7.720 144-173	162.77±6.21 156-177	1.334	0.194
Mean WT (kg)	75.27±8.004 64-90	80.62±10.05 63-98	1.567	0.129

N/B: GA: Gestational Age, BW: birth weight, HT: height, WT: weight.

The table showed the general characteristics among the groups. The means, standard deviations, ranges and the tests of significance of the parameters are as seen on the table. All the parameters were statistically not significant.

The table showed the labour intervals among the group and its statistical comparism. All the labour intervals in the induction group (P-values; total mean duration of labour = 0.978, latent phase =
0.940, active phase = 0.207, 2nd stage = 0.934 and 3rd stage = 0.555) and other parameters (mean Bishop's Score (P=0.409), mean cervical dilation on commencement of induction (P=0.850) or augmentation (P=0.261), mean oxytocin strength used (P-values: induction = 0.9059, augmentation = 0.5934); mean terminal drop per minute of oxytocin titration (P-values: induction = 0.9808, augmentation = 0.6975)) were not statistically significant.

Table II: Labour Outcomes Between the Groups

VARIABLES	A (N=15) Mean± SD Range	B (N=13) Mean± SD Range	Fisher's exact-test	P-value
Mean Bishop's Score (cm)	7.6±1.72 3-10	8.08±1.2 7-11	0.839	0.409
Mean Cervical dilation on commencement (cm)	2.8±0.41 2-3	2.8±0.44 2-3	0.409	0.850
Mean 1st stage duration (minutes)				
-Latent phase	243.0±183.7 60-660	238.2±144.8 60-486	0.077	0.940
-Active Phase	282.8±64.7 140-380	330.4±123.2 150-560	1.294	0.207
Mean 2nd stage duration (minutes)	35.6±15.9 20-80	34.7±27.4 20-150	0.085	0.934
Mean 3rd stage duration (minutes)	10±3.2 5-15	12±10.4 2-30	0.603	0.555
Mean Total duration of labour (minutes)	559.2±147.99	560.9±168.34	0.028	0.978
Mean Oxytocin used (iu)	11.33±3.5	10.8±2.8	0.1182	0.9059
- Strength	10-20	10-20		
- Terminal drops/minute	48±14.24 10-60	48.5±15.2 20-60	0.024	0.9808

Table III: Mode of Delivery Between the Two Groups

VARIABLES	A (N=15) (N)Percentage	B (N=13) (N)Percentage	X^2-test	P-value
SVD	(11)73.3%	(5)38.5%		
C/S	(4)26%	(7)53.8%	8.138	0.104
Vacuum	(0)0%	(1)7.7%		

N/B: CS: caesarean section., SVD: Spontaneous Vaginal delivery

This table showed the mode of delivery between the two groups. The percentages, frequencies and the tests of significance of the parameters are as seen on the table.

Table IV: Maternal Outcome (Pulse Rate and Blood Pressure) Among the Groups

VARIABLES	A (N=15) Mean± SD	B (N=13) Mean± SD	Fisher's exact-test	P-value
Mean PR (beat/min): Before	87.8±18.9	88.2±10.4	0.0886	0.9294
After	93.1±17.1	92±13.3	0.099	0.9211
Change in PR Before-After	t=0.2079 P=0.8353	t=0.2251 P=0.8219		
Mean SBP: Before	129.3±15.8	29.2±16.6	0.0434	0.9654
After	122.7±16.2	126.9±12.5	0.2175	0.8278
Change in SBP Before-After	t=0.2917 P=0.7705	t=0.1107 P=0.9119		
Mean DBP: Before	80±9.3	81.5±14.1	0.0916	0.927
After	78±12.07	77.7±13.01	0.1866	0.852
Change in DBP Before-After	t=0.1313 P=0.8956	t=0.1981 P=0.843		

N/B: PR: Maternal pulse rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table V: Fetal/Neonatal Outcome Between the Groups

VARIABLES	A (N=15) Mean± SD	B (N=13) Mean± SD	Fisher's exact-test	P-value
Mean FHR (beat/min): Before	148.4±8.4	143.2±17.6	0.4422	0.6583
After	150.1±6.8	142.5±18.3	0.4714	0.6374
Change in FHR Before-After	t=0.1573 P=0.875	t=0.0276 P=0.978		
Mean APGAR score at 1 min:	8.06±2.3	6.8±2.2	0.4402	0.6374
Mean APGAR score at 5 min:	9.3±1.2	8.9±1.6	0.1659	0.8682
Change in APGAR score at 1min-5min.	t=0.478 p=0.6327	t=0.772 p=0.8803		

N/B: FHR: fetal heart rate

Table VI: Neonatal Intensive Care Unit Admission Status

VARIABLES	A (N=15) N (%)	B (N=13) N (%)	X^2-test	P-value
Not admitted	10(66.7%)	8(61.5%)	2.00592	0.1567
Admitted	5(33.3%)	5(38.5%)		
Reason for admission				
None	(10)66.7%	(8)61.5%		
observation	(4)26.7%	(2)15.4%	6.340	0.160
Birth asphyxia	(1)6.6%	(3)23.1%		

N/B: NICU: neonatal intensive care unit

The table showed the maternal outcomes among the groups. The means, standard deviations and the tests of significance of the outcome measures are as seen on the table. There were no statistically significant differences in the entire outcome measure observed both in the induction and augmentation group.

The table showed the Fetal/Neonatal outcomes among the groups. The means, standard deviations and the tests of significance of the outcome measures are as seen on the table.
There were no statistically significant differences in the entire outcome measures observed.

The table showed the neonatal intensive care unit admission status among the groups. The frequencies, percentages and the tests of significance are as seen on the table. Majority of the neonates were not admitted. For those who were admitted, the reasons for admission were not statistically significant in all the groups.

Discussion

Induction of labour is usually employed following failure for natural labour to commence. However, is associated with attendant complications like prolonged labour. Therefore, eliminating its complications has necessitated studies on agents that can synergize with oxytocin and reduce its duration of exposure. Propranolol use with oxytocin during induction of labour has been found to be useful in this regard. Over the study period, a total of 28 participants who met the inclusion criteria were recruited. In this study, the general characteristics among the groups were homogenous. The Bishop scores prior to induction of labour and the cervical dilations did not show any statistically significant differences when groups were compared. These findings are in keeping with studies by Direkvand-Moghadam et al [4,] Amiri et al[14], Kashanian et al[17] and Marjani et al [9] where they also noted a homogenous population in their studies. The total mean duration was approximately equal and was statistically not significant. All other stages of labour were not statistically significantly shortened. This may be due to the short half-life of propranolol and considerably longer time it takes for induction of labour, so that within the course of induction of labour the effect of the drug should have worn off equilibrating those who did not receive propranolol. This means that when a single dose of propranolol is used in synergy with oxytocin for induction of labour, it does not shorten any of the labour intervals. Our findings corroborate with

some of the findings in a study by Amiri et al[14] who noted no difference in the duration of active phase and second stage of labour, however noted that the latent phase was shortened. This may be that both works were employed in induction of labour on nullipara but theirs used intravenous route and there was repetition of propranolol increasing the bioavailability of propranolol. This contrasts the findings in the studies by Direkvand-Moghadam et al[4], Pergialiotis et al[10], Kashanian et al[17] and Marjani et al[16] noted statistically significant differences in the duration of labour intervals. This may be that these studies had repeated dosing of propranolol with readmission and restarting if labour was not progressing, before considering caesarean section and they were not parity specific. But our study had a single dose on nullipara and induction was terminated the same day.

There were no changes in the difference in the mean strength of oxytocin and terminal drop per minute of oxytocin titration used. This may be that both groups had similar participants' characteristics. Our study is in line with the finding of Palomäkiet al[16] who noted no statistically significant differences in the oxytocin dosages when groups were compared. This may be that both our study and theirs have similar participant characteristics. In contrast, however, the studies by Kashanian et al[17] and Marshall[34] noted a reduction in the dosage of oxytocin used. This may be because of non-parity specific in the subjects and repeated dosing of propranolol used in their study compared to ours.

The majority of the participants in the propranolol group had spontaneous vaginal delivery. However, these findings did not show any statistically significant differences when groups were compared (P=0.104). This may be that though administration of propranolol was not able to make a statistical difference but may have contributed to reduction in cesarean section rate. So, propranolol may be used in labour when considering the need to reduce need for cesarean section. Our study is in keeping with the findings of Kashanian et al[17] were they noted that there was no statistically significant difference in caesarean section rate in both groups. This may be that the study had approximately the same sample size and parity was controlled before drawing conclusions. But contrast studies by Pergialiotis et al[10], Direkvand-Moghadam et al[4], Amiri et al[21] and Marjani et al[16] in induction of labour where they noted a significant difference in cesarean section rate compared to vaginal delivery. This may be that their studies were not parity specific and had repeated doses of propranolol on like our study that was on nullipara and had a single dose of propranolol.

There were not statistically significant maternal and fetal/neonatal haemodynamic changes noted. This may be because at the dose of 20 mg oral route that was the least oral route dose documented in literature within the limit of our search, propranolol had no haemodynamic effect and the oral route reduced the bioavaibility, but more effective[14]. This is in keeping with reports of some scholars who noted that propranolol has no significant maternal and foetal/neonatal haemodynamic effect when groups were compared[4,10,14-17]. This may be that these studies had approximately the same sample sizes with ours. But contrast study by LeWinter et al[35], who noted significant changes in pulse rate and blood pressure. This might be because they used 40mg while we used 20 mg oral propranolol.

Conclusion

This study showed that the administration of 20 mg oral propranolol prior to initiation of induction of labour did not accelerate labour progress. As such multiple dosing of 20 mg oral or higher single dose of oral propranolol should be studied to see if it will have effect on labour acceleration.

Conflict Of Interest: There was no conflict of interest.

Study Registration: ID: NCT05251610, ClinicalTrials.gov, https://register.clinicaltrials.gov/prs/app/action/LoginUser?ts=1&cx=-jg9qo4

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