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Low-dose vaginal misoprostol versus vaginal dinoprostone insert for induction of labor beyond 41st week: a randomized trial

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CONFLICTS OF INTERESTS

The authors declare not having potential conflicts of interest.

FUNDING

The authors are financially independent. No specific funds were needed to develop this trial.

ABSTRACT

Introduction: The aim of this study was to compare the efficacy and safety of low-dose protocol of vaginal misoprostol and vaginal dinoprostone insert for induction of labor in women with post-term pregnancies. **Material and methods:** We designed a prospective, randomized, open-labeled, blinded for the end-point evaluators trial including women of at least 41 weeks of gestational age with uncomplicated singleton pregnancies and Bishop score lower than 6. They were randomized into dinoprostone or misoprostol groups in a 1:1 ratio. Baseline maternal data and perinatal outcomes were recorded for statistical analysis. Successful vaginal delivery within 24 hours was the primary outcome variable. A p value < 0.05 was considered statistically significant. This study was registered in ClinicalTrials.gov (number NTC03744364). **Results:** We included 198 women for analysis (99 women in each group). Vaginal birth rate within 24 hours did not differ between groups (49.5% vs 42.4%; p = 0.412). When Bishop score was lower than four, dinoprostone insert showed a higher probability of vaginal delivery within 12 hours (17.8% vs 4%; p = 0.012). In dinoprostone group, it was more probable to require removal of the insert because of any adverse event (5.1% vs 14.1%; p = 0.051) and to show an abnormal fetal heart rate pattern during active labor (44.4% vs 58.6%; p = 0.047). Both groups were similar in neonatal outcomes including Apgar score, umbilical cord pH and Neonatal Intensive Care Unit admission. **Conclusions:** Low-dose vaginal misoprostol and vaginal dinoprostone insert seem to be equally effective and safe for induction of labor in pregnant women with a gestational age beyond 41 weeks.

Keywords

Induced labor, Cervical Ripening, Obstetric Labor, Misoprostol, Dinoprostone, Pregnancy

Abbreviations

CI: Confidence Interval

RR: Relative Risk

Key message

This trial compares dinoprostone and misoprostol for induction of labor in nulliparous women with postterm pregnancies. There were no differences between groups in vaginal delivery rate or perinatal outcomes. We conclude that both drugs can be equally safe and effective.

INTRODUCTION

Induction of labor is an obstetric procedure that is becoming more and more frequent through the years. Misoprostol is a synthetic prostaglandin with a variety of ways of administration with individual pharmacodynamic characteristics for each one of these administration options [1]. Dinoprostone is another pharmacological agent that can be used vaginally as a gel or as a slow-releasing insert. Both drugs are considered safe and effective for induction of labor in maternal or fetal conditions that may complicate pregnancies and make initiation of labor desirable [2].

Misoprostol is an inexpensive and thermostable drug. However, it has a long-lasting effect and it is difficult to remove in case of undesirable maternal and fetal effects. On the contrary, dinoprostone vaginal insert is a drug whose cost is higher and requires refrigeration for storage. This device can be easily removed if any complication happens, and after 30 minutes, its effect has already finished [3].

There are some studies that have evaluated different ways of induction of labor although, unfortunately, different administrations regimes and ways of administration of prostaglandin agents make it difficult to compare several options for cervical ripening. Besides, inclusion criteria for different trials comparing both induction methods are heterogeneous, including different clinical situations that may have individual patterns for induction process (i.e. rupture of amniotic membranes) [4].

Different authors have shown that misoprostol (particularly using 50 mcgr every four to six hours) can be as effective as vaginal dinoprostone insert, even achieving delivery within 24 hours in a higher proportion of women. In contrast, vaginal dinoprostone insert may be associated with a lower rate of tachysystole and uterine hyperstimulation and, consequently, a lower risk of abnormal fetal heart tracings. This type of side effects linked to the use of misoprostol seem to be reduced when using low dose regimes [5, 6].

The objective of this study was to compare the efficacy and safety of a low-dose protocol of vaginal misoprostol with a vaginal dinoprostone insert in women with post-term pregnancies scheduled for labor induction in the absence of any other risk factor.

MATERIAL AND METHODS

We designed a prospective, randomized, open-labeled, blinded for the end-point evaluators trial in Hospital Universitario Miguel Servet (Zaragoza), a Spanish tertiary hospital attending around 4000 births every year. All women with post-term pregnancies of at least 286 days of gestational age with otherwise uncomplicated singleton pregnancies were assessed in a Maternal-Fetal Unit by specialized obstetricians after a gestational care conducted by a general obstetrician and a mid-wife in a low-risk unit.

A thorough medical and obstetrical history was recorded in first visit between 40⁺⁶ and 41⁺¹ weeks, as well as a complete gynecological exploration, a non-stressing fetal test and an ultrasound assessment to confirm fetal well-being. The attending obstetrician informed and discussed with the woman usual protocols of management of induction of labor for post-term pregnancies in our hospital and confirmed if the woman met the selection criteria to be included in this trial.

Inclusion criteria were: singleton uncomplicated nulliparous women with live fetus of at least 286 days of gestational age with indication for induction of labor because of post-term pregnancy, absence of any contraindication for vaginal birth and a baseline Bishop score lower than six. Exclusion criteria were: multiple pregnancy, multiparity, stillbirth, oligohydramnios, suspected fetal distress, severe asthma, any known allergy or intolerance to prostaglandin agents or any contraindication for vaginal delivery. A verbal and written informed consent were obtained from all individual participants included in the study.

All women of this trial were admitted at the hospital between 41⁺⁴ and 41⁺⁶ weeks. At that moment, and if all selection criteria were met, women were randomized into dinoprostone or misoprostol group in a 1:1 ratio using a computerized numerical sequence. These women were allocated to one of the groups after reassuring verbal consent before starting the induction process. Induction was carefully controlled by midwives and obstetricians and regular fetal monitoring was performed to ensure fetal well-being.

A dinoprostone 10 mg insert (Propess®; Ferring S.A.U.; Orense, Spain) was placed by the attending obstetrician in the posterior fornix of the vagina for 24 hours or until a labor had started. Vaginal misoprostol tablets were administered with repeated doses of 25 mcgr (Misofar 25 mcgr ®; Laboratorios BIAL, S.A.; Zamudio, Spain) every four hours with a maximum of six doses in 24 hours. If uterine activity appeared with progressive cervical modifications, misoprostol administration was suspended for two hours and restarted if Bishop score did not improve. We considered active labor as a cervical dilation of at least three centimeters with a minimum cervical effacement of 80% and regular uterine contractions (at least one every 10 minutes).

If an abnormal fetal heart rate tracing was detected during induction period, the drug was removed and then, continuous monitoring and oxytocin induction or urgent cesarean section was performed depending on the type of abnormalities detected.

If these women did not start labor after 24 hours, a second induction could be considered using the same prostaglandin agent or using a mechanical device. Artificial rupture of membranes and oxytocin induction was used if labor did not initiate after two failed induction attempts or if Bishop score was more than five after induction.

If contractions subsequently became inadequate, oxytocin augmentation with artificial rupture of membranes was initiated at least half an hour after the removal of the dinoprostone insert or four hours after the last dose of misoprostol was administered. Epidural analgesia was provided under maternal request. Intrapartum assessment was offered as stated in our protocols based on recommendations given by Spanish Health Ministry. Continuous fetal heart rate monitoring was performed during active labor and it was considered abnormal when it was classified in categories II and III of American College of Obstetricians and Gynecologists. If needed, fetal scalp blood test was performed to confirm fetal wellbeing.

We decided to use successful vaginal delivery within 24 hours after starting induction process as the primary outcome variable. Secondary outcome variables were successful cervical ripening within 24 hours defined as Bishop score of seven or more after 24 hours, interval time from induction to delivery, need for a second induction drug/device and vaginal delivery rate. Variables regarding fetal well-being during induction and labor periods (abnormal fetal cardiotocographic tracings, need for fetal scalp blood testing or meconium-stained liquor) were recorded. Induction assessments included maternal morbidity and adverse events related with prostaglandin use.

All the information about induction, labor and perinatal period was collected on a paper form created specifically for this trial. A computerized database was designed for statistical analysis of these data using SPSS version 15.0 for Windows.

Statistical analyses

Although not many studies have been published comparing vaginal misoprostol (25 mcg every four hours) with dinoprostone 10 mg vaginal insert, we managed to establish an estimated proportion of patients that could have a vaginal delivery within 24 hours in each group by reviewing previous literature regarding comparisons between both drugs with

different dosages and ways of administration. After that, we decided to set an estimated difference between groups of 20 % in the primary outcome variable, that required at least 85 women recruited for each prostaglandin group, considering an alpha value 0.05 with 80% of statistical power and a 5% of losses to follow-up. Final analysis was performed from an intention-to-treat approach.

Descriptive statistics were calculated for all the variables. Bivariate analysis was performed with Chi-square and Fisher's exact tests for qualitative dichotomic variables. For quantitative variables, T-Student and Mann-Whitney test were used depending on the result of previous normality test for each variable. The relative risks (RRs) with corresponding 95% confidence intervals (CI) or the adjusted p-values were calculated. SPSS version 15.0 for Windows was used for statistical analysis.

Ethical approval

This study has the approval of the local ethics committee (Act N. 09/2014, Comité Ético de Investigación Clínica de Aragón, CEICA). This study was registered in ClinicalTrials.gov with registration number NTC03744364.

RESULTS

Finally, 260 women met the inclusion criteria between April 2014 and October 2017. Five of these patients refused to participate and 55 patients were excluded because of initiating spontaneous active labor before induction and randomization process. Two women, since having a Bishop score higher than six, initiated oxytocin augmentation without prostaglandin administration and they were excluded from final analysis. All remaining women were allocated to misoprostol or dinoprostone group using a computer-generated simple randomization list with a 1:1 allocation and they were included for statistical analysis (Figure 1).

Maternal body mass index was higher than 30 kg/m² in a high proportion of women (72 women, 37.3%) without differences between both groups. Regarding to other maternal-fetal data, there were no differences in baseline characteristics (Table 1). Women in the

misoprostol group received a median of three doses (interquartile range: three to four). Mean total dose of misoprostol was 81.5 mcgr (standard deviation 30.85).

Regarding to the main outcome variable, ninety-one women achieved vaginal delivery within 24 hours. Although there was a higher rate of vaginal birth within 24 hours in misoprostol group, these differences did not reach statistical significance (49.5% vs 42.4%; $p=0.412$). No differences were found regarding vaginal birth within 12 hours (13.1% vs 7.1%; $p=0.157$). There was a lower probability of needing of a second induction method in misoprostol-treated patients but without statistical significance (10.1% vs 18.2%; $p=0.103$). Furthermore, there were no differences in terms oxytocin induction, cesarean birth or operative vaginal delivery rates.

We did not found differences in the duration of the induction process (Table 2). In women with very unfavorable cervical conditions (Bishop score less than four), there was a higher proportion of delivery within 12 hours in dinoprostone group (17.8% vs 4%; $p=0.012$; RR = 2.835; CI; 95% 1.02 – 7.89). Maternal adverse events were similar for both groups. Women in dinoprostone group had higher rates of retrieval due to any adverse event without statistical significance (5.1% vs 14.1%; $p=0.051$) (Table 3).

There was a higher risk of abnormal fetal heart rate patterns during active labor in dinoprostone group (58.6% vs 44.4%; $p=0.047$; RR = 1.768; CI; 95% 1.01-3.11). During prostaglandin administration, the probability of having an abnormal fetal monitoring was similar between groups (12.1% vs 4%; $p=0.065$). Both groups were similar in meconium-stained liquor, need for fetal scalp blood test, suspected intrapartum distress, birthweight, Apgar score, umbilical cord pH or Neonatal Intensive Care Unit admission (Table 4).

DISCUSSION

Nowadays, prostaglandins (misoprostol and dinoprostone) are considered useful for induction of labor in pregnant women at term. Our data confirm that both drugs can be equally adequate for induction of post-term pregnancies. However, some differences could be found. For instance, women allocated to dinoprostone had a higher risk of abnormal fetal heart rate tracings during active labor. Despite of this fact, neonatal outcomes did not differ between groups. We observed a proportion of categories II and III tracings in both groups similar to

other studies considering the higher rate of abnormal tracings reported for women in their 41st week [6].

Several studies have compared both drugs with conflicting results. The heterogeneity in dosages, pharmacological presentations and ways of administration make it difficult to establish direct comparisons. To our knowledge, this is the first prospective trial comparing a low-dose protocol of vaginal misoprostol and a vaginal dinoprostone insert in such a homogeneous group of women. Because of a higher risk of adverse events reported in scientific literature in misoprostol-treated women with higher doses (50 mcgr or above), we implemented a low-dose protocol with 25 mcgr every four hours to minimize the risk of uterine hyperstimulation.

In our trial, we observed no differences in most variables assessed. Similarly, a trial comparing vaginal dinoprostone insert and titrated oral misoprostol with 160 women found no differences between groups in vaginal delivery within 24 hours. However, a higher probability of successful induction was observed when Bishop score was less than four in misoprostol-treated women (72.9% vs 45.0%; $p = 0.002$) [7].

Generally, higher frequencies of uterine hyperstimulation are shown with higher dose of misoprostol. A randomized trial assessed the risk of adverse events with 200 mcgr of misoprostol and vaginal dinoprostone and showed a higher risk for those included in the misoprostol group (3.2 % vs 1.9%) with higher rates of intrapartum adverse fetal events and neonates admitted to Neonatal Intensive Care Unit in misoprostol-treated group (10.4% vs 3.7%) [3].

A randomized trial that included 415 women showed that 50 mcgr of misoprostol every 6 hours resulted in a shorter induction-to-delivery time and less oxytocin augmentation compared with 3 mg of vaginal dinoprostone but higher rates of tachysystole were found [8].

Some trials have used lower doses of misoprostol to reduce the risk of hyperstimulation or fetal distress. A randomized controlled trial aimed to compare misoprostol 25 mcgr every six hours with dinoprostone gel. This study found no differences between both methods. However, because of a limited sample size (50 patients for each group), it may not have enough statistical power to detect differences [9].

The low-dose protocol of misoprostol used in our study has been already used in comparison with dinoprostone. A large trial that included 592 women allocated to vaginal dinoprostone (2mg gel), vaginal misoprostol 25 mcgr every four hours or transcervical balloon catheter. Both prostaglandins showed similar outcomes [10]. A retrospective study compared induction of labor in women with oligohydramnios not being able to confirm differences between both drugs. In this case, doses of each prostaglandin used for induction of labor were not stated in the published data [11].

Oral misoprostol has been widely used for induction of labor at term with good results. A study using oral misoprostol solution or vaginal dinoprostone including 481 women reported higher vaginal delivery rates within 12 hours (40.1% vs 21.4%; $p = 0.03$), a shorter duration of labor (15.7% vs 21.3%) and a two-fold risk to have a partus precipitatus in the dinoprostone group (5.5% vs 2.7%; $p = 0.04$). In our study, women with dinoprostone had a higher probability of showing non-reassuring fetal heart tracings (11.1% vs 7.1%; $p = 0.04$). Nevertheless, they failed to find differences in vaginal delivery [12].

Due to the amount of studies published and the diversity in dosage and posology of each prostaglandin between trials, some authors have tried to summarize that scientific evidence. A systematic review found that vaginal misoprostol achieved a higher rate of vaginal delivery within 24 hours (22 trials; average RR = 0.77; 95% CI; 0.66-0.89). However, the authors remark that this increase could only be shown in those trials with a dosage of at least 50 mcgr in the first six hours. Uterine hyperstimulation seemed to be more frequent in misoprostol-treated women (31 trials; average RR = 1.43; 95% CI; 0.97- 2.09) [6].

Besides, the authors show that oxytocin augmentation (36 trials; average RR = 0.68; 95% CI; 0.60-0.76) and epidural analgesia (eight trials; RR = 0.92; 95% CI; 0.85-0.99) was less frequent in women with misoprostol. A higher risk of meconium-stained liquor was detected in the misoprostol group (18 trials; RR = 1.35; 95% CI; 1.13-1.61) [6].

Another meta-analysis published in 2014 comparing intracervical dinoprostone with vaginal misoprostol, found that misoprostol increased the rate of vaginal delivery within 24 hours (RR = 1.27; 95% CI; 1.10-1.48; $p = 0.002$) with lower probability of oxytocin augmentation (RR=0.62; 95% CI; 0.54-0.72; $p < 0.001$) but higher risk of tachysystole (RR = 2.02; 95% CI; 1.28-3.19; $p = 0.003$) without differences in Apgar score [13].

All this evidence suggests that adverse events associated with misoprostol are dose-dependent. In fact, most articles published demonstrate higher risk of uterine hyperstimulation with higher doses of this prostaglandin although fetal distress rates are similar in the vast majority of the publications [14,15,16,17]. Some studies show that misoprostol may be more effective than dinoprostone and oxytocin for induction of labor [18,19]. Misoprostol has been proved effective in different dosage regimes even with increasing doses [20].

One of the main strengths of this study is the type of design, a randomized trial with a homogeneous group of nulliparous women in their 41st week, one of the main indications for induction of labor. These strict selection criteria were established to avoid biases due to a heterogeneous sample. Consequently, these conditions could increase the internal validity of our results, but it could reduce the possibility of extrapolating our data to other clinical contexts.

Because of the prospective design of this study, the possibility of missing data can be minimized. In addition, the variables were designed specifically to avoid bias and to avoid variability due to subjective variables. However, some variables had to be self-reported by the women and this information could be influenced by their perception of different symptoms during the induction process.

Although a triple blinding approach was not possible because of the different pharmaceutical presentation and posology for each drug, we tried to reduce the risk of biases with a blinding for the end-point evaluator. The sample size was adequate to find differences in the primary outcome variable between groups and prospective design allowed a more accurate data collection. However, the number of women included may be insufficient to evaluate infrequent events or small differences between both treatments.

Our results suggest that misoprostol and dinoprostone can be equally effective and with a low incidence of maternal-fetal complications. Stability at room temperature, simple administration and a reduced cost can make misoprostol a good option for labor induction. Intravaginal device of dinoprostone can be eventually removed easily in case of any adverse event and it has been proven safe even in women with a previous cesarean section. Furthermore, because of its slow-releasing insert, intravaginal dinoprostone does not require

a repeated administration of additional doses that may reduce discomfort for the women during the induction process.

CONCLUSION

Low-dose vaginal misoprostol and vaginal dinoprostone insert seem to be equally effective and safe methods for induction of labor in pregnant women with a gestational age beyond 41 weeks. The choice between both options should be made by the clinician, considering the advantages and disadvantages of each drug in every clinical context.

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Legends

Figure 1.- Eligibility process and randomization.

Table 1.- Baseline characteristics.

Table 2.- Labor outcomes.

Table 3.- Maternal adverse effects.

Table 4.- Neonatal outcomes.

Table 1.- Baseline characteristics.

Variable	Misoprostol (n=99)	Dinoprostone (n=99)	p value
Maternal age (years)*	33.52 (± 5.04)	33.49 (± 4.9)	0.977
Maternal height (cms) ⁺	165 (160-168)	165 (160-170)	0.412
Maternal weight (kg)*	78.12 (± 11.88)	77.39 (± 11.79)	0.665
BMI (kg/m ²)*	29.07 (± 4.57)	28.63 (± 4.29)	0.483
Gestational age (days) ⁺	292 (291-292)	292 (292-292)	0.633
Initial Bishop Score ⁺	3 (2-3)	3 (2-4)	0.412

* Data shown as mean (± SD).

⁺ Data shown as median (interquartile range: 25th centile – 75th centile).

BMI, Body Mass Index (based on term gestation maternal weight).

Table 2.- Labor outcomes.

Variable	Misoprostol (n=99)	Dinoprostone (n=99)	p value
Time to uterine activity after prostaglandin administration (h) ⁺	7 (5-12)	7 (4-12)	0.570
Time to active labor (h) ⁺	13 (8-20)	13 (9-23)	0.701
Induction-delivery interval (h) ⁺	21,6 (16.3-33.5)	21.7 (15-29.8)	0.637
Delivery ≤ 12 h [*]	7 (7.1)	16 (16.2)	0.074
Delivery ≤ 24 h [*]	57 (57.6)	55 (55.5)	0.774
Vaginal delivery ≤ 12 h [*]	7 (7.1)	13 (13.1)	0.157
Vaginal delivery ≤ 24 h [*]	49 (49.5)	42 (42.4)	0.412
Need for second preinduction [*]	10 (10.1)	18 (18.2)	0.103
Need for oxytocin induction [*]	24 (24.2)	27 (27.3)	0.626
Operative vaginal delivery [*]	37 (37.4)	28 (28.3)	0.483
Cesarean section [*]	22 (22.2)	26 (26.3)	0.507

* Data shown as n (%).

⁺ Data shown as median (interquartile range: 25th centile – 75th centile).

Table 3.- Maternal adverse effects.

Variable	Misoprostol (n=99)	Dinoprostone (n=99)	p value
Uterine hyperstimulation	7 (7.1)	10 (10.1)	0.447
Poor maternal tolerance to prostaglandin [*]	0 (0)	2 (2.0)	0.155
Need to stop prostaglandin administration (for any side effect)	5 (5.1)	14 (14.1)	0.051
Need to use tocolytic drug	9 (9.1)	10 (10.1)	0.809

Data shown as n (%).

* Including shivering, vomiting, pyrexia or unbearable pain that leads to stop the prostaglandin administration.

Table 4.- Neonatal outcomes.

Variable	Misoprostol (n=99)	Dinoprostone (n=99)	p value
Nonreassuring fetal heart rate during preinduction	4 (4.0)	12 (12.1)	0.065
Meconium-stained liquor during preinduction	2 (2.0)	3 (3.0)	0.651
Intrapartum abnormal FHR pattern	44 (44.4)	58 (58.6)	0.047
Need for fetal scalp blood test	19 (19.2)	21 (21.2)	0.723
Suspected intrapartum fetal distress*	17 (17.2)	15 (15.2)	0.699
Birthweight (g) ⁺	3482.92 (± 366.8)	3475.31 (± 359.0)	0.830
Apgar score < 4 at 1 min	1 (1.0)	1 (1.0)	1.000
Apgar score < 7 at 5 min	0 (0)	1 (1.0)	0.316
Umbilical cord pH < 7.10	11 (11.2)	9 (9.1)	0.620
NICU admission	2 (2.0)	2 (2.0)	1.000

Data shown as n (%). NICU: Neonatal Intensive Care Unit.

* Suspected fetal distress that requires ending labor process.

⁺ Expressed as mean (± SD).

Figure 1.- Eligibility process and randomization.

