

## Research Article

## Comparing the effect of oxytocin alone versus oxytocin plus intravenous and oral propranolol on labor progression: A randomized clinical trial study

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DOI: 10.5455/jrmds.2016443

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Received on: 6 August 2016

Accepted on: 10 December 2016

### ABSTRACT

**Introduction:** Cervical ripening methods are always used to prepare cervix during labor induction. The aim of this study was to compare the effects of oxytocin alone and oxytocin in combination with intravenous and oral propranolol on labor progression in natural childbirth. **Materials and Methods:** This clinical trial study was conducted on 120 pregnant women with 38-41 weeks of gestational age. They divided into three groups using triplex random blocks. The sample size in each group was 40 cases. 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 along 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. Chi-square test was used for qualitative variables. To compare the main variable of the study one-way ANOVA with Tukey post hoc test were used. The significant level of .05 was considered. **Results:** The duration of the first stage of labor in oxytocin alone group was  $197.25 \pm 66.9$  minutes which was more than oxytocin with oral propranolol ( $128.25 \pm 35.29$ ) and oxytocin with intravenous propranolol ( $122.00 \pm 23.00$ ) groups. It was a significant difference between the three groups ( $p = .0001$ ). The duration of the second stage of labor in oxytocin alone group was  $56.50 \pm 29.70$  minutes and in, oral propranolol and intravenous propranolol groups were  $42.38 \pm 17.17$  and  $54.38 \pm 23.94$  respectively. It was a significant difference between the three groups ( $p = .021$ ). **Conclusion:** Administration of propranolol with oxytocin particularly in oral method reduces the time of the first and second stages of labor in natural labor and also reduces caesarean section cases. In addition propranolol had no effect on maternal and neonatal complications.

**Keywords:** Propranolol, labor onset, labor induction, labor stages

### INTRODUCTION

The duration of normal delivery is different in women and normal delivery slow progress is very common in nulliparous women that had many fetal complications and is one of the reasons for emergency cesarean section [1]. Disruption in the normal delivery,

especially in non-advanced societies is a common problem [2]. Normal delivery failure or dystocia is responsible for 30% of cesarean sections [3]. A study showed that 30.7% of cesarean sections in Ardabil, Iran were because of dystocia [4]. Also a study which conducted in East Azarbaijan Province, Iran showed

that the lack of progress in the labor process was responsible for 25.3% of cesarean sections [5].

Induction of labor in circumstances where the cervix is inappropriate for labor is one of the obstetrical problems and cervical ripening methods are always used to prepare cervix during labor induction [6]. Elective induction of labor increases the risk of cesarean section 2 - 3 times. Various methods are used to prepare cervix for labor including; mechanical and pharmacological methods. Using prostaglandins or oxytocin is among pharmacological methods [7]. Administration of oxytocin by physicians in order to prolong the uterine contractions and to shorten the duration of labor is increasing [8, 9]. Administration of oxytocin during labor has many complications, including dystocia. The Institute for Safe Medication Practices added intravenous oxytocin to high-alert medications list and proposed reducing oxytocin dose in order to prevent the maternal and fetal complications [9]. Previous studies showed that adrenaline causes uterine muscle relaxation, in contrast noradrenaline increases the duration of uterine contractions and increases the number of contractions [2]. The reason for increasing the duration of the contractions and the number of contractions is stimulating alpha receptors and reducing contractions and uterine activity is the result of beta receptors [10].

Labor pain along with fear and anxiety, can lead to elevated levels of catecholamines in blood which decreases uterine muscle intensity contractions by stimulating beta-adrenergic receptors and impair the normal delivery [10].

Propranolol is Beta 1 and beta 2-adrenergic receptor blocker. Beta-adrenergic stimulation inhibits contractions of the uterus [11]. Propranolol can cause muscle contraction in pregnant uterus [6]. Based on laboratory studies, propranolol by blocking beta-adrenergic receptors enhances uterine contractions caused by oxytocin [7]. It has been observed that using it shortens the duration of labor induction without having detrimental effect on infant [12].

Although many studies have shown that propranolol could reduce the cesarean section rate and reduce the duration of the active phase [13], but there are other studies that showed no such findings [9]. Considering the side effects of oxytocin, finding an appropriate way to lower the dose of oxytocin and reducing the duration of labor and decrease maternal and fetal complications has always been concerned,

therefore the aim of this study was to compare the effects of oxytocin alone and oxytocin in combination with intravenous and oral propranolol on labor progression in normal childbirth.

## MATERIALS AND METHODS

This single-blind clinical trial study was conducted on 120 women with gestational age of 38-41 weeks (based on the last menstrual period or ultrasound confirmation of first trimester) and Bishop score more than or equal to 5, referred to Besat hospital in Sanandaj, Iran in 2016. Inclusion Criteria were; nulliparity, singleton, cephalic presentation, fetal heart rate between 120 to 160 beats per minute, approximate weight of 2,500 to 4,000 gr (by examination or ultrasound), the maternal heart rate between 60 to 120 beats per minutes and exclusion Criteria were ; CPD, any history of previous surgery on the uterus, fetal distress, the risk of macrosomia or polyhydramnios, SBP≤90, the maternal heart rate under 60 and more than 130 beats per minutes, any history of cardiopulmonary disease, metabolic disease of mother or taking medicine for any illness by mother, heart failure or a history of cardiac arrhythmias and long PR interval in ECG .

## Sample size and sampling method

As the main objective of this study was to compare three types of pharmacological intervention (the effects of oxytocin alone and oxytocin in combination with intravenous and oral propranolol) on the duration of the active phase of labor, the appropriate statistical analysis was using one-way ANOVA. The sample size for this analysis was calculated using the following formula:

$$\Phi = \frac{nD^2}{2a\sigma^2} \rightarrow n = \frac{2a\sigma^2\Phi}{D^2}$$

In which "a" indicates the type of pharmaceutical intervention at three levels and "D" is the mean difference between groups. If the mean difference between two groups was more than D then equality assuming of the two means is rejected. "n" is the sample size required in each group and  $\Phi$  was determined using operating characteristic curves. In a study by Sharami et al [13] they reported the difference between active time of normal delivery in the two oxytocin with propranolol and oxytocin alone groups as 75units. In this study, the assumption was that 20 units difference between the averages of the two groups is clinically significant (D = 20 is less than one standard deviation). Assuming the initial estimate

of standard deviation and active time of 30 minutes for normal delivery, we can write that:

$$n = \frac{2a\sigma^2\phi}{D^2} = \frac{2 \times 3 \times 900 \times 3}{400} = 40.5$$

Therefore the sample size was calculated as 40 cases in each group. In the above formula  $\Phi$  was considered as 3, Type I error was 0.01 and Type II error was 0.07 also test power was 93%. Total samples were 120 pregnant women who had inclusion criteria and divided into three groups using triplex random blocks.

### Data collecting

Cervical features which is called Bishop Score is a possible effective factor in the successful induction and is including; dilatation, effacement, station, consistency and position that is scored from 0 to 13. ECG was taken for all patients who entered the study. Given the exclusion criteria patients with a history of cardiac arrhythmia or arrhythmia in their ECG were excluded from study. Informed consent was taken from all cases to participate in the study. They divided into three groups using triplex random blocks.

In the oxytocin alone group, oxytocin started at 2mIU/min and every 15 minutes the same amount added to create a good contraction (3 contractions in 10 minutes) this continue maximally up to 8 hours and 36mIU. In entering the active phase of labor, induction continues to delivery, in case of no entry to the active phase (3- 4 cm dilation) induction stopped after 8 hours. If the number of contractions were more than 5 in ten minutes or more than 7 in 15 minutes and led to non-reassuring fetal heart rate pattern with diagnosis of hyper stimulation, oxytocin administration was discontinued and Ringer solution prescribed and after quenching the hyper stimulation induction repeated with half of the previous oxytocin dose. In case of re-hyperstimulation patient was excluded from the study. In the oxytocin with intravenous propranolol group, concurrent with the induction 2 mg propranolol infused intravenously and slowly and two hours after administration, patient examined vaginally. If after two hours cervical dilation did not change propranolol dose repeated just for another time and induction continues. Patients were controlled and decision made to continue induction to delivery or termination of pregnancy with cesarean section. Patient's blood pressure every hour and fetal heart rate every 15 minutes were controlled.

In the oxytocin with oral propranolol group, from beginning of induction 20 mg propranolol

administered orally, if after four hours cervical dilation did not change propranolol dose repeated just for another time and induction continues. Patients also controlled and decision made to continue induction to delivery or termination of pregnancy with cesarean section.

### Data analysis

Data were analyzed using SPSS Ver.20. Chi-square test was used for qualitative variables. To compare the main variable of the study one-way ANOVA with Tukey post hoc test were used. The significant level of .05 was considered.

### RESULTS

The results showed that the mean age in oxytocin alone group was 24.42±5.43 years and in oxytocin with oral propranolol group and oxytocin with intravenous propranolol group were 25.87±3.56 and 25.09±4.52 years respectively. There were no significant differences between three groups statistically ( $p=0.25$ ).

There were no significant differences between three groups statistically in terms of gestational age ( $p=0.08$ ). The mean gestational age in oxytocin alone group was 39.57±.97 weeks and in the oxytocin with oral propranolol group and oxytocin with intravenous propranolol group were 40.05±.81 and 40.16±.79 weeks respectively. (Table 1)

The duration of the first stage of labor in oxytocin alone group was 197.25 ± 66.9 minutes which was more than oxytocin with oral propranolol (128.25 ±35.29) and oxytocin with intravenous propranolol (122.00± 23.00) groups. It was a significant difference between the three groups ( $p = .0001$ ). There was no significant difference between oxytocin with oral propranolol (128.25 ±35.29) and oxytocin with intravenous propranolol (122.00± 23.00) groups in terms of the duration of the first stage of labor ( $p=.81$ ). The duration of the second stage of labor in oxytocin alone group was 56.50 ± 29.70 minutes and in oral propranolol and intravenous propranolol groups were 42.38 ± 17.17 and 54.38 ± 23.94 respectively. It was a significant difference between the three groups ( $p = .021$ ). Based on Tukey post hoc test in terms of the duration of the second stage of labor there were only a significant difference between oxytocin alone group and oxytocin with oral propranolol group ( $p=.27$ ) (Table 2)

According to one way ANOVA test there was significant difference between the three groups in terms of prescribed dose of oxytocin ( $p=.0001$ ). Tukey post hoc test showed that there was significant difference between the oxytocin alone group and oxytocin with intravenous and oral propranolol group ( $p=.0001$ ), but it was no significant difference between oral propranolol and intravenous propranolol groups ( $p=.93$ ). (Table 3)

The mean Apgar score 5 minutes in oxytocin alone group was  $8.93\pm.57$  and in the oxytocin with oral propranolol group and oxytocin with intravenous propranolol group were  $9.05\pm.22$  and  $8.97\pm.16$

respectively and there was no significant difference between three groups ( $p=.31$ ).

The frequency of meconium passing in oxytocin alone group was 7.5%, in the oxytocin with oral propranolol group was 15% and in oxytocin with intravenous propranolol group it was 12.5%. There was no significant difference between three groups ( $p=.57$ ).

The results also showed that the frequency of uterine atony in oxytocin alone group was 20%, in the oxytocin with oral propranolol group was 5% and in oxytocin with intravenous propranolol group it was 7.5%. There was no significant difference between three groups ( $p=.07$ ). (Table 4)

**Table 1.comparing the mean age of pregnant women in the three groups**

	Groups	Mean± SD	F	P value
Age (Year)	Oxytocin alone	24.42±5.43	1.39	.25
	Oxytocin + Oral propranolol	25.87±3.56		
	Oxytocin + Intravenous propranolol	25.09±4.52		
Gestational Age(Weeks)	Oxytocin alone	39.57±.97	5.02	.08
	Oxytocin + Oral propranolol	40.05±.81		
	Oxytocin + Intravenous propranolol	40.16±.79		

**Table 2.comparing the mean duration of the first and second stage of normal labor in three groups**

	Groups	Mean± SD	F	P value
First Stage (Minutes)	Oxytocin alone	197.25 ± 66.9	34.06	.0001
	Oxytocin + Oral propranolol	128.25 ± 35.29		
	Oxytocin + Intravenous propranolol	122.00 ± 23.00		
Second Stage (Minutes)	Oxytocin alone	56.50 ± 29.70	3.98	.021
	Oxytocin + Oral propranolol	42.38 ± 17.17		
	Oxytocin + Intravenous propranolol	54.38 ± 23.94		

**Table 3.Comparing the mean of prescribed dose of oxytocin in three groups**

Groups	Mean± SD	F	P Value
Oxytocin alone	5.53±3.13	35.05	.0001
Oxytocin + Oral propranolol	2.33±.92		
Oxytocin + Intravenous propranolol	2.48±.18		

**Table 4. The frequency of meconium passage and uterine atony in three groups**

	Groups	YES No. (%)	NO No. (%)	P value
Meconium Passage	Oxytocin alone	3(7.5)	37(92.5)	.57
	Oxytocin + Oral propranolol	6(15.00)	34(85.00)	
	Oxytocin + Intravenous propranolol	5(12.5)	35(87.5)	
Uterine Atony	Oxytocin alone	8(20.00)	32(80.00)	.07
	Oxytocin + Oral propranolol	2(5.00)	38(95.00)	
	Oxytocin + Intravenous propranolol	3(7.5)	37(92.5)	

## DISCUSSION

Propranolol increases uterine contractions in pregnant women [14]. Some studies have shown that uterine myometrium beta-adrenergic receptors in pregnant women are more than in non-pregnant women; therefore, compounds that can block adrenergic can increase uterine contractions.  $\beta_2$ -adrenergic receptor may also be reduced at the time of delivery and reducing function the of these receptors cause uterine contraction during childbirth. Propranolol blocks these receptors and increases the strength of uterine contractions and reduces the duration of active phase and second stage of labor [15-17].

The results of our study showed a significant difference between the three groups in terms of the duration of the first stage of labor and it was  $197.25 \pm 66.9$  minutes in the oxytocin alone group which was significantly more than two Oxytocin + Oral propranolol and Oxytocin + Intravenous propranolol, but there was no significant difference between intravenous propranolol group with oral propranolol group. In a study by Sharami et al. which conducted to evaluate the effect of oxytocin plus propranolol on the success of labor augmentation, the results showed that the duration of active phase of labor in propranolol group was  $324.74 \pm 71.57$  minutes which was significantly lower than placebo group ( $406.04 \pm 80.32$  minutes) [13].

In the present study it was a significant difference between the three groups in terms of the duration of the second stage of labor. It was  $56.5 \pm 26.70$  minutes in oxytocin alone group and  $42.37 \pm 17.17$  minutes in oral propranolol group. The results showed only a significant difference between oxytocin alone group and oxytocin with oral propranolol group and there was no significant difference between oxytocin with oral propranolol and oxytocin with intravenous propranolol groups. In a study by Sharami et al. duration of the second stage of labor in propranolol group  $23.03 \pm 8.31$  was also significantly lower than the placebo group  $33.83 \pm 12.33$  [13]. In a study by Ziółkowski in women who received oxytocin with propranolol the duration of delivery time 30% reduced [18]. In a study by Direkvand Moghadam et al. the mean duration of active phase and second stage of labor on the first and second days of induction in the intervention group (propranolol with oxytocin) was significantly less than the oxytocin alone group [1]. Kashanian and Zarrin showed that the mean time to achieve optimal uterine contraction in intravenous

propranolol group was significantly less than the oxytocin alone group ( $156.00 \pm 52.00$  vs  $222.00 \pm 120.00$ ) [7]. Palomäki also showed that 2-4 mg intravenous propranolol significantly shortens labor time [19]. Pergialiotis et al in a review study showed that propranolol significantly reduces the duration of labor time [20]. The results of all above mentioned studies were in consistent with ours, in other words our study confirmed that oxytocin in combination with propranolol reduced the duration of labor time.

In this study, all labors in three groups were normal and there were no cesarean section cases. In some similar studies cesarean section rate was lower in the intervention group than the control group [1, 11, 21, 22, 23], but in some studies there was no significant difference between the intervention and control groups in terms of cesarean section rate [7, 19].

The results of this study showed that in terms of Apgar score there was no significant difference between three groups. Direkvand Moghadam et al. and Sharami et al. also reported no significant between groups in terms of Apgar score [1, 13]. Adamsons reported no significant differences in Apgar scores, need for hospitalization in neonatal intensive care unit and fetal distress [10]. Sanchez-Ramos also reported that oxytocin with intravenous propranolol showed no significant difference on the Apgar score, hospitalization in neonatal intensive care unit and umbilical cord pH [11]. In another study, no significant differences in terms of Apgar score at 1 and 5 minutes and hospitalization in NICU were found between the two groups [23]. A review study showed that propranolol had no effect on Apgar score of 5 minutes and hospitalization in neonatal intensive care unit (20).

Although the frequency of meconium passage in the oxytocin alone group (7.5%) was lower than the other two groups, but there was no significant difference between three groups. The results of our study also showed that in terms of the frequency of uterine atony there was no significant difference between three groups, but its frequency in the oxytocin alone group was higher than the other two groups. This finding is in consistent with findings of Sharami's study [13].

The results of this study also showed that there was a significant difference between oxytocin alone group and oxytocin + oral propranolol and oxytocin + Intravenous propranolol groups in terms of oxytocin administered dose, but there was no significant difference between oxytocin + oral propranolol and oxytocin + Intravenous propranolol groups. Kashanian

and Zarrin showed that the required dose of oxytocin in oxytocin alone group on the first day was higher than that of oxytocin plus propranolol group [7]. In a study Sharemi et al received dose of oxytocin in the propranolol group was less than the control group [13], but in a study by Palomäki et al no significant difference was found between two groups [19].

In our study, 2 mg intravenous propranolol and 20 mg oral propranolol were administered at the beginning of the labor induction. Perhaps the differences in the results of various studies is because of dosage, interval of consumption and the way of administration (oral and IV). In the other hand, the half-life of propranolol is 2-3 hours and its highest effect is at the first hour after administration. Therefore, its repeated administration has a better impact to reduce the duration of labor time and cesarean section rate.

In majority of previous studies two groups were evaluated, but in our study we evaluated three; oxytocin alone, oxytocin in combination with intravenous propranolol and oxytocin with oral propranolol groups which is the strengths of this study. However, due to the relatively more including and excluding criteria its generalization has been reduced.

## CONCLUSION

Based on our findings the administration of propranolol with oxytocin particularly in oral method reduces the time of the first and second stages of labor in natural labor and also reduces caesarean section cases. In addition propranolol had no effect on maternal and neonatal complications.

## ACKNOWLEDGEMENTS

Authors would like to thank Vice Chancellor for research of Kurdistan University of medical sciences to support this study financially.

## CONFLICT OF INTEREST

Authors declare no conflict of interest.

## AUTHOR'S CONTRIBUTION

Study Design: Narjes Marjani, Fariba Farhadifar, Sholeh Shahgheibi, Acquisition of data: Narjes Marjani, Fariba Farhadifar Nooshin Hadizadeh, Masomeh Rezaie, interpretation of data: Fariba Farhadifar, Sholeh Shahgheibi, Masomeh Rezaie, Drafting of manuscript: Narjes Marjani, Fariba Farhadifar, Sholeh Shahgheibi, Nooshin Hadizadeh.

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