Original Article

The effect of oral propranolol plus oxytocin versus oxytocin only on the process and outcome of labor: A double-blind randomized trial

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Abstract

Background: Prolonged labor can lead to maternal and neonatal complications. The purpose of this study was to investigate the effect of oral propranolol plus oxytocin versus oxytocin only on the process and outcome of labor.

Materials and Methods: In a randomized, double-blind, controlled trial performed in Ilam Mustafa hospital, a total of 146 nulliparous pregnant women at gestational age of 40-42 weeks were randomly allocated to receive 20 mg oral dose of propranolol or placebo plus oxytocin infusion (73 participants in each group). The outcome measures were the mean duration of labor stages, type of delivery, and neonatal outcome.

Results: The mean duration of active phase and the second stage of labor were significantly shorter in the propranolol group than in the placebo group on both the first and the second days of induction. The mean duration of third stage of labor was shorter in the propranolol group than in the placebo group, but the difference was not significant statistically on the first (P = 0.159) and second (P = 0.065) days. Frequency of cesarean section deliveries significantly decreased in the propranolol plus oxytocin group compared to the placebo plus oxytocin group (P = 0.005, P = 0.015) on the first and the second days, respectively. No significant difference in the neonatal outcome measures, such as Apgar scores at 1 and 5 min and the need for neonatal intensive care unit (NICU) admission, was found between the groups.

Conclusions: This study showed that oral propranolol is an effective agent in both shortening the labor duration and reducing the frequency of cesarean section.

Key words: Cesarean section, Iran, labor, oxytocin, prolonged pregnancy, propranolol

Introduction

Labor is defined as the state of being in uterine contractions of adequate frequency, duration, and strength to cause effacement and dilation of the cervix.[1]

Prolonged labor can lead to maternal and neonatal complications,[2-4] and these adverse labor outcomes increase in prolonged pregnancy in comparison with term gestational age.[5-7] Therefore, the factors affecting labor progression have been widely studied.[1,8-12]

However, oxytocin is the best known and most widely used agent to induce and augment uterine contractions;[13] 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.[11,14]

Propranolol is well established as a β-adrenergic receptor–blocking drug that increases the uterine activity in pregnant and non-pregnant women[15] by reversing the suppressive effect of the β-agonist isoproterenol on human uterine motility.[8] Recent studies have shown the effect of oxytocin to be associated with propranolol in decreasing the time of labor induction[10] and the duration of active phase in labor dystocia.[11]

The first uncontrolled study on the use of propranolol in dysfunctional labor was conducted about four decades ago. The results showed that administration of intravenous

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propranolol causes normal uterine activity and delivery without any significant maternal or fetal complications.[16] Sanchez-Ramos *et al*. compared the effect of oxytocin plus intravenous propranolol infusion with that of oxytocin plus placebo on 96 parturients with abnormalities of the active phase of labor and reported a reduction in the need for cesarean section delivery in the propranolol group compared to the placebo group.[17] In another study, 57 nulliparous women in the active phase of labor were randomly assigned to two groups. The frequency of cesarean section due to labor dystocia was two times in the control group compared to propranolol group (13.6% and 6.25%, respectively). The neonatal and maternal outcomes were similar in both groups.[9] However, other studies showed no reduction in the rate of cesarean delivery in women receiving propranolol for labor induction[10] or augmentation.[11] However, shortening the duration of labor in order to reduce its complications is important. But recent studies have also associated elective induction in nulliparous women to increased hospital costs.[18,19]

Because of the contradicting results reported by the studies, specifically the type of delivery, we decided to evaluate the effect of propranolol on the labor duration and the delivery outcomes such as the type of delivery and Apgar score. It is well known that the half-life of propranolol is 2-3 h and its peak effect is at 1 h. Therefore, at first, we consulted with expert pharmacologists, gynecologists, and cardiologists, and then, we used oral propranolol. The drug dosage was approved by the consultation team consisting of the above-mentioned experts.

Materials and Methods

This is a double-blind, randomized, controlled trial carried out in Ilam Mostafa Hospital, Iran from March 2010 to March 2011. This study was conducted with the approval of the ethics committee of Ilam University of Medical Sciences. Participation in the study was voluntary and the participants were free to withdraw from the study whenever they wished to do so. An informed consent was obtained from all participants before they were enrolled in the study.

Using Epi Info version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and Stat Calc version 1.0.1 (AcaStat, Leesburg, VA, USA), a sample size of 150 participants was determined to have 80% power to detect significant differences between the studied groups for a confidence interval of 95%.

Elective induction of labor beyond 40 weeks of gestational age may be associated with a decrease in the risk of both cesarean delivery and meconium-stained amniotic fluid. Therefore, the induction of labor increased from 9.5% in 1990 to 22.1% in the US in 2004.[19] We studied 146 nulliparous women with singleton pregnancy of 40-42 weeks of gestational age (according to a reliable last menstrual period and ultrasound evaluation at the first trimester).

The inclusion criteria were absence of the following: a history of uterine surgery, polyhydramnios, contraindications to β–adrenergic agents, such as 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, maternal use of drug, and fetal distress. The exclusion criteria were estimated weight of the fetus more than 4 kg by ultrasound of cephalic presentation, rupture of membrane, and Bishop score of more than 5 present of uterus contraction[20] or fetal height estimated by symphsis-fundal height measurement.[21]

The participants were selected by the simple random sampling method. Then, all participants were examined by a cardiologist and a gynecologist in order to identify the conditions mentioned in the inclusion and exclusion criteria before using any intervention. Next, randomization was carried out at the obstetric triage unit on a 1:1 basis using a random number table and 73 participants were allocated in each group, as described in previous clinical trial studies.[22,23]

A checklist was used to collect the demographic and obstetric data. The participants' characteristics such as age, primary Bishop score, gestational age, body mass index (BMI), and estimated birth weight were recorded and compared between groups. The partogram was used to monitor the fetal heart rate, membrane status, cervical dilation and effacement, station of the fetus, uterine contractions, maternal pulse and respiratory rate, maternal blood pressure, maternal temperature, and Apgar scores at 1 and 5 min. Amniotomy was performed by a trained midwife when cervical dilation reached 5 cm, if the membrane had not been ruptured spontaneously.

A capsule containing 20 mg propranolol to the first group (propranolol plus oxytocin) and a similar capsule as a placebo to the second group (oxytocin plus placebo) were administrated orally by the researcher before beginning induction. Oral capsules were repeated after 8 h, if tree forceful contractions were not obtained during 10 min. Then, induction was initiated by an experienced midwife. The study was of a double-blind design.

Induction was initiated with a dose of 2 mIu/min and increased by 2 mIu/min every 15 min until tree forceful contractions were obtained for 10 min, or to a maximum dose of 30 mIu/min. Then, it was continued at this rate for 8 h. If patients entered the active phase of labor (cervical dilatation = 3–4 cm), induction was continued until delivery.

If the parturient had hyperstimulation of contractions (in a situation with more than 5 contractions/10 min, duration of contraction > 90 sec, interval of contraction less than 2 min, or fetal distress), the induction was stopped, and the parturient was kept in left lateral position and given oxygen, and intravenous dextrose. If the situation returned to normal, the induction was started with half of the previous dosage. Otherwise, the gynecologist was informed and the treatment process was chosen based on the gynecologist's decision. In the cases not entering the active phase, induction was stopped and participants were transferred to the pre-labor ward. On the second day, all interventions like those of the first day were performed. If there was no response to induction on the second day, a cesarean section was performed. The participants were followed up until delivery. All collected data were analyzed using SPSS version 14 (IBM, Armonk, NY, USA). Comparisons of means were done by *t*-test. A *P* value of 0.05 was considered statistically significant. Statistical comparisons were made using the Mann–Whitney U test, Chi-square test, and unpaired *t*-test.

Results

None of the 146 enrolled women withdrew for any reason. Participants' characteristics were not different between the groups ($P > 0.05$). Baseline characteristics of the patients are shown in Table 1.

On the first and second days of intervention, both the duration of the active phase and the second stage of labor were significantly shorter in the propranolol group. The mean duration of the third stage of labor was shorter in the propranolol group compared to the placebo group, but the difference was not significant statistically on the first ($P = 0.159$) and the second ($P = 0.065$) days. Out of 146 women enrolled for induction, 44 (30.13%) cases had cesarean section deliveries and 102 (69.87%) cases delivered vaginally. Frequency of cesarean section deliveries significantly decreased in the propranolol plus oxytocin group compared to the placebo plus oxytocin group. The results are presented in Tables 2 and 3.

No significant differences in neonates' outcomes such as Apgar scores at 1 and 5 min and the need for admission to neonatal intensive care unit (NICU) were found between the groups. The mean neonatal Apgar scores at 1 min in the propranolol and placebo groups were 8.8 ± 0.45 and 8.7 ± 0.5, respectively ($P = 0.987$). Also, the mean neonatal Apgar scores at 5 min in the propranolol and placebo groups were 9.85 ± 0.47 and 9.9 ± 0.63, respectively ($P = 0.615$). Two newborn babies (2.7%) in the propranolol group and 3 (4%) in the placebo group needed admission to NICU ($P = 0.571$). Two newborns in the propranolol plus oxytocin group and four newborns in the oxytocin alone group had an Apgar score less than 7 at the 1st minute, but there were no significant differences between groups.

Table 1: Comparison of participants' characteristics in the two groups

Characteristic	Mean±SD (*n*=73)		*P* value
	Propranolol	Placebo	
Maternal age (years)	21.5±3.5	21.9±2.2	0.865
Gestational age (days)	40.8±1.2	40.46±2.04	0.096
BMI (kg/m^2)	21.3±1.24	20.46±2.04	0.640
Bishop score	2.8±0.56	2±0.2	0.654
Birth weight (g)	3269.3±416.9	3280.8±384.5	0.532

BMI: Body mass index, SD: Standard deviations

Table 2: Comparison of labor duration in the two groups

Characteristic (min)	Mean±SD (*n*=73)		*P* value
	Propranolol	Placebo	
Duration of active phase on the first day	235.5±22	277.5±31	0.02
Duration of active phase on the second day	270±31	280.4±26.4	0.013
Duration of the second stage of labor on the first day	38.4±12	54.5±18.5	0.016
Duration of second stage of labor on the second day	21.7±8.4	38.4±11.1	0.003
Duration of third stage of labor on the first day	7.4±2.4	7.6±3.1	0.159
Duration of third stage of labor on the second day	6.9±2.9	7.1±3	0.065

SD: Standard deviation

Table 3: Comparison of the type of delivery in the two groups

Characteristic	(*n*=73)				*P* value
	Propranolol		Placebo		
	n	%	*n*	%	
Normal vaginal delivery on the first day	51	35	32	22	0.005
Cesarean section delivery on the first day	7	4.8	10	6.84	
Normal vaginal delivery on the second day	7	4.8	12	8.2	0.015
Cesarean section delivery on the second day	8	5.5	19	13	

Discussion

In recent years, investigation of new methods to reduce prolonged labor and also to prevent cesarean sections, due to uterine dysfunction, has been requested in obstetric practice because of the increased morbidity related to these problems. Therefore, in the present study, we decided to

evaluate the effect of propranolol, a β-adrenergic blocker, on labor duration and the mode of delivery. One difference between our trial and other studies performed up to now is that we used the oral form of propranolol. Our results showed that propranolol could significantly shorten both the duration of active phase and the second stage of labor.

The β_2-adrenergic receptor (β_2-AR) is a type of G protein–coupled receptor[21] which is distributed in n umerous tissues and is found widely in the smooth muscle of the vasculature, trachea, bronchi, and uterus. This receptor has an important role in smooth muscle relaxation resulting from the activation of the adenylate cyclase signaling cascade.[24] Stimulation of β2-AR causes relaxant effects on the smooth muscle of the uterus. It has been shown that the number of these receptors decreases by about 50% when the labor contraction begins.[25] Propranolol blocks β_1–β_2-ARs, but has no effect on β_3-AR of the myometrium.[10] Previous studies have shown that administration of intravenous propranolol could increase myometrial contractility in pregnant and non-pregnant women,[15] and acts against the relaxant effects of ritodrine.[26] Ziolkowski showed that use of a combination of propranolol and oxytocin in post-term pregnancies leads to reduction of labor duration by approximately 30%, which is consistent with our findings.[27] In a randomized trial by Kashanian *et al.*, when they used intravenous injection of a single dose of 2 mg propranolol 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.[10] Palomaki *et al*. reported that in cases of labor arrest due to insufficient power of contractions, adding propranolol to oxytocin could improve the power of contractions and decrease the length of labor, which is consistent with our results.[11] In a similar study on labor dysfunction, Mitrani *et al*. showed that propranolol could reinforce labor contraction by blocking the β-ARs.[16] In our study, however, the length of the third stage of labor decreased in the propranolol group, but the difference between groups was not significant; this finding is in accordance with other previous studies.[10,11] We repeated 20 mg oral propranolol after 8 h if a poor contraction was obtained. With regard to the half-life of propranolol and duration of its effect, it seems that administration of repeated doses of oral propranolol may lead to more effects.

Also, it was observed in our study that use of propranolol plus oxytocin decreased the frequency of cesarean section deliveries, confirming several previous studies.[9,17] However, the results of some other studies are not consistent with our finding.[11] In our study, propranolol had no adverse effects on neonates according to the Apgar scores at 1 and 5 min and the need for NICU admission. Safety of propranolol combined with oxytocin among neonates has been shown in several studies.[10,11,17] Oral propranolol induces long-lasting effects with no adverse effects on neonates.

Conclusion

To conclude, it was found in our study that oral propranolol, combined with oxytocin, is an effective agent both in shortening the labor duration and in reducing the frequency of cesarean section without any adverse effects on the mother and the newborn.

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