Maternal and Fetal Outcomes after Oxytocin and oral Propranolol for augmentation of labor

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Abstract: **Objective:** The purpose of this study is 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. **Patients and Methods:** 120 females were classified into 3 groups according to drug used for intervention during active phase of labor (>4 cm cervical dilatation): **Group I:** 40 patient administered Oxytocin (5 IU infusion) and 20 mg oral Propranolol. **Group II**: 40 patient administered 20mg oral Propranolol **Group III:** 40 patient administered Oxytocin (5 IU infusion). **Results:** There is a highly significant difference between the studied groups regarding duration of active phase of labor, 2nd with pvalue (0.001-0.004) respectively. There is no significant difference between the studied groups regarding 3rd stages of labor ($p < 0.05$). There is no significant difference in CTG outcome with p value (0.058) and maternal general condition and complication as well as mode of delivery ($p < 0.5$). There is no significant difference between the studied groups regarding Apgar score at 1st and 5min ($P>0.05$-0.06) respectively and neonatal admission to NICU with p value (0.089). **Conclusion:** It was found in the current study 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.
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1. Introduction

Prolonged labor can lead to maternal and neonatal complications [(1)]. It is associated with childbirth complications, concerns for fetal wellbeing, and negative birth experiences, it is one of the main indications for unplanned caesarean section in labor. These adverse labor outcomes increase in prolonged pregnancy in comparison with term gestational age [(2)].

Labor dystocia due to reduced uterine contractions is one of the main causes leading to cesarean section. In such conditions often oxytocin infusion is used for augmentation of the uterine contractions [(3)].

However, oxytocin is the best known and most widely used agent to induce and augment uterine contractions [(4)]; but the Institute for Safe Medication has termed oxytocin as a high-alert medication due to the risk of high dose or wrong prescription. This institute recommended many programs to minimize the maternal and neonatal risks of oxytocin administration [(5)].

Propranolol is well established as a β-adrenergic receptor–blocking drug that increases the uterine activity in pregnant and non-pregnant women by reversing the suppressive effect of the βagonist isoproterenol on human uterine motility. It is well known that the half-life of oral propranolol is 4 h. and appears in blood after 30 mins and its peak effect is at 1 h [(6)].

Recent studies have shown the effect of oxytocin to be associated with propranolol in decreasing the time of labor induction and the duration of active phase in labor dystocia [(7)].

The aim of this study is to evaluate 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.

2. Methods

This prospective observational interventional study was conducted from June 2017 to August 2018 on (120) pregnant ladies in labor at AL Zahraa hospital Al Azhar university and after informed a written consent was taken from every patient after explanation the benefits and risks of this trial.

Study groups:

- **Group I:** Patient administrated Oxytocin (5 IU infusion) and 20 mg oral Propranolol during active phase of labor.
- **Group II:** Patient administrated 20 mg oral Propranolol during active phase of labor (>= 4 cm).

- **Group III:** Patient administrated Oxytocin (5 IU infusion) during active phase of labor (> 4 cm).

Investigations:

- Routine investigations will be donee.g., complete blood count and blood grouping.
- Pelvi-abdominal U/S by using Samsung Medison model 2014 (Sonoacer A3) to Confirm fetal life, placental location, fetal parameters, amniotic fluid index and expected fetal weight and to exclude multiple pregnancy.

Technique:

- CTG is done for all pregnant ladies included in the study and cases with abnormal CTG pattern were excluded.
- Augmentation was initiated once cervical dilatation reach 4 cm with oxytocin intravenous drip a dose of 2 mIu/min and increased by 2 mIu/min every 15m until three forceful contraction were obtained per 10 min, or a maximum dose 30 mIU/min then, continued at this rate.
- A tablet containing 20 mg propranolol is administrated orally in the active phase of labor as a single dose once the cervical dilatation reaches 4 cm or more (in active phase). It given with oxytocin in group 1 while given only in group 2.
- CTG will be done for every patient for 30 minutes after oral propranolol administration and the CTG is repeated every 1 hours.
- Amniotomy is performed when cervical dilatation reaches 5 cm in all groups.
- The partogram will be used to monitor the fetal heart rate, membrane status, cervical dilation and effacement, station of the fetus and uterine contractions.
- If the parturient had developed hyper stimulation of contraction (in a situation with more than 5 contraction/10 min duration of contraction > 90 second, interval of contraction less than 2 min or fetal distress) the augmentation was stopped and the parturient was kept in left lateral position and given oxygen and intravenous dextrose.
- The participants are followed up until deliver y to get the labor outcomes and to detect any maternal or fetal complication and admissions to NICU.
- The data was checked to ensure quality. Pre-coded data were entered into the computer using the Statistical Package of Social Science Software program version 17 *(SPSS 17)* for statistical analysis.

3. Results

The present study was conducted on 120females. They were classified into 3 groups according to drug used for intervention during active phase of labor (>4 cm cervical dilatation).

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Table (1): General characteristics among the studied groups

Groups / Mean±SD	Group I N=40	Group II		Group III N=40	Significance	
		(A) N=24	(B) N=16		F-test	P value
Age (years)	22.3±3.9	22.8±3.3	23.3±3.9	22.3±3.5	0.4	0.75
GA (Weeks)	38.9±1	37.5±3.6	38.9±1	39.1±1	4.1	**0.01***
Bishop Score	6.8±1.2	7.1±1.2	5.9±0.9	6.6±1.3	3.1	**0.03***
HB (mg/dl)	10.4±1.4	10.7±1.6	11.1±1.1	11.1±1.1	2.1	0.1

N. B.*P value <0.05 was significant, GA: Gestational Age, HB: Hemoglobin Level.

Table (2): Mean duration of the active labor phase among the studied groups

Groups / Active phase	Group I N=40	Group II		Group III N=40	Significance	
		(A) N=24	(B) N=16		F-test	P value
• Mean ± SD • Range	2.1±0.8 (0 – 4)	4.1±1.04 (2 – 6)	2.5±0.9 (0.5-3.6)	2.6±0.8 (0.8 – 4)	26.2	**0.000***

Table (3): Mean duration of the 2nd stage of labor among the studied groups

Groups / Second stage	Group I N=40	Group II		Group III N=40	Significance	
		(A) N=24	(B) N=16		F-test	P value
• Mean ± SD • Range	21.2±6.7 (10-37)	28.4±7.3 (15-40)	26±7.3 (15-37)	23.7±7.5 (15-45)	4.7	**0.004***

Table (4): Mean duration of 3rd stage of labor among the studied groups

Groups / Third stage	Group I N=40	Group II		Group III N=40	Significance	
		(A) N=24	(B) N=16		F-test	P value
• Mean ± SD • Range	7.1±3.2 (3-15)	6.1±2.5 (2-10)	5.9±2.4 (3-10)	7.1±3.6 (2-20)	0.79	0.5

Table (5): Maternal outcome (heart rate and blood pressure) during active labor phase among the studied groups

Items \ Groups	Group I N=40	Group II (A) N=24	Group II (B) N=16	Group III N=40	Significance F	Significance P value
HR (beat/min):	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**		
Before	91.1±10.6	90.2±9.6	90.3±8.9	91.1±10.3	0.1	0.98
After	85.9±8.8	87.2±9.9	88±8.7	90.9±10.2	1.9	0.13
SBP:						
Before	110.8±7.3	112.5±7.9	109.4±8.7	110±9.6	0.1	0.61
After	109.5±8.8	111.3±8.5	109.4±7.5	109.8±9.5	0.23	0.87
DBP:						
Before	72.5±7.1	72.9±7.5	71.9±5.4	71±7.4	0.5	0.71
After	72±8.2	72.1±7.8	71.5±5.1	70.8±7.3	0.25	0.86

HR: Maternal heart rate- SBP: Systolic blood pressure- DBP: Diastolic blood pressure.

Table (6): Maternal complications among the studied groups

Complications \ Groups	Group I N=40		Group II (A) N=24		Group II (B) N=16		Group III N=40		Significance χ^2	Significance P
	No.	%	No	%	No	%	No.	%		
No	31	77.5	21	87.5	14	87.5	35	87.5	7.4	0.59
Postpartum Hge	5	12.5	3	12.5	1	6.3	5	12.5		
Uterine atony	1	2.5	0	0.0	0	0.0	0	0.0		

Table (7): Mode of delivery among the studied groups

Item \ Groups	Group I N=40		Group II (A) N=24		Group II (B) N=16		Group III N=40		Significance χ^2	Significance P value
	No	%	No	%	No.	%	No	%		
NVD	32	80	22	91.7	13	81.3	31	77.5	2.1	0.5
CS	8	20	2	8.3	3	18.8	9	22.5		

Table (8): Mean fetal heart rate during active phase of labor among the studied groups

Item \ Groups	Group I N=40	Group II (A) N=24	Group II (B) N=16	Group III N=40	Significance F	Significance P
FHR (beat/min):	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**		
Before	140±9.3	142±8.2	147.2±8.2	134.1±28.1	2.4	0.07
After	126.2±20.2	134.7±10.8	131.9±20.2	134.4±28.4	1.2	0.32
Change in FHR	t=40.7	t=4	t=2.8	t= -1		
Before-After	P =**0.000***	P =**0.001***	P =**0.02***	P =0.32		

Table (9): Distribution of fetal complications among the studied groups

Complications \ Groups	Group I N=40		Group II (A) N=24		Group II (B) N=16		Group III N=40		Signifi-cance χ^2	Signifi-cance P
	No	%	No	%	No	%	No	%		
No	29	72.5	22	91.7	12	75.0	28	70.0	0.5	0.58
Early deceleration	1	2.5	0	0.0	0	0.0	0	0.0		
Late deceleration	5	12.5	0	0.0	2	12.5	6	15.0		
Variable deceleration	2	5.0	2	8.3	1	6.3	5	12.5		
Reversible bradycardia	3	7.5	0	0.0	1	6.3	1	2.5		

Table (10): Neonatal outcome results

Items \ Groups	Group I N=40	Group II (A) N=24	Group II (B) N=16	Group III N=40	Significance F	Significance P
Apgar score at 1 min:						
Mean ± SD	6±1.1	5.9±0.9	5.7±0.9	5.7±1.2	0.79	0.51
Range	(4-9)	(4-7)	(5-7)	(3-8)		
Apgar score at 5 min:						
Mean ± SD	8±0.9	8.1±0.9	7.4±0.9	8±0.9	2.5	0.06
Range	(6-9)	(6-9)	(6-9)	(6-9)		
NICU admission:	**No (%)**	**No (%)**	**No (%)**	**No (%)**		
• Admitted	5 (12.5%)	2(8.3%)	1 (6.3%)	4 (10.0%)	χ^2	
• Not admitted	35 (87.5%)	22 (91.7%)	15 (93.8%)	36 (90.0%)	0.6	0.89

4. Discussion

Recent studies have shown the effect of oxytocin to be associated with propranolol in decreasing the time of labor induction and the duration of active phase in labor dystocia [7].

In this study we aim to evaluate the progress of labor by administration of propranolol and oxytocin during active phase and also to detect effect of oral propranolol on labor outcome.

In the current study there is significant difference between the studied groups regarding gestational age and bishop score with p value (0.01 & 0.03), respectively and there is no significant difference between the studied group regarding age and hemoglobin with p value (0.75-0.1), so all groups were matched in their age.

In the current study there is highly significant difference between the studied groups regarding the duration of active phase of labor with p value (0.00). Also, there is highly significant difference between the studied groups regarding 2nd stage of labor with p value (0.04).

These results coincide with the study of ***Direkvand-Moghadam et al.*** [8] who showed that propranolol plus oxytocin could significantly with p value (0.02 and 0.016) respectively.

Also, our results coincide with ***Kashanian et al.*** [6] study, when they used intravenous injection of a single dose of 2 mg propranolol plus oxytocin 5 IU before starting labor induction, duration of the active phase was shortened, which supports our findings. However, in their study, no significant difference was seen in the duration of second stage of labor. Use of a different dosage of propranolol in the above-mentioned study can be a possible explanation for the difference observed. The half-life of propranolol is about 2-3 h and its maximal effect is at about 1-1.5 h after injection. Perhaps use of repeated doses of propranolol may result in more effectiveness.

Palomaki et al. [9] reported that in cases of arrested labor caused by insufficient power of contractions, adding propranolol to Oxytocin could improve the power of contractions. This is coincides with our study. ***Chimura*** [10] showed similar effect to our results that they used alprenolol (a beta blocker) in vitro, produced myometrial stimulation of pregnant uterus in rats, and in another study, ***Peiker et al.*** [11] showed a similar effect of Propranolol, on relaxation of the myometrium of non-pregnant rats in vitro, but its stimulation in pregnant rats.

Oral Propranolol induces long-lasting effects on uterine contraction. In a randomized trial which was done by ***Kashanian et al.*** [6], results were congruent with our findings, but they used intravenous injection of single dose 2 mg Propranolol before starting labor induction, so both oral and intravenous propranolol route of administration had the same uterine effect.

Regarding the 3rd stage of labor, our results revealed that there was no significant difference between the studied groups with p value (>0.05).

These results coincide with the study of ***Kashanian et al.*** [6] study, when they used intravenous injection of a single dose of 2 mg propranolol plus oxytocin 5 IU which showed no significant difference in the 3rd stage between the studied groups with p value (0.065).

Also, our results coincide with ***Palomaki et al.*** [9] who showed that Propranolol (2 or 4 mg iv) combined with oxytocin was not significantly affect the duration of 3rd stage with p value (0.077).

The current study showed no significant difference between the studied groups regarding the mode of delivery as there were decrease in the rate of cesarean section but statistically non-significant. These coincide with the study of ***Palomaki et al.*** [6] who reported that no reduction in cesarean section rate was found in the propranolol plus oxytocin group 73% of the parturient in this group and 85% in oxytocin group had spontaneous vaginal delivery, RR=0.86 (95% CI 0.70-1.05), while the study of ***Moghadam et al.*** [12] revealed significant decrease in the rate of cesarean section with p value (<0.05).

Also ***Direkvand and Moghadam*** [8] stated that frequency of cesarean section deliveries significantly decrease in the propranolol plus oxytocin group compared to oxytocin group with p value (0.005 and 0.015) respectively. Use of a different dosage of propranolol in the above-mentioned study can be a possible explanation for the difference observed. The half-life of propranolol is about 2-3 h and its maximal effect is at about 1-1.5 h after injection. Perhaps use of repeated doses of propranolol may result in more effectiveness.

In this study there was no significant difference between the studied groups regarding the general condition of the mother (maternal heart rate and blood pressure). and outcome (maternal complication). These findings in agreement with the studies of ***Moghadam et al.*** [12], ***Palomaki et al.*** [9], ***Kashanian et al.*** [6] and ***Ziolkowski*** [13]. Also in agreement of our study ***Pergialiotis et al.*** [14] stated safe of propranolol for both mother and fetus In cases of arrested labor, reasons other than inadequate uterine contractility, such as disproportion, mal-presentation, malposition, fetal macrosomy or maternal anatomic abnormalities should be strictly excluded before augmentation [15].

In the current study there is a highly significant difference in the FHR before and after oral propranolol administration among group 1 with p value (0.000).

There is a highly significant difference in the FHR before and after propranolol administration in subgroup A of group II with p value (0.001) and there is significant difference in subgroup B of group II with p value (0.02).

There is no significant difference before and after oxytocin administration among group 3 with p value (0.32). The study also shows no significant difference regarding fetal complication or CTG finding and neonatal admission to NICU after oral propranolol administration comparing with group 3 which administrate oxytocin only.

Pathological CTG findings were not common in the material [9]. In their study two cases of transient bradycardia were detected in both groups, and other findings were in the placebo (control) group. Even the parturients who received two doses (4 mg) of propranolol did not show an increase in pathological CTG findings in comparison with the placebo group. These findings were coincides with our results in that indication of propranolol can be considered safe as regards intra-labor risks detected by CTG. So the percentage proportion of the augmented part of labor was significantly shorter in the propranolol group than in the placebo group (P =0.03). No differences in the required oxytocin dosage or CTG pathology were found between the groups (P > 0.05). Propranolol was found to be safe for the neonates.

In our study, Propranolol had no adverse effects on neonates according to Apgar scores of minutes 1 and 5 and need of admissions to NICU, this coincides with the findings of ***Moghadam et al.*** [12]. They found 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 (p>0.05).

This also coincides with ***Palomaki et al.*** [9]who paid special attention to close examination of the newborns after propranolol administration. No differences were found between the groups in cord blood biochemical test results, blood pressure, pulse frequency, breath frequency, blood glucose levels or need of NICU care, these findings consequently pointing to the conclusion of improbability of propranolol-related neonatal problems.

Regarding the safety, ***Pergialiotis et al.*** [14] agreed our results in that propranolol does not seem to negatively influence the fetus as the 5 min Apgar scores and the admissions to NICUs were not influenced by its administration. The 5 min neonatal Apgar scores are not influenced by its administration of propranolol compared to control groups (MD -0.07, 95 % CI -0.017, 0.02), respectively. Taking in mind these significant results, one might contemplate that propranolol might become a significant obstetrical tool for augmentation of labor in the future. The neonatal admissions to a NICU are similar to those of neonates exposed only to oxytocin (OR 0.96, 95 % CI 0.36, 2.53).

Conclusion

It was found in the current study 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.

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