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Oral Misoprostol 2 Hourly for Labor Induction

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Abstract

The objective of this study was to assess the efficacy and safety of the 2 hourly oral misoprostol for labor induction. Between May and November 2013, the hospital records of 83 women who were induced for labor and met the eligibility criteria were retrospectively reviewed. Eligibility criteria were singleton pregnancy of at least 34 weeks' gestation and a baseline Bishop score < 6. Women with a previous cesarean section or other uterine surgery, severe pregnancy-induced hypertension, and parity of 4 or more were excluded. Oral misoprostol was administered as 20 μg 2 hourly unless active labor. A maximum of 12 doses was allowed. The age of the women was 27.9 ± 5.3 years (mean ± SD). Vaginal delivery within 24 hours occurred in 38 (45.8%) women. Cesarean delivery occurred in 17 (20.5%) women. Although more parous women achieved vaginal delivery within 24 hours (52.6%) compared with nulliparous women (40.0%), the difference was not significant (P = .35). Uterine tachysystole occurred in 12 (14.5%) women. No perinatal deaths or neonatal intensive care unit admission occurred in the study group. Evidence supporting an optimal regimen is lacking, and additional research is warranted to optimize the use of oral misoprostol for the induction of labor.

Keywords

Recommended Oral Misoprostol Regimen, Induction of Labor

1. Introduction

Labor induction is a common obstetrical intervention. The natural prostaglandin E_2 (dinoprostone) and the synthetic prostaglandin E_1 analog (misoprostol) are effective pharmacological agents for inducing labor. Dinoprostone is approved by the U.S. Food and Drug Administration (FDA) for cervical ripening in pregnant women at or near term, and it has become the drug of choice in many countries [1]. It is commercially available as a vaginal suppository, vaginal and cervical gel, and vaginal insert. Misoprostol is approved by the FDA for re-

ducing the risk of non-steroidal anti-inflammatory drugs-induced gastric ulcers. The American College of Obstetricians and Gynecologists (ACOG) recommended misoprostol for cervical ripening for induction of labor and that the dose should be 25 μg [2]. The WHO recommended the use of 25 μg oral misoprostol 2 hourly or 25 μg vaginal misoprostol 6 hourly for labor induction at term [3]. These recommendations are endorsed by International Federation of Gynecology and Obstetrics (FIGO) [4]. A recent Cochrane review of randomized clinical trials (RCTs) concluded that oral misoprostol is as effective as vaginal misoprostol, results in fewer cesarean sections than vaginal dinoprostone, and the dose should be 20 to 25 μg of oral misoprostol in solution (OMS) [5]. Misoprostol was manufactured and licensed to be taken orally. Nevertheless, vaginal, sublingual, buccal and rectal routes of administration were used in clinical practice in obstetrics and gynecology. After oral misoprostol administration, uterine tonus develops which is followed by uterine contractions with repeated doses [6]. The time to onset of action is 8 minutes, and the terminal half-life is 20 - 40 minutes. The objective of this study was to assess the efficacy and safety of the recommended 2 hourly misoprostol regimen for labor induction.

2. Materials and Methods

After receiving institutional review board approval from the King Abdulaziz University Hospital, the records of women who met the eligibility requirements between May and November 2013, were reviewed. Eligibility criteria included singleton pregnancy of at least 34 weeks' gestation and a baseline Bishop score < 6. Women with a previous cesarean section or other uterine surgery, severe pregnancy-induced hypertension (abnormal liver function tests, protein > 1 g/d, blood pressure of 160/100 mmHg), parity of 4 or more were excluded. Oral misoprostol solution was administered as 20 mL from a 1 μg/mL solution prepared by dissolving a 200 mcg misoprostol tablet (Cytotec; Searle Pharmaceuticals, Leicester, UK) in 200 mL water as described before [7]. Doses were administered 2 hourly unless active labor, with uterine contractions every 3 - 5 minutes lasting 60 seconds or more, was established during the inter-dose interval. A maximum of 12 doses was allowed. If contractions subsequently became inadequate, oxytocin augmentation was provided at least 2 hours after the last misoprostol dose. The primary outcome variable was successful labor induction, defined as the proportion of women achieving vaginal delivery within 24 hours after treatment initiation. Secondary outcomes included the rate of cesarean delivery and need for augmentation with oxytocin. Safety assessments included the incidence of maternal morbidity and adverse neonatal outcomes. Uterine tachysystole was defined as more than five contractions in a 10 minute period without fetal heart rate changes and uterine hyperstimulation as tachysystolic uterine contractions associated with nonreassuring fetal heart rate pattern. Non-reassuring fetal heart rate was defined as an abnormal fetal heart rate on electronic monitoring. The data were analyzed using the Statistical Package for the Social Sciences (SPSS

Inc., Chicago, IL, USA), version 22.0.

3. Results

During the study period, 83 women met the eligibility criteria. The age of the women was 27.9 ± 5.3 years (mean ± SD), post-term pregnancy was the indication in 54 (65.1) women, and the Bishop score was ≤3 in 75 (90.4%) women (Table 1). The median dose of misoprostol was 160 μg (range, 20 - 240). Vaginal delivery within 24 hours occurred in 38 (45.8%) women. Vaginal delivery before 12 hours occurred in 11 (13.3%) women. Cesarean delivery occurred in 17 (20.5%) women. Although more parous women achieved vaginal delivery within 24 hours (52.6%) compared with nulliparous women (40.0%), the difference was not significant (P = 0.35). Uterine tachysystole occurred in 12 (14.5%) compared to 1 (1.2%) with uterine hyperstimulation (Table 2). No perinatal deaths or neonatal intensive care unit admission occurred in the study (Table 3).

Table 1. Baseline characteristics.

Variable	Misoprostol 2 hourly static dose (n = 83)
Age, y	27.9 ± 5.3 (17 - 43)
Gestation, wks	39.8 ± 1.4 (37 - 43)
BMI, kg/m^2	32.6 ± 6.6 (19.8 - 54.6)
Nulliparous, n (%)	45 (54.2)
Bishop score ≤ 3, n (%)	75 (90.4%)
Indication, n (%)	
Post-term	54 (65.1)
IUGR	4 (4.8)
PIH	11 (13.3)
Diabetes	13 (15.7)
Oligohydramnios	6 (7.2)
PROM	0
Other	7 (8.4)

Data are mean ± SD (range) or number (percentage). BMI, body mass index; IUGR, intrauterine growth restriction; PIH, pregnancy induced hypertension; PROM, premature rupture of membranes.

Table 2. Maternal adverse events.

Variable	Misoprostol 2 hourly static dose (n = 83)
Uterine tachysystole	12 (14.5)
Uterine hyperstimulation	1 (1.2)
Shivering	4 (4.8)
Vomiting	1 (1.2)
Nausea	1 (1.2)
Pyrexia	1 (1.2)

Data are number (percentage).

Table 3. Neonatal outcomes.

Variable	**Misoprostol 2 hourly static dose (n = 83)**
Nonreassuring fetal heart rate	11 (13.3)
Meconium-stained liquor	16 (19.3)
Birth weight, g	3262.8 ± 453
Preinatal death	0
Apgar score < 7 at 1 min	7 (8.4)
Apgar score < 7 at 5 min	0
NICU admission, n (%)	0

NICU, neonatal intensive care unit. Data are mean ± SD (range) or number (percentage).

4. Discussion

Although misoprostol is not approved for labor induction, its low cost, stability at room temperature, multiple administration routes, and greater acceptability among pregnant women with oral administration contributed to its widespread off-label use in Europe and most other countries [8]. Many randomized controlled trials have searched for the optimum induction of labor regimen for successful vaginal delivery with fewer adverse effects. The latest Cochrane Database of Systematic Reviews based on 76 trials (14,412 women), recommended that when using oral misoprostol, the dose should be 20 to 25 μg in solution 2 hourly [5].

In the current study, the 83 women treated with 20 μg of an oral misoprostol solution 2 hourly had lesser delivery success at 24 hours of 45.8% compared with 79.7% with 25 μg misoprostol 2 hourly for 12 doses [9]. This subject could be treated a maximum of 12 times with 20 μg oral misoprostol solution (maximum possible dose: 250 μg). Earlier studies using this dose and dose interval allowed a maximum of 4 (80 μg) Moodly [10] and 6 (120 μg) Dodd [11] doses, yet reported 24-hour vaginal delivery rates of 55.3% and 54.0%, compared with 45.8% in this cohort. The majority of recent studies examined 50 μg oral misoprostol every 4 hours, with success in at least 70% of women reported from several studies (e.g., Jindal [12], Mehrotra [13], Nagpal [14]). The discrepancy in vaginal delivery rates between these studies and the current study may be related to heterogeneity among studies. For example, eligibility for women in the study by Jindal *et al.* [12] included ruptured membranes, which have been widely studied in oral misoprostol studies. The Jindal study also required Bishop score ≤ 4, compared with ≤6 in the study by Rahman *et al.* [15]. Women in the Nagpal study [12] were given oxytocin if they were not in active labor after the maximum of 3 doses. Almost two-thirds (64.5%) had delivered during the 12-hour maximally allowed dosing interval, with only 16.1% requiring oxytocin. Although a total of 5 oral doses of 50 μg were possible in the study by Rahman *et al.* [15], the women received a mean of 2.33 doses. However, the reported mean dose (163 μg) was similar to that (165 μg) used in the current study, and both

groups had similar low 24-hour delivery. These variable women characteristics, regimens, and outcomes suggest that the optimal regimen and the population for induction of labor with oral misoprostol are not yet clarified. A more effective regimen with more consistent outcomes is needed. Therefore, the oral route is worthy of continued investigation. Also, the acceptability of introducing a recommended protocol without a parallel comparison group is consistent with any effort to get with the Guidelines. In conclusion, more research is needed to optimize the use of oral misoprostol for the induction of labor.

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