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Original article

Does Oral Propranolol Accelerate Augmentation of Labour in Synergy with Oxytocin in Nulliparous Women? A Randomized Controlled Trial in Abakaliki, Nigeria

Darlington-Peter Chibuzor UGOJI [*1], Chidi ESIKE [2], Joshua Adeniyi ADEBAYO [2], Emmanuel Chijioke UWAKWE [2], Paschal Chijioke OKOYE [1], Chidubem Philip OSUAGWU [2], Odidika Ugochukwu Joannes UMEORA [2]

[1]Department of Obstetrics and Gynaecology, David Umahi Federal University Teaching Hospital, Uburu, Ebonyi State, Nigeria.
[2]Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital Abakaliki, Ebonyi State, Nigeria.

*Corresponding Author: Darlington-Peter Chibuzor UGOJI; *darlingtonpeter2012@gmail.com*

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Abstract

Objective: Propranolol, a beta blocker has been documented in few studies to act in synergy with oxytocin to accelerate labour progress. The only available systematic review is inconclusive, hence, the need for this study. ***Methodology:*** This research is a clinical superiority open labeled randomized controlled trial that involved only nulliparous women who met the inclusion criteria and gave consent to the study. Participants were randomized from a pool of 82 participants divided into A and B. Group A received 20 mg of oral propranolol and oxytocin titration while group B received only oxytocin titration. Partograph was used to monitor their labour. SPSS software was used for analysis. Continuous variables were analyzed using students t-test while chi-square ($\chi 2$) test was used for categorical variables. A P-value of <0.05 was considered significant. ***Results:*** The total mean duration of labour was statistically significant (P<0.001). The mean duration of active phase of labour was also statistically significant (P = 0.001). However, there was no significant difference in the 2nd stage (P=0.491)} and 3rd stage of labour (P=0.753)}. ***Conclusion:*** Administration of 20mg oral propranolol prior to augmentation of labour with oxytocin accelerated the total duration of labour and active phase of labour.

Clinical Trial. gov: - NCT05251610

Keywords: ***Propranolol, Labour, Augmentation, Nulliparous***

Introduction

Labour is a physiological process which is usually progressive [1,2]. Occasionally there may be delayed progress due to inadequate uterine contraction, which commonly occurs in nulliparous women [2]. This may result in unpredictable outcomes like prolonged labour, with associated poor maternal and neonatal outcomes [2]. Therefore, shortening the duration of labour without compromising the maternal and neonatal wellbeing is the goal of every obstetrician [2]. Augmentation of labour is a common obstetric intervention which is indicated in cases of poor progress of labour due to uterine inertia1 and this is routinely done using oxytocin titration [3].

The modern trend in labour management involves interventions that improve the progress of labour rather than watchful waiting [4]. Some agents have been used in labour with the aim of preventing prolonged labour [1,4,5]. Oxytocin, an uterotonic, is used conventionally in Obstetrics for augmentation of labour. However, prolonged labour and its sequale still occur; thus, necessitating the search for new agents like beta-receptor antagonists such as propranolol, which has been shown to work in synergy with oxytocin to shorten the duration of labour without compromising maternal and neonatal outcomes [5-11]. This method applies because of the role of uterine contractions and concomitant cervical dilatation in the labour process [12,13]. Labour pain and the associated anxiety increase adrenalin secretion, and this leads to dysfunctional uterine contractions through beta-adrenergic receptor stimulation. These receptors are inhibited by the use of beta-blockers like propranolol [10].

Data from studies have demonstrated the effectiveness of propranolol, a non-selective beta-blocker and the oldest beta receptor antagonist with wide therapeutic index in augmentation of labour [5-11]. This pool of evidence suggests a significant reduction in the duration of labour and a more coordinated uterine contraction that is able to cause an increase in cervical dilatation rate and descent

of the fetus with none or minimal side effects in patients who receive propranolol in labour [5-11]. However, this has only been evaluated in two randomized controlled studies in Africa, within the limits of literature search- one in South Africa [10] and the second in Egypt [9]. More so epinephrine, which is a tocolytic and secreted more with stress and anxiety of labour, is found more in black than white women [10,12,17-20]. The introduction of a beta blocker which antagonizes epinephrine effect might eliminate the effect of epinephrine and lead to improved labour outcome. The effect of this drug on labour augmentation has not been demonstrated among Nigerian nulliparous women. This study is therefore designed to assess the effects of this drug on labour augmentation among nulliparous women in Abakaliki, Nigeria.

Methodology

This was a clinical superiority open labeled, randomized controlled trial on the effectiveness of oral propranolol in shortening the duration of labour during augmentation of labour in nulliparous women at the department of Obstetrics and Gynaecology of Alex Ekwueme Federal University Teaching Hospital Abakaliki (AEFUTHA) and Mile 4 Hospital Abakaliki, all in Ebonyi State, Nigeria. The study included only nulliparous women who met the inclusion criteria and consented to the study. A total of 82 nulliparous women were recruited for the study. Randomization was done using a computer-generated random numbers with the aid of the software Research Randomizer. Patients were recruited into the appropriate arms. Participants in group A received 20 mg of Propranolol orally before the commencement of oxytocin titration, while those in group B received only oxytocin titration. Labour was monitored with partograph according to departmental protocol for augmentation of labour.

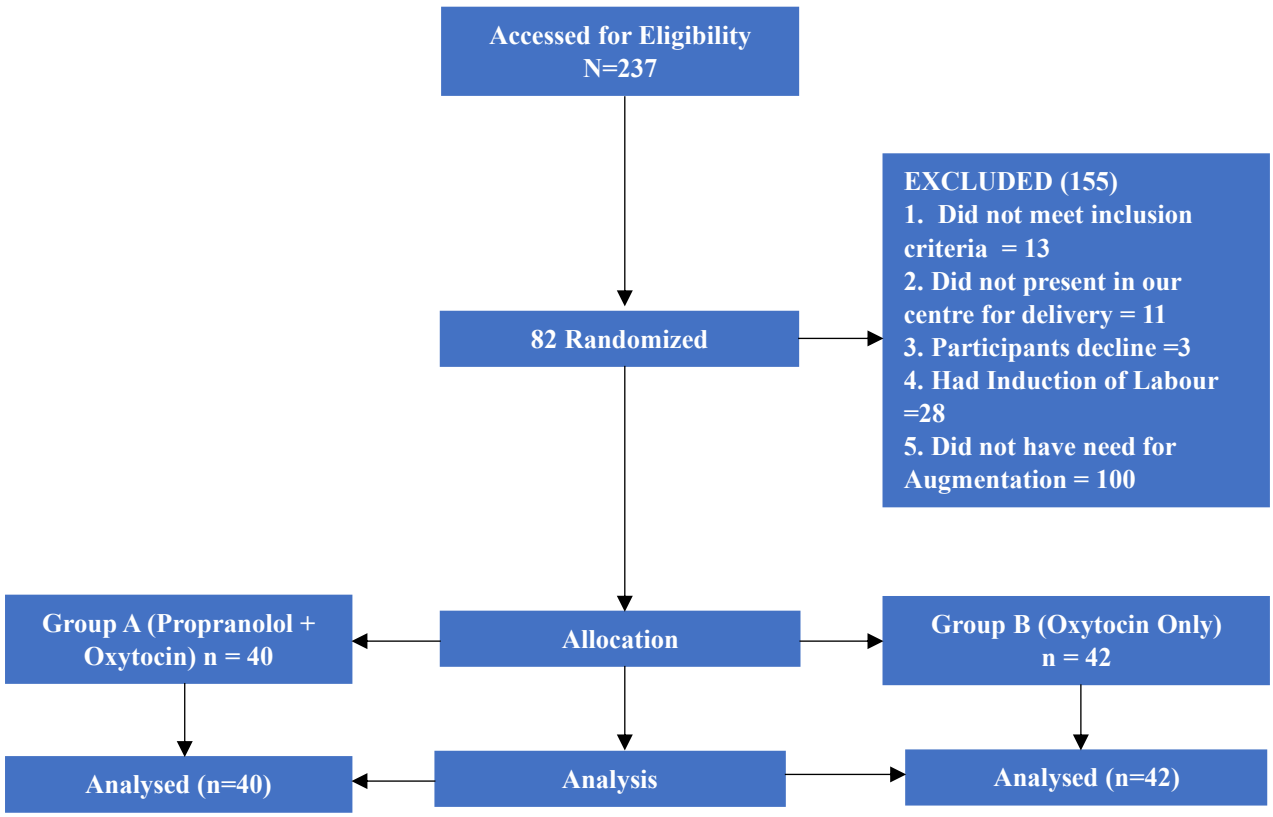
The primary outcome measures were the total mean duration of labour and the mean durations of 1st, 2nd and 3rd stages of labour. Secondary outcomes were; total mean dosage of oxytocin used, mode of delivery, Maternal outcome (mean pulse rate and blood pressure), fetal outcome (mean fetal heart rate), 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 recorded 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. Independent student's-test was used for comparison between groups of continuous variables while chi-square (χ^2) test was used for categorical variables. P-value of <0.05 was taken as significant.

Results

Consort Diagram



Over the study period, a total of 82 participants who met the inclusion criteria were recruited into the study as seen in the consort diagram above. The subjects were distributed between group A = 40 (oxytocin and propranolol for induction and augmentation of labour) and group B = 42 (oxytocin only for induction and augmentation of labour).

Table I: General characteristics among the groups

VARIABLES	A (N=40) Mean± SD Range	B (N=42) Mean± SD Range	t-test	P-value
Mean Age (years)	24.73±3.56 14-32	25.36±4.05 18-40	0.749	0.456
Mean GA (weeks)	39.23±1.36 $36-42^{+2}$	39.61±1.36 $36^{+4}-42^{+4}$	1.273	0.207

Mean BW (kg)	3.04±0.427 2-4	3.07±0.447 2-4	0.394	0.695
Mean HT (cm)	160.13±6.3 147-175	159.45±8.3 146-178	0.413	0.681
Mean WT (kg)	74.18±13.8 54-130	73.5±11.10 55-101	0.245	0.808

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.

Table II: Labour outcomes between the groups

VARIABLES	A (N=40) Mean± SD Range	B (N=42) Mean± SD Range	t-test	P-value
Mean Cervical dilation on commencement (cm)	5.7±1.3 4-8	5.4±1.3 4-9	1.132	0.261
Mean Active Phase duration (minutes)	222.3±133.7 20-1850	353.7±189.0 30-645	3.620	**0.001**
Mean 2nd stage duration (minutes)	33.2±22.5 5-135	37.9±31.7 15-180	0.692	0.491
Mean 3rd stage duration (minutes)	9.8±4.4 1-20	22.5±7.1 2-45	0.316	0.753
Mean Total duration of labour (minutes)	262.6±140.1	399.4±193.8	3.649	**<0.001**
Mean Oxytocin used (iu) - **Strength**	10.3±1.6 10-20	12.9±4.6 10-20	0.5338	0.5934
- **Terminal drops/minute**	33±16.8 10-60	42.4±17.4 10-60	0.3886	0.6975

The table showed the labour intervals among the group and its statistical comparison. The total mean duration of labour was A=262.6±140.1minutes and B=399.4±193.8 minutes; the difference was statistically significant (P<0.001). The mean duration of active phase of labour was A = 222.3±133.7 minutes compared to the control group B = 353.7±189.0 minutes. These were statistically significant (P = 0.001). There were no statistical difference in 2nd (P=0.491) and 3rd stages (P=0.753) of labour. Mean oxytocin strength used (P-values = 0.5934); mean terminal drop per minute of oxytocin titration (P-values = 0.6975)) were not statistically significant.

Table III: Mode of delivery between the two groups

VARIABLES	A (N=40) (N)Percentage	B (N=42) (N)Percentage	X^2-test	P-value
SVD	(32)80%	(30) 71.4%	4.281	0.379
C/S	(7)17.5%	(11) 26.2%		
Vacuum	(1)2.5%	(1) 2.4%		

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=40) Mean± SD	B (N=42) Mean± SD	t-test	P-value
Mean PR (beat/min): **Before**	90.3±12.4	88.9±9.8	0.0185	0.9852
After	89.9±12.4	88.4±8.7	0.0508	0.9595
Change in PR **Before-After**	**t**=0.0228 **P**=0.9818	**t**=0.0382 **P**=0.9696		
Mean SBP: **Before**	126.5±16.9	125.6±12.05	0.0044	0.9965
After	123.5±14.8	118±20.5	0.2053	0.8374
Change in SBP **Before-After**	**t**=0.1335 **P**=0.8938	**t**=0.3196 **P**=0.7493		
Mean DBP: **Before**	80.5±10.6	81.7±7.7	0.0296	0.9764
After	77±7.9	79.02±7.4	0.0169	0.9865
Change in DBP **Before-After**	**t**=0.1668 **P**=0.8675	**t**=0.2509 **P**=0.8019		

N/B: PR: Maternal pulse rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Before and After propranolol administration.

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.

Table V: Fetal/Neonatal outcome between the groups

VARIABLES	A (N=40) Mean± SD	B (N=42) Mean± SD	t-test	P-value
Mean FHR (beat/min): **Before**	147.2±6.9	141.9±9.8	0.2666	0.7897
After	147.3±7.7	142.1±7.9	0.3893	0.6971
Change in FHR Before-After	**t**=0.0097 **P**=0.9923	**t**=0.0159 **P**=0.9873		
Mean APGAR score at 1 min:	8.6±1.4	7.5±2.07	0.3959	0.6922
Mean APGAR score at 5 min:	9.5±1.01	9.2±1.5	0.200	0.8415
Change in APGAR score at 1min-5min.	**t**=0.5213 **p**=0.6021	**t**=0.665 **p**=0.8682		

N/B: FHR: fetal heart rate, Before and After propranolol administration

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.

Table VI: Neonatal Intensive care Unit admission status

VARIABLES	A (N=40) N (%)	B (N=42) N (%)	X^2-test	P-value
Not admitted	35(87.5%)	32(76.2%)	0.07977	0.7776
Admitted	5(12.5%)	10(21.4%)		
Reason for admission				
None	(35)87.5%	(32)76.2%	5.372	s0.258
Observation	(3)7.5%	(5) 11.9%		
Birth asphyxia	(2)5.0%	(5)11.9%		

N/B: NICU: neonatal intensive care unit

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

The need to prevent prolonged labour, thereby eliminating its complications, has necessitated studies on agents that can synergize with oxytocin and reduce its duration of exposure during augmentation of labour. This has necessitated scholars trying to discover newer agents like propranolol that can help shorten the duration of labour when used in synergy with oxytocin in labour. In this study, the general characteristics of participants in both groups were homogenous. This finding is in keeping with studies by Hanafy et al [9] and Sharami et al [11] who noted a homogenous population in their studies.

The total duration of labour was significantly shorter in the study group compared to the control group. This may be because propranolol's effect on the myometrium is more effective in the active phase of labour, which is more dependent on the strength of uterine contraction. This effect is translated to the total duration of labour, as other factors come into play in the 2nd stage and 3rd stage of labour. The similarity may be because these studies had approximately the same sample size and however, similar methodology parity was neither considered nor controlled for in these studies. Since the current study was only on nullipara whose pelvis (which is one of the determinants for labour progress) has not been tested. Also, this study corroborated a Meta-analysis by Pergialiotis et al [8] where he noted that propranolol shortened the total duration of labour without any effect on the 2nd and 3rd stages of labour. This study however is in contrast with the findings by Cilliers et al [10] in South Africa that concluded that propranolol did not reduce the duration of labour in their population. This may be because of their small sample size used in the study, as compared to this one; as well as the methodology for Propranolol and oxytocin administration.

There were no difference in the mean strength of oxytocin and terminal drop per minute of oxytocin titration used. This may be due to the fact that both groups had similar participants' characteristics. Our study is in line with the finding of Palomäki et al [7] who noted no statistically significant differences in the oxytocin dosages when groups were compared. This may be as a result of the similarities in the characteristics of the participants in both studies. In contrast, however, the studies by Cilliers et al [10] in South Africa, Marshall [35] and Sharami et al [11] 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.

In this study, there was no statistically significant difference in the mode of delivery between the two groups. This may be due to the fact that propranolol only had effects on uterine contraction, as shown on its effect in first stage of labour. It could not influence other factors that might impact on the second stage which involves the passage and the passenger. Our study is in keeping with the findings of Palomäkiet al [7] in augmentation of labour were they noted that there was no statistically significant difference in caesarean section rate in both groups. This corroborates the effects of propranolol on uterine contraction but not on other factors contributing to the process of labour. This was in contrast to studies by Sanchez-Ramos et al [6], Hanafy et al [9] in Egypt, Cilliers et al [10] in South Africa and Sharami et al [11] in augmentation of labour where they noted a significant difference in cesarean section rate compared to vaginal delivery. This might possibly be due to their studies being not parity-specific and also because the participants had repeated doses of propranolol unlike our study that was on nulliparous and had a single dose of propranolol.

There were no statistically significant differences in maternal and fetal/neonatal outcomes. This infers that 20mg oral propranolol single dose is safe both for mother and fetus and therefore may be useful in reducing the duration of augmentation of labour with oxytocin. This is in keeping with reports of some scholars who noted that propranolol had no significant maternal and fetal/neonatal haemodynamic effect when groups were compared [5-11]. This might be due to the similarity in sample size and methodology employed by both studies. This was however contrary to the findings by LeWinter et al [33], who noted significant changes in maternal pulse rate and blood pressure. This might be due to higher dosage (40mg) used in their study as against 20mg in our

study. Their study also had smaller sample size compared to ours. This might have had significant impact on the findings.

Conclusion

This study showed that the administration of 20mg oral propranolol prior to initiation of augmentation of labour shortened the duration of active phase and the total duration of labour but had no effects on the duration of second and third stages of labour. As such 20mg oral propranolol may be considered as an adjunct to oxytocin during augmentation of labour.

Informed Consent

A signed consent was obtained by the researcher and research assistants before recruitment of the participants into the study after appropriate counselling.

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. Patients signed written and informed consent form after careful explanation of the objectives, procedure and full implication of participation in the study. This study was conducted in compliance with the ethical standards of our institution on human subjects as well as with the Helsinki Declaration.

Clinical Trial Registration

The work was registered with the ClinicalTrials.gov with clinical trial number; - NCT05222646

Conflict of Interest

There was no conflict of interest.

Presentation

Award winning presentation at the 2022 International Conference of the Society of Gynaecology and Obstetrics of Nigeria (SOGON)

Funding Statment

The entire financial burdens were burn by the researchers.

Author Contributions

Darlington-Peter Chibuzor UGOJI: The principal investigator

Odidika Ugochukwu Joannes UMEORA, **Chidi ESIKE and Joshua ADEBAYO:** Supervised the work and helped in literature search.

Paschal Chijioke OKOYE, Chidubem Philip OSUAGWU and Emmanuel Chijioke UWAKWE were involved in the literature search and day to day conduct of the work till conclusion.

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Data Availability

Data would be available upon reasonable request.

List of Abbreviations

SPSS: Statistical package for social sciences
<: Lessthan
X^2: Chi-square
= Equal to
2nd: Second
1st: First
3rd: Third
AEFUTHA: Alex Ekwueme Federal Teaching Hospital Abakaliki
Mg: Miligram
5th: Fifth
N: Number
SD: Standard deviation
GA: Gestational Age
BW: Birth weight
Kg: Kilogram
HT: Height
CM: Centimeter
Iu: International Unit
CS: Caesarean section
SVD: Spontaneous vaginal delivery
PR: Pulse rate
SBP: Systolic blood pressure
DBP: Diastolic blood pressure
Min: Minutes
FHR: Fetal heart rate
NICU: Newborn intensive care unit
HREC: Hospital and Research Committee
SOGON: Society of Gynaecology and Obstetrics of Nigeria

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