Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

Comparing the Efficacy and Safety of Oral and Vaginal Isosorbide Mononitrate, with Oral Propranolol in Cervical Ripening and Labor Induction

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Article Info

10.24200/jogcr.11.8.689

Received: 2025/02/02
Accepted: 2025/04/05
Published Online: 28 Jun. 2026

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ABSTRACT

Background & Objective: Nitric oxide stimulates the release of prostaglandins and cyclooxygenase, leading to cervical collagen rearrangement and cervical softening. Propranolol inhibits uterine beta-adrenergic receptors and induces uterine contractions. This study compared the efficacy and safety of oral and vaginal Isosorbide Mononitrate (IMN) and oral propranolol for cervical preparation.

Materials & Methods: This randomized clinical trial was conducted on 120 pregnant women with an unfavorable cervix. They were assigned to four groups: vaginal IMN 40 mg, oral IMN 40 mg, oral propranolol 40 mg, and vaginal placebo tablets. In all groups, the specified agents were placed in the posterior fornix and administered every 4 hours up to a maximum of four doses. If labor did not start spontaneously, induction was performed with oxytocin.

Results: The Bishop score in the vaginal IMN group increased significantly compared with the other groups (P<0.001). The interval from induction to the active phase and the mean duration of the active phase did not differ significantly among the four groups. Mild headache was significantly more frequent in the vaginal IMN group than in the other groups (P>0.001). The use of vaginal and oral isosorbide mononitrate tablets and oral propranolol had no adverse effects on the five-minute Apgar score or neonatal pH.

Conclusion: Vaginal IMN is an effective, simple, and low-cost method for cervical preparation that can improve the Bishop score and shorten the induction period before the onset of the active phase.

Keywords: Isosorbide mononitrate, Propranolol, Cervical ripening

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1. Introduction

Labor induction is indicated in certain situations involving maternal or fetal compromise. Cervical status is crucial at the time of induction. If the cervix is considered unfavorable based on the Bishop score, a ripening method is employed. A Bishop score of four or less indicates an unfavorable cervix and may warrant cervical preparation **(1,2)**. Therefore, numerous investigations have been conducted to evaluate methods for cervical preparation before the initiation of uterine contractions **(3, 4)**.

Two primary techniques are used for cervical ripening: 1) mechanical methods, such as laminaria hygroscopic dilators, intracervical Foley catheters, artificial rupture of membranes, and extra-amniotic saline infusion (1); and 2) pharmacologic interventions, such as prostaglandins **(5)**. Various studies have shown adverse maternal and fetal outcomes associated with uterine contractions induced by prostaglandins **(6,7)**. Therefore, it is ideal to use agents for induction and cervical preparation that minimize adverse maternal and fetal effects **(8)**.

Recently, nitric oxide-releasing drugs, which are endothelium-dependent relaxing agents and important biological mediators, have gained attention. Evidence shows that vaginal application of nitric oxide releasers is effective in preparing the cervix before labor induction. Nitric oxide acts directly and through stimulation of the release of prostaglandins, cyclooxygenase (COX-2), and cytokines, leading to cervical collagen rearrangement and cervical softening **(9)**, which results in cervical preparation for labor **(10)**.

Although previous studies **(11-13)** have demonstrated that nitric oxide agents are safe during human pregnancy, the only potential risk associated

with these agents is dilation of the uterine vessels, which can lead to a drop in blood pressure and, if severe, fetal hypoxia **(8)**.

On the other hand, evidence indicates that stimulation of beta-adrenergic receptors promotes relaxation of the uterine smooth muscle. These receptors decrease by 50% at the onset of labor **(14)**. Propranolol, as a beta-blocker, inhibits uterine beta-adrenergic receptors and induces uterine contractions **(15)**. The administration of propranolol enhances uterine contractile activity in both pregnant and non-pregnant women **(16)**.

The current study assessed the efficacy and safety of both oral and vaginal administration of isosorbide mononitrate, as well as oral propranolol, for cervical preparation and labor induction.

2. Materials and Methods

This study was a double-blind, placebo-controlled randomized clinical trial. The study population consisted of pregnant women with an unfavorable cervix who were referred to Yas Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran, during 2020-2021.

After explaining the purpose of the study and obtaining informed consent, a detailed clinical history was taken at the beginning of the study. In addition, vaginal and abdominal examinations were performed, followed by a routine obstetric ultrasound. The initial evaluation, including vaginal examination and NST assessment, was conducted by a senior resident.

Inclusion criteria were as follows: nulliparous women with a term, live fetus in cephalic presentation, singleton pregnancy, gestational age between 38 and 41 weeks, unfavorable cervix (Bishop score of 4 or less), estimated fetal birth weight of 2000 to 4000 grams, and reassuring fetal heart monitoring.

Exclusion criteria included the presence of a uterine scar, history of cervical conization, polyhydramnios (MVP>8), placenta previa or vasa previa, presence of regular uterine contractions, suspected chorioamnionitis, history of asthma, active genital herpes, systolic blood pressure less than 90, cardiovascular disease, severe preeclampsia, alcohol addiction, and a history of headache in the mother.

The patients were randomly divided, using a table of random numbers generated by Microsoft Excel, into four groups of 30: vaginal Isosorbide Mononitrate (IMN) 40 mg, oral IMN 40 mg, oral propranolol 40 mg (two 20 mg tablets every twelve hours until the required dose), and a control group receiving a vaginal placebo tablet.

In the vaginal IMN group, two 20 mg tablets of IMN were placed in the posterior fornix every 4 hours, up to a maximum of four doses, until the onset of labor. For women who had not reached the active stage of labor 6 hours after the last dose of IMN, oxytocin infusion was initiated. In the oral IMN group, two 20 mg tablets were administered orally, with the dose repeated as in the vaginal group. In another group, 40 mg of oral propranolol was administered, with the dose repeated as in the other groups. In the placebo group, one placebo tablet was placed vaginally as described above. In all groups, after receiving four doses of the drug, induction was performed with oxytocin if labor did not start spontaneously.

The primary outcomes assessed included time to induction of labor and time to delivery. Secondary outcomes included maternal complications, the need for oxytocin augmentation, fetal outcomes and related morbidities, mode of delivery, incidence of cesarean delivery, fetal Apgar score at five minutes, meconium passage, umbilical cord pH, and the rate of NICU admission across the four groups. Maternal complications, such as hypotension and headache, were recorded in all four groups.

In this study, the frequency of qualitative variables was calculated, while for quantitative variables, the mean, median, and standard deviation were determined. Parametric tests were used for normally distributed data, and nonparametric tests were used for non-normal distributions. The t-test was applied to compare quantitative variables between two groups, and the chi-square test was used for comparisons of qualitative variables. In this study, a significance level of less than 0.05 was considered significant.

3. Results

A total of 120 women participated in this study. There were no significant differences in baseline demographic characteristics among the four groups (Table 1). The highest increase in the Bishop score was observed in the vaginal IMN group (80%), while the lowest increase was noted in the oral propranolol group (17%) (Figure 1).

Regarding the termination of pregnancy, 87 participants had NVD, accounting for 80% in the vaginal isosorbide mononitrate group, 77% in the oral isosorbide mononitrate group, 60% in the propranolol group, and 73% in the control group. A total of 33 participants underwent cesarean delivery. This rate was 20% for vaginal isosorbide mononitrate (6 cases), 23% for oral isosorbide mononitrate (7 cases), and 27% (8 cases) for the control group. The highest cesarean rate was observed in the propranolol group, with 12 cases (40%).

In total, 33 cesarean sections were performed: 10 cases due to lack of progress, 6 cases due to meconium passage, 3 cases due to cephalopelvic disproportion, 7 cases due to fetal distress, and 7 cases due to complete abortion. The differences observed in the mode of delivery among the four groups were not statistically significant (P=0.325). Regarding the need for augmentation, no significant difference was observed

among the four groups (P=0.440). The average time from the administration of vaginal and oral IMN tablets and oral propranolol to 6 cm dilation was 10.7 hours for vaginal isosorbide mononitrate, 11 hours for oral isosorbide mononitrate, and 10.8 hours for oral propranolol tablets.

The minimum time observed in all four groups oral and vaginal isosorbide mononitrate, oral propranolol, and the control group was 5 hours, while the maximum time in the control group was 24 hours. The difference in dilation times up to 6 cm among the four groups was not statistically significant (P=0.130). As shown, there was no statistically significant difference among the four groups in the duration from the 6 cm examination to full dilation (P=0.058). The minimum time from the 6 cm examination to full dilation across all four groups was 1 hour, with a maximum of 4 hours.

On average, the time from full dilation to the birth of the baby was 41.5 minutes in the vaginal isosorbide mononitrate group, 49.83 minutes in the oral isosorbide mononitrate group, 40 minutes in the oral propranolol group, and 33.83 minutes in the control group. The observed difference was not statistically significant (P=0.165). The minimum time from full dilation to delivery across the four groups was 5 minutes, while the maximum time was 120 minutes.

The side effects of isosorbide mononitrate mainly included headache, flushing, low blood pressure, and nausea. Mild headache was more frequent in the group receiving vaginal isosorbide mononitrate than in the oral isosorbide group. The observed differences in the frequency distribution of other complications among the four groups were not statistically significant (P>0.001).

In total, 115 cases had an Apgar score >7 and 5 cases had an Apgar score <7; among these, 1 case was in the first group, 1 case in the second group, 2 cases in the oral propranolol group, and 1 case in the control group. Overall, there was no significant difference in neonatal Apgar scores among the four groups (P=0.890). The umbilical cord pH of the newborns was also not significantly different among the four groups (P=0.629).

A total of 13 cases were admitted to the NICU: 2 cases in the vaginal isosorbide mononitrate group, 3 cases in the oral isosorbide mononitrate group, and 4 cases each in the oral propranolol and control groups. Overall, there was no statistically significant difference in neonatal complications among the four groups.

Six cases had meconium passage: 2 cases were in the vaginal isosorbide mononitrate group, 2 cases were in the oral propranolol group, and 2 cases were in the control group. There were no cases of meconium passage in the oral isosorbide mononitrate group. These findings did not show a significant difference (P>0.05).

The duration of the second and third stages of labor was not significantly different among the four groups. The highest increase in the Bishop score was observed in the vaginal isosorbide mononitrate group, where 24 out of 30 participants (80%) showed significant progress. The lowest increase in the Bishop score was observed in the oral propranolol group, with 5 participants (17%).

The incidence of a Bishop score above six after the full prescribed dose was higher in the IMN groups than in the propranolol and control groups (P<0.001) (Table 2).

Table 1. Baseline Characteristics of Study Participants

Variables	Vaginal IMN	Oral IMN	Oral Propranolol	Placebo	P-value
Age	30.37±5.08	29.87±5.32	30.57±4.4	28.9±4.42	0.545
BMI	32.03±2.85	29.77±2.84	29.87±2.45	30.7±2.73	0.605
Gravidity	1.2±0.41	1.2±0.41	1.13±0.35	1.1±0.31	0.648
Gestational age	39.27±0.98	39.37±0.93	39.57±0.97	39.4±0.89	0.667

Table 2. Outcome comparison of Study Participants

Variables	Vaginal IMN	Oral IMN	Oral Propranolol	Placebo	P-value
Time of latent phase	10.7	11	10.8	12.9	0.130
Time of first stage of labor	2.43	3.2	2.73	2.8	0.058
Time of second stage of labor	41.5	49.8	40	33.8	0.165
Headache	15(20)	7(23)	1(3)	0	<0.001
Antonia	2(7)	4(13)	5(17)	6(20)	0.494
Decreased blood pressure	1(3)	2(7)	1(3)	2(7)	0.873
Nausea and flashing	4(13)	2(7)	1(3)	1(3)	0.545
Apgar score <7	1(3)	1(3)	2(7)	1(3)	0.890
Neonatal PH < 7.2	1(3)	0	1(3)	1(3)	0.629

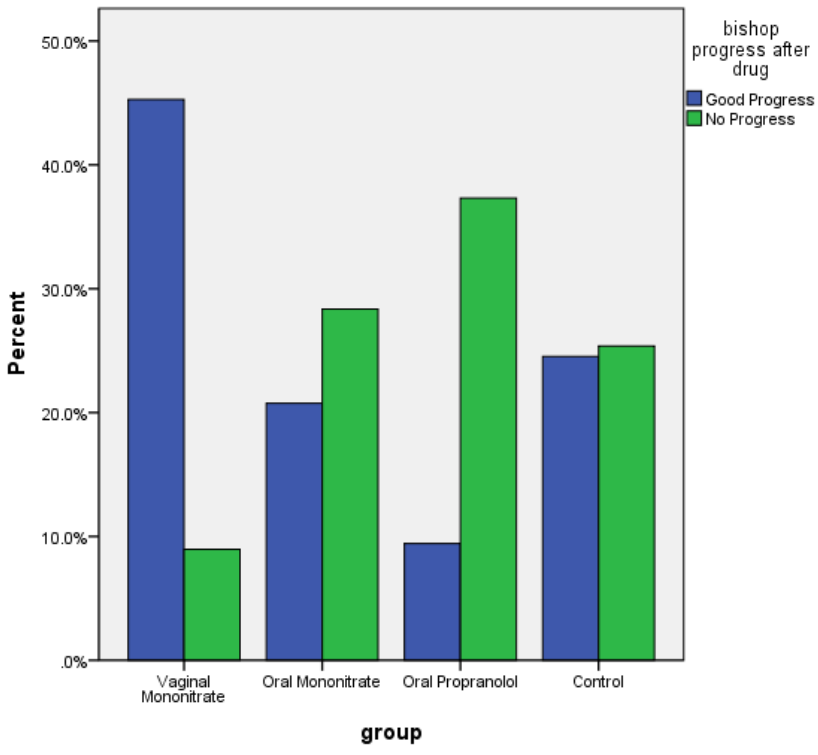


Figure 1. Bishop's score changing in four groups

4. Discussion

Nitric Oxide (NO) is a common product of arginine metabolism in many tissues and appears to be an important vasodilator; it may also be involved in cell death and neurotransmission **(17)**. NO is also released from the molecules of several vasodilator drugs. It is released from many important drugs such as nitroprusside, nitrates, and nitrites **(18)**. This substance is a potent vasodilator in all vessels and a powerful relaxant in most muscles. Its mechanism of action in this context involves activation of guanylate cyclase and the production of cyclic Guanosine Monophosphate (cGMP), which in turn causes dephosphorylation and deactivation of myosin light chains, leading to relaxation of smooth muscle **(19)**.

Stimulation of beta-adrenergic receptors causes relaxation of the smooth muscles of the uterus; these receptors decrease by 50% at the onset of labor **(26)**. Propranolol blocks beta-1 and beta-2 adrenoreceptors and does not affect beta-3 myometrial receptors. By inhibiting beta-adrenergic receptors, propranolol increases uterine contractions and consequently may induce labor **(18)**.

The findings obtained in this research were analyzed based on the study objectives, and the following results were obtained. The main aim of this study was to compare the effects of vaginal and oral isosorbide mononitrate tablets and oral propranolol tablets on cervical preparation before hospitalization of pregnant women in the first stage of labor. In our study, the effects of vaginal and oral isosorbide mononitrate tablets and oral propranolol tablets for cervical preparation and labor induction were compared. To eliminate confounding effects, the groups were similar in terms of maternal age, BMI, gravidity, number of previous births, number of previous abortions, gestational age, and Bishop score, and there was no statistically significant difference in these variables.

The mean age of the mothers in our study was 29.9 years, and the mean BMI was 30, which is similar to the findings reported by Yazdizadeh et al., in 2012 **(20)**. Considering that our objective in this study was to investigate women with a Bishop score of less than 2, the four groups were comparable and showed no significant difference in this regard.

In the current study, although there was no statistically significant difference in the Bishop score before drug administration among the four groups vaginal and oral isosorbide mononitrate, oral propranolol, and the control group (P=0.939) a statistically significant difference was observed after drug administration. This increase was greater in the vaginal isosorbide mononitrate group than in the oral isosorbide mononitrate and oral propranolol groups. This result is consistent with the study by Samia Mokhah et al., **(21)**.

In our study, the Bishop score in the isosorbide mononitrate groups increased significantly compared with the control group, which received no intervention. The highest increase in the Bishop score was observed in the vaginal isosorbide mononitrate group, where 24 out of 30 participants (80%) showed a significant improvement.

In the study by Yazdizadeh et al., (2012), administration of isosorbide mononitrate compared with placebo significantly increased the Bishop score and decreased the time interval from induction to the active phase of labor **(20)**, which is consistent with the results of our study. The present study shows that, in the absence of other medical or mechanical methods, isosorbide mononitrate can significantly increase the Bishop score.

Ramiz et al., and Bularbo et al., in separate studies, compared the effect of isosorbide mononitrate with placebo **(22,23)**. In the study by Ramiz et al., the change in the Bishop score in the drug group was greater than in the placebo group, which is consistent with the present study. However, in the study by Bularbo et al., except for 22% in the drug group and 8% in the placebo group who went into spontaneous labor before 24 hours, no change in the Bishop score was observed in the rest of the participants, which is not consistent with the present study.

In a study conducted by Othman et al., **(24)**, isosorbide mononitrate tablets were compared with prostaglandin E2 gel. The average time from the start of treatment to delivery in the isosorbide mononitrate group was longer than in the prostaglandin E2 gel group. The results of their study indicate that prostaglandin E2 was more effective than isosorbide mononitrate tablets in cervical preparation **(24)**. In our study, isosorbide mononitrate resulted in a significant increase in the Bishop score after administration compared with the oral propranolol and control groups.

In the studies conducted by Habib et al., **(25)** and Bularugada et al., **(26)**, it was shown that the average hospitalization time until delivery was shorter in the isosorbide mononitrate tablet group than in the placebo group. In the studies by Ramiz et al., Bularo et al., and Akerhood et al., several reports indicated that, compared with placebo, isosorbide mononitrate tablets were more effective in cervical preparation **(22,23,26)**. These studies are consistent with the results of our study.

In Chanrachakol's study (2000), which compared two drugs isosorbide mononitrate and misoprostol the time interval from induction to the active phase was longer in the isosorbide mononitrate group than in the misoprostol group **(27)**, indicating the greater effectiveness of prostaglandins in labor induction and cervical preparation. The present study shows that, if other medical and mechanical methods are not used, isosorbide mononitrate can shorten the induction time until the start of the active phase (or the latent phase of labor).

In our study, the mean time interval from the administration of vaginal and oral isosorbide mononitrate tablets and oral propranolol to 6 cm dilation was 10.7 hours with vaginal isosorbide mononitrate, 11 hours with oral isosorbide mononitrate, and 10.8 hours with oral propranolol tablets. The minimum time observed in all four groups oral and vaginal isosorbide mononitrate, oral propranolol, and the control group was 5 hours, while the maximum time in the control group was 24 hours.

The observed difference in dilation times up to 6 cm among the four groups vaginal and oral isosorbide mononitrate, oral propranolol, and the control group was not statistically significant (P=0.130), which is consistent with the study by Bulapragada et al., **(26)** conducted in 2009. As shown, there was also no statistically significant difference among the four groups in the duration from the 6 cm examination to full dilation (P=0.058).

The minimum time interval from the 6 cm examination to full dilation in all four groups was 1 hour, and the maximum time was 4 hours. On average, the time interval from full dilation to the birth of the baby was 41.5 minutes in the vaginal isosorbide mononitrate group, 49.83 minutes in the oral isosorbide mononitrate group, 40 minutes in the oral propranolol group, and 33.83 minutes in the control group. The observed difference was not statistically significant (P=0.165). The minimum time from full dilation to delivery in the four groups was 5 minutes, and the maximum time was 120 minutes.

In the study by Deirkund Moghadam et al., **(3)**, the effect of propranolol combined with oxytocin was compared with placebo. The results showed that, in the propranolol group compared with the placebo group, the duration of the latent phase, the time to onset of effective contractions on the first and second days, and the cesarean section rate were significantly lower, which is not consistent with our study.

In the study by Sharmi et al., **(4)**, administration of oxytocin in combination with propranolol significantly shortened the duration of the active stage of labor, the duration of the second stage, and the cesarean section rate compared with placebo.

In the present study, there was no significant difference in the duration of the first, second, and third stages of labor among the studied groups, which is not consistent with the results of other studies by Deirkund et al., **(3)** and Sharmi et al., **(4)** in this field.

Another objective of this study was to determine the mode of delivery according to the treatment method in the four groups, and the results showed that the mode of delivery, including cesarean and vaginal delivery, was not significantly different among the four groups.

In the present study, regarding the termination of pregnancy, a total of 87 participants had a natural vaginal delivery, accounting for 80% in the vaginal isosorbide mononitrate group, 77% in the oral isosorbide mononitrate group, 60% in the propranolol group, and 73% in the control group.

Cervical ripening before induction may not reduce the rate of cesarean section in nulliparous women with an unfavorable cervix **(26)**, which is not consistent with the results of our study, because the cesarean section rate did not increase significantly in our study.

Regarding the side effects of the drugs used in the current study (isosorbide mononitrate and propranolol) in the four studied groups, the results showed that the most common complication in the isosorbide mononitrate group was headache. In the vaginal isosorbide mononitrate group, the headache rate was higher than in the oral group, and headaches improved with rest and acetaminophen.

Moreover, in the control group, none of the participants experienced headaches, which is consistent with the studies by Samia Mokhah et al., **(21)** and Habib et al., **(25)**.

The results of the present study showed that the use of vaginal and oral isosorbide mononitrate tablets and oral propranolol had no negative effect on the five-minute Apgar score or the pH of newborns, and no serious neonatal or maternal morbidity was reported. These findings are consistent with the results of studies by Ghosh et al., **(17,19)**.

The sampling method used in this research (double-blind, simple randomization) is considered one of the strengths of experimental studies. All participants included in the study were nulliparous, whereas in many previous studies multiparous mothers were also included. In addition, all stages of the study including sample selection, initial evaluations, induction, delivery, and assessment of secondary outcomes were performed by the researcher, except for the hospitalization of participants during the night shift, which was carried out with the assistance of the research team. This approach increased the accuracy of the research.

Among the limitations of this study are biological differences and varying responses to induction among individuals, which were beyond the control of the researcher. In addition, it was not possible to evaluate individual differences such as pelvic shape, soft tissue characteristics, and their resistance to fetal passage, which may influence the duration of labor.

5. Conclusion

This study showed that vaginal isosorbide mononitrate is an effective, simple, and low-cost method for cervical preparation that can improve the Bishop score and shorten the induction period until the onset of the active phase. In addition, it had no adverse effects on the fetus or the mother. Due to the effect of propranolol on beta-adrenergic receptors, we expected it to cause uterine contractions and consequently

reduce the duration of labor and the number of cesarean sections; however, in this study, it did not affect the duration of delivery and increased the number of cesarean sections.

6. Declarations

Acknowledgments

We would like to thank all participants of this study.

Ethical Considerations

The study protocol was approved from the Ethics Committee of Tehran University of Medical Sciences with ethical code of IR.TUMS.IKHC.REC.1398.641. Furthermore, the study was registered with the Iranian Registry for Clinical Trials (code: IRCT20201003048910N1).

Authors' Contributions

M. SH. and F. R.: Study concept and design. M.T., B. S. and F. G.: Data collection. K. J.: statistical analysis N. S. and M. A.: Writing and editing article.

Conflict of Interest

The authors declare no competing interests.

Fund or Financial Support

The authors declare no financial support for this study.

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How to Cite This Article:

Shirazi M, Tajpour M, Jafarabadi K, Rahimi-Sharbaf F, Sahebdel B, Golshahi F, et al. Comparing the efficacy and safety of oral and vaginal isosorbide mononitrate, with oral propranolol in cervical ripening and labor induction. J Obstet Gynecol Cancer Res. 2026;11(8):689-696.

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