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Beta-Blocker Role in Induction of Labor: A Randomized Clinical Trial

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ABSTRACT

Background: Induction of labor when compared to expectant management, there is a noticeable decrease in perinatal mortality when labor is induced at or after 37 weeks of gestation. Additionally, it lowers the rate of Neonatal Intensive Care Unit (NICU) hospitalizations and cesarean section rates (CS) without increasing the number of operational vaginal births.

Objective: To evaluate the outcome of adding propranolol to misoprostol for induction of labor compared to misoprostol alone.

Subjects and methods: This is Randomized Clinical Trial that was performed in the Department of Obstetrics and Gynecology, Faculty of Medicine, Minia University. A total of 160 pregnant women candidates for induction of labor for different obstetric indications were divided into two groups. Group I: included 80 patients and labor was induced using misoprostol preceded by placebo pills. Group II: 80 patients and labor was induced using misoprostol preceded by propranolol.

Result: The duration of the active phase, the induction-delivery interval, and the latent phase varied statistically significantly across the groups under study. Regarding the units of oxytocin and misoprostol needed to produce a sufficient uterine contraction, there was no statistically significant difference between the groups under study but their doses needed to achieve adequate uterine contractions is decreased in propnalol group .

Conclusion: Propranolol, when administered alongside misoprostol for labor induction, enhances the efficacy of misoprostol and greatly reduces the induction-delivery interval, thereby serving as an adjuvant to misoprostol.

Keywords: Minia Maternity, Hospital, Induction of labor, Propranolol, Misoprostol.

INTRODUCTION

In everyday practice, the most frequent obstetric technique is induction of labor. When compared to expectant management, inducing labor between weeks 37 and 41 of gestation is clearly related with a lower rate of perinatal mortality. Additionally, it lowers CS rates without causing more surgical vaginal births or NICU hospitalizations [(1)].

Nonetheless, it was discovered that induction failure might reach 23.7% in multiparas and 41.2% in nulliparas. Induction rates vary greatly throughout government and private facilities, non-teaching hospitals, and teaching (tertiary) care hospitals in Egypt. In Egypt, the high rate of CS, which reached 54% of all births, is attributed in part to induction failure [(2-4)].

Given these realities, every attempt is made to reduce the time between induction and delivery while minimizing morbidities for both mothers and newborns. Induction of labor has a greater risk of failure when the cervix is immature and the Bishop score is low. A variety of techniques, including mechanical and pharmacological ones like oxytocin or prostaglandins, are employed to get the cervix ready for labor [(5-7)].

By relaxing the cervical muscles and contracting the smooth muscle fibers in the myometrium, misoprostol, a synthetic PGE1, exerts uterotonic effects that promote cervical dilatation and effacement. Misoprostol may have a number of benefits over other prostaglandins. It may be administered in a variety of ways, is inexpensive, and stable at room temperature [(6,8)].

In many investigations, the non-selective beta blocker propranolol was investigated for its ability to cause uterine contractions. Isoproterenol's inhibitory impact on human uterine motility can be reversed by propranolol, a medication that blocks β-adrenergic receptors. A thorough examination of the existence of beta receptors in the human myometrium and their function in myometrial contractility was prompted by this [(7,9)]. Propranolol cardiovascular adverse effects include bradycardia, hypotension, heart block, and worsening of acute heart failure, especially in sensitive individuals or those using concomitant AV-nodal blocking medications. It may also worsen vasospastic angina by unopposed alpha-mediated vasoconstriction [(10-12)].

The objective of this randomized clinical trial was to evaluate the outcome of adding propranolol to misoprostol for induction of labor compared to misoprostol alone in Minia University Maternity Hospital.

PATIENTS AND METHODS

This is Randomized Clinical Trial was performed in the Department of Obstetrics and Gynecology, Faculty of Medicine, Minia University from June to December 2024, on 160 pregnant women candidates for induction of labor for different obstetric indications.

Inclusion criteria:

- Full-term pregnant women indicated for induction of labor for different obstetric indications
- Either nulliparous or multiparous women
- Singleton pregnancy

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- Cephalic presentation
- Average fetal weight and Bishop score 4-6.

Exclusion criteria:

- The cases were in active labor.
- Instances when induction of labor is not appropriate, such as active genital herpes or placenta previa; situations where CS is recommended; and a history of prior uterine surgery.
- Allergy to prostaglandins.
- Liver, kidney, or asthma problems.
- An irregular ECG indicating a known heart condition.
- Heart block and severe hypotension as examples of propranolol contraindications.

All patients were subjected to:

1) ***Complete history taking:***
2) ***Physical examinations:***
   - General examination:
     To exclude systemic diseases.
     - Vital signs (BP, temp., HR, RR).
     - Signs of (pallor, cyanosis, jaundice, and LN enlargement).
   - Local exam.
   - Abdominal exam.:
     - Abdominal palpation.
     - Abdominal percussion.
     - Abdominal auscultation.
   - Pelvic examinations.
   - Bishop scoring.

Study design:

• ***Candidates were classified into 2 groups:***

- **Group I:** Receiving misoprostol 25 ug tablets vaginally to be repeated after 4 hours for a total of 4 doses.
- **Group II:** Receiving two pills of oral propranolol hydrochloride 10 mg (Inderal, AstraZeneca, Egypt) 30 minutes before the commencement of the induction procedure with misoprostol, then misoprostol 25 ug tablets repeated vaginally after 4 hours for 4 doses.

• Then each candidate was assessed individually by monitoring: follow up Bishop score, need for more doses of misoprostol and oxytocin, duration of the latent phase, active phase, induction delivery interval then finally mode of delivery.

• Candidates were evaluated for potential amniotomy or oxytocin infusion in those candidates who responded well to induction (at least three vigorous uterine contractions lasting 30 to 50 seconds and verified cervical changes).

Ethical approval:

The Ethics Committee of the Minia Faculty of Medicine has given its approval to this project. Each participant completed a permission form when all information was received. Throughout its implementation, the study complied with the Helsinki Declaration.

Statistical analysis:

Version 20.0 of the SPSS program was used to do the statistical analysis. Frequency and percentage denote categorical data, whereas mean. ± SD denotes continuous data. An independent sample t-test was used for continuous variables, and the X^2-test was used to compare the two groups with respect to categorical data. Statistical significance was defined as P values less than 0.05.

RESULTS

The groups under study did not differ statistically significantly in terms of age, BMI, parity, gestational age, or initial Bishop score (Table 1).

Table (1): Comparison of personal and obstetric characteristics between the studied groups

	Group one (Misoprostol+ placebo) N=80	**Group Two (Misoprostol+ Propranolol) N=80**	**P value**
Age (years) Mean ± SD	22.6 ±2.5	23.2±3.5	0.38
BMI (kg/m^2) Mean ± SD	26.8±2.6	26.41±2.8	0.52
Parity Mean ± SD	1.9±0.8	1.95±0.8	0.78
Gestational age (weeks) Mean ± SD	40.2±0.95	40.3±0.91	0.63
Initial Bishop score Mean ± SD	4.6±0.49	4.6±0.49	1

P>0.05: not significant., P<0.05: statistically significant. SD: stander deviation.

The study groups did not differ statistically significantly in terms of the mode of delivery or the indication of induction; however, the follow-up Bishop score did differ statistically significantly (Table 2).

Table (2): Comparison of labor characteristics between the studied groups.

		Group one (Misoprostol+ placebo) N=80	Group Two (Misoprostol+ Propranolol) N=80	P value
Indication of induction	Post date	56(70%)	48 (60%)	0.23
	ROM	12 (15%)	24 (30%)	
	HTN	12 (15%)	6 (7.5%)	
	Others	0 (0%)	2 (2.5%)	
Mode of delivery	CS	18 (22.5%)	8 (10%)	0.12
	NVD	62 (77.5%)	72 (90%)	
Follow up Bishop score Mean ± SD		7.5±0.6	4.8±0.5	<0.001

P>0.05: not significant. P<0.05: statistically significant.

The duration of the active phase, the induction-delivery interval, and the latent phase varied statistically significantly across the groups under study (Table 3).

Table (3): Comparison of duration of different phases of labor between studied groups

	Group one (Misoprostol+ placebo) N=80	Group Two (Misoprostol+ Propranolol) N=80	P value
Duration of latent phase (hours) Mean± SD	9.6± 4.9	6± 4.5	**0.001***
Duration of active phase (hours) Mean± SD	5.5± 2	4± 1.2	**<0.001***
Induction-delivery interval (hours) Mean± SD	12.45± 6.12	11.5± 5.45	**0.049**

P>0.05: not significant. P<0.05: statistically significant.

Regarding the units of oxytocin and misoprostol needed to produce a sufficient uterine contraction, there was no statistically significant difference between the groups under study (Table 4).

Table (4): Doses of misoprostol and oxytocin in cases who delivered vaginally in the studied groups.

		Group one (Misoprostol+ placebo) N=62	Group Two (Misoprostol+ Propranolol) N=72	P value
Misoprostol dose	1 dose	20 (32.25%)	24 (33.3%)	0.38
	2 doses	32 (54.83%)	46 (64%)	
	3 doses	4 (6.45%)	2 (2.7%)	
	4 doses	4 (6.45%)	0 (0%)	
Oxytocin dose (units)	0 units	4 (6.45%)	2 (2.7%)	0.34
	5 units	50 (80.65%)	62 (86.2%)	
	10 units	4 (6.45%)	8 (11.1%)	
	15 units	4 (6.45%)	0 (0%)	

P>0.05: not significant. P<0.05: statistically significant.

DISCUSSION

One of the most popular obstetrical treatments carried out worldwide is induction of labor. In order to achieve delivery before spontaneous labor begins, methods for inducing uterine contractions are referred to as induction of labor. In a patient who is in labor and not making enough progress, augmentation of labor is the process of increasing the frequency and intensifying the uterine contractions that are already occurring in order to achieve vaginal birth [(12)].

Currently, the two primary prostaglandin formulations used for cervical ripening and labor induction are misoprostol (prostaglandin E1 [PGE1]) and dinoprostone (prostaglandin E2 [PGE2]). Uterine contractions are caused by these prostaglandins binding to smooth muscle cells in the decidua. Cervical ripening results from these contractions' breakdown of collagen in the cervical stroma's connective tissue. Uterine contractility rises more with PGE1 than with PGE2 [(13)].

Propranolol, a novel medication that enhances prostaglandin activity, will aid in the induction process and lower CS rates. Propranolol has been utilized in labor augmentation by a number of researchers [(10)].

The main results of this study were as follows:

Our results showed that the groups under study did not differ statistically significantly in terms of age, BMI, parity, gestational age, or initial Bishop score.

In agreement with our results **Abdel Hamid *et al.*** [(14)] who randomized 128 pregnant full-term primigravid women into two groups in order to test propranolol plus misoprostol with misoprostol alone for labor induction in primigravids. Each candidate received 25 µg of vaginal misoprostol to induce labor. Group II was given sweet pills as a placebo, whereas group I was given 20 mg of propranolol tablets. With p-values of 0.533, 0.141, 0.094, and 0.549, respectively, they found no statistically significant differences between the groups under study in terms of age, BMI, Bishop score, and gestational age.

In order to assess the rates of CD in patients with protracted labor who were randomly assigned to receive propranolol vs a placebo, **McCoy *et al.*** [(15)] recruited 164 participants and randomized them, placing 84 in the propranolol group and 80 in the placebo group. They found age, BMI, and gestational age did not differ statistically significantly across the groups they studied. **Sobhy *et al.*** [(8)] conducted research to assess the effects of oral propranolol as a supplemental agent to oxytocin on the induction and outcome of labor with the control group, which was given oxytocin alone. They reported that the age distribution was 28.24 (SD 4.54) and 27.03 (SD 4.64) for each group, with no discernible difference between them. Additionally, the groups' BMI, parity, gestational age, and Bishop score did not differ significantly.

In our study, as regarding indication of induction, ROM (12 in group I vs. 24 in group II), HTN (12 in group I vs. 6 in group II), post-date (56 in group I vs. 48 in group II), and others (0 in group I and 2 in group II) did not differ statistically significantly between the groups under study (P value 0.23).

As regarding mode of delivery in our research, the study groups did not differ statistically significantly in terms of the mode of delivery (P value 0.12) ; however, the follow-up Bishop score did differ statistically significantly (7.5 ± 0.6 in group I vs 4.8 ± 0.5 in group II, P value <0.001). So, the number of successful induction in 2nd group was more than 1st group (72 in group II **vs** 62 in group I) and number of CS (due to fetal distress, failure of progress or failed induction) decreased in 2nd group compared with 1st group (8 (10%) in group II vs 18 (22.5%) in group I).

Consistent with our findings **Abdel Hamid *et al.*** [(14)] discovered that neither the mode of delivery nor the indication of induction differed statistically significantly among the groups under study. Post-date (60.9% in group 1 vs. 68.8% in group 2), ROM (28.1% in group 1 vs. 15.6% in group 2), HTN (9.4% in group 1 vs. 14.1% in group 2), and others (1.6% in group 1 and 1.6% in group 2) were the indicators of induction in both groups. Like our results, **Moghadam *et al.*** [(9)] discovered that the propranolol group had noticeably decreased CS rates.

In our research, regarding duration of latent phase, the differences between the groups under study were statistically significant (9.6± 4.9 in group I vs 6± 4.5 in group II, p value 0.001) with shorter latent phase in 2nd group than 1st group. Also, regarding duration of active phase, the differences between the groups under study were statistically significant (5.5± 2 in group I vs 4± 1.2 in group II, p value <0.001) with shorter duration in 2nd group than 1st group. Regarding induction-delivery interval, the differences between the groups under study were statistically significant (12.45± 6.12 in group I vs 11.5± 5.45 in group II, p value 0.049). So, the duration decreased in 2nd group compared to 1st group. Our findings are supported by **Abdel Hamid *et al.*** [(14)] who discovered that group I (Misoprostol and propranolol) experienced a significantly shorter latent phase of labor (7.9± 5.6h. vs. 9.2± 6.03h.) in comparison to group II (Misoprostol and placebo) and a significantly shorter induction-delivery interval (11.8± 8.1h. vs. 12.6± 8.9h.). While, in contrast with our results the length of the active phase of work did not differ statistically significantly between the two groups.

In the study of **Sobhy *et al.*** [(8)] they found that the active phase duration did not significantly differ between the groups under research, however the study group's latent phase duration was much shorter. Also, **Amiri *et al.*** [(16)] concurs with our research, which discovered that propranolol can shorten the latent phase's duration.

In our study, regarding the doses of misoprostol and oxytocin needed to achieve adequate uterine contractions, the groups under study did not

differ statistically significantly (with P value: 0.38, 0.34 respectively) but the need for further doses of misoprostol and oxytocin decreased in 2nd group than in 1st group.

Our findings are supported by **Abdel Hamid *et al.* (14)** who discovered that both groups (Misoprostol and propranolol group) and (Misoprostol and placebo group) had no significant differences regarding the total number of misoprostol doses to achieve successful induction or the total doses of oxytocin to maintain adequate uterine contractions with p-value 0.79 and 0.834, respectively.

Bigelow *et al.* (7) discovered that the dosage of misoprostol did not change statistically significantly between the groups under investigation (the propranolol group and the placebo group; P=0.6). Like our results, **Sobhy *et al.* (8)** reported that the oxytocin dosage required to produce adequate contractions (three contractions every ten minutes) was significantly lower in the experimental group than in the control group.

Regarding complication of propranolol, there was no side effects (such as bradycardia, and hypotension) reported in our study.

Consistent with our findings **Vatanchi *et al.* (17)** examined the impact of misoprostol alone versus propranolol + misoprostol in inducing labor. They discovered that, in terms of delivery problems, there was no discernible difference between the two groups (P=0.397). Propranolol pills did not cause bradycardia or hypotension as adverse effects.

Consistent with our findings **Abdel Hamid *et al.* (14)** found that group I did not have any negative effects with propranolol, including dizziness.

CONCLUSION

In contrast to misoprostol alone, our study assessed the effects of mixed misoprostol and propranolol on labor induction.

Propranolol can be utilized as an adjuvant to misoprostol since it increases the activity of misoprostol and resulting in a much shorter induction delivery interval when taken with misoprostol to induce labor. To verify these findings across a range of groups and therapeutic contexts, more research is recommended.

RECOMMENDATION

We need to involve larger sample size in next studies for more evaluation.

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