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Efficacy of Intravaginal Administration of Isosorbide Mononitrate Together with Misoprostol versus Misoprostol Alone in The Induction of Labor in Postdate Women

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ABSTRACT

Background: Many studies proved that the administration of isosorbide mononitrate in combination with misoprostol might increase the success rates of abortion and delivery and help in the reduction of side effects of misoprostol.

Objective: To ascertain if misoprostol and intravaginal isosorbide mononitrate (IMN) intravaginally administered together can reduce the time needed to induce labor in postdate women.

Patients and Methods: One hundred postdate pregnant women with unfavourable cervixes who were due for labor induction, in Labor Ward, Ain Shams Maternity Hospital, were selected and randomly allocated to receive IMN 40 mg with misoprostol 25 µg or misoprostol 25 µg alone by vaginal administration. The duration of induction to the active phase is the primary result. To match the two groups, Bishop's score, gestational age, parity, and mother's age were taken into consideration.

Results: Women who took IMN with misoprostol had substantially shorter induction to active phase lengths (10.6±1.5 against 8.8±1.3 p 0.001) and from the beginning of induction to the time of delivery (17.2±2.3 versus 12.2±2.7 p 0.001) than those who got misoprostol alone. There was no statistically significant difference between the two groups regarding uterine contractile anomalies including tachysystole, hypertonus, and hyperstimulation. The risk of maternal side effects such flushing, hypotension, tachycardia, diarrhea, or postpartum hemorrhage was not significantly different between the two groups, despite the presence of a substantial variation in the rate of headache. 2 patients (4%) had headache in group A (misoprostol alone), compared to 15 (or 30%) in group B (IMN with misoprostol).

Conclusion: The use of IMN in combination with misoprostol in the induction of labor is effective in the reduction of the duration of induction and safe on the mother and fetus.

Keywords: Misoprostol, Induction, IMN.

INTRODUCTION

Even if the perfect method for starting labor is yet aways ahead, it is now a crucial part of contemporary obstetrics. The outcome of labor induction is determined by a number of factors. A ripening cervix is one of the essential components to a successful induction. The inflammatory cascade and the active cervical ripening process are similar. A number of degradative enzymes breakdown and disorganize the collagen framework, increase the amount of extracellular and intracellular water, reorganise the extracellular matrix proteins, and raise the water content of the cells [(1)].

Typically, cervical ripening medicines are used to treat women with an unripened cervix, which is commonly defined as having a Bishops score of less than six. Prostaglandins (PGs) have been the primary cervical ripening agents since the late 1960s, and they have been administered to induce labor in a variety of methods with comparable outcomes. Even if there are a number of additional agents, pharmacological and non-pharmacological (mechanical) techniques have been utilised to speed up cervical ripening and induce labor [(2)].

Nevertheless, in recent years misoprostol [(3,4)], and donors of nitric oxide (NO) have both been used to soften the cervix and start labor[(5,6)]. Contrary to prostaglandins, NO donors boost rather than reduce uterine blood flow and promote rather than inhibit uterine myometrial contractions. Because of this, NO donors like IMN appear to be the best cervical ripening agent before labor induction [(7)]. Numerous studies have also shown that IMN given vaginally has no discernible negative effects on either hemodynamics of mother or fetus [(8)]. Furthermore, there aren't many research that have looked into how well NO donors work for cervix priming and labor induction.

AIM OF THE WORK

To determine if IMN and misoprostol are effective at cutting the time it takes for post-date women to induce labor.

MATERIALS AND METHODS

The study's participants were 100 post-term pregnant women who were hospitalized for labor induction at Ain Shams Maternity Hospital between January and July 2019. This study employed a prospective, randomised, double-blind, controlled trial.

Age (twenty, thirty-five years), a single fetus, gestation age > 40 weeks based on LMP or first-trimester ultrasonography, not in labor (six contractions in 1 hour), Bishop's score seven, and no medical condition were included as inclusion criteria.

Gestational age 40 weeks, ripe cervix (Bishop's score > 6), membranes rupture, suspicious with chorioamnionitis, placenta previa, or unexplained vaginal bleeding, hx of major uterine operation, hypertonic uterine pattern, severe preeclampsia, renal or hepatic dysfunction, contraindications to receiving PG, and general medical disorder diseased women (e.g., diabetes, hypertension), were considered as exclusive criteria.

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The treatment plan for the study's subject population, which was randomly split into two groups, was packaged, sealed, and numbered by a neutral medical staff member working under the direction of Department clinicians. The recruited women in Group A received misoprostol pill a (25 μg) through vagina in the posterior fornix every four hours, up to a maximum of five doses. The recruited women in Group B received a maximum of 5 doses of 40 mg of IMN administered through the vaginal in the posterior fornix every 4 hours along with a tablet of misoprostol (25 μg).

The patients were reevaluated four hours after the initial application, and depending on the clinical response, either no medication was given, a second dose of misoprostol (25 μg), or IMN (40 mg) and misoprostol (25 μg), respectively, were given to the two groups. The medicine dose was repeated every 4 hours for as long as the Bishop score is higher than 6, or up to the maximum of 5 doses (125 μg + 160 mg). If six hours have passed after the fifth dosage and the Bishop score has not increased, the induction was judged ineffective, and the patient was sent in for a CS birth.

By using cardiotocography, patients' fetal heart sounds were monitored. The departmental procedure for labor induction was followed, and fetal heart rate and uterine activity were monitored. Every 30 minutes during the first two hours following the start of therapy, the mother's blood pressure and pulse rate were measured. Augmentation was done by oxytocin drip 0.5 – 1 mUnit/minutes then titrate 1-2 mUnit/minutes every 30 minutes until 3 or more uterine contractions of 40 - 60 seconds in 10 minutes. Artificial membrane rupture was done when the cervix is 4 – 6 cm dilated according to the station of the fetal head. Maternal demographic profile was recorded. Regarding labor characteristics, we looked at labor length, unfavourable maternal effects, newborn outcomes, and the interval between induction and actual labor.

Sample size:

Using the STATA programme, setting alpha error at 5 percent and power at 80 percent. Results from a prior study [9] indicated that the mean induction to active phase interval for groups A and B was 8.6 ± 1.7 and 5.6 ± 1.7, respectively, with a mean difference of (3 hours), Assuming a lower difference (1 hour) between the two groups produced a minimal sample of (46) cases per group; total (92) cases and to avoid drop out of patients (4) cases were added to each group so each group contained (50) cases; total (100) cases.

Ethical approval:

Ain Shams Medical Ethics Committee of the Ain Shams Faculty of Medicine gave its approval to this study. All participants gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

SPSS version 20.0 was used to analyse the data that were obtained. Qualitative data were represented using frequency and percentage and were compared by Chi square test (X^2). Quantitative data were expressed as mean and standard deviation (SD) and were compared by the independent samples t-test. The following statistical tests were also used: Odds ratio, Relative risk (risk ratio), Kaplan-Meier survival analysis, and Log rank test. P values below 0.05 were considered significant.

RESULTS

In terms of demographic characteristics, the mothers of the two groups were equivalent in age, parity, gestational age, and the body mass index (Table 1).

Table (1): Comparison between group A and group B according to demographic data

Variable	Group (A) n=50 mean±SD m	Group (B) n=50 mean±SD	P
Age (years)	26.6±2.0	25.9±2.0	0.083
Gestational age (weeks)	41.2±0.9	41.1±0.7	0.537
BMI (kg/m^2)	30.4±2.3	29.8±2.7	0.235
Parity	2.8±1.04	2.4±0.9	0.117

According to the first Bishop score, table (2) doesn't demonstrate any statistically significant differences between the groups.

Table (2): Correlation of groups A and B based on the initial Bishop score

Variable	Group (A) n=50 mean±SD m	Group (B) n=50 mean±SD	P
Initial Bishop score	3.8±0.7	3.7±0.5	0.122

Group B had a lower statistically significant mean than group A in terms of the mean times from induction to the active phase interval and the mean times from induction to delivery, but there was not a significant distinction between the two groups when it comes to the manner of delivery (Table 3).

Table (3**):** Comparing group A with group B based on the results of the labor

Variable	**Group (A) n=50 mean±SD**	**Group (B) n=50 mean±SD**	**P**
Average time from induction to active phase	10.6±1.5	8.8±1.3	0.037*
Mean duration of induction to delivery	17.2±2.3	12.1±2.7	0.021*

Mode of Delivery	**Group (A) n (%)**	**Group (B) n (%)**	**Odds ratio**	**Relative risk**	**NNT**	**p-value**
Vaginal delivery	41 (82%)	44 (88%)	1.609 (0.527-4.919)	1.500 (0.577-3.901)	16.667	0.401
Caesarean section	9 (18%)	6 (12%)				

*: Significant

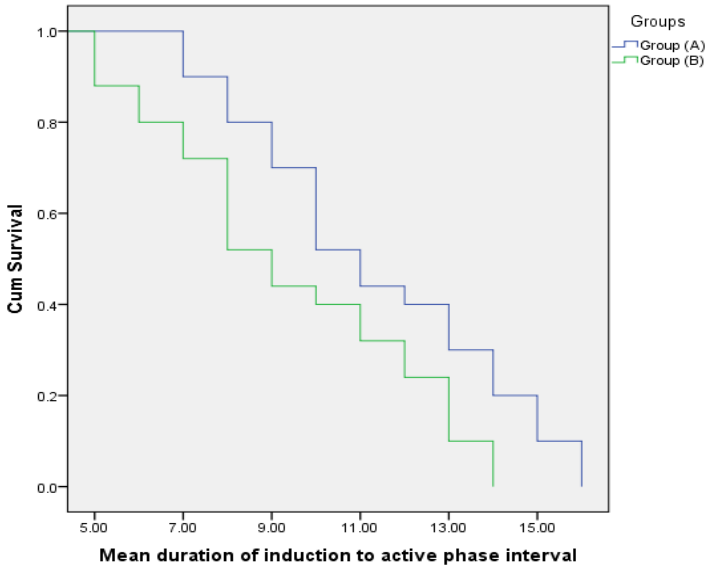

Fig. (1**):** Kaplan-Meier survival curves in Group A and group B

Table (4) shows statistically significant difference in headache frequency between groups. There was no obvious difference between the two groups in terms of uterine contractile abnormalities, in the incidence of flushing, hypotension, tachycardia, diarrhea, and bleeding after delivery.

Table (4): Comparing between group A and group B in terms of any negative consequences on the mother

Maternal Side Effects		**Group (A) n=50 n (%)**	**Group (B) n=50 n (%)**	**P**
a) Flushing		0 (0%)	1 (2%)	0.135
b) Hypotension		0 (0%)	0 (0%)	0.148
c) Tachycardia		0 (0%)	0 (0%)	0.895
d) Headache		2 (4%)	15 (30%)	0.035*
e) Diarrhea		0 (0%)	0 (0%)	0.277
f) Post-Partum hemorrhage		1 (2%)	0 (0%)	0.206
g) Uterine contractile abnormalities	Tachysystole	0 (0%)	0 (0%)	1.000
	Hyperstimulation	2 (4%)	1 (2%)	0.892
	Hypertonus	0 (0%)	0 (0%)	1.000

*: Significant

Table (5) reveals that there was no statistically significant difference between both groups in terms of weight, Apgar scores at one and five mins, or NICU admission.

Table (5): Based on fetal outcome, group A and group B are compared

Variable	Group (A) n=50 mean±SD	Group (B) n=50 mean±SD	P
Weight (kg)	2.88±0.53	2.82±0.40	0.253
Apgar one minute	7.7±1.4	8.4±1.2	0.186
Apgar five minutes	8.9±0.4	9.0±0.2	0.405
Variable	**Group (A) N (%)**	**Group (B) N (%)**	**P**
NICU admission	3 (6%)	1 (2%)	0.235

DISCUSSION

Many studies proved that the administration of isosorbide mononitrate in combination with misoprostol might increase the success rates of abortion and delivery and help in the reduction of side effects of misoprostol [(10)].

Many studies talked about the comparison between prostaglandins and NO donors in the cervical ripening during labor induction [(8-10)]. Other studies proved that the nitric oxide donors are more effective than the placebo in the ripening of the cervix [(11)].

The main point of strength in our study is that we had blinding in our methodology and the blinding leading to reduction in the bias rate of the results of the study, and **Noor *et al.*** [(9)] and **Abdellah *et al.*** [(12)] studies didn't have blinding in methodology.

There were some limitations represented in two points; the first one was the small size of our sample (100 cases) in comparison with **Abdellah *et al.*** [(12)] study (290), and the second one, we didn't use placebo instead of isosorbide mononitrate in group of induction with misoprostol alone in comparison with **Abdellah *et al.*** [(12)] study, which used placebo.

In the current study, the mean time from the start of induction to delivery was (12.1 ± 2.7) in group B vs (17.2 ± 2.3) in group A. The mean time from the commencement of induction to active phase interval was (8.8 ± 1.3) in group B versus (10.6±1.5) in group A. The difference between these results was statistically significant.

This result matched with **Noor *et al.*** [(9)], who studied 100 postdate pregnant women. The study was a randomised clinical trial in which the pregnant women were split into two groups and were given either 50 µg vaginally or 40 mg of isosorbide mononitrate every six hours for a total of four doses in the second group. The results of this study concluded that there was the significantly shorter duration of induction to the active phase (8.6 ± 1.7 versus 5.6 ± 1.7 p<0.001) and induction to labor interval (20.8 ± 2.9 versus 14.2 ± 2.7, p<0.001) in misoprostol and IMN group versus misoprostol alone.

Additionally, this outcome was consistent with **Abdellah *et al.*** [(12)], whose study involved 290 full-term pregnant women. In this randomised clinical trial, the pregnant women were divided into two groups and given either placebo or misoprostol 50 µg intravaginally or 40 mg of IMN every six hours up to four times. The results of this study concluded a statistically significant shorter induction duration than the active phase (10.97 ± 2.87 versus 13.91 ± 2.16, p<0.001) and induction to labor interval (19.56 ± 3.96 23 ± 2.62, p<0.001) in misoprostol and IMN group versus misoprostol alone.

These findings did not agree with those of **Collingham *et al.*** [(13)], whose investigation involved pregnant women whose gestational ages ranged from 32 to 42 weeks. The study was a prospective, randomised experiment in which pregnant women were separated into two groups and given IMN 40 mg intravenously along with 50 µg misoprostol orally in the second group. The interval between induction and delivery for the two groups did not significantly differ.

This result didn't match with **Wölfler *et al.*** [(14)], who studied nulliparous pregnant women at term. The study was a prospective randomized trial in which the pregnant women were divided into two groups; one group were administrated 3 mg dinoprostone vaginally and the second group were administrated 3 mg dinoprostone in addition to isosorbide mononitrate 40 mg vaginally every 12 hours for 4 doses. Between the two groups, there was no discernible difference in the time from induction until delivery.

In the current study, according to the caesarean section rates in group A, which was 9 cases, and group B, which was 6 instances, statistically significant difference between the two groups was not found. This result matched with **Noor *et al.*** [(9)] and **Abdellah *et al.*** [(12)]**.** While in the study of **Chanrachakul *et al.*** [(5)], despite a greater proportion of non-reassuring FHR in the misoprostol group (9 (56 percent) versus 3 (15 percent)), there was a higher rate of dystocia in the IMN 9 (45%) versus 6 (37.5%) in the misoprostol group.

When it comes to uterine contractile abnormalities, which included tachysystole, hypertonus, and hyperstimulation, there was not a significant distinction between the two groups in this research. This result matched with **Noor *et al.*** [(9)] and **Abdellah *et al.*** [(12)]**.**

In the present study, there was no discernible difference between the two groups according to the maternal side effects in form of flushing, hypotension, tachycardia, diarrhea and postpartum hemorrhage, but there was a substantial difference in headache frequency. In group B (IMN and misoprostol) 15 (30%) versus group

A (misoprostol alone) 2 (4%). This result was matched with **Abdellah *et al.* [12].** This result didn't match with **Noor *et al.* [9]**. This result showed that there was no discernible difference between the two groups in terms of the adverse effects on the mother.

In our research, there was no significant difference between the two groups in terms of the fetal outcome as determined by birth weight, Apgar scores at 1 and 5 minutes, and admission to the neonatal critical care unit. This result was matched with **Noor *et al.* [9]** and **Abdellah *et al.* [12].**

CONCLUSION

The use of IMN in combination with misoprostol in the induction of labor is effective in the reduction of the duration of induction and safe on the mother and fetus.

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REFERENCES

1. **Meier K, Parrish J, D'Souza R (2019):** Prediction models for determining the success of labor induction: A systematic review. Acta Obstet Gynecol Scand., 98(9):1100-1112.
2. **Kelly A, Kavanagh J, Thomas J (2003):** Vaginal prostaglandin (PGE2 and PG F2a) for induction of labour at term. doi: 10.1002/14651858.CD003101.
3. **Wing D, Paul R (1996):** A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. Am J Obstet Gynecol., 175: 158-164.
4. **Nunes F, Rodrigues R, Meirinho M (1999):** Randomized comparison between intravaginal misoprostol and dinoprostone for induction of labor. Am J Obstet Gynecol., 181: 626-629.
5. **Chanrachakul B, Herabutya Y, Punya-Vachira P (2002):** Randomized trial of isosorbide mononitrate versus misoprostol for cervical ripening at term. Int J Gynaecol Obstet., 78: 139-145.
6. **Ekerhovd E, Bullarbo M, Andersch B *et al.* (2003):** Vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening at term: A randomized controlled study. Am J Obstet Gynecol., 189: 1692-1697.
7. **Ghosh A, Lattey K, Kelly A (2016):** Nitric oxide donors for cervical ripening and induction of labour. Cochrane Database Syst Rev., 12: CD006901. doi: 10.1002/14651858.CD006901.
8. **Nicoll A, Machenzie F, Greer I *et al.* (2001):** Vaginal application of the nitric oxide donor isosorbide mononitrate for preinduction cervical ripening: A randomized controlled trial to determine effects on maternal and fetal hemodynamics. Am J Obstet Gynecol., 184: 958-64.
9. **Noor N, Sharma A, Parveen S *et al.* (2017):** Intravaginal administration of misoprostol alone versus misoprostol and isosorbidemononitrate for cervical ripening and labour induction. Journal of Applied and Advanced Research, 2: 37-42.
10. **Abd-El-Maeboud Karim H, Ghazy A, Nadeem A *et al.* (2008):** Effect of vaginal pH on the efficacy of vaginal misoprostol for induction of midtrimester abortion. Journal of Obstetrics and Gynaecology Research, 34: 78-84.
11. **Bullarbo M, Orrskog M, Andersch B *et al.* (2007):** Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labor induction postterm: a randomized controlled study. American Journal of Obstetrics and Gynecology, 196: 50. doi: 10.1016/j.ajog.2006.08.034.
12. **Abdellah M, Hussien M, Aboalhassan A (2011):** Intravaginal administration of isosorbide mononitrate and misoprostol for cervical ripening and induction of labour: a randomized controlled trial. Archives of Gynecology and Obstetrics, 284: 25-30.
13. **Collingham J, Fuh K, Caughey A *et al.* (2010):** Oral misoprostol and vaginal isosorbide mononitrate for labor induction: a randomized controlled trial. Obstetrics & Gynecology, 116: 121-126.
14. **Wölfler M, Facchinetti F, Venturini P *et al.* (2006):** Induction of labor at term using isosorbide mononitrate simultaneously with dinoprostone compared to dinoprostone treatment alone: A randomized, controlled trial. American Journal of Obstetrics and Gynecology, 195: 1617-1622.