

Original Article

Vaginal administration of isosorbide mononitrate for cervical ripening prior to induction of labor for postdated pregnancy: a randomized controlled trial

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Abstract

Introduction: Induction of labor is commonly practiced intervention in modern Obstetrics. The aim of induction of labor is to initiate labor when maternal and fetal conditions necessitate delivery before the onset of spontaneous contraction with purpose to achieve safe vaginal delivery. Induction of labor is one of the most commonly practiced interventions in the Department of Obstetrics and Gynecology every day. The success of this obstetric practice is highly dependent upon the condition of the cervix which is assessed with Bishop's Score and it is well known that unfavorable cervix is associated with failure of induction and cesarean section. In the recent years, there has been a considerable interest in the use of nitrous oxide donors for cervical ripening and labor induction.

Objective: To evaluate whether isosorbide mononitrate administered vaginally prior to induction in postdated pregnancy is effective for pre-induction cervical ripening and thus, improves the process of induction of labor.

Methods: One hundred and twenty women scheduled for labor induction were recruited and assigned randomly to isosorbide mononitrate or placebo followed by misoprostol 25µg. The efficacy of the medication was evaluated by predetermined outcome variables for cervical ripening and induction of labor and delivery.

Results: The groups were comparable with respect to age, gestational age and Bishop's score. Women receiving isosorbide with misoprostol didn't show any improvement in the Bishop's score compared to misoprostol and placebo. There was no significant difference between the two groups regarding time of delivery and onset of active stage of labor from induction. Cesarean delivery rates were similar between the two groups; however, the indications of the cesarean section were different between the two groups which were significant statistically. Neonatal outcome were similar between the two groups.

Conclusion: The addition of vaginal isosorbide mononitrate to oral misoprostol for cervical ripening and labor induction did not reduce time to vaginal delivery and didn't help in improving pre-induction cervical score.

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Introduction

Induction of labor is an intervention to expedite delivery when there is concern about pregnancy and is usually performed when the benefits to the mother outweighs the risk of continuing pregnancy. Since the late 1960's prostaglandins have been used for the induction of labor at term, and their analogs have been administered by various routes to induce labor with mostly comparable results.¹ Although several other agents have been proposed to be useful in inducing labor and cervical ripening like: oxytocin, corticosteroids, estrogen, relaxin and nitricoxide donors (NOD),^{1,2} the standardized cervical priming and induction of labor is predominantly achieved by means of Prostaglandins administration. However, in the last years, there has been a considerable interest in the use of misoprostol³⁻⁵ and NOD^{6,7} for cervical ripening and labor induction. NOD have been shown to stimulate prostaglandin production in the human cervix after topical administration.⁸

Similar kind of study done by Rameez et al. have shown that vaginally administered isosorbide mononitrate was effective for pre-induction cervical ripening.⁹ Another study done by Mohamad S. Abdellah et al.¹⁰ have also concluded that isosorbide and misoprostol is more efficient than misoprostol alone in terms of fast cervical ripening and shortening of induction-labor

interval. Nitric oxide appears to be safe in term pregnancy but do affect maternal and fetal hemodynamics when applied vaginally, albeit without clinical significance.¹¹

The present study was undertaken with an objective of evaluating the efficacy of Nitric oxide donor i.e.; isosorbide mononitrate for cervical ripening prior to induction of labor. If the result of the study comes positive, then, there will be less number of patients undergoing cesarean section for failed Induction.

Methods

This study was a prospective, randomized, single blinded, placebo-controlled and was carried out at the Department of Obstetrics and Gynecology, B. P. Koirala Institute of Health Sciences, Dharan, from October 2013 to September 2014. This study was granted approval from the institute ethical review board before its initiation.

This study considered 95% Confidence interval and 80% power for sample size calculation. According to the study done by Abdellah MS et al.,¹⁰ it was found that women receiving isosorbide plus misoprostol showed significant changes in the Bishop score compared to misoprostol plus placebo (8.57 ± 1.46 vs 7.6 ± 1.39) Standard deviation was found to be 1.42.

Now using the formula that is T test for 2 sample mean

$$\begin{aligned} n &= 2x (S.D)^2 \times (Z_b + Z_{a/2})^2 / (\text{Mean1} - \text{Mean1})^2 \\ &= 2x (1.4)^2 \times (0.842 + 1.96)^2 / (8.57 - 7.6)^2 \\ &= 36 \end{aligned}$$

For reducing various types of bias, we added 10% in sample size, so, the sample size became 40 in each arm. But, this study considered 60 in each arm, that is case and control arm. To recruit this number of patients, a 12 month inclusion period was anticipated.

So, a total number of 120 women scheduled for labor induction were recruited in this study. Sixty patients were recruited in misoprostol group and 60 patients were recruited as control group received pyridoxine.

Inclusion Criteria

- Nulliparity
- Postdated pregnancy (≥ 41 weeks)

Exclusion Criteria

- Pre labor rupture of membrane
- Oligohydramnios (AFI ≤ 5 cm)
- Preeclampsia
- IUGR

The study took place in the Antenatal ward of Department of Obstetrics and Gynecology at BPKIHS. All the patients who were eligible for the study on the basis of inclusion criteria were enrolled in the study.

All the participants were fully informed about the nature and scope as well as potential risk of the study. After consenting for the study, patients were randomized according to computer generated random number table to receive either isosorbide mononitrate (40mg) or placebo (pyridoxine 40mg) 1day prior to planned induction with misoprostol. The patient did not know whether they are receiving the treatment or placebo, only the doctor randomizing the patient knew about whether the patient was receiving treatment or placebo. Randomization was done by on duty doctor and Bishop's score was documented.

Maternal pulse and blood pressure were assessed every 30 minutes during the 1st two hours after instilling isosorbide mononitrate, then, every 4 hourly, it was measured by the same doctor who randomized the patient. Any adverse or side effects were documented. The next day, all the patients were induced with misoprostol 25 μ gm, Bishop's score was documented again. The next day, the randomized patients were induced with misoprostol. Three doses of misoprostol were given every 4 hourly. Patients not entering into active phase of labor after 4 hours of last dose of misoprostol were diagnosed as failed induction and cesarean section was carried out. Those patients who progressed after any dose of

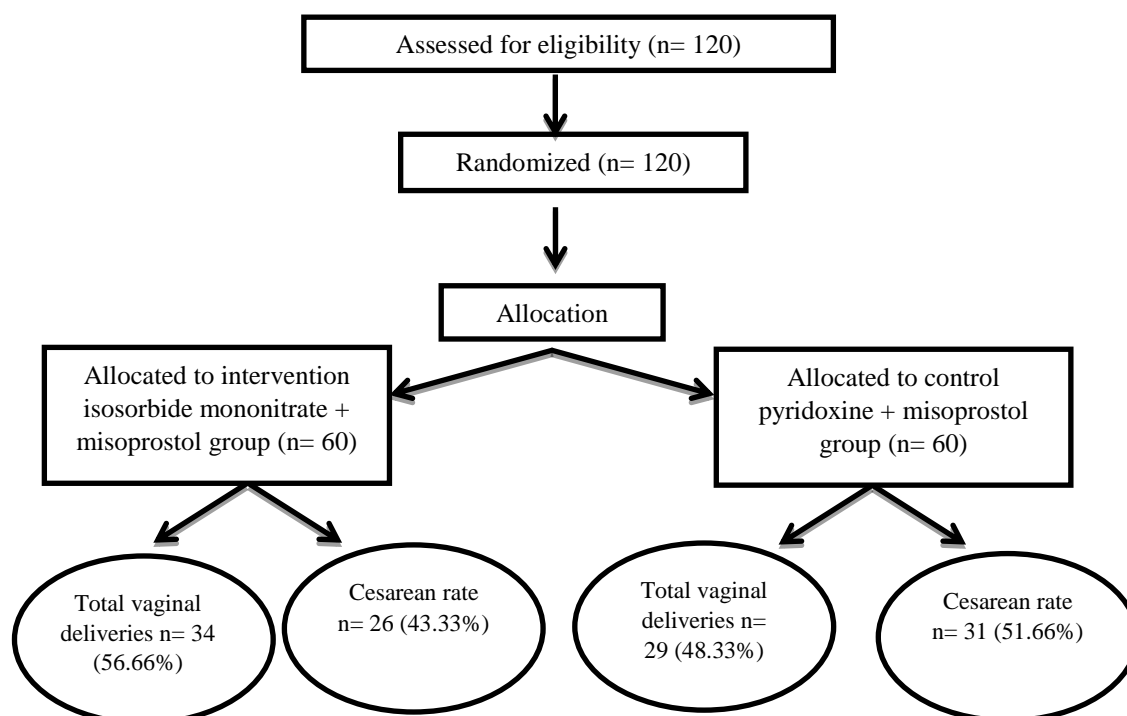
misoprostol was managed according to labor room protocol.

The efficacy of the medication was evaluated by predetermined outcome variables for cervical ripening and induction of labor and delivery. Cervical ripening was assessed by the change in Bishop's Score found 16 hours after the initial application. Labor induction was assessed by measuring time from initial dose to beginning of the active phase of labor and time from initial dose to delivery.

Maternal safety was evaluated by the occurrence of various adverse effects: Tachy-systole (> 5 contractions in 10 min), uterine hypertonus, headache and hypotension. Fetal safety was evaluated by Apgar score and need for neonatal intensive care unit admission.

Statistical analysis was done using the SPSS software for windows, version 11.5. The *t* test and Chi-square test were applied to find out the significant difference for inferential statistics. $P < 0.05$ was considered statistically significant.

Figure 1: Consort diagram of the trial



Results

A total of 120 women who gave consent for the study were enrolled in study. The two groups were comparable with respect to age, parity, gestational age, indication for induction and Bishop’s score. All the

patients were primi gravida according to inclusion criteria and indication for induction of labor was postdated pregnancy. The baseline characteristics are shown in table 1.

Table1: Baseline Characteristics of both groups

	Misoprostol plus IMN (n= 60)	Misoprostol plus placebo (n= 60)	P values
Age (years)	23.25 ± 2.7	22.73 ± 3.07	0.336
Gestational age (weeks)	41.1 ± 0.399	41.1 ± 0.44	1.000
Initial Bishop’s Score	3.07 ± 0.312	3.20 ± 0.632	0.146

Values are given as mean ±S.D

Women receiving IMN plus misoprostol didn’t show significant changes in the Bishop’s score 1day after administration when compared with misoprostol plus placebo (3.08 ± 0.334 vs. 3.35 ± 0.732, P= 0.120). The median time from initial dose to beginning of active labor and time from initial dose to delivery remained statistically insignificant (table 2).

Table 2: Outcome Variables

	Misoprostol plus IMN (n= 60)	Misoprostol plus placebo (n= 60)	P-value
Bishop’s score before induction	3.08 ± 0.334	3.35 ± 0.732	0.120
Time from initial dose to beginning of active labor (hour)	9.189 ± 3.4	8.7 ± 3.3	0.561
Time from initial dose to delivery (hour)	12.78 ± 4.03	14.33 ± 4.69	0.550

Values are given as mean ±S.D

There were no significant differences in the incidence of maternal adverse effects. No significant differences were found in the incidence of cesarean delivery in the two groups. However, regarding indications of cesarean section, fetal distress and meconium stained liquor were more common in isosorbide group and failed induction was more common in placebo group which was statistically significant ($P= 0.013$). There was no statistical difference between the neonatal outcomes and neonatal Intensive care admission between the two groups.

Discussion

Labor induction in the presence of unfavorable cervix is a common indication for the use of prostaglandins. Prostaglandins and their analogues have been used for induction of labor since 1960s.

Recently nitric oxide donors such as isosorbide mononitrate have been shown to stimulate prostaglandin production in the human cervix after topical administration.⁸ Therefore, a combination of both should accelerate the process of cervical ripening and labor induction and possibly potentiate the efficacy of each agent alone without major maternal and fetal adverse effects. The study was conducted to find out whether the addition of isosorbide to the routine administration

of misoprostol is more efficient for cervical ripening than misoprostol alone in our setup.

The present study was a randomized controlled trial. One hundred and twenty patients were enrolled in the study and randomized into isosorbide and placebo groups. All subjects in the study received the assigned treatment. All of the 120 patients completed the study.

Till date many studies have shown that Nitric Oxide donor like isosorbide can induce cervical ripening and thus, helps in improving the pre-induction cervical Bishop's Score. Nunes et al.¹² found that length of induction to delivery was reduced from approximately 27 to 22 hours when inpatient administration of glyceryl trinitrate, a nitric oxide donor, was combined with vaginal prostaglandin dinoprostone. However, the present study fails to show any benefit for cervical ripening and labor induction in terms of reducing the length of time to vaginal delivery by addition of vaginal isosorbide mononitrate with misoprostol for induction of labor.

This is in agreement with study conducted by Justin P. Collingham et al.¹³ who concluded that addition of isosorbide mononitrate to misoprostol for cervical ripening and labor induction did not

reduce time to vaginal delivery and was associated with a greater incidence of headache. However, they had given oral misoprostol which was different from this study. In the present study, we have chosen vaginal misoprostol because the duration between the use of isosorbide mononitrate and misoprostol was one day which will eliminate the potential for pharmacological interaction between vaginal misoprostol and vaginal isosorbide mononitrate.

Study done by Ekerhovd et al.⁷ showed statistically significant reductions in maternal blood pressure and increase in maternal pulse with isosorbide mononitrate use at term though clinically insignificant. This study found no difference in the incidences of maternal tachycardia or hypotension between the two groups which is consistent with the findings of Nunes et al.¹² Headache is one of the most commonly reported symptoms in patient who had received isosorbide mononitrate for cervical ripening in other studies. However, in this study, only one patient complained of headache in isosorbide group which was clinically not significant. This may be because only one dose of isosorbide mononitrate was used.

Conclusion

In conclusion, the present study shows that addition of nitric oxide donor like

Isosorbide mononitrate to misoprostol for pre-induction cervical ripening has no advantage of improving cervical findings in terms of Bishop's score and neither does it help in reducing induction to delivery time, suggesting a limited role for isosorbide mononitrate in in-patient cervical ripening and labor induction.

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