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The Effect of Oral Propranolol plus Oxytocin Versus Oxytocin alone on Induction and Outcome of Labor

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ABSTRACT

Background: Labor is a state of uterine contractions having adequate frequency, duration, and strength resulting in cervical effacement and dilatation. Prolonged labor could cause maternal and neonatal medical issues and these unfavorable labor clinical outcomes are elevated in prolonged gestations in comparison with term pregnancies. The present study aimed to evaluate the effect of oral propranolol supplementary agent to oxytocin on induction and outcome of Labor and compare it with the control group (oxytocin alone).

Patients and methods: This was a randomized controlled clinical trial which was conducted in Zagazig University Hospital and Zagazig General Hospital in the period between January 2021 and December 2021 to compare the efficacy of propranolol and oxytocin vs. oxytocin alone for induction of labor at 38-41 week gestational age. The study was conducted on 106 pregnant women; divided into two groups each group contain 53 pregnant women.

Results: Duration of latent phase and duration of 3rd stage was significantly shorter among study group but there was no significant difference in duration of active phase and 2nd stage between two groups. Dose of oxytocin at which sufficient contractions occurred (3 contractions per 10 minutes) was significantly lower among the study group than the control group. Normal vaginal delivery was more frequent among the study group than among the control group: 41 cases (77.4%) versus 32 controls (60.4%). Cesarean section mode was less in the study group than the control group ($p>0.05$).

Conclusion: Administration of oral propranolol combined with oxytocin during latent phase of labor is an effective agent in shortening the labor duration and decreasing the rate of cesarean section with no considerable side effects neither to the mother nor to her newborn has been recorded during the study.

Keywords: Oral Propranolol, Oxytocin, Outcome of Labor, Pregnancy, randomized controlled clinical trial.

INTRODUCTION

When there are enough uterine contractions that cause the cervical dilatation and effacement, the condition is known as labor [(1)].

These adverse labor clinical outcomes are more common in protracted gestations when compared to term pregnancies, and prolonged labor may result in medical problems for the mother and the newborn. Because of this, the factors affecting and controlling the advancement of labor have been well studied [(2, 3)].

International study data indicates that rates of cesarean sections have increased over the past few decades. Previous investigations have demonstrated and demonstrated a potential correlation between labor induction and increased rates of cesarean sections. These rates are impacted by advanced mother age and gestational age at delivery in cases of multiparity as well as nulliparity. Accordingly, a low Bishop score level and an anticipated baby birth weight of raise the clinically indicated likelihood of a failed induction 3.5 kg. It's interesting to note that for the past ten years, the impact of labor trials on the rates of cesarean sections has been the subject of dispute and disagreement in the scholarly community. However, interestingly recent research meta-analyses show that it has little impact on these rates. [(4, 5)].

A variety of agents are used to enhance and induct labor. In practical application, the most typically used agents are oxytocin and prostaglandins. Although the research-based information in this problem is contradictory, intravaginal misoprostol which is delivered either intracervically or intravaginally seems to be more economical and efficacious than dinoprostone. Nonetheless, because uterine hyperstimulation and tachysystole occur less frequently with dinoprostone, researchers observe that it appears to have a safer clinical profile. When used off-label, intravaginal dinoprostol has essentially replaced intravaginal misoprostol. Given the possible side effects of misoprostol and the costly issues related to dinoprostone, it would be imperative to investigate the effectiveness of other agents in this area of obstetric practice [(6)].

Despite being the most often used medication to induce and enhance Some writers consider oxytocin to be a high-alert medication for uterine contractility because of the elevated clinical risk that comes with it with excessive dosage or incorrect prescribing [(7)].

It has been discovered that the P-adrenergic receptor-blocking drug propranolol causes both pregnant and non-pregnant women to have increased uterine activity. It does this by removing the P-agonist isoproterenol's suppressive effect on human uterine motility. Propranolol has a maximum effect of one hour and a pharmacological half-life of approximately two to three hours. Recent studies have demonstrated the effectiveness of an oxytocin agent in conjunction with propranolol to shorten the duration of the active phase

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of labor and the time it takes to induce labor in clinical settings involving labor dystocia [8].

The work's objective was to compare the effects of oral propranolol as a supplemental drug to the effects of oxytocin on the induction of labor; with the control group received only oxytocin.

PATIENTS AND METHODS

This randomized controlled clinical trial was conducted at Zagazig University Hospital and Zagazig General Hospital between January 2021 and December 2021, to assess the effectiveness of propranolol and oxytocin against oxytocin alone for inducing labor at 38–41 weeks gestation. 106 pregnant women were involved in the study; they were divided into two groups of 53.

Inclusion criteria: The following criteria must be met: age between 20 and 35 years, gestational age between 38 and 41 weeks (based on a reliable last menstrual period and first trimester ultrasound), singleton pregnancy, cephalic vertex presentation, intact membranes, Bishop score > 5, Fetal well-being status, primigravida status, or history of one or two vaginal births; mother's BMI between 18 and 30 kg/m2.

Exclusion criteria: age range: over 35 years old to under 20 years old; multiple pregnancies; multiple births by vaginal delivery; non-cephalic presentation; uterine contractions; history of uterine surgery (e.g., Cesarean section, myomectomy, pre-labor membrane rupture); non-reassuring status of fetal well-being; contraindications to P-adrenergic agents, such as bronchial asthma; systolic blood pressure less than 100 mmHg or pulse rate between 60 and 120 beats per minute).

Randomization: Patients fulfilling the inclusion criteria were randomized into two groups:

Study Group: There were 53 ladies in this group that were having labor induction. Patients in this cohort were given oral propranolol (20 mg; two 10 mg tablets) two hours prior to intravenous oxytocin administration.

Control Group: There were 53 ladies in this group that were having labor induction. Patients in this group received intravenous oxytocin only.

Drugs, dosage and regimen:

Active Drug: Tablet of propranolol hydrochloride 10 mg (Inderal® 10 mg, AstraZeneca, Egypt).

Dose and Regimen: Two 10 mg propranolol pills (20 mg) were taken two hours before beginning labor induction. Tablets are repeated after 8 hours if enough contractions are not obtained [8].

Low-dose protocol of To simulate a physiological method, oxytocin was administered by intravenous drip[9].

Regimen:

- Start at 1-2 milliseconds per minute and increase every 30 minutes until you reach 3 contractions per ten minutes.
- A maximum of 32 milligrams per minute could be administered.

All patients were subjected to the following:

- Accurately recording history.
- The clinical assessment was finished:
- Exam general.
- Examining the abdomen.
- The altered pelvic examination score by Bishop.
- Standard tests such as CBC, RBS, urine, blood type, and Rh typing were performed.

An ultrasound scan of the abdomen and pelvis.

Constant cardiac tocography.

Assessment of maternal-fetal status every 15 minutes during oxytocin administration (or at least every 30 minutes if oxytocin dosage remains stable), with documented in the patient medical record.

If patients entered the active phase of labor (four centimeter cervical dilation), the active management of labor commenced. When cervical dilatation reached 5 cm and the membranes had not broken spontaneously, an amniotomy was performed. The mother's pulse, blood pressure, temperature, fetal heart rate, membrane status, cervical dilatation and effacement, fetal station, and uterine contractions were all recorded during the partogram.

If the patients did not enter the active phase the induction was terminated after eight hours, and the patients were taken to the pre-labor ward. On the next day, all interventions were performed in the same manner as on the first. A cesarean section was performed on the second day if there was no response to induction.

Primary Outcome: Propranolol's effectiveness in inducing labor as a complement to oxytocin is assessed and measured, and the results of labor in the two groups are compared.

Secondary Outcomes:

Labor outcomes including: The length of the second stage, the active phase, the latent period, and the delivery mechanism.

Neonatal Outcomes including: The NICU admittance requirement, fetal birth weight, and the APGAR scores at one and five minutes.

Protocol approval:

Following authorization from the Institutional Review Board, Zagazig University (IRB-ZU), the search was approved by the OB/GYN Department. Every patient provided informed consent to participate in the trial after being informed about its purpose and possible outcomes. This study was carried out in accordance with the Declaration of Helsinki, the World Medical Association's code of ethics for research involving humans.

Statistical Analysis:

Basic clinical examination, laboratory testing, and outcome assessments are all done with Microsoft Excel, along with coding, entering, and analyzing historical

data. Subsequently, the information was entered into the social science statistical software. (SPSS version 20.0) program in order to be analyzed. Numbers and percentages were used to summarize qualitative data, while mean ± SD was used to summarize quantitative data, depending on the type of data. Student's t test was used to compare continuous variables between two independent groups. For the examination of qualitative variables, the Fisher's exact test or the Chi square test (X2) was selected. P values were established at less than 0.05, 0.01 and less than 0.001 for significant, high, and very high, respectively, results.

RESULTS

The age distribution was 28.24 (SD 4.54) and 27.03 (SD 4.64) for each group, with no discernible difference between them. Additionally, there was no discernible difference in the groups' BMI, parity, gestational age, or bishop score (Table 1).

Table (1): Basic demographic and obstetric history distribution between studied groups.

Variables		Study group (N=53)	Control group (N=53)	T test	P value
Age (years)	**Mean±SD**	27.03±4.64	28.24±4.54	1.352	0.179
	Range	20.0-35.0	20.0-35.0		
BMI (kg/m^2)	**Mean±SD**	25.14±1.98	24.28±3.94	1.420	0.158
	Range	21.5-28.4	20.1-28.5		
Parity	**Mean±SD**	1.02±0.81	1.21±0.82	1.201	0.232
	Range	0.0-2.0	0.0-2.0		
GA (weeks)	**Mean±SD**	39.03±0.62	39.21±0.54	1.593	0.114
	Range	38.0-41.0	38.0-41.0		
Bishop score	**Mean±SD**	7.4±0.6	7.5±0.6	1.473	0.143
	Range	6.0-8.0	6.0-8.0		

There was no significant difference in the duration of the active phase and the second stage, while the study group's duration of the latent phase and third stage was much shorter. (Table 2).

Table (2): Duration of different phases distribution between studied groups.

Variables	Study Group Mean±SD	Control Group Mean±SD	T test	P value
Duration of Latent Phase by hours	6.51±1.82	7.70±2.41	2.868	0.005*
Duration of Active Phase by Hours	2.78±0.41	2.89±0.47	1.260	0.211
Duration of 2nd satge by minutes	47.01±14.43	51.30±12.16	1.652	0.102
Duration of 3rd stage by min	6.73±1.34	8.05±1.44	4.865	0.00**

Dose of oxytocin at which sufficient contractions (3 contractions every 10 min) was substantially lower among study group than control group (Table 3).

Table (3): Dose of Oxytocin by mIu/min. between studied groups.

Variable	Study group Mean±SD	Control group Mean±SD	T test	P value
Dose of Oxytocin By miu/min	14.88±3.25	19.63±4.32	6.396	0.00**

Delivery mode revealed that CS mode was lower in the study group, though not considerably (Table 4).

Table (4): Distribution of studied groups according to mode of delivery.

Variable			Groups		X^2	P value
			Study group	Control group		
Mode of Delivery	**CS**	N	12	21	3.56	0.059
		%	22.6%	39.6%		
	NVD	N	41	32		
		%	77.4%	60.4%		
Total		N	53	53		
		%	100.0%	100.0%		

There was no discernible difference between the groups based on the distribution of maternal morbidity between the analyzed groups (Table 5).

Table (5): Maternal Morbidity distribution between studied groups.

Variable			Groups		X^2	P value
			Study Group	Control Group		
Maternal Morbidity	No	N	47	46	1.23	0.86
		%	88.6%	86.7%		
	Blood Transfusion	N	1	2		
		%	1.9%	3.8%		
	Hypotension	N	4	2		
		%	7.5%	3.8%		
	Postpartum Hemorrhage	N	1	3		
		%	1.9%	5.6%		
Total		N	53	53		
		%	100.0%	100.0%		

There was no discernible difference between the groups based on the distribution of fetal outcomes between the analyzed groups (Table 6).

Table (6): Fetal outcome distribution between studied groups.

Variable			Study Group Mean±SD	Control Group Mean±SD	t/ X^2	P
Birth Weight			3124.33±273.92	3137.73±168.76	0.303	0.762
Apgar score at 1 minute			7.35±0.68	7.11±1.31	1.209	0.230
Apgar score at 5 minutes			9.21±1.38	8.82±1.24	1.831	0.061
NICU	No	N	50	48	0.54	0.46
		%	94.4%	88.4%		
	Yes	N	3	5		
		%	5.6%	11.6%		
Total		N	53	53		
		%	100.0%	100.0%		

DISCUSSION

About forty years ago, the first uncontrolled study on propranolol use in labor disorders was carried out. Consistent with our investigation, the research outcomes demonstrated that the injection of propranolol results in normal uterine activity and the subsequent birth without any statistically significant difficulties for either the mother or the fetus. A previous research team found that the propranolol research group required fewer cesarean section deliveries than the oxytocin research group when comparing the effects of 96 studies comparing oxytocin alone with propranolol + oxytocin participants [(10)]. Similar to this, our research revealed that the propranolol research group required fewer cesarean sections and had shorter active phase durations, although the differences were not statistically significant.

Our findings are consistent with the research conducted by **Marjani *et al.*** [(11)] on 120 pregnant women between the ages of 38 and 41 weeks gestation. Subjects were divided into three groups. To induce labor, oxytocin was administered alone to the first group, in combination with intravenous propranolol for the second group, and oral propranolol for the third group. Measurements were made for three groups: uterine atony, meconium passage, Apgar score, and first and second stage labor length. It was discovered that the oral method of propranolol and oxytocin administration reduces the frequency of cases requiring cesarean sections and the duration of the first and second stages of labor in natural labor. Moreover, propranolol had no effect on problems for new moms or babies.

Also, **Amiri *et al.*** [(12)]**;** concurs with our research, which discovered that propranolol can shorten the latent phase's duration.

Although there was a greater rate of cesarean sections the difference did not reach statistical significance in the control group. **Moghadam *et al.*** [(13)] discovered that, in line with our findings, oral propranolol was helpful in initiating labor and may lower the number of cesarean deliveries without endangering mothers or babies. The mean duration of the initial latent phase was shorter in the Propranolol group. Propranolol with Oxytocin group was superior to the Oxytocin group experienced a substantial drop in the frequency of cesarean deliveries.

No discernible variations were observed in the neonatal outcomes across the groups in terms of Apgar

scores at minutes 1 and 5 or the requirement for NICU admissions.

Kashanian *et al.* [14] conducted 150 nulliparas with a gestational age of 39–41 weeks of pregnancy and a Bishop score of five were used in a randomized controlled trial. The initial team (oxytocin group = 75) underwent oxytocin-only labor induction. One hundred and fifty patients made up the second group (the propranolol group), which received two milligrams of propranolol slowly injected intravenously before oxytocin started.

This study supports our findings, which indicate that propranolol may cut the time needed for induction of labor and shorten the amount of oxytocin required. In the propranolol group, getting good contractions took an average of less time. In the propranolol group, there was a shorter mean gap between the beginning of the induction process and the first day of the active phase. The mean interval between the beginning of induction and delivery was shorter in the propranolol group. For induction, less oxytocin was needed in the propranolol group.

Pergialiotis *et al.* [15] agrees with our studies, which found that propranolol shortens the latent phase and maybe the duration of labor in general.

In a different study, 57 nulliparous instances that were were arbitrarily split into two study groups during the active stage of labor. The frequency of cesarean sections owing to labor dystocia was twice as high in the propranolol research group compared to the control research group (13.6% and 6.25%, respectively). This supports the value of propranolol in lowering the rate of cesarean sections, which is thought to be a worldwide obstetric concern, and further demonstrates concordance and similarity with the findings of our study. The study's research team also found that the maternal and neonatal outcomes were similar in both groups, and our results were very similar to theirs in that regard, with no statistically significant difference between the two groups supporting the safety of propranolol use on neonatal clinical outcomes [8].

Our study results are very comparable to those of another randomized research experiment that used intravenous injection of a single dosage of 2 mg propranolol prior to beginning induction of labor, which resulted in a shorter duration of the active phase of labor. A comparable earlier investigation has shown that the administration of oxytocin plus propranolol in post-term gestations results in a about 30% reduction in labor duration [10].

Hanafy *et al.* [16] carried out a second trial to examine the effects of oral propranolol on labor outcomes and the progression of labor by giving oxytocin and propranolol orally during the active phase of labor. They discovered that giving oral propranolol and oxytocin during the early active phase of labor is the most efficient way to reduce the labor interval; nonetheless, the combination is preferred because propranolol alone does not shorten the labor interval as much as oxytocin alone. The rate of cesarean section is decreased by oral propranolol use, yet this effect is statistically insignificant. Neither the mother nor her newborn experienced any significant negative effects during the research.

Additionally, propranolol was found to strengthen labor contractions by blocking P-adrenergic receptors in another investigation on labor dysfunction [17].

Nevertheless, a research by **Bigelow *et al.* [18]** discovered no proof that oxytocin plus propranolol during labor induction reduces the amount of time it takes to deliver a baby or the frequency of cesarean deliveries. Propranolol, on the other hand, dramatically decreased composite maternal morbidity without having a negative impact on newborns.

CONCLUSION

When given orally during the latent phase of labor, a combination of propranolol and oxytocin can effectively shorten labor durations and lower the rate of cesarean sections. The mother and her unborn child do not experience any noteworthy adverse effects from this medication.

RECOMMENDATIONS

If there are no contraindications, women undergoing induction of labor may add propranolol to oxytocin. Due to the paucity of research studies, more should be done in the future, accounting for racial and ethnic disparities in cases as well as multicentric design comparisons. As a result, we think that propranolol should only be used in clinical research trials at this time for labor induction and augmentation.

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