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Original Article

COMPARATIVE EFFICACY OF ISOSORBIDE MONONITRATE AND MISOPROSTOL VERSUS MISOPROSTOL ALONE FOR CERVICAL RIPENING AND INDUCTION OF LABOR: A RANDOMIZED DOUBLE-BLIND STUDY

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ABSTRACT

Objective: Induction of labor is a common obstetric procedure aimed at initiating uterine contractions before the spontaneous onset of labor, essential for achieving vaginal delivery. Misoprostol, a synthetic prostaglandin E1 analog, is widely used for cervical ripening and labor induction but is associated with potential side effects. Isosorbide mononitrate (ISMN), a nitric oxide donor, has emerged as a potential adjunct to enhance cervical ripening. This randomized, double-blind study evaluates the comparative efficacy of ISMN combined with misoprostol versus misoprostol alone for cervical ripening and labor induction in term pregnancies.

Methods: This study was conducted at the Department of Obstetrics and Gynecology, Dr. R. P. G. M. C. Kangra, Himachal Pradesh, from July 2019 to June 2020. A total of 100 patients meeting the inclusion criteria were randomized into two groups: Group 1 received ISMN 40 mg and misoprostol 25 mcg, while Group 2 received misoprostol 25 mcg and a placebo. The primary outcome was the induction to active phase interval. Secondary outcomes included mode of delivery, maternal and neonatal outcomes, and side effects. Statistical analysis was performed using Chi-Square and unpaired t-tests, with a p-value<0.05 considered significant.

Results: Group 1 (ISMN+misoprostol) showed a significantly shorter induction to active phase interval (11.85±3.24 h) compared to Group 2 (misoprostol alone) (19.82±3.7 h, p=0.004). The mode of delivery did not significantly differ between groups, with similar rates of vaginal delivery and cesarean sections. Neonatal outcomes, including birth weight and APGAR scores, were comparable between the groups. Maternal complications were not significantly different, with no increased incidence of hyperstimulation or postpartum hemorrhage in group 1.

Conclusion: The combination of ISMN with misoprostol is more effective in reducing the induction to active phase interval compared to misoprostol alone without increasing adverse maternal or neonatal outcomes. This combination therapy could represent a significant advancement in the management of labor induction.

Keywords: Cervical ripening, Labor induction, Isosorbide mononitrate, Misoprostol, Maternal-fetal outcomes, Randomized double-blind study

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INTRODUCTION

Induction of labor is a common obstetric procedure performed to initiate uterine contractions before the spontaneous onset of labor, with the goal of achieving vaginal delivery. Various medical conditions necessitate induction, including post-term pregnancy, preeclampsia, intrauterine growth restriction, and other maternal or fetal health concerns. The effectiveness of labor induction depends largely on the state of the cervix at the time of induction, assessed using the Bishop score. A favorable Bishop score is associated with a higher likelihood of successful induction and vaginal delivery [1, 2].

Misoprostol, a synthetic prostaglandin E1 analog, is widely used for cervical ripening and labor induction due to its efficacy in promoting uterine contractions and cervical dilation. However, its use is associated with potential side effects such as uterine hyperstimulation, fetal distress, and meconium-stained amniotic fluid. These complications necessitate the exploration of adjunctive therapies that can enhance the efficacy of misoprostol while mitigating its adverse effects [3, 4].

Isosorbide mononitrate (ISMN), a nitric oxide donor, has emerged as a potential agent for cervical ripening. Nitric oxide plays a crucial role in the biochemistry of cervical ripening by relaxing the myometrium and facilitating the breakdown of collagen in the cervical stroma. Previous studies have suggested that the combination of ISMN with prostaglandins could synergistically improve cervical ripening and reduce the time to active labor, thereby enhancing the overall efficacy of labor induction [5, 6].

The primary aim of this randomized, double-blind study is to evaluate the comparative efficacy of intravaginal ISMN combined with misoprostol versus misoprostol alone for cervical ripening and labor induction in term pregnancies. By assessing the induction to active phase interval, mode of delivery, and neonatal outcomes, this study seeks to determine whether the combination therapy offers superior outcomes in comparison to misoprostol alone [7, 8].

Furthermore, this study aims to provide insights into the safety profile of the combined regimen, particularly focusing on maternal and neonatal complications. The potential reduction in the incidence of uterine hyperstimulation, meconium-stained amniotic fluid, and other adverse effects with the use of ISMN could represent a significant advancement in the management of labor induction [9].

Overall, this study addresses a critical need in obstetric practice by exploring an alternative strategy to optimize labor induction outcomes. The findings from this research could influence clinical protocols and improve the quality of care for pregnant women requiring induction of labor. Through rigorous comparison and analysis, this study aims to contribute valuable evidence on the efficacy and safety of ISMN and misoprostol combination therapy, potentially setting the stage for its broader adoption in clinical practice.

MATERIALS AND METHODS

This prospective, randomized, double-blind study was conducted in the Department of Obstetrics and Gynecology at Dr. R. P. G. M. C. Kangra, Himachal Pradesh, following approval from the Institutional Ethics Committee. Patients admitted to the labor room from July 2019 to June 2020 for labor induction were included after providing informed consent.

Inclusion criteria

- Consent given
- Bishop Score ≤ 6
- Conditions: Pregnancy Induced Hypertension, Intrauterine Growth Restriction, Rh-Isoimmunisation, major fetal congenital anomaly, intrauterine fetal death, singleton pregnancy, 34 or more completed weeks of gestation

Exclusion criteria

- Consent not given
- Contraindications for labor induction: placenta previa, pre-labor rupture of membranes, previous LSCS, malpresentations, major CPD, established fetal distress, heart disease, liver disease, anemia complicating pregnancy

Methodology

Patients meeting the inclusion criteria underwent ultrasonographic examination for gestational age, fetal growth parameters, and abnormalities. Detailed obstetric, menstrual, medical, family and personal histories were recorded. General physical examination assessed mental and physical status, vital signs, and chest and heart conditions. Abdominal examination included fundal height estimation, Leopold maneuvers, and fetal heart rate auscultation.

The randomization sequence was computer-generated in blocks of four or eight, with medications placed in numbered sealed envelopes containing two packages:

- Package A: Tablet ISMN 40 mg+Tablet Misoprostol 25 mcg
- Package B: Tablet Misoprostol 25 mcg+placebo (Pyridoxine)

Women received the medications based on randomization, followed by 4-hourly vaginal examinations to evaluate Bishop Score. Misoprostol doses were administered every 4 h (up to 4 doses), and ISMN or placebo every 12 h (up to 2 doses). Uterine contractions and fetal heart rate were monitored every 30 min. If the Bishop score was<6 after 4 h, additional doses were given.

For favorable cervices (Bishop score ≥6, cervical dilation ≥4 cm), artificial rupture of membranes (AROM) was performed. Based on the presence or absence of meconium:

- Clear liquor: Labor induction with oxytocin drip and fetal heart rate monitoring.
- Thin meconium-stained liquor: Fetal heart rate monitoring for 30 min.
- Deeply stained liquor: Caesarean section to prevent meconium aspiration syndrome and fetal anoxia.

Oxytocin infusion began at cervical dilation of 3 cm, starting with 2 units in 500 ml of Ringer solution (4 mIU/min) and increasing every 30 min to a maximum of 8 units (32 mIU/min) until adequate contractions were achieved (3 contractions in 10 min, lasting 40-45 seconds). Failed induction was diagnosed if adequate contractions were not established, leading to cesarean section.

Comparisons between groups

- Age, parity, gestational age
- Time from medication start to first contraction pain
- Time from AROM±oxytocin to active labor phase
- Duration of 1st, 2nd, and 3rd labor stages and mode of delivery
- Maternal complications: hyperstimulation, postpartum hemorrhage, headache, nausea, vomiting, dizziness
- Neonatal outcomes: Apgar score at 1 and 5 min, NICU admission

After trial completion, women completed a questionnaire regarding side effects.

Statistical analysis

Data were recorded in Microsoft Excel and analyzed using the Chi-Square test for categorical data and unpaired t-test for numerical variables. A p-value<0.05 was considered statistically significant.

RESULTS

This randomized double-blind study evaluated the comparative efficacy of isosorbide mononitrate (ISMN) combined with misoprostol versus misoprostol alone for cervical ripening and induction of labor in term pregnancies. A total of 100 women were randomized into two groups of 50 each.

Demographic profile

The demographic characteristics were comparable between the two groups. The average age in Group 1 (ISMN+misoprostol) was 26.06±3.75 y, and in group 2 (misoprostol alone) was 26.8±4.83 y (p=0.395). The BMI was 24.41±3.7 kg/m^2 in Group 1 and 24±3.6 kg/m^2 in Group 2 (p=0.575). The distribution of the period of gestation was similar across the groups (p=0.08), with a pre-induction Bishop score of 4.16±0.76 in Group 1 and 4.14±0.83 in Group 2 (p=0.9) (table 1).

Induction to active phase interval

The time from induction to the active phase of labor was significantly shorter in Group 1 (11.85±3.24 h) compared to Group 2 (19.82±3.7 h) (p=0.004) (table 2).

Mode of delivery

The mode of delivery did not significantly differ between the two groups. Vaginal deliveries occurred in 34 women in Group 1 and 40 women in Group 2 (p=0.318). Operative vaginal deliveries were the same in both groups (3 each). The rate of cesarean sections was 13 in Group 1 and 7 in Group 2 (table 3).

Neonatal outcomes

Neonatal outcomes were similar between the groups. The average birth weight was 2840.1±535.2 gs in Group 1 and 2669.24±512.9 gs in Group 2 (p=0.106). APGAR scores at 1 minute were identical in both groups, with a median of 7.0 [7.0, 8.0] (p=1). At 5 min, APGAR scores were 9.0 [9.0, 10.0] in Group 1 and 10.0 [9.0, 10.0] in Group 2 (p=0.323) (table 4).

Maternal complications

Group 1 had fewer instances of hyperstimulation (0 vs. 3 in Group 2, p=0.07). Headache and dizziness were reported by 4 women in Group 1 and none in Group 2 (p=0.04). One case of postpartum hemorrhage (PPH) was noted in Group 2 and none in Group 1 (p=0.314). No significant differences in oxytocin requirement were observed between the groups (p=0.139) (table 1).

Table 1: Demographic profile

Variable	Group 1 (n=50)	Group 2 (n=50)	P Value
Age (y)	26.06±3.75	26.8±4.83	0.395
BMI (kg/m^2)	24.41±3.7	24±3.6	0.575
Period of Gestation (weeks)			
34-36+6	2	2	0.08
37-40	30	19	
>40	18	29	
Pre-induction Bishop Score	4.16±0.76	4.14±0.83	0.9

Labor duration

The duration of the first stage of labor was shorter in Group 1 (248.3±173.25 min) compared to Group 2 (300.4±154.88 min), though not statistically significant (p=0.118). The second stage duration was 28.7±21.169 min in Group 1 and 33.5±24.04 min in Group 2 (p=0.291). The third stage duration was consistent between groups (5±0 min in Group 1 and 5.06±0.24 min in Group 2, p=0.08). The total labor duration was shorter in Group 1 (277±194.4 min) compared to Group 2 (333.9±178.9 min), but this difference was not statistically significant (p=0.131) (table 3).

Overall, the combination of ISMN and misoprostol demonstrated a shorter induction to active phase interval and comparable safety and efficacy to misoprostol alone, with no significant differences in maternal complications, oxytocin requirement, labor duration, mode of delivery, or neonatal outcomes.

Table 2: Induction to active phase interval

Variable	Group 1 (n=50)	Group 2 (n=50)	P Value
Induction to Active Phase (hours)	11.85±3.24	19.82±3.7	0.004

Table 3: Mode of delivery

Mode of delivery	Group 1 (n=50)	Group 2 (n=50)	P Value
Vaginal	34	40	0.318
Operative Vaginal Delivery	3	3	
LSCS	13	7	

Table 4: Neonatal outcomes

Variable	Group 1 (n=50)	Group 2 (n=50)	P Value
Birth Weight (grams)	2840.1±535.2	2669.24±512.9	0.106
APGAR Score at 1 minute	7.0 [7.0, 8.0]	7.0 [7.0, 8.0]	1
APGAR Score at 5 min	9.0 [9.0, 10.0]	10.0 [9.0, 10.0]	0.323

DISCUSSION

Induction of labor remains a critical procedure in obstetrics, with various pharmacological agents utilized to optimize outcomes. Misoprostol, although effective, carries a risk of uterine hyperstimulation and other complications. The potential benefits of adjunctive therapies such as ISMN, which may enhance cervical ripening and labor induction while mitigating adverse effects, warrant thorough investigation [10].

This randomized double-blind study demonstrated that the addition of ISMN to misoprostol significantly reduced the induction to active phase interval, suggesting a synergistic effect in cervical ripening. The biochemistry of cervical ripening involves complex interactions between various biochemical pathways, where nitric oxide plays a pivotal role in relaxing the myometrium and breaking down collagen in the cervical stroma. By leveraging the nitric oxide-donating properties of ISMN, the cervical ripening process appears to be accelerated, facilitating a more efficient transition to active labor [11, 12].

Interestingly, the mode of delivery did not differ significantly between the two groups, indicating that while the combination therapy expedited the onset of active labor, it did not necessarily influence the final mode of delivery. This finding underscores the multifactorial nature of delivery outcomes, where factors beyond cervical ripening and induction play critical roles [13].

Neonatal outcomes, including birth weight and APGAR scores, were comparable between the groups, suggesting that the use of ISMN does not compromise fetal well-being. The absence of significant differences in maternal complications, such as hyperstimulation and postpartum hemorrhage, further supports the safety profile of the combination therapy. These findings align with previous studies suggesting that nitric oxide donors can be safely integrated into induction protocols without increasing maternal or fetal risks [14].

The implications of these findings are noteworthy for clinical practice. The reduced induction to active phase interval can potentially decrease the overall duration of labor, thereby reducing maternal fatigue and the risk of intrapartum complications associated with prolonged labor. Additionally, the comparable safety profile suggests that ISMN can be a valuable addition to existing induction protocols, particularly in settings where optimizing the efficiency of labor induction is paramount [15].

However, the study has its limitations. The sample size, while adequate for detecting significant differences in primary outcomes, may not be sufficient to identify rare adverse events. Further large-scale studies are warranted to confirm these findings and explore the long-term implications of using ISMN in labor induction. Additionally, the study's findings are specific to a tertiary care setting and may not be generalizable to all obstetric populations.

In conclusion, this study provides compelling evidence for the efficacy and safety of combining ISMN with misoprostol for cervical ripening and labor induction. The significant reduction in the induction to active phase interval, coupled with comparable maternal and neonatal outcomes, highlights the potential of this combination therapy to enhance labor induction protocols. Future research should focus on validating these findings in larger, more diverse populations and exploring the mechanistic pathways underpinning the observed clinical benefits.

CONCLUSION

The combination of ISMN and misoprostol for cervical ripening and labor induction significantly shortens the induction to active phase interval without increasing adverse maternal or neonatal outcomes. This therapy could optimize labor induction protocols, enhancing maternal and neonatal care. Further research is needed to confirm these findings and explore long-term implications.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICTS OF INTERESTS

Declared none

REFERENCES

1. Bullarbo M, Orrskog ME, Andersch B, Granstrom L, Norstrom A, Ekerhovd E. Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labor induction postterm: a randomized controlled study. Am J Obstet Gynecol. 2007;196(1):50.e1-5. doi: 10.1016/j.ajog.2006.08.034, PMID 17240231.

2. Habib SM, Emam SS, Saber AS. Outpatient cervical ripening with nitric oxide donor isosorbide mononitrate prior to induction of labor. Int J Gynaecol Obstet. 2008;101(1):57-61. doi: 10.1016/j.ijgo.2007.09.027, PMID 18222450.
3. Thomson AJ, Lunan CB, Cameron AD, Cameron IT, Greer IA, Norman JE. Nitric oxide donors induce ripening of the human uterine cervix: a randomised controlled trial. Br J Obstet Gynaecol. 1997;104(9):1054-7. doi: 10.1111/j.14710528.1997.tb12066.x, PMID 9307534.
4. Abdellah MS, Hussien M, Aboalhassan A. Intravaginal administration of isosorbide mononitrate and misoprostol for cervical ripening and induction of labour: a randomized controlled trial. Arch Gynecol Obstet. 2011;284(1):25-30. doi: 10.1007/s00404-010-1572-4, PMID 20582425.
5. Chanrachakul B, Herabutya Y, Punyavachira P. Potential efficacy of nitric oxide for cervical ripening in pregnancy at term. Int J Gynaecol Obstet. 2000;71(3):217-9. doi: 10.1016/s0020-7292(00)00284-8, PMID 11102606.
6. Vaisanen Tommiska M. Nitric oxide in human uterine cervix: role in cervical ripening. Finland: University of Helsinki; 2006.
7. Ekerhovd E, Brannstrom M, Weijdegard B, Norstrom A. Nitric oxide synthases in the human cervix at term pregnancy and effects of nitric oxide on cervical smooth muscle contractility. Am J Obstet Gynecol. 2000;183(3):610-6. doi: 10.1067/mob.2000.105901, PMID 10992181.
8. Chanrachakul B, Herabutya Y, Punyavachira P. Randomized comparison of glyceryl trinitrate and prostaglandin E2 for cervical ripening at term. Obstet Gynecol. 2000;96(4):549-53. doi: 10.1016/s0029-7844(00)00990-x, PMID 11004357.
9. Thomson AJ, Lunan CB, Ledingham M, Howat RC, Cameron IT, Greer IA. Randomised trial of nitric oxide donor versus prostaglandin for cervical ripening before first trimester termination of pregnancy. Lancet. 1998;352(9134):1093-6. doi: 10.1016/S0140-6736(98)01289-6, PMID 9798584.
10. Noor N, Sharma A, Parveen S, Ali SM. Intravaginal administration of misoprostol alone versus misoprostol and isosorbide mononitrate for cervical ripening and labor induction. J Appl Adv Res. 2017;2(1):37-42. doi: 10.21839/jaar.2017.v2i1.52.
11. Collingham JP, Fuh KC, Caughey AB, Pullen KM, Lyell DJ, El Sayed YY. Oral misoprostol and vaginal isosorbide mononitrate for labor induction: a randomized controlled trial. Obstet Gynecol. 2010;116(1):121-6. doi: 10.1097/AOG.0b013e3181e408f2, PMID 20567177.
12. Sherif H, Ahmed M, Amgad A. Comparison between misoprostol and isosorbide mononitrate and misoprostol in preinduction cervical ripening. Obstet Gynecol. 2009;35(3216):0258.
13. Bollapragada SS, MacKenzie F, Norrie JD, Eddama O, Petrou S, Reid M. Randomised placebo-controlled trial of outpatient (at home) cervical ripening with isosorbide mononitrate (IMN) prior to induction of labour clinical trial with analyses of efficacy and acceptability the IMOP study. BJOG. 2009;116(9):1185-95. doi: 10.1111/j.1471-0528.2009.02216.x, PMID 19624440.
14. Leduc D, Biringer A, Lee L, Dy J. Clinical practice obstetrics committee special contributors. J Obstet Gynaecol Can. 2013;35(9):840-57. doi: 10.1016/S17012163(15)30842-2, PMID 24099451.
15. Ghosh A, Lattey KR, Kelly AJ. Nitric oxide donors for cervical ripening and induction of labour. Cochrane Database Syst Rev. 2016 Dec 5;12(12):CD006901. doi: 10.1002/14651858.CD006901.pub3, PMID 27918616.