OBSTETRICS

Randomized clinical trial between hourly titrated oral misoprostol and vaginal dinoprostone for induction of labor

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OBJECTIVE: The objective of the study was to compare the efficacy and safety of hourly titrated oral misoprostol with vaginal dinoprostone insert.

STUDY DESIGN: Subjects were randomized into hourly titrated oral misoprostol or dinoprostone 10 mg vaginal insert. Misoprostol was given as 20 μg hourly for 2 doses. In the absence of regular uterine contractions, the dose was increased to 30 μg hourly for 3 doses and then 40 μg for 1 dose, 50 μg for 1 dose, and 60 μg hourly for 4 doses. Before the 40 and 50 μg doses, 1 more hour of observation was given. The primary outcome variable was vaginal delivery within 24 hours. Safety assessments included the incidence of maternal morbidity and adverse neonatal outcomes.

RESULTS: A total of 160 women was enrolled in the study. The groups were similar for demographic and clinical factors. Vaginal delivery was achieved within 24 hours in 100 women (62.5%): 44 in the dinoprostone group (55.0%) and 56 in the misoprostol group (70.0%) ($P = .05$). The proportion of women who achieved vaginal delivery within 24 hours was significantly greater for nulliparous women in the misoprostol group (24 of 51, 58.5%) compared with the dinoprostone group (12 of 36, 33.3%; $P = .0270$). Significantly more women with baseline Bishop score of 3 or less in the misoprostol group had successful induction (43 of 59, 72.9%) compared with the dinoprostone group (27 of 60, 45.0%; $P = .002$). Frequencies of maternal adverse events were similar between groups.

CONCLUSION: Hourly titrated oral misoprostol can provide an efficacious and safe substitute for the expensive dinoprostone vaginal insert.

Key words: hourly, misoprostol, oral, titrated

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Induction of labor for both elective reasons and clinical indications continues to increase worldwide. Misoprostol, a synthetic prostaglandin E1 analog, can be administered orally, sublingually, buccally, intravaginally, or rectally and is used for both cervical ripening and labor induction. According to the American College of Obstetricians and Gynecologists (ACOG), there is extensive clinical experience with misoprostol, and a large body of published reports supports its safety and efficacy when used appropriately.[1]

A Cochrane review of 56 randomized clinical trials (RCTs) of oral misoprostol with a total of 11,590 women concluded that this treatment is as effective as vaginal misoprostol for inducing vaginal delivery and results in fewer caesarean deliveries compared with vaginal dinoprostone.[2] Based on their review, the authors recommended a dose of oral misoprostol in solution (OMS) of 20-25 μg; however, a specific regimen was not supported, and trials that included fixed and titrated doses were pooled.

The World Health Organization recommendation of a fixed OMS dose of 25 μg every 2 hours for labor induction based on moderate-quality evidence and strong recommendation[3] was recently supported by the International Federation of Gynecology and Obstetrics.[4] However, trials continue in efforts to identify the optimum treatment regimen.

Misoprostol has a short half-life (20-40 minutes) following oral administration. It reaches peak serum concentration in 30 minutes, followed by a rapid decline to low levels by 120 minutes, with a more gradual decline thereafter.[5] Compared with 2 hour dosing, hourly titrated oral misoprostol dosing may provide a more steady state drug level within the zone of therapeutic efficacy, which may result in improved clinical outcome. There are limited data, however, regarding the use of hourly titrated oral misoprostol. Based on pharmacokinetics, previously published regimens, and the incidence of side effects, we hypothesized that stepwise hourly titrated oral misoprostol is efficacious and safe.

The objective of this study was to compare the efficacy and safety of a stepwise protocol of hourly titrated oral misoprostol with vaginal dinoprostone insert in women scheduled for labor induction.

Materials and Methods

This open-label randomized trial was approved by the King Abdulaziz

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University Hospital (KAUH) Institutional Review Board. All women admitted to the KAUH (Jeddah, Saudi Arabia) for whom induction of labor was indicated by their attending obstetrician, who met the eligibility criteria, and from whom written informed consent was obtained by the physician were enrolled. Inclusion criteria included singleton pregnancy of at least 34 weeks' gestation and a baseline Bishop score less than 6. Women with contraindications for use of either drug, previous cesarean section or other uterine surgery, severe pregnancy-induced hypertension (abnormal liver function tests, protein >1 g/d, blood pressure of ≥160/100 mm Hg), parity of 4 or more, or with uterine contractions were excluded.

Women were randomized into the misoprostol or dinoprostone groups (1:1) using computer-generated numbers, with allocation concealed in opaque envelopes distributed by the obstetrics ward nurse. Labor management at the KAUH is standardized and includes electronic fetal monitoring performed 1 hour before and 1 hour after the start of induction, which is continued after the beginning of uterine contractions until delivery. Intramuscular or intravenous analgesia is given for pain relief during labor. Delivery is conducted by in-house staff, usually residents and senior residents under the care of the on-call consultant.

Oral misoprostol was administered from a 1 μg/mL solution prepared from a 200 μg misoprostol tablet (Cytotec; Searle Pharmaceuticals, Leicester, UK) dissolved in 200 mL of water, following the procedure described in other studies.[2] Cutting the tablets is difficult and imprecise, and oral misoprostol in solution not only allows precise dosing, but also the misoprostol remains active in solution for 24 hours.[2] The starting dose was 20 μg hourly for 2 doses. In the absence of regular uterine activity, the dose was increased to 30 μg hourly for 3 doses and then 40 μg for 1 dose, 50 μg for 1 dose, and 60 μg hourly for 4 doses. Before administering the 40 μg and 50 μg doses, 1 more hour of observation was given.

Regular uterine activity is defined as regular uterine contractions every 3-5 minutes and lasting 60 seconds or more. At any time, if establishment of active labor was achieved, no further misoprostol was given. If contractions subsequently became inadequate, oxytocin augmentation was provided at least 2 hours after the last misoprostol dose. Dinoprostone 10 mg vaginal insert (Propess; Controlled Therapeutics, East Kilbride, Scotland) was placed manually in the posterior fornix for a maximum of 24 hours or until the establishment of regular uterine activity and then was removed. If contractions subsequently became inadequate, oxytocin augmentation was provided at least half an hour after removal of the insert.

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 interval to delivery from first treatment (hours), 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 5 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. Nonreassuring fetal heart rate was defined as an abnormal fetal heart rate on electronic monitoring.

Statistical Analysis

Several studies comparing oral misoprostol with vaginal prostaglandins for the induction of labor failed to show a statistically significant difference in rates of vaginal delivery within 24 hours, with success rates ranging from 54% to 74%.[1] In the study by Cheng et al, [6] however, 94% of subjects delivered within 24 hours after oral titrated misoprostol, compared with 54% after vaginal misoprostol. Using an intermediate projection of 60% delivery within 24 hours for dinoprostone and 80% for misoprostol would require 82 subjects per group at alpha = .05 with 80% power. Analysis was performed on an intent-to-treat basis. Dichotomous variables were compared between groups using χ^2 analysis, and continuous variables using the independent Student t test, with $P < .05$ indicating statistical significance.

Results

A total of 160 women were enrolled between January 2011 and July 2012, of whom 80 were randomized to the misoprostol and 80 to the dinoprostone vaginal insert groups (Figure). The groups were similar for demographic and clinical factors (Table 1). They were 28.8 ± 5.5 years of age. Approximately half had previous deliveries. Three fourths of the women had a Bishop score of 3 or less at baseline, and postterm was the primary induction indication for 93 (58.1%) women.

Women in the misoprostol group received a median of 9 (range, 2–11) doses (median dose, 340 μg; range, 40–460 μg). In the entire cohort, vaginal delivery was achieved within 24 hours in 100 subjects (62.5%): 44 (42 normal vaginal deliveries and 2 ventouse extractions) in the dinoprostone vaginal insert group (55.0%) and 56 (55 normal vaginal deliveries and 1 ventouse extraction) in the misoprostol group (70.0%) ($P = .05$; power, 50%; relative risk relative risk [RR], 1.5, 95% confidence interval [CI], 0.99–2.27) (Table 2).

Proportions with vaginal delivery within 12 hours and interval from first treatment to vaginal delivery were not significantly different between groups. Proportions achieving vaginal delivery within 24 hours were similar between groups for women with previous childbirth ($P = .313$); however, the proportion of women successfully induced was significantly greater for nulliparous women in the misoprostol group (24 of 51, 58.5%) compared with the dinoprostone vaginal insert group (12 of 36, 33.3%; $P = .027$).

In addition, proportions were similar between groups for women with indications for induction other than status postterm, whereas significantly more misoprostol-treated postterm women delivered vaginally within 24 hours (37 of 48, 77.1%) compared with dinoprostone-treated women (25 of 45, 55.6%; $P = .028$). Although more women in the dinoprostone vaginal insert group whose Bishop score at baseline was 4 or 5 had successful induction (17 of 20, 85.0%)