

The efficacy and safety of intravaginal misoprostol for the induction of labor in patients with obstetrical or medical indication for labor induction

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Summary

Background: Labor induction is becoming one of the most frequent procedures in maternity hospitals. However, the optimal agent for labor induction has not yet been established. Misoprostol, a prostaglandin E1 analogue, is receiving much attention due to its labor induction properties. **Objective:** The aim of this study was to evaluate the efficacy and safety of 25 and 50 mcg of intravaginal misoprostol, every four hours, for the induction of labor. **Materials and Methods:** This was a randomized controlled study to compare two different regimens of vaginal misoprostol, in women with obstetrical or medical indication for induction of labor. Participants received either a 25- or 50-mcg dose of misoprostol inserted into the posterior vaginal fornix repeated every four hours (maximum six doses), until adequate labor was established. Close monitoring of uterine activity and fetal heart rate was performed in all patients. Data were collected prospectively on epidemiological, obstetric, and care aspects. **Results:** Both regimens of misoprostol were effective in the induction of labor and most of the women had normal vaginal deliveries (81.08%). Although the mean time intervals from induction to the onset of active labor, and from induction to vaginal delivery for the 50-mcg regimen were lower, there was no significant difference between the two regimens. There were very few complications, with one case of uterine tachysystole in each treatment regimen. **Conclusion:** The results of the present study show that both regimens of misoprostol appear to be effective for the induction of labor in patients with indication, with few fetal complications.

Key words: Cervical ripening; Labor; Induced; Administration; Intravaginal; Misoprostol.

Introduction

The induction of labor, in term pregnant women with unfavorable cervix, remains one of the great challenges of modern obstetrics [1]. According to the literature, the optimal agent for uterine cervix maturation and induction of labor has not yet been established [2]. However, in recent years, labor induction has become one of the most frequent procedures performed in US maternity hospitals [3].

Misoprostol is a prostaglandin E1 analogue, which has been recently receiving a great amount of attention due to its labor induction properties [4-6]. Misoprostol has several potential advantages over other synthetic prostaglandin analogues, such as it is stable at room temperature, it is relatively low cost, and it can be administered via several routes (oral, vaginal, sublingual or buccal), making it an ideal agent for induction of labor [7-11].

Since standard doses of misoprostol for labor and induction of labor in pregnant women with live fetuses are not well established in the literature, the objective of this study was to evaluate the efficacy and safety of 25 and 50 mcg of intravaginal misoprostol, every four hours, for the induction of labor, in patients with obstetrical or medical indication for labor induction.

Materials and Methods

This was a randomized controlled trial to compare the efficacy and safety of two different regimens of intravaginal misoprostol (25 and 50 mcg) every four hours (to a maximum of six doses) for induction of labor.

This study was approved by the Ethics Committee for Research at the Federal University of Ceará following the ethical principles established by the National Health Council Resolution #466/2012, with necessary prior written consent from participants. Medical support was available upon request.

All women with obstetrical or medical indication for labor induction, and who met inclusion criteria, were invited to participate in the trial. Participants were enrolled with the use of a written informed consent form.

The inclusion criteria included obstetrical or medical indication for labor induction (hypertensive disorders of pregnancy, premature rupture of membranes (PROM), diabetes mellitus, post-date pregnancy, and hyperthyroidism), non-favorable cervix (Bishop score[12] ≤ 6 and absence of active labor), parity less than five, gestational age > 37 weeks, singleton live fetus, cephalic presentation, and reactive fetal heart rate pattern. Women with prior uterine scars, pathological fetuses, contraindications to vaginal delivery, and the use of prostaglandin analogue (asthma, glaucoma, heart disease, renal and liver dysfunction), altered fetal heart rate pattern, and vaginal bleeding were excluded from the study.

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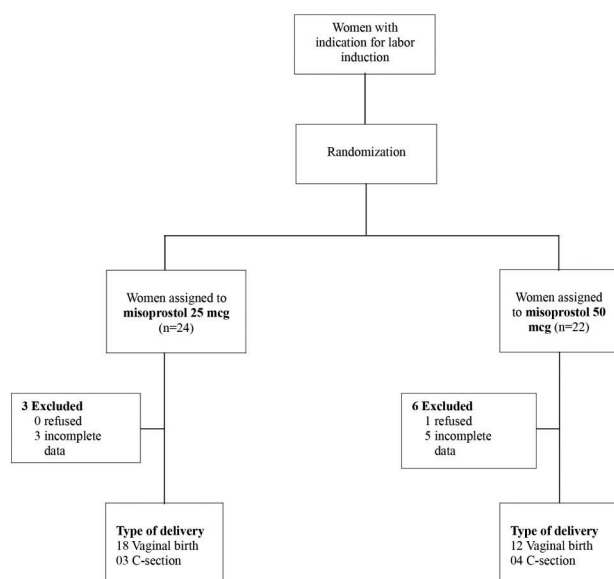


Figure 1. — Study profile.

This was a convenience sample of 46 women admitted for labor induction; participants were randomly allocated to receive either 25 or 50 mcg of vaginal misoprostol. Randomization was performed using a table of random numbers by the doctor on call before induction. A pre-induction Bishop score and a non-stress test were performed (Figure 1).

This study was conducted during the period from January 2013 to December 2014 at the maternity unit of the *Santa Casa de Misericórdia de Sobral* hospital, a reference hospital located in a mid-sized city in the northeast of Brazil.

Women received either a 25- or 50-mcg dose of misoprostol inserted into the posterior vaginal fornix repeated every four hours, until adequate labor was established (at least three contractions in ten minutes). The maximum number of doses was limited to six; for which, sequentially numbered sealed opaque envelopes containing the misoprostol tablets were prepared. Close monitoring of uterine activity and fetal heart rate was performed in all patients.

The following data were collected prospectively on a standardized form: epidemiological aspects (age and gestational age), obstetric history (number of previous pregnancies and type of previous deliveries), and care aspects (indication for the interruption of pregnancy, Bishop score, type of delivery, time of induction, onset of active labor, time of delivery, number of doses of misoprostol used, and complications).

At baseline, to identify statistical significance between the groups, the authors used an unpaired *t*-test for age, gestational age, and initial Bishop score; Fisher's exact test (two-tailed) for parity, and indication for labor induction (post-date, PROM, preeclampsia, and patient's choice).

During the study, Fisher's exact test (two-tailed) was used to compare delivery method, complications, vaginal delivery times (< 12 hours, 12 – 24 hours, and > 24 hours), and cesarean section. The unpaired student's *t*-test was used to assess the difference in mean time intervals from induction to delivery (induction to onset of active labor, onset of active labor to vaginal delivery, and induction to vaginal delivery).

The statistical software package SPSS, version 17.0, was used for all analyses. The limit for statistical significance was set at $p = 0.05$.

Table 1. — Maternal demographic characteristics.

Variables	25 mcg (n=24)	50 mcg (n=22)	<i>p</i> -value
Age (years ± SD)	25.6±7.96	23.9±5.45	0.39 ^a
Parity (N:M)	12:12	12:10	0.78 ^b
Gestational age (weeks ± SD)	39.5±1.59	40.0±1.59	0.38 ^a
Initial Bishop score (score ± SD)	3.33±0.96	3.52±0.98	0.52 ^a
Indication for labor induction			
<i>Post-date</i> (%)	11 (45.8)	13 (59.1)	0.39 ^b
<i>PROM</i> (%)	8 (33.3)	5 (22.7)	0.52 ^b
<i>Preeclampsia</i> (%)	5 (20.8)	4 (18.2)	1.00 ^b
<i>Patient's choice</i> (%)	0	2 (9.1)	0.22 ^b

^a Student's *t*-test; ^b Fisher's exact test (two-tailed); SD Standard deviation; N: nulliparous; M: multiparous; PROM: premature rupture of membranes.

Table 2. — Delivery method and complications.

Variables	25 mcg (n=21)	50 mcg (n=16)	<i>p</i> -value
Delivery			0.44 ^a
<i>Spontaneous vaginal</i> (n, %)	18 (85.71)	12 (75.00)	
<i>Cesarean section</i> (n, %)	3 (14.29)	4 (25.00)	
Complications			1.00 ^a
<i>Uterine tachysystole</i> (n, %)	1 (4.76)	1 (6.25)	

^a Fisher's exact test (two-tailed)

Table 3. — Vaginal delivery and cesarean section variables

Variables	25 mcg	50 mcg	<i>p</i> -value
Interval times (hours ± SD)			
<i>Induction - onset of active labor</i>	5.40±3.60	4.40±3.23	0.44 ^a
<i>Onset of active labor - Vaginal delivery</i>	7.27±5.11	7.83±5.46	0.78 ^a
<i>Induction - Vaginal delivery</i>	12.70±5.75	12.20±5.40	0.83 ^a
Vaginal delivery			
< 12 hours (n, %)	11 (61.11)	6 (50.0)	0.71 ^b
12 – 24 hours (n, %)	6 (33.33)	6 (50.0)	0.46 ^b
> 24 hours (n, %)	1 (5.56)	0	1.00 ^b
Cesarean section			0.43 ^b
<i>Nulliparous</i> (n, %)	2 (66.67)	4 (100.0)	
<i>Multiparous</i> (n, %)	1 (33.33)	0	

SD: standard deviation; ^a Student's *t*-test; ^b Fisher's exact test (two-tailed).

Results

Forty-six women met eligibility criteria and were enrolled in the study. After entering the trial, nine women were excluded due to missing data on medical records. The women were randomly assigned to treatment (25 mcg of vaginal misoprostol every four hours, n=24; 50 mcg of vaginal misoprostol every four hours, n=22).

Upon enrollment, maternal demographic characteristics and indications for labor induction were recorded and analyzed: age, parity, gestational age, initial Bishop score, and

indication for labor induction (post-date, PROM, preeclampsia, and patient's choice). However, there were no statistically significant differences between the treatment regimens. Post-date pregnancy was the primary indication for labor induction in both groups, 11 out of 24 (45.8%) in the 25 mcg group and 13 out of 22 (59.1%) in the 50 mcg group, $p = 0.39$ (Table 1).

In the 25 mcg group, the vaginal delivery rate was 18/21 (85.71%) and 12/16 (75.0%) in the 50 mcg group, $p = 0.44$. Potential adverse effects of misoprostol such as allergic reactions, fainting, fever, headaches, diarrhea, nausea, etc., were not observed in either group. In relation to complications, only two cases of uterine tachysystole were observed, one in each group; in both cases the delivery was normal without any other complications (Table 2).

The mean time interval between induction and the onset of active labor was higher in the 25 mcg group, 5.40 ± 3.60 hours compared to 4.40 ± 3.23 hours in the 50 mcg group, $p = 0.44$. The time interval between the onset of active labor and vaginal delivery was 7.27 ± 5.11 hours in the 25 mcg group and 7.83 ± 5.46 hours in the 50 mcg group, $p = 0.78$. There was also no statistically significant difference for the mean time interval between induction and vaginal delivery, $p = 0.83$.

In the 25 mcg group, vaginal delivery within 12 hours was achieved in 11 out of 18 women (61.11%), and between 12 and 24 hours in six women (33.33%); in the 50 mcg group, vaginal delivery within 12 hours occurred in six out of 12 women (50.00%), and in the other six women during the next 12 hours. There was no significant difference between the groups concerning induction and vaginal delivery.

In both induction groups, most of the women who had cesarean sections were nulliparous, 66.77% and 100%, respectively, $p = 0.43$ (Table 3).

Discussion

The results of the present study show that both 25 and 50 mcg of intravaginal misoprostol, every four hours, were effective in the induction of term labor; and most of the women had a normal vaginal delivery, with few complications.

In the 25 mcg group 85.71% of women and 75.0% in the 50 mcg group were delivered vaginally. This is comparable to the study by Loto *et al.* [13] in which 88.7% of the patients in the 25 mcg group and 93.7% in the 50 mcg group achieved vaginal delivery, as also in the study by Azubuike *et al.* [14] in which 32 out of 40 women in the 25 mcg group, and 32 out of 43 women were delivered vaginally, (80.0% and 74.4%, respectively). However, in a systematic review by McMaster *et al.* [15], the investigators found that 25 mcg of vaginal misoprostol was significantly less efficacious than 50 mcg: 66.6% compared to 74%.

In the present study, complications were similar in both

groups, one case of uterine tachysystole was registered in each; however, both women were delivered vaginally, without interurrences. Other investigators found similar results, Girija and Manjunath [16] reported that potential adverse effects of misoprostol, such as uterine rupture, nausea, vomiting, diarrhea, and fever were not observed in the study population, and that there was no significant difference in the variables such as the use of oxytocin augmentation, uterine contraction abnormalities, abnormal cardiograph, modes of delivery, and postpartum hemorrhage. Another study by Szczesny and Sandvik [17], with 181 nulliparous women, also reported that all fetuses/infants tolerated well treatment with both 25 and 50 mcg of vaginal misoprostol. Nevertheless, Adeniyi *et al.* [18] identified that labor complications such as precipitate labor, tachysystole, and abnormal fetal heart rate patterns were greater among participants that received 50 mcg of vaginal misoprostol and Andresen *et al.* [19] reported a 10% risk of uterine hyperstimulation compared to induction with 25 mcg of misoprostol and 3 mg of minprostin.

In the cases in which cesarean section was indicated, it was due to cephalopelvic disproportion, preeclampsia with signs of imminent eclampsia, no response to misoprostol (no effective uterine contractions) after the sixth dose, and patient's refusal to continue induction. Cesarean rates among the groups were similar, which is consistent with other studies [13, 14, 16, 20]

Although the mean time interval from induction to the onset of active labor, and from induction to vaginal delivery for the 50-mcg regimen was lower, there was no statistically significant difference between the two misoprostol regimens; normal vaginal delivery was achieved in approximately 12 hours. Induction failure was similar in both groups, with only one woman in each group (data not shown). Other studies have found similar results, in one study by Girija *et al.* [16], the time interval from induction to the onset of active labor was 8.25 ± 3.71 hours in the 25 mcg group, and 11.92 ± 10.15 hours in the 50 mcg group; mean induction delivery interval was 14.42 ± 13.2 hours in the 25 mcg group, and 18.58 ± 13.73 hours in the 50 mcg group ($p = 0.73$). In another study by Meydanli *et al.* [21], in which 120 women not in active labor with a gestational age > 41 weeks were randomized to receive either 25 mcg or 50 mcg of intravaginal misoprostol; the results showed that there was no significant difference between the groups with regards to the mean time interval from induction to vaginal delivery. These results were also confirmed by a systematic review which identified that although the time interval from induction to vaginal delivery was shorter in the 50 mcg group, these results were not statistically significant. [15]

This current study demonstrated the importance of misoprostol for the induction of labor in patients with obstetrical or medical indication for labor induction. Since misoprostol is a relatively inexpensive drug, its use pro-

vides a low-cost alternative for labor induction avoiding unnecessary cesarean sections, wound infections, and extended hospital stays, while promoting more humanized practices.

The limitations of this study included a limited number of patients in this trial, and since paper-based medical records were used to register patient information, some records were considered ineligible, inaccurate, and incomplete by the researchers. Furthermore, potential confounding factors need to be identified and examined on how these may have modulated the response of the patient under different conditions.

In conclusion, although larger trials are needed, the results of this study show that both regimens of vaginal misoprostol appear to be effective for the induction of labor in patients with obstetrical or medical indication for labor induction, with few fetal complications.

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