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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 significance 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

Labor is a state of uterine contractions having adequate frequency, duration, and strength resulting in cervical effacement and dilatation **(1).**

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. For that reason, the aspects influencing and regulating progression of labor have been extensively investigated **(2, 3)**.

The cesarean section rates are rising during the last decades according to international research data. Prior research studies have revealed and displayed that labor induction could be correlated with raised cesarean section rates. Advanced maternal and gestational age at the time of delivery influence and impact these rates both in nulliparous and multiparous cases. Correspondingly, the existence of a low Bishop scoring level and an expected neonatal birth-weight (3.5 kg) raise the clinical estimated probability of failed induction. Interestingly the effect of trial of labor on the rates of cesarean section has become an issue of controversy and research debate throughout the previous decade. Interestingly updated research meta-analyses, on the other hand denote that it does not affect these rates **(4, 5).**

Numerous agents are implemented for labor induction and augmentation prostaglandins and oxytocin are the most widely used agents in practice. Intravaginal misoprostol Appears to be more effective and less costy than dinoprostone which is administered intracervically or intravaginally, even though research-based evidence in this issue show contradiction on the other hand researchers mention that dinoprostone appears to have a safer clinical profile due to lower frequency of uterine hyperstimulation and tachysystole. Recently, intravaginal dinoprostone have greatly replaced the off-label usage of intravaginal misoprostol. Keeping in mind the possible side effects of misoprostol and the costly issues of dinoprostone it would be crucial to investigate the effectiveness of other agents within this field of obstetric practice **(6)**.

Though, oxytocin agent is the most widely implemented drug for induction and augmentation of uterine contractility however oxytocin is considered by various authors as a high-alert medication caused by the elevated clinical risk of high dosage or inappropriate prescription **(7).**

Propranolol a β-adrenergic receptor–blocking agent that have been shown and demonstrated to raise uterine activity among pregnant and non-pregnant females acting by withdrawing the suppressive impact of the β-agonist isoproterenol on uterine motility in humans. The pharmacological half-life of propranolol is around 2 to 3 hours and its maximum effect is at one hour. Up dated research studies have displayed that the impact of oxytocin agent in linkage and conjunction with propranolol in reducing labor induction time and active phase duration in clinical scenarios of labor dystocia **(8).**

The aim of the work was to study the effect of oral propranolol supplementary agent to oxytocin on

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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.

Inclusion criteria: Age between 20 years and 35 years, gestational age 38 - 41 weeks (according to a reliable last menstrual period and ultrasound evaluation at first trimester), singleton viable pregnancy, cephalic vertex presentation, intact membranes, Bishop score > 5, reassuring fetal well-being status, maternal BMI between (18-30kg/m^2), and primigravida, or Previous one or previous two vaginal delivery.

Exclusion criteria: age more than 35 years or less than 20 years, multiple pregnancy, multigravida more than two vaginal delivery, non-cephalic presentation, presence of uterine contractions, history of uterine surgery e.g., Cesarean section, myomectomy, pre-labor rupture of membranes, non-reassuring fetal well-being status, contraindications to β-adrenergic agents, such as bronchial asthma, systolic blood pressure less than 100 mmHg or pulse rate less than 60/min and more than 120/min, history of any known cardiac disease, mother's pulmonary or metabolic disorders, fetal distress, and estimated weight of the fetus more than 4 kg by ultrasound of cephalic presentation.

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

Study Group: This group included 53 women undergoing induction of labor. In this group, the patients received (two tablets of 10mg) 20 mg propranolol orally two hours before adding intravenous oxytocin.

Control Group: This group included 53 women undergoing induction of labor. In this group, patients received intravenous oxytocin alone.

- Drugs, dosage and regimen:

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

Dose and Regimen: Two tablets of 10 mg of propranolol (20 mg) two hours before starting induction of labor. Tablets repeated after 8 hours, if adequate contractions are not achieved [(8)].

Low-dose protocol of oxytocin by intravenous drip was attempted to mimic a physiologic approach [(9)].

- Regimen:

- A starting dose was 1-2 milliunits per minute.
- Increased by 1-2 milliunits per minute every 30 minutes until 3 contractions/10 minutes were achieved.
- The maximum dose used was not exceeding 32 milliunits per minute.

All patients were subjected to the following:

- Proper history taking.
- Clinical examination was done:
  - General examination.
  - Abdominal examination.
  - Pelvic examination: Modified Bishop score
  - Routine investigations were done, e.g. CBC, RBS, Urine, Blood group,Rh typing.
  - Pelvi-abdominal U/S.
  - Continuous Cardiotocography.

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

If patients entered the active phase of labor (cervical dilatation 4 cm), active management of labor was started. Amniotomy was performed when cervical dilatation reached 5 cm, if the membranes had not been ruptured spontaneously, Using Partogram to monitor the fetal heart rate, membrane status, cervical dilatation and effacement, station of the fetus, uterine contractions, maternal pulse, maternal blood pressure and maternal temperature.

If the patients did not enter the active phase after 8 hours, the induction discontinued and the patients were transferred to the pre-labor ward; and on the second day, all interventions were performed similar to the first day. If there was no response to induction on the second day, a caesarean section was performed.

Primary Outcome: Evaluation and measurement the efficacy of Propranolol supplementary agent to oxytocin in induction of labor and compare between Labor outcome in Both groups.

Secondary Outcomes:

Labor outcomes including: duration of latent phase, duration of active phase, duration of second stage, and mode of delivery

Neonatal Outcomes including: Fetal birth weight, APGAR score at 1 and 5 minutes, and need for NICU admission.

Protocol approval:

After Institutional Review Board, Zagazig University (IRB-ZU) permission, OB/GYN Department gave their approval to the search. After hearing about the study's goal and potential consequences, each patient gave informed consent to participate. This research was carried out in line

with the World Medical Association's Code of Ethics (Declaration of Helsinki) for human studies.

Statistical Analysis:

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) **(**Statistical Package for the Social Sciences) software for analysis. According to the type of data, qualitative data were summarized as number and percentage, and quantitative data were summarized by mean ± SD. Continuous variables were compared by student's t test between two independent groups. Chi square test (X^2)/Fisher's exact test was chosen for analysis of qualitative variables. P value was set at $\leq$0.05 for significant results, <0.01 for high significant results and<0.001 for very high significant results.

RESULTS

Age was distributed as 27.03 (SD 4.64) and 28.24 (SD 4.54) respectively with no significant difference between the groups. Also there was no significant difference between the groups regarding BMI, parity, gestational age and 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		

Study group was significantly shorter regard Duration of Latent Phase and Duration of 3rd stage but there was no significance difference in duration of active phase and 2nd stage (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 per 10 min) was significantly 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**

According to mode of delivery CS mode was less in study group but not significantly (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%		

According to maternal morbidity distribution between studied groups there was no significant difference between 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%		

According to fetal outcome distribution between studied groups there was no significant difference founded between groups (Table 6).

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

			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

The first uncontrolled research study on the usage of propranolol within dysfunctional labor was performed around four decades ago. The research results revealed that propranolol administration results in normal uterine activity and subsequent delivery without any statistically significant maternal or fetal complications that shows harmony with our research study results. A prior research team conducted a comparison of the impact of oxytocin plus propranolol with that of oxytocin alone on 96 study subjects observed a decrease in the requirement for cesarean section delivery in the propranolol research group in comparison to the oxytocin research group. Similarly, our study has shown reduced cesarean section requirement and reduced duration of active phase duration in propranolol research group but the difference was not statistically significant [10].

Our results resemble the study made by **Marjani *et al.*** [11]; in this clinical trial study was conducted on 120 pregnant women with 38-41 weeks of gestational age. They divided into three groups. The Induction of labor started for the first group using oxytocin alone, the second group received oxytocin in combination with intravenous propranolol and the third group received oxytocin alone with oral propranolol. The duration of first and second stages of labor and Apgar score, meconium passing and uterine atony were recorded for three groups and found that administration of propranolol with oxytocin particularly in oral method reduces the time of the first and second stages of labor in natural labor and reduces caesarean section cases. In addition, propranolol had no effect on maternal and neonatal complications.

Also, **Amiri *et al.*** [12]**;** agrees with our study and found that Propranolol has been able to reduce the duration of latent phase.

The cesarean section rate in the control group was higher, but the difference was not statistically significant. In concordance with our study, **Moghadam *et al.*** [13] found that oral Propranolol was effective for labor induction and that it could decrease the frequency of caesarean deliveries without producing any adverse effects on mothers or neonates. The mean duration of latent phase was shorter in the first in Propranolol group. In Propranolol plus Oxytocin group, frequency of cesarean deliveries significantly decreased than in the Oxytocin group.

There was no significant differences in neonate outcome, such as Apgar scores of minutes 1 and 5 and need of admissions to NICU, were found between the groups.

Kashanian *et al.* [14] performed a randomized controlled trial on 150 nulliparas with a gestational age of 39–41 weeks of pregnancy and a Bishop score of five. In the first group (oxytocin group = 75), oxytocin alone was used for induction of labor. In the second group (propranolol group = 75 cases), before the beginning of oxytocin, 2 mg propranolol was slowly injected intravenously then the oxytocin was initiated.

This study agrees with our study and found that Propranolol may shorten the induction duration and labor and reduce the amount of necessary oxytocin. The mean duration for obtaining good contractions was shorter in the propranolol group. The mean interval between the beginning of induction until the beginning of active phase at the first day of induction was shorter in the propranolol group. The mean interval between the beginning of induction until delivery was shorter in the propranolol group. The amount of necessary oxytocin of induction was less in the propranolol group.

Pergialiotis *et al.* [15] agrees with our study and found that Propranolol shortens the latent phase and possibly the total duration of labor

Another research study involved 57 nulliparous cases within the active phase of labor in which they were randomly categorized to two research groups. The cesarean section frequency arising from labor dystocia have been two times among the control research group in comparison to propranolol research group (13.6% and 6.25%, consecutively). That furthermore shows harmony and similarity to our study results and justifies the usefulness of propranolol to reduce cesarean section rates that is considered a global obstetric issue. Additionally the research team revealed in that study that the neonatal and maternal outcomes were similar in both research groups and that finding was revealed great similarity with our study as there was no statistical significant difference between both research groups in that aspect justifying the safety of propranolol usage on neonatal clinical outcomes [8].

A similar previous research study have shown that the usage of a propranolol and oxytocin combination in post-term gestations causes a decreased duration of labor by around 30%, and another a randomized research trial used intravenous injection of a single dose of 2 mg propranolol before beginning induction of labor, that resulted in shortened duration of the active phase of labor, these research findings show great similarity to our study findings [10].

Another study was done by **Hanafy *et al.* [16]** to evaluate the progress of labor by administration of oral Propranolol and Oxytocin during active phase of labor and to detect effect of oral Propranolol on labor outcomes found that administration of oral Propranolol together with Oxytocin during early active phase of labor is effective method in shortening the labor interval but Propranolol alone not shorten it as Oxytocin alone, so combination is better. Using oral Propranolol decreases rate of cesarean section but it is statically non-significant. No considerable side effects neither to the mother nor to her newborn has been recorded during the study.

Furthermore, another study on labor dysfunction, it was revealed that propranolol could strengthen labor contractions by blockage the β-adrenergic receptors [17].

However, a study carried out by **Bigelow *et al.* [18]** found there was no evidence that the addition of propranolol to oxytocin in induction of labor decreases time to delivery or the rate of cesarean delivery. However, propranolol significantly reduced composite maternal morbidity without adverse neonatal effects.

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; no considerable side effects to the mother or to her newborn.

RECOMMENDATIONS

If no contraindications, Propranolol can be used as a supplementary agent to oxytocin in women undergoing induction of labor. The low number of research studies calls for further research efforts in the future, taking into account racial, ethnics differences among cases besides considering multicentric design in comparison. Therefore, we believe that the use of propranolol for labor induction and augmentation must be only considered currently in the level of clinical research trials.

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