A prospective randomized trial of labor induction with vaginal controlled-release dinoprostone inserts with or without oxytocin and misoprostol+oxytocin

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Summary

Objective: This study was designed in an aim to compare the efficacies of three labor induction methods, dinoprostone (PGE2) vaginal insert with or without concomittant oxytocin and misoprostol (PGE1) combined with oxytocin infusion. *Methods:* This was a prospective observational trial of nulliparous women undergoing labor induction from December 2006 to January 2007. Inclusion criteria were: gestational age between 36 to 42 weeks, singleton cephalic presentation of the fetus, intact membrane and unfavorable cervical Bishop score < 6, and absence of spontaneous uterine contractions. Participants were then randomly assigned to preinduction cervical ripening with a dinoprostone vaginal insert (10 mg) administered into the posterior fornix for a total of 12 hours without oxytocin (group I); with oxytocin (group II), and with misoprostol (50 μg) intravaginally in the posterior fornix with repeat dosing at 6-hour intervals with a maximum dose of four with oxytocin (group III). *Results:* A total number of 106 women met the inclusion criteria without distribution for 19 cases in group I, 44 and 43 cases in groups II and III, respectively. There were no statistically significant differences in terms of the demographic characteristics, indication of labor induction, interval from-induction-to-delivery, cardiotocographic abnormalities and neonatal outcomes and mode of deliveries among the three groups ($p > 0.05$). *Conclusions:* Three methods of labor induction were equally efficient in achieving succesful delivery without any maternal and fetal adverse outcomes.

Key words: Labor induction; Oxytocin; Controlled-release dinoprostone vaginal insert: Misoprostol.

Introduction

Labor induction is an obstetric challenge for women with an unfavorable cervix. The aim of labor induction is straightforward vaginal delivery within 12-24 hours of induction. In an attempt to optimize labor induction, there has been a concerted effort to elucidate the role of several agents available for cervical ripening) in achieving a successful vaginal delivery, including mechanical and pharmacological methods like cervical stripping, an extra-amniotic foley catheter, oxytocin, a controlled-release dinoprostone vaginal insert (PGE_2), misoprostol (PGE1), and mifepristone [1-5]. Prostaglandin analog studies in the last decade have demonstrated that both oral and local administration of these compounds shortened induction-to-delivery intervals, and lowered maximum dose of oxytocin compared to a placebo [6-8]. However, the most significant adverse effects of PGE_1 or PGE_2 were uterine hyperstimulation and systemic side-effects [1, 5, 9].

The ideal agent must effectively induce labor, needs to be safe, easy to administer, and acceptable to the patient. The most frequent pharmacological method for labor induction is intravenous oxytocin [1].

The purpose of this study was to determine whether the administration of a controlled-release dinoprostone vaginal insert with or without oxytocin and misoprostol with oxytocin would result in shorter induction times, and to assess the undesirable outcomes of each regimen such as uterine hyperstimulation, vaginal delivery not achievable within 24 hours, fetal heart rate abnormalities, neonatal morbidity assesed by Apgar score, and admission to the nenatal intensive care unit (NICU).

Materials and Methods

Approval for this study was obtained form the Institutional Ethical Board and all the authors conformed to the Declaration of Helsinki during the study period. (No author had any financial conflict of interest with drug companies related to products used in the current investigation).

This was a prospective, double-blinded observational trial of nulliparous women undergoing labor induction from December 2006 to January 2007. All women with a medical or obstetric indication for labor induction were eligible for the study. Inclusion criteria were gestational age between 36 to 42 weeks, singleton cephalic presentation of the fetus, intact membrane and unfavorable cervical Bishop score < 6, and absence of spontaneous uterine contractions. Exclusion criteria were known sensitivity to prostaglandins, ruptured membranes, parity more than five, suspected chorioamnionitis, previous cesarean delivery (CS) or history of uterine surgery, and previous attempted induction of labor for index pregnancy. For the purpose of the study, we defined induction as successful only if vaginal delivery occurred by induction protocols within 24 hours of labor induction.

All study participants were admitted to the labor ward 12 hours before scheduled induction of labor, and cardiotocography was performed to rule out fetal distress and presence of

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uterine contractions. A cervical Bishop score was assigned on admission by a single-blinded physician for all patients. Prior to cervical ripening, all ultrasound examinations were made by using a Toshiba Sonolayer SSA 250 (Toshiba, Tokyo, Japan) ultrasound machine equipped with a 5 MHz transvaginal probe by a single-blinded investigator. Ultrasound measurement of cervical length was made in the sagittal plane along the length of the endocervical canal with simultaneous visualization of the internal and external cervical os. The shortest of three measurements was taken as the cervical length. Randomization was done independently through the hospital pharmacy by random allocation. Administration of labor induction agents was made by an on-call physician in the labor ward and not by the physician who assigned the Bishop scores.

The controlled-release PGE2 vaginal insert was a 0.8 mm thick semi-opaque polymeric insert, consisting of a biodegradable polymeric drug delivery device with a constant rate of 0.3 mg/hours or a total dose of 5 mg over the recommended dosage period of 12 hours [9]. All nulliparous women allocated to prostaglandin analogs remained in bed for two hours following insertion. Cardiotocographic (CTG) recordings were continued during the first hour of insertion and thereafter when the contractions occurred. Prostaglandin analogues were inserted into the posterior fornix of the vagina.

CTG tracings were independently reviewed by a blinded investigator and abnormalities were coded as hypertonus, tachysystole, and hyperstimulation. Hypertonus was defined as a single contraction with duration of at least two minutes; tachysystole as the presence of at least six contractions in ten minutes for two consecutive ten minute periods; and hyperstimulation as the presence of tachysystole or hypertonus associated with fetal tachycardia, late deceleration, fetal bradycardia, and/or loss of long-term variability. Continuous fetal heart rate and tocodynamic monitoring were performed during labor.

Participants were then randomly assigned to a dinoprostone vaginal insert (Propess® Vitalis Saglik Urunleri Danismanlik ve Ticaret Ltd., Turkey, in collaboration with Controlled Therapeutics Ltd., Scotland) 10 mg administered into the posterior fornix for a total of 24 hours (10 mg every 12 hours) without oxytocin (group I), with oxytocin (group II), and with misoprostol (Cytotec®, 200 µg tablets, Ali Raif, Turkey) 50 µg intravaginally in the posterior fornix with repeat dosing at six hour-intervals with a maximum dose of four with oxytocin (group III). If the Bishop score was ≥ 5 oxytocin was started followed by amniotomy. Oxytocin (Synpitan forte®, 5 IU, Deva, Turkey) was started with a dose of a 2 mU/min increment at 20-min intervals to a maximum of 30 mU/min for all cases with Bishop scores > 6 following cervical ripening with prostaglandin analogues.

Demographic characteristics, mode of delivery, time from induction-to-delivery, indications of induction, CTG abnormalities and neonatal outcomes were determined. Neonatal complications noted were Apgar scores of < 7 at 5 min and the rate of admission to NICU.

Statistical analysis was performed using the SPSS 10.0 (SPSS10.0, Chicago, IL, USA) statistical package. Results are presented as the mean ± SD or median with 25th-75th percentile values, where appropriate. Test of normality was performed by the one-way Kolmogorov-Smirnov test. Patient demographic characteristics were analyzed by the Student's t-test and the chi-square and Fisher's exact test or Wilcoxon rank sum test where apropriate. One-way ANOVA was used for group comparisons of continuous variables. Kaplan-Meier curves were compared by using the Wilcoxon log-rank test. A two-sided p value < 0.05 was set to be statistically significant.

Results

A total number of 106 women met the inclusion criteria without distribution for 19 cases in group I, 44 and 43 cases in groups II and III, respectively. There were no statistically significant differences in terms of demographic characteristics and indication of labor induction (Table 1), as well as fetal and neonatal characteristics, cardiotocographic abnormalities and neonatal outcomes, and mode of deliveries among the three groups (Table 2). Duration of oxytocin use and time interval from induction to delivery also did not differ among the three groups ($p > 0.05$) (Figure 1). Interestingly, in all three groups high percentages of abnormal CTG patterns (hypertonus, tachysystole or hyperstimulation) were observed. In terms of number of patients that remained undelivered within 24 hours of labor induction, no statistically relevant differences were depicted between three groups (Mantel-Cox log-rank, χ^2: 1.5, df = 2, p = 0.454).

Table 1. — *Characteristics of women who received a controlled-release dinoprostone vaginal insert only (group I), dinoprostone + oxytocin (group II) and misoprostol + oxytocin (group III).*

Characteristics	Group I (n = 19)	Group II (n = 44)	Group III (n = 43)	p value
Maternal age (yrs)	29.1 ± 2.3	29.4 ± 3.2	27.9 ± 1.2	0.31
Maternal weight (kg)	82.2 ± 3.4	84.2 ± 2.5	82.3 ± 1.8	0.54
Gestational age (wks)	39.3 ± 1.7	38.6 ± 2.1	39.4 ± 1.5	0.33
Indications for induction (%)				
Postdates	5	11	10	0.55
Oligohidramnios	2	4	4	0.63
Hypertensive disorders	8	18	17	0.76
Diabetes mellitus	1	3	3	0.32
Term PROM*	–	1	1	0.79
Other	3	7	8	0.12

*premature rupture of membrane.

Table 2. — *Labor characteristics and neonatal outcome in groups I, II and III, respectively.*

Characteristics	Group I (n = 19)	Group II (n = 44)	Group III (n = 43)	p value
Birthweight (g)	3270.3 ± 482.8	3210.3 ± 562.4	3186.6 ± 534.2	0.85
Bishop score (n)				
≤ 6	18	44	36	0.80
> 6	1	3	4	
Initial cervical length (mm)	33.7 ± 3.7	33.0 ± 1.8	30.3 ± 4.5	0.18
Duration of oxytocin use (hr) median (25^{th}-75^{th} percentiles)	–	6 (4-9)	6 (5-8)	0.49
Vaginal delivery n (%)	10 (52.6)	27 (61.4)	25 (58.1)	0.81
Cesarean delivery n (%)	9 (47.4)	17 (38.6)	18 (41.9)	
Time from induction to delivery (hrs) median (25^{th}-75^{th} percentiles)	10 (4-15)	10 (7-18)	11 (8-15)	0.50
Abnormal CTG tracings*	17	33	35	0.40
5 min Apgar score < 6	1	2	–	0.39
NICU** stay (days)	3.1 ± 0.2	4.1 ± 1.2	3.9 ± 0.3	0.23
Maternal hospital stay (days) median (25^{th}-75^{th} percentiles)	4 (2-6)	3 (2-3)	4 (2-6)	0.02

*hypertonus, tachysystole or hyperstimulation; **neonatal intensive care unit.

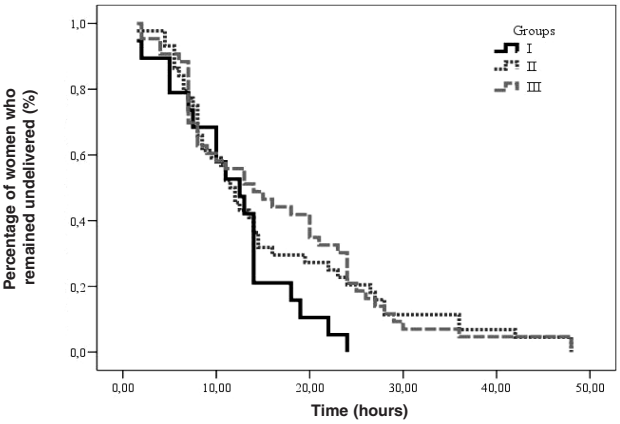

Figure 1. — Percentage of nulliparous women in groups I, II and III who remained undelivered (y-axis) within 24 hours of labor induction (x-axis). (Mantel-Cox log-rank, χ^2: 1.5, p = 0.454).

Discussion

Based on the results of the current investigation, a dinoprostone controlled release vaginal insert with or without oxytocin and misoprotol with oxytocin protocols had similar efficacy in achieving vaginal delivery within 24 hours of infection with similar adverse maternal and fetal outcomes. As seen in Table 1, duration of oxytocin dose and induction-to-delivery interval did not differ among the three groups.

There are considerable numbers of prospective, randomized controlled studies in the literature comparing prostaglandin analogues and oxytocin with each other or a placebo [1, 11-15]. These studies have demonstrated that prostaglandin analogues with or without oxytocin signifiantly increased Bishop score, shortened the time from induction-to-delivery and reduced the incidence of cesarean delivery.

In a retrospective analysis by Lapaire *et al*. [16], 98 patients were retrospectively analyzed. A total of 47 patients received 3 mg dinoprostone suppositories every six hours (max 6 mg/24 h) whereas 51 patients in the misoprostol group received either 50 µg misoprostol vaginally every 12 hours. The authors concluded that there was a three-fold chance for vaginal delivery in the misoprostol than in the dinoprostone whereas more cesarean sections were performed in the dinoprostone group due to failed induction without any significant differences in adverse maternal outcome. However, in contrast to the results of the present study, more neonates of the dinoprostone group were admitted to the NICU.

The potential development of uterine hyperstimulation is of particular concern with regard to prostaglandin analogues. Ramsey *et al*. [17], through a study of 111 cases randomized to 50 µg misoprostol every six hours for two doses and 0.5 mg dinoprostone gel every six hours for two doses, found that CTG abnormalities occurred more frequently following misoprostol administration compared to dinoprostone analogues. One distinct advantage of vaginally inserted dinoprostone compared to tablet form was stated to be the easy removal of the drug and reversibility of uterine hyperstimulation, as well as a single dosing scheme [18]. Although the present study did not show any difference in CTG abnormalities, dinoprostone vaginal inserts seemed to confer a benefit over misoprostol. Le Roux *et al*. [7] conducted a multicenter, randomized control trial for 573 women admitted for induction of labor and randomized to vaginal misoprostol (50 µg every 6 hours x 4 doses) or dinoprostone gel (1 mg), and stated that despite there being no difference in the rates of vaginal delivery within 24 hours of induction between the two groups, more tachysystole and cesarean section for fetal distress were performed compared to the dinoprostone group. However, they also pointed out that oral misoprostol resulted in fewer cesarean deliveries without any increased CTG abnormalities. Although the current investigation yielded a similar efficacy of different prostaglandin analogues for succesful labor induction, Nanda *et al*. [19] concluded that misoprostol is cheaper, stable at room temperature, has a shorter mean induction-to-delivery interval and requires less oxytocin. As for the last, the authors emphasized that this issue is more important in tropical countries.

In a systematic review by Crane *et al*. [20], misoprostol (oral or vaginal) in women at term with an unfavorable cervix and intact membranes was more effective than dinoprostone (intracervical or vaginal) in achieving vaginal delivery within 24 hours. The same authors stated that misoprostol increased the rates of tachysystole and hyperstimulation. In a recent randomized study, comparing the safety and efficacy of vaginal misoprostol versus dinoprostone vaginal inserts for cervical ripening and labor induction, 200 cases were randomized to either 50 µg intravaginal misoprostol every three hours or a 10 mg dinoprostone insert every 12 hours for a maximum dose of 24 hours [21]. In contrast to the results of the current investigation, the authors concluded that misoprostol resulted in a shorter interval from induction to delivery with a high rate of non-reassuring fetal heart rate tracing. In a prospective randomized controlled trial by Rowland *et al*. [22], comparing misoprostol versus dinoprostone for cervical ripening in 126 women recruited into the study, there was no difference in the percentage of women who delivered vaginally or by cesarean section, but more hyperstimulation was observed in the misoprostol group. Again, neonatal outcome in respect to low cord pH or Apgar score as well as admissions to NICU were similar between the two groups.

Similar to the present investigation, Bolnick *et al*. [23] studied pregnancies that underwent labor induction at ≥ 37 weeks of gestation with an unfavorable cervix (Bishop score, ≤ 6) were randomly assigned to receive vaginally either a single dose of sustained-release dinoprostone (Cervidil) with concurrent low-dose oxytocin or multidosing of misoprostol (25 µg every 4 hours) followed by high-dose oxytocin. They concluded that neither mean time from the initiation of induction to vaginal delivery nor the percentage of patients who were delivered vaginally differed between the two groups. CTG abnormalities were similar between the two groups, as also found in the current investigation.

The cost-benefit of misoprostol over dinoprostone also has to be taken into account. Although it was not the intention of the present study to do a comparison of the three groups in terms of cost, the duration of hospital stay was found be lower in the dinoprostone+oxytocin group, compared to the dinoprostone only and misoprostol + oxytocin groups. Although not shown in this study, the hospital cost of cases in group III (miso+oxytocin) was lower compared to the dinoprostone groups (groups I and II).

Ramsey *et al*. [24] compared the relative efficacy and cost of three commercially available prostaglandin analogues, intravaginal misoprostol (50 μg dose at 6-hour internals), and dinoprostone inserts (10 mg for a total time of 12 hours), as labor preinduction agents in 111 women with an unfavorable cervix who underwent labor induction. They finally concluded that induction-to-delivery intervals, however, were significantly shorter among women who were treated with misoprostol compared with dinoprostone inserts. Moreover, the overall mean cost per patient that was incurred by labor induction was significantly less for the misoprostol group compared to the dinoprostone insert group which is an important finding that needs further evaluation in detail.

In conclusion, although there were no differences in the efficacy of labor induction and neonatal outcomes among the three groups, a more detailed analysis regarding the cost-effectiveness of each regimen needs to be determined in a larger case series with sufficient power. In addition, the use of prostaglandin analogues with different doses and way of administration (oral, intracervival, intravaginal) have to be evaluated. Moreover, although different from the current investigation, the concurrent use of oxytocin with prostaglandin analogues needs to be assessed. The latter issue seems to be beneficial in shortening the delivery time without considerable maternal and perinatal adverse outcomes [25].

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