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ORIGINAL ARTICLE

What is the optimal duration of oral misoprostol treatment for cervical ripening?

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Abstract

Objectives: To evaluate the number of misoprostol tablets needed to obtain a Bishop score (BS) ≥ 6 or a significant cervical change (≥ 2 points in BS) during cervical ripening.
Methods: Retrospective study of women with term singleton pregnancies and a BS < 6 taking oral misoprostol (20 μg first 2 doses followed by 40 μg every 2 h) for cervical ripening.
Results: We included 400 women, 72% nulliparous, mean age of 31.3 ± 5.9 years and 70% with a baseline BS ≤ 2. During cervical ripening, 61 (15.3%) achieved a BS ≥ 6 and 205 (51.3%) a significant change in BS. The incremental risk to achieve a BS ≥ 6 after 4 tablets was low (+3.25%) with an incremental probability of +12.75% for painful uterine contractions and +0.5% for abnormal fetal tracing (AFT). The incremental probability to achieve a significant change in BS after 7 tablets was low (+2.0%). 24.3% women delivered by cesarean section which likelihood significantly increased with maternal age <35 years, BMI ≥ 30, nulliparity, AFT, and baseline BS ≤ 2.
Conclusions: The marginal benefit of giving more than 7 misoprostol tablets (14 h) during cervical ripening is very low.

Keywords

Oral misoprostol, dosing, duration, induction of labor, cervical ripening

History

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Introduction

Misoprostol, a methyl ester of prostaglandin E_1 (PGE_1), as well as dinoprostone (PGE_2), are efficacious for cervical ripening in women with an unfavorable cervix prior to induction of labor (IOL) [1–4]. Currently, only PGE_2 is approved by the U.S. Food and Drug Administration for cervical ripening, whereas PGE_1 recommended by the American College of Obstetricians and Gynecologists (ACOG) as an alternative agent, is used in USA and in many European countries as an off-label medication [5,6].

Misoprostol has several advantages compared to PGE_2 [7]. It is cheap, stable at room temperature, easy to use, and without many digestive side effects [8]. Several studies comparing the effectiveness of prostaglandins for cervical ripening suggest that misoprostol is more effective than PGE_2 with a significant decrease in the cesarean section rate [9–12]. The World Health Organization, the International Federation of Gynecology and Obstetrics, and the ACOG allow the use of misoprostol for IOL under certain conditions [13].

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Misoprostol can be administered by various routes: oral, sublingual, intravaginal, or intrarectal [14]. The oral route may result in improved clinical outcomes over the vaginal route [10,11], and women's convenience and comfort also seem to be increased [15–18]. The regimens most frequently used were either 20–25 μg every 2 h for a maximum of 12 doses (24 h), or 50 μg every 4 h for a maximum of 6 doses (24 h). Irrespective of the existence of studies investigating the administration route and dosage, the duration of the procedure has not been studied and has been arbitrarily chosen [18–26]. Long-lasting labor induction can be exhausting, lead to psychological sequelae and requires medical surveillance, implying extra costs that need to be considered [27].

In this study, we aimed to evaluate the incremental effect of each misoprostol tablet to obtain a Bishop score (BS) ≥ 6 or a significant cervical change (≥ 2 points in BS) during cervical ripening in women undergoing IOL. Furthermore, we assessed the associations between clinical and obstetrical factors and cervical ripening efficacy, but also the risk factors for cesarean section.

Materials and methods

We conducted a retrospective cohort study analyzing data from pregnant women undergoing cervical ripening prior to

IOL with oral misoprostol during 2010 at the Geneva University Hospitals (HUG). This study was approved by the local institutional review board. Written informed consent was not required for participation in this trial.

At our institution, where induction rate is around 30%, we perform cervical ripening with prostaglandins (dinoprostone or misoprostol) in women with a BS <6, otherwise labor is directly induced with oxytocin [28]. Included cases were consecutive women admitted in the labor suite for IOL, with term (≥37 gestational weeks) singleton pregnancies and having a BS <6, assessed by vaginal examination. Exclusion criteria to receive misoprostol were a uterine scar, suspected fetal distress, or genital bleeding. Our protocol was as follows: 20 µg tablets for the first 2 doses followed by 40 µg tablets orally every 2 h with a maximum of 320 µg (9 tablets/18 h). Tablets were produced by our pharmacy. External electronic fetal monitoring was performed 30 min before and after administration of medication. Before giving an additional dose of misoprostol, a cervical examination was performed, except in the absence of uterine contractions (UC). No further dose was given if there were regular (≥3 in 10 min) or painful UC (used as risk sign for uterine rupture), a BS ≥ 6, spontaneous rupture of membranes, or abnormal fetal tracing (AFT). If labor had not started after 9 tablets, oxytocin infusion was given at increasing doses (0.08 UI/h up to a maximum of 2.5 UI/h). Fetal heart rate (FHR) and uterine activity were monitored in all women during labor. FHR patterns were analyzed according to the United Kingdom National Institute for Health and Care Excellence guidelines [29].

The primary outcome was the achieving a BS of ≥6. Secondary outcomes were: (1) achieving a significant change of the cervix defined as an increase of at least 2 points on the BS and (2) the risk of cesarean section. We also collected data on the following variables: maternal age; parity; gestational age; indications for labor induction; oxytocin use; epidural analgesia use; indication for cesarean section; uterine hyperstimulation (≥5 UC in 10 min) or hypertonia (UC of ≥2 min); amniotic fluid at delivery (clear; stained: greenish or tinted; meconial: thick meconium); 5-min Apgar score; arterial umbilical pH; AFT (complicated variables or late decelerations, fetal tachycardia [>160 bpm] or bradycardia [<100 bpm]); newborn weight; neonatal or maternal complications, postpartum hemorrhage (>500 ml for vaginal delivery and >1000 ml for cesarean section); and time between the beginning of induction and a significant BS change and delivery.

Sample size calculation

We hypothesized that approximately 25% of the 4000 women delivering yearly in HUG would have an indication for misoprostol and that 5% would have exclusion criteria, leading to a potential number of 931 women. We anticipated that the prevalence of women who will obtain a BS ≥ 6 on misoprostol would be 10%, based on a pilot study conducted in our service and including 100 women. With the expected number of 400 women having cervical ripening with misoprostol prior to IOL, we could estimate a proportion of 10% women who will obtain a BS ≥ 6 on misoprostol with a precision of ±3%.

Statistical analysis

Continuous data are presented by their mean standard deviation (SD), and categorical variables by their number and relative proportion. We calculated the cumulative risk to achieve a BS ≥6 or a significant change in the BS per 2 h periods of time per 100 patients versus the cumulative competing risks of painful UC or AFT. We performed competing risk Cox regression analysis according to the method of Fine and Gray to assess the factors associated with our main outcomes versus painful UC or AFT [30]. Times considered in these analyses were the duration from the start of misoprostol and the occurrence of the outcome of interest. As misoprostol was given in a standardized frequency every 2 h, information on the number of tablets and time of observation were the same and the number of misoprostol tablets could not be assessed as a risk factor in our models.

We assessed the risk factors for delivery by cesarean section using a competing risk Cox regression model with vaginal delivery (spontaneous and instrumental deliveries) as a competing event of interest. The potential risk factors tested: initial BS (≤ 2 versus >2), maternal age (<35 versus ≥35 years); significant change of the BS (no versus yes); rupture of membranes (yes versus no); parity (nulliparous versus parous); AFT and intrauterine fetal growth restriction. All tests were two-tailed and p values < 0.05 were regarded as significant. We used Stata (version intercooled 13.0) for all analyses.

Results

Among the 3922 deliveries in our hospital within 2010, 1295 (33%) had labor induction with misoprostol, dinoprostone, or oxytocin. The characteristics, labor, and delivery data of participants are shown in Table 1. Maternal age ranged between 17 and 46 years. Women were more frequently nulliparous (288; 72%) and had a mean BMI of 29.37 (± 4.90). At rupture of membranes, amniotic fluid was stained in 22 cases (5.5%), while thick meconium was observed once. Three quarters (303, 75.7%) of deliveries were vaginal, including 212 (53%) spontaneous deliveries. Indications for CS were AFT ($n = 12$), failure of IOL with misoprostol and oxytocin ($n = 15$), or other indications ($n = 70$). Maternal and neonatal complications are described in Table 2. The risk of tachysystole/hypertonia was low and there were no cases of uterine rupture. Newborns had a mean weight of 3358 g (±515.3) and a low risk of complications. There were no cases of sepsis, seizure, or neonatal death.

Women took a mean number of 3.6 (range 1–9) misoprostol tablets (corresponding to 104 µg). Among them, 61 (15.3%) achieved a BS ≥ 6 and 205 (51.3%) had a significant BS change during cervical ripening. Mean duration between the first misoprostol tablet and a significant BS change was 7.1 h (±4.3), while mean induction to delivery time was 20.5 h (±9.2).

The incidence of a BS ≥ 6 after 1 misoprostol tablet was 3% and increased to 12% with 4 tablets. The incremental probability to achieve a BS ≥ 6 after 4 tablets was low (+0.5% with an additional tablet and +3.25% between 5 and 9 tablets). The incremental probability of competing events significantly increased with the number of tablets: +37.5%

Table 1. Characteristics of the study participants ($n = 400$) and obstetrical outcomes.

Maternal characteristics	
Maternal age (years): median (IQR range*)	31 (27–35)
Gestational age (weeks): median (IQR range*)	40 (39–41)
Indications for induction of labor, *n* (%)	
Post-term†	93 (23.3)
Oligohydramnios†	68 (17.0)
Prelabor rupture of membranes >12 h	66 (16.5)
Maternal age >40 years	29 (7.3)
Intra-uterine fetal growth restriction	24 (6.0)
Other§	120 (30)
Bishop score at baseline: median (IQR range*)	2 (1–3)
Women with Bishop score ≤2, *n* (%)	279 (69.9)
Obstetrical outcomes	
Epidural analgesia, *n* (%)	369 (92.3)
Oxytocin use after misoprostol, *n* (%)	327 (81.8)
Mode of delivery, *n* (%)	
Vaginal	303 (75.7)
Cesarean	97 (24.3)
Amniotic fluid at delivery, *n* (%)	
Clear	366 (91.7)
Stained	22 (5.5)
Meconial	11 (2.8)
Mean umbilical cord arterial pH at delivery (SD)	7.21 (±0.06)
Apgar score at 5 min: mean (SD)	9.7 (±0.8)

*IQR: interquartile range: 25th percentile, 75th percentile; SD: standard deviation.

†Post-term: gestational age $> 41 + 3$ weeks.

‡Oligohydramnios: amniotic fluid index < 5 at term.

Table 2. Maternal and fetal/neonatal side effects and complications.

Variables	Number (%)
Tachysystole/hypertonia	13 (3.3)
Abnormal fetal heart rate	32 (8.0)
Maternal complications	
Hemorrhage*	38 (9.5)
Fever	6 (1.5)
Hospitalization >5 days	62 (15.5)
Neonatal complications	
pH <7.10	14 (3.9)
NICU† hospitalization	10 (2.5)
Apgar <7 at 5 min	13 (3.3)
Respiratory distress syndrome	5 (1.25)

*Hemorrhage: blood loss of >500 ml after vaginal delivery or >1000 ml after cesarean section.

†NICU: neonatal intensive care unit.

risk of UC from 1 to 4 tablets and +12.75% between 4 and 9 tablets; for the risk of AFT, it increased by +2.75% from 1 to 4 tablets and +0.5% between 4 and 9 tablets (Figure 1a). By contrast, the probability to achieve a significant change in the BS after 1 tablet was 6.25% and this increased to 49.25% after 7 tablets. The incremental probability to achieve a significant change in the BS after 7 tablets was low (+2.0% between 8 and 9 tablets). The incremental risk of UC was low with +0.25% with a eighth tablet and no increase thereafter; there was no change in the risk of AFT between 7 and 9 tablets (Figure 1b).

In the multivariate analysis, we showed that the only two risk factors associated with obtaining a $BS \geq 6$ were a baseline score above 2 and the presence of pre-labor rupture of membranes (Table 3). Neither maternal age nor parity was significantly associated with our primary outcome. On the contrary, the hazard to have a significant BS change was decreased when the baseline score was above 2. The presence of pre-labor rupture of membranes increased the hazard for a significant BS change, while high maternal age or parity did not. Finally, the hazard for delivering by cesarean section was significantly increased with nulliparity, $BMI \geq 30$, AFT, and baseline $BS \leq 2$. It was also increased in the absence of a significant change of the BS during cervical ripening (Table 4).

Discussion

Studies assessing the effectiveness of oral misoprostol for cervical ripening have used a range of doses (10–200 μg) and time periods ranging between 12 and 48 h [18–26]. All studies have concluded that it is an effective medication for this indication [10–12]. WHO recommends that cervical ripening with misoprostol should have a maximum duration of 24 h [31]. To our knowledge, there is no study reporting on the incremental benefice of each additional misoprostol tablet and therefore on the optimal duration of misoprostol treatment for cervical ripening. We have shown here that the risk of achieving a $BS \geq 6$ after 4 tablets (8 h) of misoprostol or a significant change in the BS after 7 tablets (14 h) was very low.

In our study, we have used the dose of 20 μg for the first 2 doses followed by 40 μg misoprostol orally every 2 h, based on a prior study performed in our unit which showed that this regimen was safe and efficient [19]. This dosage falls into the category of low dosing (< 50 μg) which has demonstrated good efficacy and few side effects [10]. The mean dose of oral misoprostol needed for cervical ripening was 104 μg, corresponding to previous results ranging from 103 μg when using 50 μg/4 h to 272 μg when using 100 μg/3 h [24,25]. Mean induction to delivery time was 20.5 h and similar to that reported by Thaisomboon et al. (18.8 or 21.2 h depending on the regimen), Faucett et al. (21.9 h), Dodd et al. (21.2 h), and Dallenbach et al. (21.75 h), using regimens ranging from 20 μg/h to 100 μg/4 h [7,18,19,25]. Pongsatha et al. reported that using a higher dose of oral misoprostol (100 μg every 3 or 6 h) dramatically decreased the induction to delivery interval (13.82 or 17.66 h depending on the regimen), with no difference on rates of women achieving vaginal birth within 24 h, but with an increase in side effects [24]. Rates of vaginal deliveries (75.7%) and delivery within 24 h of initiation of labor induction (65%) in our study are also similar to those reported in the literature, even if we take into account that two-thirds of included women had an initial $BS \leq 2$ [7,18,19,23,25]. However, our study differs in that our findings tend to prove that there is no benefit in giving more than 7 tablets of misoprostol, even if the BS remains unfavorable. Therefore, the duration of cervical ripening can be significantly reduced to a maximum of 14 h. Besides reducing the time in the delivery room, medical staff and costs, limiting the duration of cervical ripening might also impact the psychological burden of long labor (tiredness, stress, and psychological sequelae) [27].

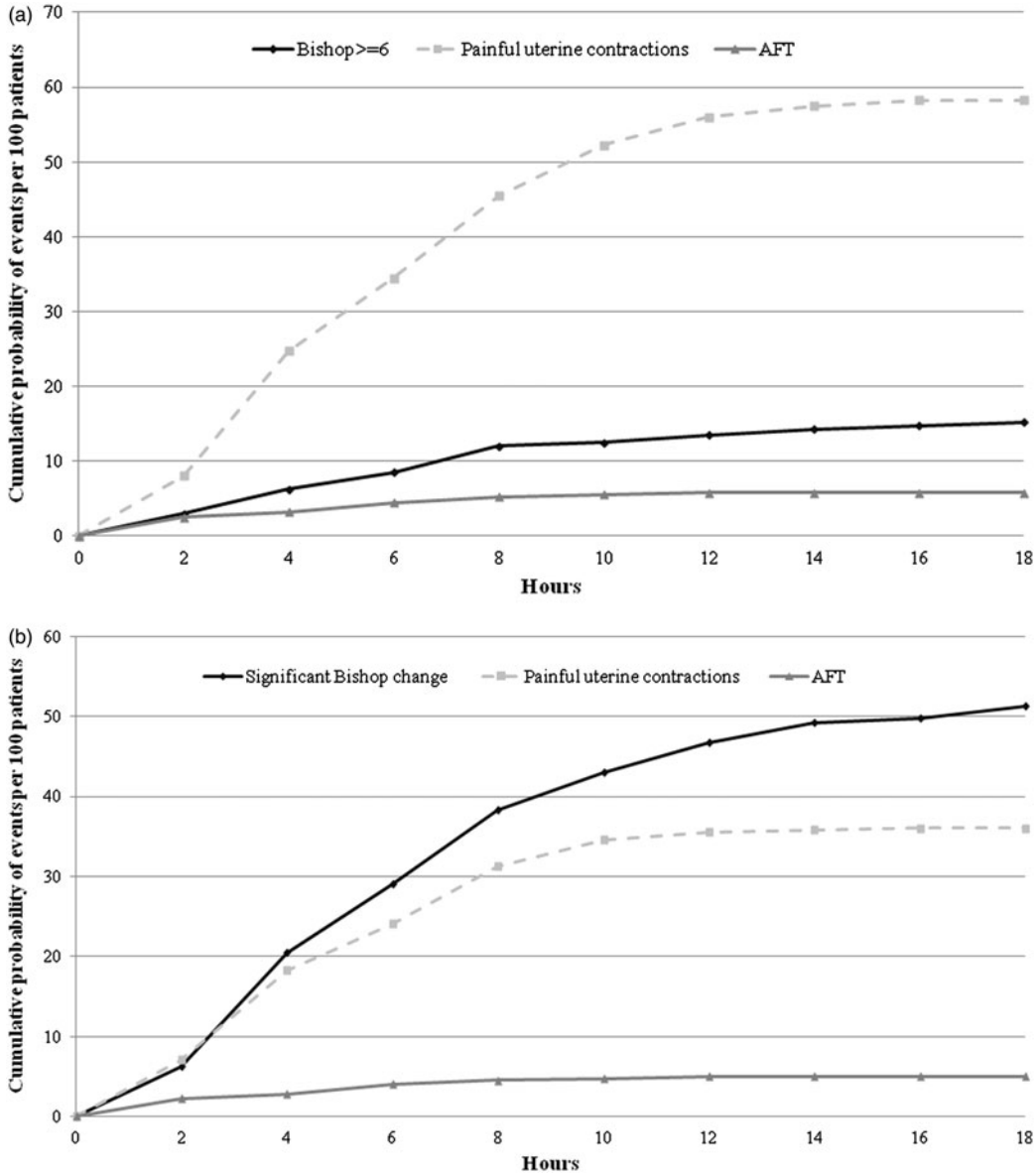

Figure 1. Incremental probability of achieving (a) a Bishop score ≥6, or competing events across time per 100 patients and (b) a significant change in the Bishop score, or competing events across time per 100 patients. AFT: abnormal fetal tracing.

Table 3. Demographical and clinical factors associated with achievement of a Bishop score ≥ 6 (Model 1) and a significant Bishop score change (Model 2)*.

	Model 1			Model 2		
Variables	HR†	95% CI‡	*p*	HR	95% CI	*p*
Maternal age ≥35 years (reference, <35 years)	0.90	0.51–1.58	0.706	0.97	0.73–1.28	0.812
Parity (reference nulliparity)	1.45	0.85–2.48	0.168	1.30	0.96–1.75	0.090
Bishop >2 at misoprostol start (reference, ≤2)	2.41	1.46–3.98	0.001	0.50	0.35–0.72	<0.001
Pre-labor rupture of membranes (reference, no rupture of membranes)	1.87	1.05–3.32	0.032	1.96	1.42–2.71	<0.001
BMI <30 (reference, ≥30)	1.11	0.67–1.85	0.681	0.90	0.69–1.17	0.433

*Results from the competing risks model.

†HR: hazard ratio.

‡CI: confidence interval.

We showed that the factors influencing positively a significant change in the BS were an initial BS ≤ 2 and pre-labor rupture of the membranes. Factors associated with cesarean delivery were nulliparity, BMI ≥ 30, or the presence of AFT. It was also significantly increased in the absence of a significant change of the BS during cervical ripening and when BS was below 2 at misoprostol start. By contrast, the status of the membranes at the time of initiation of cervical ripening was not associated with a higher risk of cesarean section, which is in contradiction with the results of previous

Table 4. Factors associated with cesarean section (versus vaginal delivery)*.

Characteristics	HR	95% CI	*p* values
Maternal age <35 years (reference, ≥35 years)	1.60	0.98–2.61	0.063
Nulliparous (reference, parous)	4.07	1.96–8.48	<0.001
BMI ≥30 (reference, <30)	2.25	1.49–3.40	<0.001
No significant change of the Bishop score (reference, significant change of the Bishop score)	1.53	1.01–2.32	0.047
Bishop ≤2 at misoprostol start (reference, >2)	1.90	1.07–3.37	0.028
Prelabor rupture of membranes (reference, no rupture of membranes)	1.34	0.76–2.38	0.311
AFT† (reference, normal fetal heart rate)	2.42	1.31–4.47	0.005
IUGR‡ (reference, no IUGR)	0.75	0.30–1.83	0.523

*Results from the competing risks model.

†AFT: abnormal fetal heart rate.

‡IUGR: intrauterine fetal growth restriction.

studies [32,33]. Regarding maternal and neonatal side effects and complications, we showed that the use of misoprostol was not associated with severe complications except a high percentage of post-partum hemorrhage, which is comparable to the one described in a recent review paper [34].

The strength of our study is that it was conducted in a university setting where cervical ripening is daily practice with a standardized protocol. Due to the pragmatic context of the study, the definition of the time of occurrence for a BS ≥ 6 or for a significant change in the BS was identical for all women and standardized at every 2 h. This allows decreasing the number of gynecological examinations and improves the quality of care management of the women. In addition, painful UC (indicating risk of uterine rupture) and AFT (indicating fetal distress) were considered as competing events to stop misoprostol earlier and were taken into account by means of a competing risk Cox regression model [30]. By not taking into consideration these competing events, we could have overestimated the cumulative incidence of the outcome under evaluation. However, we used a retrospective cohort and we could not exclude a possible bias inherent to all observational studies. The dose of 40 µg (starting with a tapering dose of 20 µg) of misoprostol might be viewed as a limitation as it is not the most frequently used in some countries such as the USA. On the other hand, it is counter logic to expect a positive effect with a lower dose when there is not with a higher one.

In conclusion, our study shows no benefit in giving more than 7 tablets of oral misoprostol and therefore of prolonging cervical ripening for more than 14 h.

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Declaration of interest

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