Comparison Effect of Oral Propranolol and Oxytocin Versus Oxytocin Only on Induction of Labour in Nulliparous Women (A Double Blind Randomized Trial)

ASHRAF DIREKVAND-MOGHANDAM\textsuperscript{1}, MOLOUK JAFAPOUR\textsuperscript{2}, ALI KHAN\textsuperscript{3}

ABSTRACT

Background and Aim: Today, research on new methods for preventing caesarean sections owing to labour induction, have been requested in obstetric practice, because of the increased morbidity related to caesarean section. Therefore, the aim of this study was to compare the effect of Oral Propranolol and Oxytocin versus Oxytocin only on induction of labour in nulliparous women.

Material and Methods: A double blind randomized controlled trial was performed at the Ilam Mostafa Hospital, Ilam, Iran, from March 2010 to March 2011 on 146 nulliparous pregnant women who had gestational age of 40–42 weeks of pregnancy and a Bishop score of ≤5. Participants were divided in two groups (with 73 participants in each group). In the first group (placebo plus Oxytocin group = 73), Oxytocin was used for the induction of labour. In the second group (Propranolol plus Oxytocin group = 73 cases), before the use of Oxytocin, 20 mg Propranolol was administrated orally and then the Oxytocin was initiated. Twenty mg Propranolol was repeated after 8 hours if good contraction was not obtained.

Results: The mean duration for obtaining good contractions was significantly shorter in the Propranolol group than in the placebo group, on both the first and second day of induction (p<.05). The mean duration of latent phase was shorter in the first in Propranolol group (p<.05). In Propranolol plus Oxytocine group, frequency of cesarean deliveries significantly decreased than in the placebo plus Oxytocin group (21% versus 39.7%). 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>.05)

Discussion and Conclusion: Our study showed that oral Propranolol was effective for labour induction and that it could decrease the frequency of caesarean deliveries without producing any adverse effects on mothers or neonates.

Key words: induction of labour, Propranolol, Caesarean delivery, Oxytocin

INTRODUCTION

Induction of labour is defined as stimulation of uterine contractions before they occur spontaneously and its prevalence has increased in the United States from 9.5% of births in 1990 to 22.1% of births in 2004 [1]. Although induction of labour has recently been on the rise for purposes of convenience or to accommodate busy schedules, the main reasons include prolonged pregnancies and maternal and foetal indications [2]. Prolonged pregnancies can result in development of oligohydramnios, macrosomia, and intravertebral foetal demise at a later gestational age [3]. Induction of labour is thought to be advantageous for the mother or baby [4]. Induction of labour is directly relevant to the health related Millennium Development Goals (MDGs) and it may also contribute to lowering of caesarean section rates [5]. Labour can be induced by mechanical and pharmacological methods such as use of prostaglandins [6] and Oxytocin [7]. Oxytocin can be used alone or in combination with other agents for labour induction. Propranolol is one of these agents which have been suggested for assisting labour induction [8]. In several studies, it was seen that Propranolol could induce contractions in the pregnant uterine musculature [9,10]. Propranolol, as a β-adrenergic receptor-blocking drug, can reversed the inhibitory effect of β-agonist isoproterenol on human uterine motility [11]. In a study, its intravenous use once or twice in a 2 mg dose was found to shorten the duration of labour induction, without any significant adverse effects on neonates [12]. In other study, intravenous Propranolol was found to increase uterine activity in pregnant and in the non-pregnant participants [13]. No poor effect on neonatal outcome was found with use of Propranolol [11,12]. The purpose of the present study was to evaluate the effect of Oral Propranolol plus Oxytocin in comparison with Oxytocin alone on induction of labour.

MATERIAL AND METHODS

This was a double blind randomized controlled trial that was performed at the Ilam , Mostafa Hospital, Ilam, Iran, from March 2010 to March 2011. We studied 146 pregnant women with prolonged pregnancies. The eligibility criteria were singleton pregnancies with gestational age of 40–42 weeks of pregnancy (according to a reliable last menstrual period and ultrasound evaluation at first trimester), nulliparity, cephalic presentation, intact membrane, and Bishop's score of less than [5]. Exclusion criteria were uterus contraction, any previous surgical operation on the uterus, sign of foetal distress, suspicious macrosomia, polyhydramnios, systolic blood pressure of <100 mmHg, pulse rates of < 60/min and more than 120/min, history of any known cardiac disorder, mother's pulmonary or metabolic disorders, or maternal use of drugs.

A total of 146 pregnant women were investigated in a randomized clinical trial, as was previously described for other clinical trial studies [13,14] (73 participants in each group). In the first group (Propranolol plus Oxytosine), a capsule consisted of 20 mg Propranolol was
administered and in the second group (Oxytocin plus placebo), a similar capsule as a placebo was administrated orally by researcher before beginning of induction of labour. Oral capsules were repeated after 8 hours if good contraction (3 forceful contractions within 10 min) was not obtained. Then, induction was initiated by experienced midwife who knew nothing about the method of intervention; the patients were also blinded to it (double blind).

Induction and the control of patients were monitored. Induction was initiated at a dose of 2 mlu/min and it was increased 2 mlu / minute every 15 minutes until good contractions were obtained (3 forceful contractions within 10 minutes) or to a maximum dose of 30 mlu/min; then, it was continued at this rate for 8 hours. If patients entered the active phase of labour (cervical dilation = 3-4 cm), induction continued until delivery. If the participants did not enter the active phase, the induction was discontinued and the patients were transferred to the pre-labour 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. Blood pressures and heart rate of the parturients and foetal heart rates were monitored every 15 minutes. The participants’ characteristics, age, primary Bishop score, gestational age, the number of deliveries on the first day of induction and caesarean sections, timing of the beginning good contractions after induction, duration of latent phase (interval between the beginnings of good contractions until cervical dilatation of 3–4 cm were obtained), type of delivery and Apgar scores of minutes 1 and 5, need of admissions to NICU and neonatal weights were recorded and compared in the two groups. The participants were followed up until delivery.

### Statistical Analysis
All collected data were analysed by using SPSS, version 14 (IBM, Armonk, NY, USA). Comparisons of means were done by t-test. A p-value of 0.05 was considered as statistically significant. Statistical comparisons were determined by using the Mann-Whitney U test, unpaired t-test.

### Ethical Evaluation
This study was undertaken with the approval of the ethics committee of the Ilam University of Medical Sciences. Participation in the study was voluntary and the participants were free to withdraw from the study whenever they wished. Informed consents were obtained from all participants before their enrolment into the study.

### Results
None of the 146 enrolled women withdrew from the study for any reason. Baseline patient characteristics have been shown in [Table/Fig-1]. Participant characteristics were not different among groups. On the first and second days of intervention, the intervals between the beginning of induction and until good contractions were obtained were significantly shorter in the Propranolol group. On the first and second days of intervention, the intervals between the beginning of induction and until good contractions were obtained were significantly shorter in the Propranolol group. Between the beginning of induction and until good contractions were obtained were significantly shorter in the Propranolol group.

### Discussion
Elective labour induction has been introduced as main cause of caesarean deliveries. Now-a-days, research on new methods for preventing caesarean sections owing to labour induction or uterine hypocontractility have been requested in obstetric practice, because of the increased morbidity related to caesarean sections. Therefore, in the present study, we decided to evaluate the effect of Propranolol as beta adrenergic blocker on success of labour induction.

One difference in our trial, as compared to that in other studies which have been performed up to now, is that we used oral form of Propranolol. As per our results, Propranolol could significantly shorten both the timing of start of good forceful contractions and duration of latent phase. Results of several studies are consistent with our results. In a randomized trial which was done by Kashanian et al., results were congruent with our those of study, in that they used intravenous injection of single dose 2 mg Propranolol before starting labour induction [8]. Palomaki et al., reported that in cases of arrested labour caused by insufficient power of contractions, adding propranolol to Oxytocin could improve the power of contractions [12]. Chimura showed that the use of alpenrolol (a beta blocker) in vitro, produced myometrial stimulation of pregnant uterus in rats [15], and in another study, Peiker et al, showed a similar effect of Propranolol, on relaxation of the myometrium of non-pregnant rats in vitro, but its stimulation in pregnant rats [10]. In another study [16], Propranolol inhibited the relaxant effect of Ritodrine in isolated myometrial strips that were obtained during elective caesarean deliveries. The beta-2 adrenergic receptor, a member of the super family of G protein-coupled receptors [17] is distributed in numerous tissues and is manifested 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

### Tables

#### Table/Fig-1
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Propranolol puls Oxytocin (n=73)</th>
<th>Placebo puls Oxytocin (n=73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years)</td>
<td>21.5 ± 3.5</td>
<td>21.9 ± 2.2</td>
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<td>Gestational age (day)</td>
<td>40.8 ± 1.2</td>
<td>20.46 ± 2.04</td>
<td>0.0985</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>21.3 ± 1.24</td>
<td>20.46 ± 2.04</td>
<td>0.640</td>
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<tr>
<td>Bishop score</td>
<td>2.8 ± 0.56</td>
<td>2x ± 0.2</td>
<td>0.654</td>
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<tr>
<td>Birth weight (g)</td>
<td>3269.3± 416.9</td>
<td>3280.8 ± 384.5</td>
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#### Table/Fig-2
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<tr>
<th>Characteristic</th>
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<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interval until good contractions in first day, min</td>
<td>176.2±11.2</td>
<td>190.3±21.4</td>
<td>0.000</td>
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<tr>
<td>Duration of latent phase in first day, min</td>
<td>115.5±9.2</td>
<td>185±28.6</td>
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<tr>
<td>Duration of latent phase in second day, min</td>
<td>198.4±16.3</td>
<td>259.2±24.4</td>
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#### Table/Fig-3
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<th>Placebo puls Oxytocin (n=73)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal Apgar score minute 1</td>
<td>8.8±.45</td>
<td>8.7±.5</td>
<td>0.987</td>
</tr>
<tr>
<td>Neonatal Apgar score minute 5</td>
<td>9.8±.47</td>
<td>9.9±.63</td>
<td>0.615</td>
</tr>
</tbody>
</table>

*Continuous variables displayed as mean ± standard deviations
** Neonatal Intensive Care Unit, Number, Percent

### References
1. Peiker et al, showed a similar effect of Propranolol, on relaxation of the myometrium of non-pregnant rats in vitro, but its stimulation in pregnant rats [10]. In another study [16], Propranolol inhibited the relaxant effect of Ritodrine in isolated myometrial strips that were obtained during elective caesarean deliveries. The beta-2 adrenergic receptor, a member of the super family of G protein-coupled receptors [17] is distributed in numerous tissues and is manifested 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 [18]. Engstrom et al., reported that beta-2 adrenergic receptor number in pregnant rats decreases linearly throughout the gestational period [19]. However, Legrand et al., showed that the concentration of beta-2 adrenergic receptor in pregnant rat myometrium, decreased just 6 hours before the delivery [20]. Chanrachakul et al., in their study, concluded that diminished beta-2 adrenergic receptor levels, along with the apparent desensitization of the beta-2 adrenergic receptors at term gestation, would tend to promote myometrial contractility, thereby initiating labour, probably in concert with other mechanisms [21]. With respect to these studies, it seems beta adrenergic blockers such as Propranolol can increase the uterine contractions in term pregnant uteri. Also, our study showed that use of Propranolol plus Oxytocin decreased the frequency of caesarean deliveries and this was confirmed several previous studies [11, 22]. However, these findings of other studies were not consistent with our findings [12]. Different dosages of Propranolol which were used in these studies was one possible explanation for this difference. The half life of Propranolol is about 2–3 hours and its maximal effect is about 1–1.5 hours after injection [23]. We used oral Propranolol that induces long-lasting effects on uterine contraction.

In our study, Propranolol had no adverse effects on neonates because of Apagar scores of minutes 1 and 5 and need of admissions to NICU. According to classification of the Food and Drug Administration (FDA), Propranolol is in C group. Propranolol administration which was done for labour stimulation produced no adverse effects on foetal heart rate and general condition of the mother [24]. Safety of Propranolol use in neonates has been shown in several studies [8,11,12]. We used 20 mg oral Propranolol at start of induction and it was repeated in the same dose after 8 hours if good contractions were not obtained. In spite of the fact that oral Propranolol induces long-lasting effects, we found no adverse effects on neonates.

CONCLUSIONS

If a need of induction of labour is considered as a sufficient indication for use of medication, with respect of our study, we suggested that Propranolol is effective for successful labour induction and is safe for mother and newborn.

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Conflict of interest: The authors have no conflicts of interest to disclose.

REFERENCES


