Original Article

Comparative Study Between Oral and Vaginal Misoprostol for Induction of Labor in Nulliparous Pregnant Women at or Beyond Completed 41 Weeks

Mahmoud Abdelhameed, Heba El Sawah, Marwa Sharaf, El Sayed Omran and Sally A. El-Attar

Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Egypt.

ABSTRACT

Background: Misoprostol applied vaginally has been shown to be an effective method of inducing labor; nevertheless, pregnant women may be resistant to digital examination and there is a possibility of infection. Therefore, oral misoprostol was attempted to induce labor.

Objective: The aim of this study was to evaluate the safety and effectiveness of vaginal versus oral misoprostol for inducing labor in nulliparous women at or after 41 completed weeks of pregnancy.

Materials and Methods: Eighty nulliparous women, divided into two groups, were eligible for labor induction at 41 weeks or more. In Group 1, 40 pregnant women got 25 µg vaginal misoprostol every six hours until a response was achieved, with a maximum of four doses. For Group 2, 40 pregnant women took oral misoprostol at a dose of 25 µg every six hours until a response was obtained, with a maximum of four doses.

Results: Oral and vaginal misoprostol were comparable regarding the duration from inducing labor to onset of the active stage, interval from inducing labor to the delivery, cesarean deliveries, dosage requirements, and maternal and neonatal outcomes. However, the process of labor augmentation with oxytocin was dramatically reduced in the vaginal group.

Conclusion: 25 µg oral misoprostol is as effective and safe as 25 µg vaginal misoprostol for inducing labor in nulliparous women with an unripe cervix at or beyond completed 41 weeks.

Key Words: Labor induction, misoprostol, nulliparous women.

Received: 29 November 2023, **Accepted:** 4 December 2023

Corresponding Author: Mahmoud Ahmed Ismail Abdelhameed, MD, Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Egypt, **Tel.:** 01003457468, **E-mail:** Dr_mahmoud_ahmed2015@hotmail.com

ISSN: 2090-7265, February 2024, Vol.14, No. 1

INTRODUCTION

Labor induction is performed for a variety of reasons, including those pertaining to the mother and the fetus. Prolonged pregnancy is one of the most prevalent reasons for this procedure[1]. Recent research has shown that there is an increased risk of perinatal morbidity and maternal complications if the pregnancy continues past 41 weeks[2]. Therefore, there is mounting evidence supporting labor induction at forty-one weeks, rather than the current practice of expectant management[3].

Prenatal use of the prostaglandin E1 analogue "misoprostol", while helpful in preventing stomach ulcers, results in uterine muscle contractions. By capitalizing on this side effect, researchers have proven that misoprostol is superior to the traditional induction approaches, leading to shorter induction-to-delivery intervals without an increase in unfavorable outcomes[4].

It is advantageous in that it is inexpensive, unaffected by changes in temperature, and simple to deliver via a variety of methods, including vaginal, oral, and sublingual administration[5].

Oral misoprostol may have different pharmacokinetics than vaginal misoprostol, which may account for the observed differences in clinical outcomes among the 2 administration routes. The half-life of misoprostol, an active metabolite of oral misoprostol, is only 20-40 minutes, and its absorption from the gastrointestinal tract is fast, peaking at 15 minutes. Misoprostol is eliminated rapidly in the first 120 minutes and then at a slower rate for the rest of the time. In contrast, misoprostol's concentration in the blood rises slowly after the vaginal insertion, reaching a peak 70-80 minutes later and then being removed slowly, with plasma levels remaining detectable 6 hours later[6].

The aim of the research was to evaluate the safety and effectiveness of vaginal versus oral misoprostol for inducing labor in nulliparous women at or after 41 weeks of gestation.

 DOI:10.21608/EBWHJ.2023.251942.1279

PATIENTS AND METHODS

This randomized clinical trial was conducted in the casualty department of obstetrics and gynecology (Kasr El-Aini Hospital -Faculty of medicine – Cairo University) during the period from December 2021 to the end of May 2022. Eighty nulliparous pregnant women were recruited for induction of labor at or after 41 weeks. The ClinicalTrials.gov registration number for this study is NCT05696574, and the Cairo University Research Ethics Committee approved it (MS-35-2022).

Sample size calculation: Induction-to-delivery intervals for oral and vaginal misoprostol-treated women were contrasted to determine the sample size. In the previous research[7], the mean ± SD induction-to-delivery interval for oral misoprostol was 12 ± 0.7 hours, while for vaginal misoprostol, it was 10 ± 0.8 hours. We determined that a minimum sample size of 36 women per group was required to detect a 0.5-hour difference with 80% power at the $\alpha = 0.05$ level using the Student test for independent samples. Sample size calculation was done using PS Power and Sample Size Calculations 3.0.11 for MS Windows (William D. Dupont and Walton D., Vanderbilt University, Nashville, Tennessee, USA).

Inclusion criteria: Woman is considered a nullipara if she has never carried a pregnancy beyond 20 weeks. She might not have been pregnant at all, or she might have had one or more abortions or an ectopic pregnancy[8]. Other criteria include single living pregnancy, cephalic vertex presentation, reactive fetal non-stress test (NST) and Bishop's score of six or less.

Exclusion criteria: Fetal macrosomia (greater than 4kg). Intrauterine growth restriction (IUGR) [Estimated fetal weight (EFW) less than the tenth percentile for gestational age][9]. Oligohydramnios [Amniotic fluid index (AFI) less than the 5th percentile] or ruptured membrane. Uterine contractions on a regular basis. Previous uterine scarring or any other contraindication to vaginal birth, such as placenta previa (full or partial covering of the internal cervical os with the placenta)[10]. Any maternal diseases or pregnancy-related medical conditions that pose a risk to the mother's or her fetus's health or life.

After explaining the goal of the research, all participants provided informed consent to participate in the study. All cases were subjected to: a thorough history, complete physical and obstetrical examination. Vaginal examination was performed to assess the Bishop's score. Obstetric ultrasound was done to evaluate the fetal weight, amniotic fluid and rule out any fetal abnormalities.

Candidates are divided into two equal groups:

Group 1: involved forty pregnant women who were given vaginal misoprostol (put in the posterior vaginal fornix) at a dose of 25 micrograms (µg) to be repeated every six hours if no response was obtained with a maximum of four doses of the medication.

Group 2: Forty pregnant women took oral misoprostol at a dose of 25 µg, with further doses given every 6 hours if necessary (up to a total of 4 doses).

The following conditions resulted in the subsequent dose being withheld: the active phase of labor which was characterised by cervical dilation greater than 3 cm and regular contractions in the uterus, the patient had at least 3 regular uterine contractions in ten minutes, the cervix was favorable for an amniotomy (Bishop's score greater than eight), or there were complications concerning either the pregnant woman or the fetus.

An amniotomy was carried out shortly after engagement of the fetal head and cervical dilatation greater than 3 cm. If the frequency of contractions was fewer than three per ten minutes, oxytocin augmentation was then administered.

Oxytocin was given 6 hours following the last dose of misoprostol, starting at the dose of one mU/minute and increasing by one mU/minute every 20 minutes until sufficient contractions occurred. If the induction failed (defined as an unfavourable cervix with a Bishop's score of equal or less than six after four doses of misoprostol, assessed six hours following the final dosage), caesarean section was performed.

Continuous Cardiotocography (CTG) monitoring of the uterine activity and fetal heart rate and rhythm was conducted for 20 minutes before the start of labor induction and before every dose. Frequency of intermittent fetal heart rate auscultation was 15 minutes in the first stage of labor and 5 minutes in the second stage. Uterine hyperstimulation and misoprostol adverse effects as nausea, diarrhoea, vomiting, and fever were listed.

Neonatal assessment included: Neonatal birth weight, Apgar score at one and five minutes and the need for transfer to neonatal intensive care unit (NICU). Abnormal perinatal outcomes consisted of one-min and five-min Apgar scores < 7 and NICU admission > 24 hours. The abnormal neonatal outcome category involved women who had at least one unsatisfactory result.

Outcomes:

Duration to onset of the active stage of labor was the main outcome. Secondary outcomes included: interval from labor induction to the delivery, delivery mode, the number of misoprostol doses administered, the number of pregnant women who received oxytocin and any maternal, fetal, or neonatal adverse events.

Statistical analysis:

The information was entered and coded using SPSS version 28 (IBM Corp., Armonk, NY, USA). Quantitative data were represented by mean and standard deviation, whereas qualitative data were summarized by frequency counts and percentages. When comparing the two groups, an unpaired t test was employed[11]. Sets of nominal or category variables were compared utilizing the Chi-square (x2) test. The exact test was applied when the expected frequency was below five[12].

RESULTS

Table (1) demonstrates that there was no discernible difference among the both groups concerning maternal age, BMI and number of previous abortions. There was no significant distinction among the both examined groups regarding Bishop score and estimated fetal weight (EFW) by ultrasound (U/S).

Table (2) shows that there was no significant distinction among the two studied groups concerning the number of needed doses of misoprostol. However, the incidence of use of oxytocin for augmentation was significantly lower in females who received vaginal misoprostol when compared with females who received oral misoprostol. There was no significant distinction among the both examined groups regarding the duration to onset of active stage of labor or the interval from induction to delivery.

Table (3) illustrates that 31 patients in the group 1 delivered vaginally while 9 patients delivered by cesarean section (CS) [3 failed inductions, 2 obstructed labors, 2 non-reassuring NSTs, 2 maternal complications]. On the other hand, 30 patients in the group 2 delivered vaginally while 10 patients delivered by CS [4 failed induction, 2 obstructed labor, 2 non-reassuring NST, 2 maternal complications]. There was no statistically significant variation in the incidence of maternal adverse events between the two groups.

Table (4) demonstrates that there was no discernible difference in the reported misoprostol adverse effects between the two study groups.

Table (5) shows that there was no significant variance among both groups regarding neonatal birth weight and adverse neonatal outcomes.

Table 1: Participants characteristics, Bishop score and EFW by U/S in group (1) versus group (2).

Item	Group 1 (vaginal) Mean ±SD	Group 2 (oral) Mean ±SD	*P value*
Maternal age (years)	24.8± 4.87	23.53±4.4	*0.223*
BMI (kg/m²)	30.13±2.16	29.95±1.68	*0.687*
Previous abortions	0.18± 0.50	0.20±0.56	*0.834*
Bishop score	5.45±0.68	5.32±0.62	*0.390*
EFW by U/S (gm)	3609±135.34	3559±232.62	*0.244*

Table 2: Comparison among study groups as regard number of needed doses of misoprostol, augmentation with oxytocin, duration to onset of active stage of labor and induction to delivery interval.

Item	Group 1 (vaginal)	Group 2 (oral)	*P value*
Number of misoprostol doses (Mean ±SD)	2.75 ± 1.03	2.7 ± 1.09	*0.834*
Oxytocin augmentation (Number of cases)	12 (30%)	25 (62.5%)	*0.004*
Duration to onset of active stage of labor (hours) (Mean ±SD)	13.89±5.44	13.14±5.96	*0.574*
Induction to delivery interval (hours) (Mean ±SD)	20.84±6.18	19.87±6.21	*0.489*

Table 3: Comparison between study groups regarding failed induction, vaginal delivery and maternal obstetric adverse events.

Item	Group 1 (vaginal) Number of cases (%)	Group 2 (oral) Number of cases (%)	*P value*
Vaginal delivery	31 (77.5%)	30 (75%)	*1*
Failed induction	3 (7.5%)	4 (10%)	*1*
	Maternal obstetric adverse events		
Antepartum bleeding	2 cases (5%)	2 cases (5%)	*1*
Postpartum bleeding	3 cases (7.5%)	4 cases (10%)	*1*
Uterine Hyperstimulation	3 cases (7.5%)	2 cases (5%)	*1*

Table 4: Adverse effects of misoprostol between the two study groups.

Item	Group 1 (vaginal)	Group 2 (oral)	*P value*
Nausea	5 cases (12.5%)	7 cases (17.5%)	*0.531*
Vomiting	4 cases (10%)	3 cases (7.5%)	*1*
Diarrhoea	4 cases(10%)	2 cases (5%)	*0.675*
Hyperthermia	2 cases (5%)	2 cases (5%)	*1*

Table 5: Neonatal birth weight and adverse neonatal outcome in both groups.

Variable	Group 1 (vaginal)	Group 2 (oral)	*P value*
Neonatal birth weight (gm) (Mean ±SD)	3657.5 ± 112.97	3662.5 ± 107.86	*0.840*
Adverse neonatal outcome			
Apgar score at 1 min <7	8 cases (20%)	6 cases (15%)	*0.556*
Apgar score at 5 min <7	1 case (2.5%)	2 cases (5%)	*1*
NICU admission >24 hours	1 case (2.5%)	2 cases (5%)	*1*

DISCUSSION

The use of medical methods to induce labor has increased globally in recent decades. More than twenty percent of births in the United States and Europe are induced. Without a corresponding increase in resources in the delivery wards, the induction rate in Finland has doubled in the past two decades and is now at about 27%. As a result, there is a rising need for a safe and effective induction technique that may bring about a vaginal delivery without endangering the health of either the mother or the fetus[13].

The findings of our research indicated that there was not a substantial distinction between the oral and vaginal misoprostol regarding either the duration from induction to onset the active stage of labor or induction to the delivery interval.

There was no statistically distinction among the proportion of women who delivered vaginally within the first day: 31 (77.5%) in the vaginal group and 30 (75%) in the oral group. When comparing between the two study groups, there was no any substantial variations in the number of misoprostol doses required. However, oxytocin augmentation was needed in 25 (62.5%) cases in the oral group in comparison to 12 (30%) cases in the vaginal study group. There was no statistically significant distinction among the vaginal and oral groups in terms of maternal or neonatal complications.

According to the findings of our research, the effectiveness of 25 micrograms of misoprostol delivered vaginally versus 25 micrograms of oral misoprostol in terms of our primary objective is equivalent. In the current research, the usage of oxytocin was found to be much less common in the misoprostol vaginal group as opposed to the misoprostol oral group. Aside from that, there were no distinctions noted among the 2 groups in terms of the time until the beginning of the active stage of labor, the interval between induction and delivery, the rate of cesarean section, or poor outcomes for the mother or the neonate.

In line with our study, Mehta and colleagues carried out a research on 100 women who needed induction. Both oral misoprostol at 25 micrograms and vaginal misoprostol at twenty-five micrograms every four hours, up to a maximum of five doses, have been demonstrated to induce labor safely and effectively. In contrast to our findings, they claimed that the vaginal approach takes less time and requires fewer dosages than the oral route[14].

Consistent with our findings, Ambika and his coworkers studied two groups of one hundred female patients each. Misoprostol was administered in two different ways: vaginally in one group and orally in the other. In both groups, participants received 50 micrograms every six hours, for a total of four doses. The newborn outcomes of the two groups in the Ambika *et al*. study did not differ statistically. However, in contrast with our study, Ambika and his co-workers reported that the number of misoprostol doses necessary for a favorable labor results in the vaginal group was much lower than the amount required in the oral study group. Moreover, the interval from induction to the delivery was shorter in the vaginal study group than in the oral group. They concluded that when provided in equal amounts, vaginal misoprostol delivery is more efficacious than oral misoprostol administration in inducing labor[15].

In contrast with our study, Bagariya and colleagues study on 196 women showed that the vaginal route is favorable compared to the oral route for inducting labor when used at the same dosage of 25 µg in primigravida; they reported a lower number of dosages required, a shorter induction to delivery interval, a lower incidence of failed induction, a lower rate of caesarean deliveries,

a lower requirement of labor augmentation with oxytocin, and fewer maternal adverse effects of the drug in the vaginal route of administration compared to the oral route. Bagariya and colleagues attributed the increased efficacy related to vaginal misoprostol to the local cervical effect of the vaginal administration[16].

Furthermore, contrary to our findings, Kaur and colleagues' study of 100 pregnant women who were admitted for induction of labor showed that oral misoprostol had a superior safety record than the vaginal route due to a significantly higher incidence of uterine hyperstimulation in the vaginal group, even though there were no notable variations in the outcomes for mothers and newborns[17].

Although the current study has accomplished its goals, but there are still certain limitations. The small sample size led to low statistical power in between the groups of comparison. Additional limitations might include the absence of blinding in our investigation as each participant has been informed of the study's purpose. In order to be more representative and remove any potential bias, future research should consider expanding the study base by increasing the sample size and trial duration.

CONCLUSION

The current study concluded that 25 µg of orally administered misoprostol is just as effective and safe as 25 µg of vaginal misoprostol for inducing labor in nulliparous pregnant women with an unripe cervix at or after 41 weeks of gestation.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Hussain A, Yakoob M, Imdad A and Bhutta Z. Elective induction for pregnancies at or beyond 41 weeks of gestation and its impact on stillbirths: a systematic review with meta-analysis. BMC public health, 2011; 11(3), 1-12.

2. Muglu J, Rather H, Arroyo-Manzano D, Bhattacharya S, Balchin I, *et al*. Risks of stillbirth and neonatal death with advancing gestation at term: A systematic review and meta-analysis of cohort studies of 15 million pregnancies. PLoS medicine, 2019; 16(7), e1002838.

3. Wennerholm U, Saltvedt S, Wessberg A, Alkmark M, Bergh C, *et al*. Induction of labour at 41 weeks versus expectant management and induction of labour at 42 weeks (SWEdish Post-term Induction Study, SWEPIS): multicentre, open label, randomised, superiority trial. bmj, 2019; 367.

4. Tang J, Kapp N, Dragoman M, De Souza J. WHO recommendations for misoprostol use for obstetric and gynecologic indications. International Journal of Gynecology & Obstetrics, 2013;121(2), 186-189.

5. Rahman H, Pradhan A, Kharka L, Renjhen P, Kar S, *et al*. Comparative evaluation of 50 microgram oral misoprostol and 25 microgram intravaginal misoprostol for induction of labour at term: a randomized trial. Journal of Obstetrics and Gynaecology Canada, 2013; 35(5), 408-416.

6. Bygdeman, M. Pharmacokinetics of prostaglandins. Best Practice & Research Clinical Obstetrics &Gynaecology, 2003; 17(5), 707-716.

7. Handal-Orefice R, Friedman A, Chouinard S, Eke A, Feinberg, B, *et al*. Oral or vaginal misoprostol for labor induction and cesarean delivery risk. Obstetrics and gynecology, 2019; 134(1), 10.

8. GleicherN. Why are reproductive cancers more common in nulliparous women?. Reproductive biomedicine online, 2013; 26(5), 416-419.

9. Perng W, Rifas-Shiman S, Kramer M, Haugaard L, Oken E, *et al*. Early weight gain, linear growth, and mid-childhood blood pressure: a prospective study in project viva. Hypertension, 2016; 67(2), 301-308.

10. Wang Y, Hu C, Pan N, Chen C, Wu R. Prophylactic uterine artery embolization in second-trimester pregnancy termination with complete placenta previa. Journal of International Medical Research, 2019; 47(1), 345-352.

11. Chan Y. Biostatistics 102: quantitative data–parametric and non-parametric tests. blood Press, 2003; 140(24.08), 79.

12. Chan Y. Biostatistics 103: qualitative data-tests of independence. Singapore Med J, 2003; 44(10), 498-503.

13. Vogel J, Gülmezoglu A, Hofmeyr G, Temmerman M. Global perspectives on elective induction of labor. Clinical obstetrics and gynecology, 2014; 57(2), 331-342.

14. Mehta R, Patel B, Shah A, Jani S, Patel V, *et al*. A comparative study of vaginal misoprostol versus oral misoprostol for induction of labour. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 2020; 9(6), 2520-5.

15. Ambika H, Bhat S, Lepakshi B, Savitha C. Comparative study of efficacy and safety of vaginal

misoprostol versus oral misoprostol in induction of labour when used in equal doses. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 2017; 6(9), 3828-3832.

16. Bagariya S, Samariya M, Samariya A. A comparative study of 25mcg of oral and vaginal misoprostol in induction of labour at term gestation in primigravida. International Journal of Clinical Obstetrics and Gynaecology, 2020; 4(2), 396-401.

17. Kaur P, Goel P, Takkar N, Huria A. Randomised controlled trial to compare safe safety and efficacy of vaginal versus oral route of misoprostol for induction of labour in term pregnancy with unfavourable cervix. International Journal of Reproduction, Contraception, Obstetrics and Gynecology, 2015; 4(6),1988-1993.