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ORIGINAL ARTICLE

# Isosorbide Mononitrate a Nitric Oxide Donor: A Study of Its Efficacy and Safety as an Agent for Cervical Ripening

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## Abstract

*Objective* To study the efficacy and safety profile of isosorbide mononitrate (IMN) as an agent for cervical ripening.

*Methodology* This study was conducted in the Department of Obstetrics and Gynecology, M Y Hospital & M G M Medical College Indore from September 2011 to February 2013. Pregnant women attending the antenatal clinics were screened for possible participation in the study after explaining the nature of the study. This study was conducted on 150 patients. An initial dose of 40 mg IMN was applied in the posterior vaginal fornix, and the same dose was repeated after 6 h. Cervical ripening was assessed by the change in Bishop Score 12 h after the initial application.

*Results* In a study of 150 cases, mean maternal age was 22.2 ± 2.6 years (range 19–35 years) and mean gestational age was 40.5 ± 1.07 (range 40–42 weeks). 52 women were primigravidas, while 98 were multigravidas. The mean Bishop Score—before drug administration was 1.94 ± 1.3 (range 0–5), and mean fetal heart rate was 137 ± 6.2 bpm. The mean of Bishop scores before IMN administration was 1.94 ± 1.3, while mean of Bishop score after drug administration was 6.7 ± 2.2; mean difference was equal to 4.76. *P* value was equal to 0.0001. By conventional criteria, this difference is considered to be statistically significant. The mode of delivery 96 (64 %) delivered vaginally, while 54 (36 %) were delivered by Cesarean section. Mean Apgar score at 1 min was 8.2 ± 0.9 SD (range 7–10), while mean Apgar score at 5 min was 9.4 ± 0.6 (range 8–10). The only side effect noted was headache, and 30 cases (20 %) complained of headache.

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*Conclusion* IMN seems to be effective, safe, inexpensive, and well-tolerated agent for cervical ripening. It is cost effective and safe with minimal side effects.

**Keywords** Isosorbide mononitrate · Cervical ripening

## Introduction

Although most of the patients have a spontaneous onset of labor at term, on occasions, the natural course of labor may have to be induced for various reasons. Induction of labor is now an integral part of modern day obstetrics. The aim of induction of labor is to achieve a successful vaginal delivery. The baby should be born in a good condition within acceptable time frame and with minimal maternal side effects. Several factors influence the outcome of induced labor. Unfavorable cervix is one of the main causes of failed induction. In order to over come this, cervix needs to be ripened.

Labor induction in the presence of cervical immaturity is a common indication for the use of prostaglandins. Since the late 1960s, prostaglandins (PG) have been used for the induction of labor at term, and PG and their analogs have been administered by various routes to induce labor with mostly comparable results. However, several other agents have been proposed to be useful in inducing labor and cervical softening, like oxytocin, corticosteroids, estrogen, relaxin, and nitric oxide (NO) donors [1, 2]. The standardized cervical priming and induction of labor are predominantly achieved by means of PG administration. However, in the recent years, there has been a considerable interest in the use of misoprostol [3–5] and NO donors [6, 7] for cervical ripening and labor induction.

No donors have been shown to stimulate prostaglandin production in the human cervix after topical administration [7]. Local application of nitric oxide donors effectively induces cervical ripening by rearranging the cervical collagen and ground substance which soften the cervix and does not have severe adverse effects as dinoprostone.

There are limited studies on Nitric oxide donors for cervical ripening; in this context, Isosorbide mononitrate is one such agent which has been studied in outpatient setting but there are conflicting results. More studies are required to prove its usefulness for cervical priming, especially in low resource setups where cost does matter. The aim of our study was to find out efficacy and safety profile of Isosorbide Mononitrate as an agent for cervical ripening.

## Materials and Methods

This study was carried out in the Department of Obstetrics & Gynecology of MGM Medical College and M.Y. Hospital, Indore. Study period extended from May 2012 to Oct. 2013. Pregnant women attending the antenatal clinics were screened for possible participation in the study after explaining the nature of the study. This study was conducted on 150 patients. An initial dose of 40 mg isosorbide mononitrate was applied in the posterior vaginal fornix, and the same dose was repeated after 6 h. Cervical ripening was assessed by the change in Bishop Score 12 h after the initial application.

In accordance with departmental protocol for induction of labor, FHR and uterine activity were monitored after the application of the medication, after the beginning of regular uterine contractions, and during the active phase and second stage of labor by cardiotocography. Maternal blood pressure and pulse rate were assessed every 30 min, starting from 2 h after initiation of treatment. All maternal or fetal adverse effects were documented. The efficacy of the medication was evaluated by predetermined outcome variables for cervical ripening and induction of labor and delivery. Labor induction was assessed by measuring the time interval from the initial dose to the beginning of the active phase of labor.

The Inclusion criteria were Term Nulliparous/Multiparous women with singleton pregnancy and intact membranes. High-risk cases which were included were cases with Post-term pregnancy, IUGR, IUD, Hypertensive disorders, Diabetes mellitus, and Oligohydramnios.

The High-risk cases which were excluded were cases with PROM, Multiple pregnancies, Polyhydramnios, Cephalopelvic disproportion, Non-cephalic presentation, pregnancy with previous uterine scar, previous uterine perforation, previous history of cone biopsy, history of allergy to prostaglandins, or glyceryl trinitrate.

## Statistical Analysis

Appropriate statistical analysis was done with the help of SPSS version 11. Data were analyzed by Unpaired Student's $t$ test and $\chi$ square test. $P$ value $< 0.05$ was considered significant.

## Observations

We arrived at the following observations which have been tabulated:

In a study of 150 cases, the demographic variables—as in Table 1— include maternal age and gestational age, whose mean were 22.2 ± 2.6 years (range 19–35 years) and 40.5 ± 1.07 (range 40–42 weeks), respectively.

Out of 150, 52 women were primigravidas, while 98 were multigravidas. The mean ± SD of Bishop Score

**Table 1** Demographic variables of all cases

| Variable | Frequency | Mean ± SD |
|---|---|---|
| Age | | 22.23 ± 2.6 |
| Gestational age (wk) | | 40.5 ± 1.07 |
| Parity-primi | 52 (35.6 %) | |
| Multi | 98 (65.3 %) | |
| Total | 150 | |
| Bishops score before IMN | | 1.94 ± 1.3 |
| FHR before IMN | | 137.9 ± 6.2 |

**Table 2** Mean & mean difference of Bishops score before & after administration of IMN

| Mean bishops before IMN | Mean bishops after IMN | Mean difference | *P* value |
|---|---|---|---|
| 1.94 ± 1.31 | 6.70 ± 2.2 | 4.76 | 0.0001 |

* *P* value is significant

**Table 3** Frequency & percentage of cases with significant change in bishops score

| Bishops score change | Frequency | % |
|---|---|---|
| <4 points | 43 | 28.6 |
| >4 points | 107 | 71.3 |
| Total | 150 | 100 |

before drug administration was 1.94 ± 1.3 (range 0–5) and Fetal Heart Rate mean was 137 ± 6.2 bpm.

Table 2 shows the mean Bishop scores before isosorbide mononitrate (IMN) administration which was 1.94 ± 1.3, while mean Bishop score after drug administration was 6.7 ± 2.2; mean difference was equal to 4.76. *P* value was equal to 0.0001. By conventional criteria, this difference is considered to be statistically significant.

Table 3 and Fig. 1 show the frequencies of cases that their Bishop scores showed significant clinical changes after IMN administration. From the total of 150 cases, only 107 (71.3 %) had their Bishop scores changed by more than 4 points.

The mode of delivery (Table 4) shows that out of 150 cases, 96 (64 %) delivered vaginally, while 54 (36 %) were delivered by Cesarean section.

In Table 5, mean Apgar score at 1 min was 8.2 ± 0.9 SD (range 7–10), while teh mean Apgar score at 5 min was 9.4 ± 0.6 (range 8–10).

The only side effect noted was headache. Out of 150 cases, 30 cases (20 %) complained of headache (Table 6).

## Discussion

In this research, IMN was studied in a formulation which is cheap and widely available. 150 cases were enrolled to take IMN vaginally up to two doses 6 h apart. The primary outcome was a change in the Bishop score.

There were significant changes in the Bishop score, mean of Bishop Score before IMN was 1.94 ± 1.3, while mean ± SD of Bishop Score after IMN was 6.7 ± 2.2. *P* value was 0.0001 which is significant.

This result was in agreement with study done in Sweden by Ekerhovd et al. [7] which was a randomized controlled study. Title was "Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at

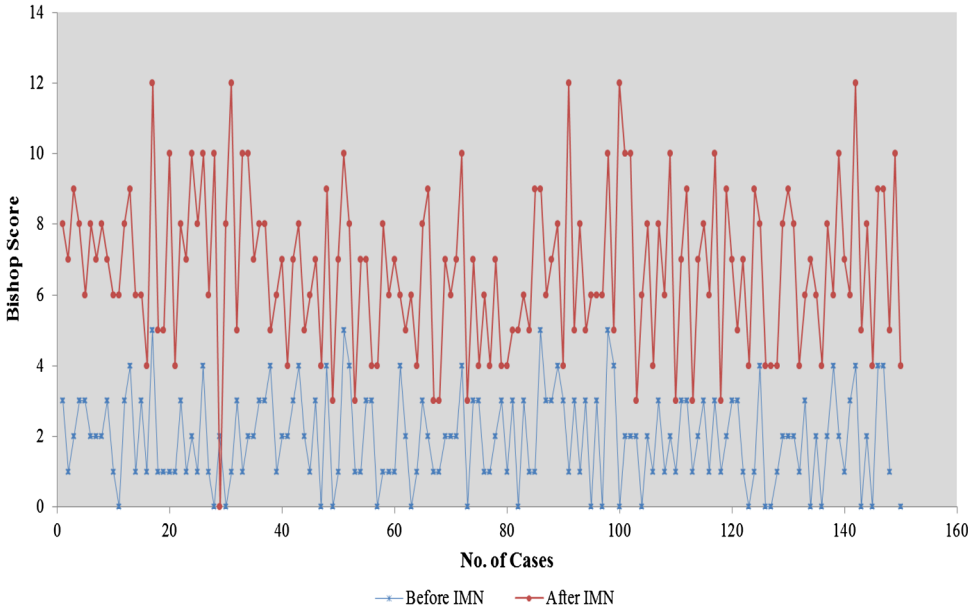


**Fig. 1** The bishop score of the cases before and after IMN administration: before IMN was between 0 and 5 score, while after IMN the range was between 0 and 12

**Table 4** Mode of delivery

| Mode of delivery | Frequency | % |
|---|---|---|
| Vaginal | 96 | 64 |
| Cesarean | 54 | 36 |
| Total | 150 | 100 |

**Table 5** Mean apgar score at 1 and 5 min

| | mean ± SD | Range | Median |
|---|---|---|---|
| Apgar at 1 min | 8.2 ± 0.9 | 7–10 | 8 |
| Apgar at 5 min | 9.4 ± 0.6 | 8–10 | 9 |

**Table 6** Frequency of a complication headache

| Headache | Frequency | % |
|---|---|---|
| Yes | 30 | 20 % |
| No | 120 | 80 % |
| Total | 150 | 100 |

term." Sixty women were included in their study; women were randomized to either 40 mg IMN or placebo vaginally, 4 h before elective C section. They found a clear effect on the distensibility of the uterine cervix in the study group, the force necessary to dilate the cervix was significantly lower than the placebo group ($P < 0.0001$).

Our result also agrees with a study by Rameez et al. [8] which was entitled "Nitric oxide donor isosorbide mononitrate for pre-induction cervical ripening at 41 weeks." In another study by Bullarbo et al. [10], IMN had a clear and significant effect on cervical distensibility (cumulative force to dilate cervix from 5 till 10 mm).

In our study, from 28 cases who were delivered vaginally, 24 (85 %) of them were those who had favorable cervix after IMN ($P = 0.012$ significant). This means that the rate of l decrease of Bishop score is more than 6. This result disagrees with the study done in France by Gabriel et al. [9]. Their study was conducted prospectively in 179 women who required induction of labor; cervical length was measured before induction, and they found that Bishop score was not predictive of the delivery mode, although C section for failure to progress was more frequent when Bishop score was <6. However, in women who had a Bishop score <6 but a cervical length <26 mm, there was a lower C/S rate (20.6 vs. 42.9 %; $P = 0.006$).

This means that Bishop score alone is not a good predictor of the risk of C Section. This disagreement in the present study may be due to comparatively small sample size.

In our study, no significant changes were observed in the FHR before and after IMN. The mean of FHS before IMN was 137 ± 6.2, while mean of FHS after IMN and before induction was 138 ± 4.7 ($P = 0.7$ not significant).

This result agrees with study done in Israel (2002) by Thaler et al. [11]. They studied the effect of nitric oxide donors on FHR patterns in patients with hypertension; they included 20 women with pregnancy-induced hypertension. 30 min recordings of FHR and fetal movement before and after IMN were done. The baseline FHR did not differ significantly, and it was 140.9 ± 2.0 and 137.5 ± 2.1 bpm, respectively.

In a study by Ekerhovd et al. [7], fetal well-being was evaluated intermittently by cardiotocography, FHR being specifically recorded at baseline and after 210 min. They found that all cardiotocographics intermittently performed were normal and without any signs of fetal distress, and FHR being within normal range (110–150 bpm) in all participants.

In our study, Apgar score was assessed at 1 and 5 min, which was all within normal range. At 1 min, mean was 8.2 ± 0.9 with the range of 7–10 and median 8. 5-min mean ± SD Apgar score was 9.4 ± 0.6 with the range of 8–10 and median 9. This result is comparative with Ekerhovd et al. [7] who reported 9.0 ± 0.6 (7–10), 9.8 ± 0.4 (9–10), and 10.0 ± 0 (10–10) mean ± SD at 1, 5, and 10 min, respectively.

In our study, the main side effect was headache which was experienced by 30 cases (20 %), but nearly all of them had mild headache which was tolerable. This result is lower than what Osman et al. [12] reported in their study "A randomized comparison of prostaglandin E2 gel with nitric oxide donors isosorbide mononitrate for cervical ripening before the induction of labor at term." In this study, IMN group received 40 mg single dose; they found that from 195 cases who received IMN 172 (88 %) developed headache, while in prostaglandin group from 188 cases, only 19 of them developed headache. $P$ value was less than 0.0001. Ekerhovd et al. [7] also reported headache in 24 cases from total 30 (80 %).

Difference in this result between the present and other studies may be due to the fact that in these two studies, it is mentioned that all participating women were informed about possible side effect before giving their informed consent; there is difference in the dose regime also.

## Conclusions

IMN is an effective, safe, inexpensive, and well-tolerated agent for cervical ripening. IMN is an attractive alternative agent as it has no maternal major side effects and absolutely no fetal side effects. Induction delivery interval is

reduced after giving IMN plus inducing agents. It is also cost effective compared to other agents for cervical ripening specially Prostaglandins which are being commonly used. However, more studies are required on more number of patients to prove it to be an ideal agent for cervical ripening. Because of its comparitive low cost, it may prove to be useful, especially in low resource set ups.

**Compliance with ethical requirements and Conflicts of interests** The research is in compliance with ethical standards. Permissions have been taken and is approved by the intitutional ethical committee. The authors have no conflicts of interest.

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