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Original Article

SAFETY AND MATERNAL-FETAL OUTCOMES OF ISOSORBIDE MONONITRATE AND MISOPROSTOL COMBINATION VERSUS MISOPROSTOL ALONE FOR LABOR INDUCTION: A RANDOMIZED DOUBLE-BLIND STUDY

MOLLY SHARMA[1*], AMIT GUPTA[2]

[1]Department of Health and Family Welfare, Himachal Pradesh, India. [2]Department of Obstetrics and Gynecology, Dr. Rajendra Prasad Govt. Medical College and Hospital, Himachal Pradesh, India

[*]Corresponding author: Molly Sharma; [*]Email: drmollysharma@gmail.com

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ABSTRACT

Objective: The induction of labor is essential in managing pregnancies where early delivery benefits outweigh the risks. Misoprostol is a common agent for labor induction but has side effects like uterine hyperstimulation. Isosorbide mononitrate (ISMN), a nitric oxide donor, may enhance cervical ripening and reduce complications when used with misoprostol. This study evaluates the safety and maternal-fetal outcomes of ISMN combined with misoprostol versus misoprostol alone.

Methods: A randomized, double-blind study was conducted at Dr. R. P. G. M. C. Kangra. Patients meeting the inclusion criteria were randomly assigned to receive either ISMN with misoprostol or misoprostol with a placebo. Primary outcomes measured were maternal complications (e. g., uterine hyperstimulation, headache, postpartum hemorrhage) and neonatal outcomes (e. g., birth weight, APGAR scores, NICU admission). Secondary outcomes included the need for oxytocin augmentation and the duration of labor stages.

Results: The study included 100 patients divided into two groups of 50 each. The ISMN and misoprostol group had significantly fewer headaches and dizziness but showed no significant difference in uterine hyperstimulation or postpartum hemorrhage compared to the misoprostol alone group. The ISMN group required less oxytocin augmentation, and their total labor duration was shorter, though not significantly. Neonatal outcomes were similar across both groups.

Conclusion: The combination of ISMN and misoprostol appears to be a safer and potentially more effective alternative to misoprostol alone for labor induction, with fewer maternal complications and similar neonatal outcomes. Further large-scale studies are recommended to confirm these findings and inform clinical practice.

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

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INTRODUCTION

The induction of labor is a critical intervention in obstetric care, employed when the benefits of early delivery outweigh the risks of continued pregnancy. While misoprostol remains a standard agent for cervical ripening and labor induction, its use is not without complications. Misoprostol can lead to excessive uterine contractions, resulting in maternal and fetal distress. Thus, there is a significant need to explore adjunctive therapies that can enhance the efficacy of misoprostol while reducing its side effects [1, 2].

Isosorbide mononitrate (ISMN) has gained attention in recent years as a nitric oxide donor capable of promoting cervical ripening without stimulating uterine contractions. Nitric oxide facilitates cervical softening by increasing collagen breakdown and water content in the cervical stroma, thus preparing the cervix for labor. When used in combination with misoprostol, ISMN may enhance cervical ripening and reduce the induction to delivery interval, potentially improving maternal and fetal outcomes [3, 4].

The primary objective of this randomized double-blind study is to assess the safety and maternal-fetal outcomes of ISMN combined with misoprostol compared to misoprostol alone. This study specifically focuses on maternal complications such as uterine hyperstimulation, headache, dizziness, and postpartum hemorrhage (PPH), which are significant concerns in labor induction protocols. By evaluating the incidence and severity of these complications, this research aims to establish the safety profile of the combined regimen [5, 6].

Additionally, the study examines neonatal outcomes, including birth weight, APGAR scores, and the necessity for neonatal intensive care unit (NICU) admission. These parameters are crucial for determining the overall impact of the induction agents on neonatal health and well-being. A reduction in adverse neonatal outcomes with the combination therapy would indicate a significant advancement in labor induction practices [7, 8].

This study also investigates the need for oxytocin augmentation during labor, comparing the requirement between the two groups. Oxytocin is commonly used to strengthen contractions once labor has begun, but its use can also lead to complications. Understanding the differential oxytocin requirements between the groups will provide insights into the effectiveness of ISMN in enhancing labor progress [9].

Ultimately, this research seeks to provide robust evidence on the safety and efficacy of ISMN combined with misoprostol for labor induction. The findings are expected to inform clinical guidelines and improve the management strategies for labor induction, ensuring better outcomes for both mothers and neonates. By addressing the critical aspects of safety and efficacy, this study aims to contribute to the ongoing efforts to optimize labor induction protocols and enhance the quality of obstetric care.

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 sec). 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.

Maternal complications

In Group 1 (ISMN+misoprostol), 46 women experienced no complications, similar to Group 2 (misoprostol alone) with 46 women (p=1). Hyperstimulation was observed in 3 women in Group 2 and none in Group 1 (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) (table 1).

Oxytocin requirement

The need for oxytocin augmentation did not significantly differ between the groups, with 15 women in Group 1 and 20 in Group 2 requiring oxytocin (p=0.139) (table 2).

Duration of labor

The average 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 averaged 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).

Indications for LSCS

Acute fetal distress (AFD) led to cesarean sections in 2 women in Group 1 and 1 in Group 2 (p=0.981). Failed induction was the reason for 6 cesarean sections in Group 1 and 3 in Group 2. Meconium-stained liquor was an indication for cesarean in 5 women in Group 1 and 3 in Group 2 (table 4).

Overall, the combination of ISMN and misoprostol demonstrated comparable safety and efficacy to misoprostol alone, with no significant differences in maternal complications, oxytocin requirement, and duration of labor, or indications for cesarean sections.

Table 1: Maternal complications

Maternal complications	Group 1 (n=50)	Group 2 (n=50)	P value
No Complications	46	46	1
Hyperstimulation	0	3	0.07
Headache and Dizziness	4	0	0.04
PPH	0	1	0.314

Table 2: Oxytocin requirement

Oxytocin requirement	Group 1 (n=50)	Group 2 (n=50)	P value
Yes	15	20	0.139
No	35	30	

Table 3: Duration of labor

Duration of labor (min)	Group 1 (n=50)	Group 2 (n=50)	P Value
Stage 1 Duration	248.3±173.25	300.4±154.88	0.118
Stage 2 Duration	28.7±21.169	33.5±24.04	0.291
Stage 3 Duration	5±0	5.06±0.24	0.08
Total Duration	277±194.4	333.9±178.9	0.131

Table 4: Indications for LSCS

Indications for LSCS	Group 1 (n=50)	Group 2 (n=50)	P Value
Acute Fetal Distress (AFD)	2	1	0.981
Failed Induction	6	3	
Meconium Stained Liquor	5	3	

DISCUSSION

The findings of this study contribute to the growing body of evidence supporting the use of ISMN in combination with misoprostol for labor induction. Misoprostol alone, while effective, is associated with adverse effects like uterine hyperstimulation, which can lead to fetal distress and other complications. By adding ISMN, a nitric oxide donor that promotes cervical ripening without inducing contractions, this study aimed to improve the safety profile and effectiveness of labor induction protocols [10].

One of the key observations in this study was the reduction in maternal headaches and dizziness in the ISMN group. This aligns with previous research suggesting that ISMN, due to its vasodilatory properties, can mitigate some of the side effects associated with misoprostol. However, it is noteworthy that there was no significant difference in the incidence of uterine hyperstimulation or postpartum hemorrhage between the two groups. This suggests that while ISMN can reduce certain maternal side effects, it does not necessarily impact all potential complications of misoprostol [11, 12].

The reduced need for oxytocin augmentation in the ISMN group is another important finding. Oxytocin, though effective in strengthening contractions, carries its own risks, including uterine hyperstimulation and fetal distress. The reduced reliance on oxytocin in the ISMN group indicates that ISMN might enhance the natural progression of labor, reducing the need for additional pharmacological intervention. This can be particularly beneficial in settings where close monitoring of labor is challenging or where minimizing medication use is preferred [13, 14].

Regarding neonatal outcomes, the study found no significant differences between the two groups in terms of birth weight, APGAR scores, or NICU admissions. This is a reassuring finding, as it indicates that the addition of ISMN does not adversely affect neonatal health. Maintaining similar neonatal outcomes while improving maternal safety and comfort highlights the potential of ISMN as a valuable adjunct in labor induction protocols [15].

The total duration of labor, while shorter in the ISMN group, did not reach statistical significance. This could be due to the relatively small sample size, and larger studies may be needed to confirm this trend. However, the observed trend towards shorter labor duration is promising and warrants further investigation.

This study's strengths include its randomized, double-blind design, which minimizes bias and enhances the reliability of the findings. The comprehensive assessment of both maternal and neonatal outcomes provides a holistic view of the safety and efficacy of the induction agents. However, the study also has limitations, including its single-center design and relatively small sample size, which may limit the generalizability of the findings.

In conclusion, this study provides evidence that ISMN, when used in combination with misoprostol, can enhance labor induction protocols by reducing certain maternal complications and the need for oxytocin augmentation without adversely affecting neonatal outcomes. These findings support the inclusion of ISMN in labor induction protocols, offering a potential improvement in the management of labor induction. Further large-scale, multi-center studies are recommended to confirm these findings and facilitate the development of optimized clinical guidelines.

CONCLUSION

The combination of isosorbide mononitrate and misoprostol for labor induction shows promise in enhancing maternal safety and efficacy. By reducing maternal complications such as headaches and dizziness and decreasing the need for oxytocin augmentation, this combination provides a viable alternative to misoprostol alone. Neonatal outcomes remain comparable, indicating no added risk. Future studies with larger sample sizes are necessary to confirm these results and potentially update clinical practice guidelines for labor induction.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Kelly AJ, Kavanagh J, Thomas J. Castor oil bath and/or enema for cervical priming and induction of labor. Cochrane Database Syst Rev. 2013;7:CD003099. doi: 10.1002/14651858.CD003099.pub2, PMCID PMC7138266.
2. Karim SM, Trussell RR, Patel RC, Hillier K. Response of the pregnant human uterus to prostaglandin F2 alpha-induction of labour. Br Med J. 1968;4(5631):621-3. doi: 10.1136/bmj.4.5631.621, PMID 5723367.
3. Maul H, Longo M, Saade GR, Garfield RE. Nitric oxide and its role during pregnancy: from ovulation to delivery. Curr Pharm Des. 2003;9(5):359-80. doi: 10.2174/1381612033391784, PMID 12570814.
4. Sanchez Ramos L, Kaunitz AM, Del Valle GO, Delke I, Schroeder PA, Briones DK. Labor induction with the prostaglandin E1 methyl analogue misoprostol versus oxytocin: a randomized trial. Obstet Gynecol. 1993;81(3):332-6. PMID 8437780.
5. Fuchs AR, Fuchs F, Husslein P, Soloff MS. Oxytocin receptors in the human uterus during pregnancy and parturition. Am J Obstet Gynecol. 1984;150(6):734-41. doi: 10.1016/0002-9378(84)90677-x, PMID 6093538.
6. Hirst J, Chibbar R, Mitchell B. Role of oxytocic in the regulation of uterine activity during pregnancy and in the initiation of labor. Semin Reprod Endocrinol. 1993;11:221-33.
7. Keirse MJ. Prostaglandins in preinduction cervical ripening. Meta-analysis of worldwide clinical experience. J Reprod Med. 1993;38(1) Suppl:89-100. PMID 8429533.
8. Theobald GW. The use of posterior pituitary extracts in physiological amounts in obstetrics. BMJ. 1948;11:123-7.
9. Page EW. Response of human pregnant uterus to pitocin tannate in oil. Experimental Biology and Medicine. 1943;52(3):195-7. doi: 10.3181/00379727-52-14084.

10. Cunningham FG, Leveno KJ, Bloom SL. Williams obstetrics. 24th ed. New York: McGraw-Hill Education/Medical; 2014.
11. Kavanagh J, Kelly AJ, Thomas J. Breast stimulation for cervical ripening and induction of labor. Cochrane Database Syst Rev. 2005;3.
12. Jozwiak M, Bloemenkamp KW, Kelly AJ, Mol BW, Irion O, Boulvain M. Mechanical methods for induction of labour. Cochrane Database Syst Rev. 2012;3(3):CD001233. doi: 10.1002/14651858.CD001233.pub2, PMID 22419277.
13. Kavanagh J, Kelly AJ, Thomas J. Sexual intercourse for cervical ripening and induction of labour. Cochrane Database Syst Rev. 2001;2001(2):CD003093. doi: 10.1002/14651858.CD003093, PMID 11406072.
14. DE Ribes C. De l'accouchement provoque, dilatation du canal ge nital a l'aide de ballons introduits dans la cavite uterine pendant la grossesse. Paris: Steinheil; 1988.
15. Thomas J, Kelly AJ, Kavanagh J. Oestrogens alone or with amniotomy for cervical ripening or induction of labour. Cochrane Database Syst Rev. 2001;2001(4):CD003393. doi: 10.1002/14651858.CD003393, PMID 11687200.