Labor induction at term: a comparison of the effects of 50 μg and 25 μg vaginal misoprostol

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Summary

Purpose of investigation: To compare the effects of 50 μg of vaginal misoprostol with 25 μg for labor induction at term.

Methods: One hundred and forty-seven pregnant women with indications for labor induction and cervical Bishop's score of ≤ 6 were randomly assigned to receive either 50 μg (n = 74) or 25 μg (n = 73) of vaginal misoprostol every four hours until either a Bishop's score of ≥ 8 or adequate uterine contraction frequency had been achieved. Induction-to-vaginal-delivery time was considered the primary outcome measure.

Results: Mean induction-to-vaginal-delivery time was significantly shorter in the 50-μg group than in the 25-μg group (526 ± 141 min vs 745 ± 218 min, respectively); oxytocin was administered to 65.8% of the patients in the 25-μg group and to 35.1% in the 50-μg group ($p < .05$). The incidence of tachysystole was significantly higher in the 50-μg group than in the 25-μg group (12% vs 2.7%, $p < .05$). We found no statistically significant difference between the two groups with respect to the rate of primary cesarean section, incidence of hyperstimulation syndrome, or neonatal outcome ($p > .05$).

Conclusion: Fifty micrograms of vaginally administered misoprostol is an effective and inexpensive means of inducing labor at term. Uterine tachysystole may be associated more frequently with a 50-μg dose of vaginal misoprostol than with a 25-μg dose. Clinicians must accurately document the frequency and intensity of uterine contractions before every 50-μg dose of misoprostol is administered.

Key words: Labor induction; Neonatal outcome; Uterine tachysystole; Vaginal misoprostol.

Introduction

Labor induction is the stimulation of uterine contractions before the spontaneous onset of labor for delivery. Oxytocin and prostaglandins are widely used to induce labor at term [1]. Although oxytocin is a safe and effective initiator of uterine contractions, its effectiveness depends on the condition of the cervix at the beginning of labor induction [2].

Prostaglandins are the agents most frequently used for labor induction at term in women with an unfavorable cervix [1]. Prostaglandin E2 (PGE2) is the only pharmacologic agent approved by the US Food and Drug Administration for cervical ripening and labor induction at term; however, it is expensive and is not easily administered.

Misoprostol is a synthetic prostaglandin E1 (PGE1) analog that has been approved by the US Food and Drug Administration to be taken orally for the prevention and treatment of gastric ulcers associated with the use of nonsteroidal anti-inflammatory drugs [3]. That agent is also effective for cervical ripening and labor induction at term [4-6]. It is inexpensive, easily administered orally or vaginally, and can be stored at room temperature [5].

Many reports show that vaginal administration of misoprostol is more effective than oral administration for cervical ripening and labor induction at term [6,7]. However, the optimal dose of intravaginal misoprostol for that purpose is controversial. A few studies have indicated the safety and the efficacy of 50-μg vaginal doses of misoprostol as opposed to 25-μg vaginal doses [8-12]. Our aim in this study was to compare the findings in patients undergoing labor induction via 50-μg or 25-μg vaginal misoprostol.

Materials and Methods

This randomized controlled study was conducted at the Department of Obstetrics and Gynecology, Baskent University, Ankara, Turkey between June 2004 and March 2006. An independent Ethics Committee approved the work and written informed consent from the patients was obtained before they participated in the study. Inclusion criteria for enrollment were as follows: singleton pregnancy with vertex presentation and no contraindication to vaginal delivery, obstetric indications for labor induction, and a reactive fetal heart rate (FHR) pattern. Exclusion criteria included a Bishop score of > 6, prior cesarean delivery, placenta previa or unexplained vaginal bleeding, and contraindications or an allergic reaction to the use of prostaglandins. A total of 521 women delivered during the study period. One hundred and eighty-five women were eligible subjects for labor induction. Thirty-eight women declined to participate in the study. Therefore, 147 women at term (≥ 37 weeks' gestation) with an indication for labor induction and a cervical Bishop score of ≤ 6 were randomly assigned to receive either 50 μg or 25 μg of vaginal misoprostol (Cytotec, G.D. Searle & Co., UK; and Ali Raif Co., Turkey). Seventy-four patients received 50 μg of vaginal misoprostol and 73 patients received 25 μg of vaginal misoprostol administered every four hours until either a Bishop score of ≥ 8 or adequate uterine contraction frequency (≥ 3 contractions in a 10-minute period) was achieved. A maximum of six doses of either dosage was administered.

Postdate pregnancy was defined as gestational age ≥ 41 weeks, and oligohydramnios was considered if the amnionic fluid index was ≤ 5 cm.

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Initially, a vaginal examination was performed and the patient's Bishop score was determined; the dose of misoprostol was then inserted into the posterior fornix. Bishop score was determined before each subsequent misoprostol dose was administered. Initial and serial Bishop score assessments were performed by the same obstetrician who designed the study. The 50-μg dose was prepared by quartering a 200-μg misoprostol tablet with a pill cutter, and the 25-μg dose was prepared by splitting a 50-μg piece in half. The dosages of the misoprostol were also prepared by the same obstetrician mentioned above. To randomize patients, envelopes were filled with pieces of paper with the names "50-μg" or "25-μg"; these were subsequently pulled by hospital residents after the patients were admitted for labor induction.

Pelvic examination was performed every one to two hours. "Active" labor was defined as cervical dilatation of 3 to 4 cm or more in addition to regular uterine contractions. "Ineffective" labor was considered when the cervix dilated at a rate of < 1 cm/hr during the active phase of labor. Amniotomy was performed in those patients and labor progress was again evaluated after two to three hours in women with unruptured membranes. Patients whose labor progress was poor received low-dose oxytocin, but not within four hours after a dose of misoprostol had been administered. Oxytocin infusion was initiated at a dose of 1 mU/min and was increased by 1 mU/min every 30 minutes to a maximum of 20 mU/min [13]. Uterine activity after oxytocin administration was deemed satisfactory when a cervical dilatation rate of 1 to 2 cm/hr was achieved. If the Bishop score had not changed or if adequate labor (≥ 3 uterine contractions in a 10-minute period) did not occur after six doses of misoprostol, a diagnosis of failed induction was made, and the patient was offered the option of delivery via cesarean section.

All patients underwent continuous electronic fetal heart rate (FHR) monitoring and external tocodynamometry. FHR patterns were evaluated as described by Kubli and colleagues [14]. Tachysystole was defined as the occurrence of at least six uterine contractions in ten minutes for two consecutive 10-minute periods, and hypertonus was defined as any one contraction that lasted ≥ 2 min [15]. Hyperstimulation syndrome was defined as tachysystole or one prolonged uterine contraction lasting ≥ 2 min in addition to FHR abnormalities (fetal tachycardia, late decelerations, loss of beat-to-beat variability) [5]. If either tachysystole or hypertonus occurred in the presence of a normal FHR pattern, the oxytocin infusion was decreased. If hyperstimulation syndrome developed, the administration of oxytocin was terminated and the patient was turned onto her left side. A bolus of 500 ml of a crystalloid solution was then infused, and 8 l/min oxygen was supplied via a nasal cannula. Ritodrine hydrochloride was used as a tocolytic agent. Vaginal lavage was performed to remove the previously administered misoprostol tablet.

The induction-to-vaginal-delivery time was considered the primary outcome measure. Other outcome measures were defined as follows: the need for oxytocin augmentation, method of delivery, number of misoprostol doses required, rate of vaginal delivery after one dose of misoprostol, incidence of induction to vaginal delivery within 12 hours, incidence of tachysystole and uterine hyperstimulation, and neonatal outcome measures such as Apgar scores, cord pH values, and a cord pH value of < 7.16. A cutoff value of < 7.16, which represents two standard deviations below the mean, was chosen for the umbilical artery pH value [16]. Data were analyzed by means of SPSS software (Statistical Package for the Social Sciences, version 11, SSPS Inc, Chicago, IL, USA). The Student's *t*, chi-square, and Fisher exact chi-square tests were used to determine whether statistically significant differences occurred between the two groups. A p value of < .05 was considered statistically significant.

Results

A total of 147 patients participated in the study. The women did not differ with regard to maternal age, parity, height, weight, gestational age at the onset of the study, or preinduction Bishop score (p > .05) (Table 1). Indications for labor induction were similar between the two groups, and postdate pregnancy was the most frequent indication for labor induction in both groups (p > .05) (Table 2). The mean dose of misoprostol required was similar in both groups (p > .05) (Table 3).

Table 1. — *Maternal characteristics.*

	50-μg group* (n = 74)	25-μg group* (n = 73)	p value**
Age (yrs)	28.2 ± 4.7	28.0 ± 4.4	0.791
Parity	0.4 ± 0.6	0.3 ± 0.5	0.164
Height (cm)	164 ± 6	163 ± 4	0.875
Weight (kg)	70.9 ± 9	68.8 ± 10	0.270
Nulliparity	49 (66.2%)	52 (71.2%)	0.512
Gestational age (wks)	39.3 ± 0.9	39.4 ± 0.9	0.321
Initial Bishop score	3.0 ± 1.0	2.7 ± 1.5	0.264

* Values are expressed as mean ± SD or as number and percent.
** Student's t-test, chi-square test, and Fisher's exact chi-square tests were used.

Table 2. — *Indications for labor induction.*

	50-μg group* (n = 74)	25-μg group* (n = 73)	p value**
Postdate pregnancy	37 (50.0%)	36 (49.3%)	0.718
Oligohydramnios	12 (16.2%)	7 (9.6%)	0.718
Hypertension/preeclampsia	9 (12.2%)	13 (17.8%)	0.718
PROM	10 (13.5%)	11 (15.1%)	0.718
Other	6 (8.1%)	6 (8.2%)	0.718

* Values are expressed as number and percent.
** Chi-square test was used.
PROM = premature rupture of membranes.

The mean induction-to-vaginal-delivery time was significantly different in the two groups (p < .05) (Table 3). There was also a significant difference regarding the duration of first and second stages of labor between the two study groups (p < .05) (Table 3).

There were 49 (66.2%) nulliparous women in the 50-μg group and 52 (71.2%) in the 25-μg group (p > .05) (Table 1). Among the nulliparous women, the mean time from induction to vaginal delivery was shorter in the 50-μg group than it was in the 25-μg group (p < .05) (Table 3). Among the multiparous women, the mean time from induction to vaginal delivery was also shorter in the 50-μg group than it was in the 25-μg group (p < .05) (Table 3).

Among the women in the 50-μg group, 53 (71.6%) patients delivered vaginally, and 54 (74.0 %) of the women in the 25-μg group underwent vaginal delivery (p > .05) (Table 3). Forty women (54.1%) delivered vaginally after having received a single dose of misoprostol in the 50-μg group as opposed to subjects in the 25-μg group, 23 (31.5 %) of whom underwent vaginal delivery after a single dose of misoprostol (p < .05) (Table 3).

Table 3. — *Labor outcomes.*

	50-μg group* (n = 74)	25-μg group* (n = 73)	p value**
The mean dose of misoprostol	1.7 ± 1.3	2.0 ± 1.2	0.242
Oxytocin augmentation	26 (35.1%)	48 (65.8%)	0.0001
Meconium in labor	6 (8.1%)	4 (5.5%)	0.745
Uterine tachysystole	9 (12.0%)	2 (2.7%)	0.03
Uterine hyperstimulation	1 (1.4%)	0 (0%)	1.0
The duration of first stage of labor (min)	315 ± 100	464 ± 120	0.0001
The duration of second stage of labor (min)	35 ± 25	52 ± 35	0.003
Induction-to-vaginal delivery time (min)	526 ± 141	745 ± 218	0.0001
Induction- to-vaginal delivery time (nulliparous women) (min)	531 ± 156	797 ± 234	0.0001
Induction-to-vaginal delivery time (multiparous women) (min)	517 ± 109	626 ± 123	0.005
Vaginal delivery after 1 dose	40 (54.1%)	23 (31.5%)	0.006
Vaginal delivery within 12 h	51 (68.9%)	38 (52.1%)	0.03
Cesarean delivery	17 (23.0%)	14 (19.2%)	0.573
Vaginal delivery	53 (71.6%)	54 (74.0%)	0.593
Operative vaginal delivery	4 (5.4%)	5 (6.8%)	0.745

* Values are expressed as mean ± SD or as number and percent.
** Student's t-test, chi-square test, and Fisher's exact chi-square tests were used.

More women in the 25 μg group received oxytocin compared to the 50 μg group (Table 3).

The rate of cesarean section did not differ between the two groups ($p > .05$) (Table 3). Indications for cesarean delivery were similar in the two groups (Table 4). More women in the 50-μg group delivered within 12 hours of the induction of labor (Table 3). No difference was found between the two study groups with respect to the proportion of patients in whom induction of labor failed (Table 4).

Table 4. — *Indications for cesarean delivery.*

	50-μg group* (n = 17)	25-μg group* (n = 14)	p value**
Fetal distress	1 (5.9%)	0 (0%)	0.645
Failure to progress	11 (64.7%)	10 (71.4%)	0.645
Failed induction	5 (29.4%)	4 (28.6%)	0.645

* Values are expressed as number and percent.
** Chi-square test, and Fisher exact chi-square tests were used.

Table 5. — *Neonatal outcome.*

	50-μg group* (n = 74)	25-μg group* (n = 73)	p value**
Birthweight (g)	3256 ± 306	3334 ± 440	0.165
Apgar score < 7 at 1 minute	0	1 (1.4%)	0.497
Apgar score < 7 at 5 minutes	0	0	
Mean cord pH	7.26 ± 0.05	7.27 ± 0.05	0.746
Cord pH < 7.16	3 (4.1%)	3 (4.1%)	0.357
NICU admission (%)	0 (0)	0 (0%)	

* Values are expressed as mean ± SD or as number and percent.
** Student's t test, chi-square, and Fisher's exact chi-square tests were applied.
NICU= neonatal intensive care unit.

No statistically significant differences were noted between the two groups with respect to the incidence of uterine hyperstimulation syndrome and neonatal outcome ($p > .05$) (Tables 3 and 5). The incidence of uterine tachysystole was significantly higher among women in the 50-μg group than those in the 25-μg group ($p < .05$) (Table 3). The mean birth weight of neonates did not differ between the two groups ($p > .05$) (Table 5). There was no difference in the mean cord pH value between the two groups, and the incidence of newborns with a cord pH value < 7.16 was similar in both groups ($p > .05$) (Table 5). We found no differences in the Apgar score < 7 at 1 and 5 min between the groups, and no infant from either group was admitted to the neonatal intensive care unit (Table 5). Maternal adverse effects (nausea, vomiting, diarrhea) were not detected in any patients.

Discussion

Many randomized controlled trials and three meta-analyses have been performed to compare the safety and effectiveness of vaginal misoprostol for cervical ripening and labor induction [4, 5, 8-12, 17-19]. In this study, we have demonstrated that to induce labor at term, a 50-μg dose of intravaginally administered misoprostol is more effective than a 25-μg dose. In addition, we did not find a dose-related increase in maternal adverse effects or perinatal morbidity, except that the incidence of tachysystole was higher in the 50-μg group than in the 25-μg group.

It has previously been shown that 50 μg of vaginally administered misoprostol causes a shorter induction-to-delivery interval than does the 25-μg dose [8, 9, 11, 12]. In our patients, 50 μg of vaginal misoprostol also shortened the duration of labor. The mean induction-to-vaginal-delivery time was approximately four hours longer in patients who received 25 μg of misoprostol than in those who received 50 μg. Although we found no significant differences in cesarean or operative vaginal delivery rates between the two groups, the proportion of patients who were delivered vaginally within 12 hours after the induction of labor was significantly higher in the 50 μg group (Table 3).

Farah *et al.* [8] also compared the safety and effectiveness of vaginally administered misoprostol at doses of 50 μg and 25 μg for labor induction. A total of 399 patients were enrolled in their study. Those investigators showed that the incidence of vaginal delivery after one dose of misoprostol was significantly higher in the 50-μg group than in the 25-μg group. Farah and colleagues [8] and Srisomboon *et al.* [9] also found that a greater proportion of patients who received 25 μg of vaginally administered misoprostol required oxytocin augmentation. Those findings are consistent with the results of our study, in which a greater proportion of patients delivered after a single misoprostol dose in the 50-μg group, and less frequent oxytocin augmentation was required by patients in the 50-μg group than by patients in the 25-μg group.

A systematic review by Sanchez-Ramos and coworkers [18] revealed that the incidence of uterine tachysystole was significantly higher in women who received 50 μg of vaginally administered misoprostol than in those who received 25 μg. The rates of tachysystole ranged from 1.6% to 15.6% in women administered 25-μg doses of vaginal misoprostol and from 3.2% to 32.8% in those who received 50-μg vaginal doses. Paungmora and colleagues also reported that the rate of tachysystole was 17.1% in women who were administered 50-μg of vaginal misoprostol for labor induction [20]. In our study, there was a statistically significant difference in the incidence of uterine tachysystole between the two groups. The rate of uterine tachysystole was 2.7% for women in the 25-μg group and 12% for those in the 50-μg group. The incidence of hyperstimulation syndrome did not differ between the two study groups. One patient had hyperstimulation syndrome in the 50-μg group but no patient in the 25-μg group had the syndrome. Farah *et al.* [8] also found a higher incidence of tachysystole in women receiving 50 μg of vaginal misoprostol in their studies. However, no significant differences were detected between the two groups regarding the incidence of hyperstimulation syndrome, the need for neonatal resuscitation, or required neonatal admissions to the neonatal intensive care unit. The findings of our study correlate with the results mentioned above. However, sufficient numbers are necessary to exclude the possibility of a dose-related increase in maternal adverse effects or perinatal morbidity including hyperstimulation syndrome in our population.

An increase in the incidence of uterine tachysystole and hyperstimulation syndrome seem to be dose-dependent and may be related to the number of doses of misoprostol administered. It is therefore important to assess uterine activity properly before administering additional doses of misoprostol.

Although in our study the rate of tachysystole was significantly higher in patients who received 50 μg of misoprostol we did not find a significant difference between the two groups with respect to neonatal outcome, including the rate of cesarean delivery, the mean cord pH value, the incidence of newborns with a cord pH value < 7.16, and number of neonates admitted to the neonatal intensive care unit.

In conclusion, this study demonstrates that 50 μg of vaginal misoprostol is an effective and inexpensive agent for inducing labor at term. However, the numbers in this study were not sufficiently large to the make a definite conclusion about the safety of 50 μg of vaginal misoprostol. The higher incidence of uterine tachysystole may be dose-dependent and may be related to the number of doses of misoprostol administered. To prevent uterine contraction abnormalities, clinicians must accurately document the frequency and intensity of uterine contractions before every 50-μg dose of misoprostol is administered.

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