Randomized Comparison of Sustained-Release Dinoprostone Vaginal Insert Versus Oxytocin for Cervical Priming/Labor Induction in Post-Term Pregnants with Unfavorable Cervix

Olgunlaşmamış Serviksi Olan Miadını Geçmiş Gebelerde Kontrollü Salınımlı Dinoproston Vajinal Ovül İle Oksitosinin Doğum Eylemi Üzerine Olan Etkilerinin Randomize Olarak Karşılaştırılması

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ABSTRACT Objective: To compare the efficacy and safety of sustained-release dinoprostone vaginal insert with low-dose oxytocin infusion for cervical ripening/labor induction. **Material and Methods:** Patients were randomly assigned to receive either vaginally two doses of a dinoprostone vaginal insert (dinoprostone group, n=64) or two doses of intravenous low-dose oxytocin (oxytocin group, n=63) at 12 hr intervals. The main outcomes were vaginal delivery by ≤24 hrs and overall cesarean delivery rates. Secondary outcomes included changes in Bishop's score by 12 hr, the rate of uterine hyperstimulation syndrome, duration of stages of labor, immediate neonatal complications including meconium-stained amniotic fluid, 5-min Apgar score ≤ 7 and the rate of admission to neonatal intensive care unit. **Results:** Patients achieved vaginal delivery by ≤ 24 hours in the dinoprostone group (53.1 %) was similar to those patients in the oxytocin group (53.9 %). Overall cesarean delivery rate was 42.6 % in the oxytocin group and 32.8% in the dinoprostone group (P>0.05). There were no statistically significant differences between the groups regarding secondary outcomes. **Conclusions:** Both dinoprostone vaginal insert and low-dose oxytocin infusion were similar in efficacy for cervical priming/labor induction and safety for maternal and fetal outcomes. Moreover time to delivery in oxytocin group was more likely to be shorter; however, cesarean delivery rate in dinoprostone group was more likely to be lower.

Key Words: Parturition; birth intervals; oxytocin

ÖZET Amaç: Postterm gebeliği ve elverişsiz serviksi olan hastalarda, serviks olgunlaşması/doğum eylemi indüksiyonu için yavaş serbestleşen dinoproston vajinal ovül ile düşük doz intravenöz oksitosin infüzyonunun doğum eylemi üzerine olan etkinliği ve anne ile fetüs için güvenliğini karşılaştırmak. **Gereç ve Yöntemler:** Hastalar 12 saat ara ile 2 doz PGE2 vajinal ovül (n=64) veya intravenöz oksitosin (n=63) almak üzere rastgele iki gruba ayrıldı. Ana sonuç ölçütleri sezaryen doğum oranı ve ≤ 24 saatte vajinal doğumdu. Ölçülen sekonder ölçütler şunlardı: 12 saatte Bishop puanındaki değişikler; uterus hiperstimülasyon sendromu oranı; doğum eylemi evrelerinin süresi; mekonyum boyanmış amniyon sıvısını, 5. dakika Apgar puanı ≤ 7 ve neonatal yoğun bakım ünitesine yatış oranını içeren erken neonatal komplikasyonlardı. **Bulgular:** İlk 24 saatte, vajinal yolla doğum gerçekleştiren dinoproston grubundaki hastalar (%53,1), oksitosin grubundaki vajinal yolla doğum yapan hastalardan (%53,9) istatistiksel olarak farklı değildi (P=1,00). Genel sezaryen oranı oksitosin grubunda % 42,6 ve dinoproston grubunda % 32,8 idi (P>0.05). Sekonder ölçüm parametreleri açısından iki grup arasında istatistiksel olarak anlamlı fark yoktu. **Sonuç:** Olgunlaşmamış serviksi bulunan postterm gebelerde, yavaş salınımlı dinoproston vajinal ovül ve düşük doz oksitosin, doğum eylemi üzerine olan etkileri, maternal ve fetal yan etkileri açısından benzer özelliklere sahipti. Ayrıca, oksitosin grubunda doğuma kadar geçen süre daha kısa iken dinoproston grubunda sezaryen doğum oranı daha düşüktü.

Anahtar Kelimeler: Doğum; doğum aralığı; oksitosin

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Prolonged pregnancy is a common high-risk problem and of major concern in obstetrics today. Postterm pregnancy (beyond 41 to 42 weeks gestation) constitute approximately 10% of all pregnancies and they have an increased risk of perinatal death, intrapartum fetal heart rate (FHR) abnormalities, meconium staining, macrosomia, and cesarean delivery.[1]

Low-risk postterm women with favorable cervix as determined by Bishop score,[2] are usually managed by induction of labor. Nonetheless, induction of labor in women with unripe cervix remains a challenge for the obstetrician. The advantages of preinduction cervical maturation by topical application of prostaglandins have been known for several years.[3] Prostaglandin E_2 (PGE_2) is available in a variety of formulations, including vaginal tablets, endocervical gels, and it is administered using various dosing regimens.[4]

A slow-release dinoprostone vaginal insert is now available and, efficacy and safety of this formulation on cervical priming and labor induction in singleton gestations at term were compared with an alternative vaginal [5,6] or cervical[7,8] prostaglandins in previous randomized trials. In a recent meta-analysis, Hughes et al[9] found no clinically significant differences between the effects of this preparation and of other standard prostaglandin preparations.

When the uterine cervix is unfavorable, oxytocin, with or without amniotomy, is frequently ineffective whereas vaginal PGE_2 is widely recognized and accepted as a standard method of labor induction.[10] Nonetheless no randomized prospective study was carried out to compare the effectiveness of dinoprostone vaginal insert with intravenous oxytocin infusion in prolonged pregnancy with unfavorable cervix.

Aim of this randomized prospective clinical trial was to compare the efficacy and safety of sustained release PGE_2 vaginal insert with low-dose oxytocin infusion for cervical ripening/labor induction in the presence of unfavorable cervix in patients with postterm pregnancy.

METHODS

This study was carried out from August to October 2005 at the Perinatology Unit of Zekai Tahir Burak Women's Health Education and Research Hospital after approval was obtained from our Institutional Human Research Review Committee.

Otherwise uncomplicated pregnant women who had a gestational age of 290 days were screened for eligibility. All of the patients were informed about the study protocol and a signed informed consent was obtained from each participant.

Inclusion criteria were singleton gestation, cephalic presentation, intact membranes, unfavorable cervix (Bishop's score ≤ 6) and reassuring FHR pattern. Exclusion criteria included previous uterine surgery, active vaginal bleeding, placenta praevia, estimated fetal weight > 4000 g, suspicion of cephalopelvic disproportion (CPD).

Women scheduled for induction of labor were randomly allocated to receive either a PGE_2 vaginal insert (Propess, Vitalis Sağlık Ürünleri ve Tic. Ltd. Şti., Kavaklıdere, Ankara, Turkey) or intravenous oxytocin (Postuitrin, İ.E. Ulugay, İlac Sanayii Türk A.Ş., Topkapı, İstanbul, Turkey).

Randomization was performed with use of a computer generated random number table. Group allocation was predetermined and placed in consecutively numbered opaque, sealed envelopes. The next consecutive envelope was drawn after the patient consented to randomization.

Those patients assigned to the dinoprostone group received vaginal insert which was a hydrogel polymer matrix containing 10 mg dinoprostone. The pessary releases PGE_2 at a constant rate of 0.3 mg/h over 12 hour. It was inserted into the posterior vaginal fornix of the vagina in transverse position and the patient was asked to remain recumbent for an hour to allow the vaginal insert to swell. Vaginal insert was removed after 12 hours. It was only to be removed earlier in the case of onset of active labor (at least 4 cm cervical dilation with regular uterine contractions), the rupture of the membranes, or hyperstimulation syndrome.

Women, who were allocated for oxytocin group, received low-dose oxytocin infusion which was begun at a rate of 2 mU/min and increased by 2 mU/min every 15 minutes. If contractions reached a frequency of 4 per 10 minutes for 2 consecutive 10-minute windows, the oxytocin infusion was not increased further unless the frequency of contractions diminished. The maximum allowable dose of oxytocin was 40 mU/min.

In both dinoprostone and oxytocin groups: continuous external electronic FHR and tocodynamic monitoring was used throughout the labor; artificial rupture of membranes was performed as early as safely possible once the cervix became ≥ 3 cm dilated while the head was applying; gynecological examination was performed once at 6th hour during the passive phase and per 2 hours in active phase of labor. While oxytocin infusion was stayed until the end of second stage of labor in oxytocin group, no augmentation was done in any stage of labor in dinoprostone group.

The treatment period was followed by 12 hrs rest in both groups. If the patient did not reach an active labor spontaneously, treatment was repeated once more with the same dosages 24 hour after the start of therapy. At 36 th hour, the treatment was defined as failed induction if the patient still was not in the active phase. In case of failed induction again after 12 hours of rest, the patients in both groups were induced by oxytocin with the same regimen once more. If even active labor was not entered after the 3rd induction, the patients were underwent cesarean delivery.

In case of hyperstimulation syndrome, treatment was ceased and it was restarted if the pattern resolved. The diagnosis and treatment of hyperstimulation syndrome were performed as in the previous literature.[11] Late decelerations, moderate and severe variable decelerations and bradycardia were the abnormalities considered on the FHR tracing. Main outcome measures were vaginal delivery at ≤24 hours and overall cesarean delivery rate.

There was no literature to be based on for sample size calculation. Therefore, using information from our pilot study (30 women in each group), the sample size was estimated with the assumption of a Type-I error (α) of 0.05 (with the use of a 1-sided equivalence test), a power of 0.80 (1-β; Type-II error) and a 22.5% difference in outcome between the two groups, the sample size for each group in the study should be 63. We recruited 127 women totally; 64 in dinoprostone group and 63 in oxytocin group.

Numeric values were expressed as mean ± SD and ordinal values were expressed as number (percentage). The normality of distributions of variables was analyzed by the Kolmogorov–Smirnov distribution equality test. The Student's t test was used for statistical significance of differences in normally distributed variables between groups. The Chi-Square test, Mann–Whitney *U*-test and two-sided difference test between two proportions were used for statistical significance of differences in non-normal distributed variables between groups. The statistical significance of differences between before and after values of variables between groups was analyzed using Covariance Analysis (ANCOVA). A *P*-value of <0.05 was considered to be statistically significant. The SPSS 11.0 statistical package was used for statistical analysis.

RESULTS

There were 137 eligible candidates owing to inclusion criteria during the study period but nine of them refused to participate. Therefore, a total of 128 otherwise healthy postterm women with unfavorable cervix were enrolled in and completed the study; 64 were randomized to receive slow-release dinoprostone vaginal insert and 63 received low-dose oxytocin.

As summarized in Table 1, baseline characteristics of both dinoprostone and oxytocin groups were similar with respect to maternal and gestational age, body mass index, gravidity, parity, preinduction Bishop's score and amniotic fluid index (AFI).

Table 2 illustrates the comparison of main outcome measures. Overall delivery rate by ≤ 24 hrs was 68.8% in dinoprostone group and 87.3% in the oxytocin group (*P*<0.05); however, patients in the

TABLE 1: Baseline characteristics of patients

Characteristics	Dinoprostone(n=64)	Oxytocin(n=63)
Maternal age (year) *	24.8 ± 4.1	25.1 ± 4.3
Gestational age (day) *	292.3 ± 1.3	291.6 ± 1.4
BMI (kg/m2) *	28.7 ± 3.4	28.9 ± 3.8
Gravidity (n) †	1.5 ± 0.8	1.8 ± 1.1
Parity (n) †	0.3 ± 0.6	0.6 ± 1.0
Preinduction Bishop's score †	2.4 ± 1.4	2.1 ± 1.6
AFI < 50 (mm) ‡	24 (38.1 %)	26 (40.6 %)

Data are presented as mean ± S.D. or n (%), * Student's t test, † Mann-Whitney U test, ‡ Fisher's exact test, BMI; Body mass index, AFI; Amniotic fluid index, P > 0.05 for all comparisons.

TABLE 2: Comparison of main outcome measures and indications for cesarean deliveries

Main outcome measures	Dinoprostone (n=64)	Oxytocin (n=63)	P value *
Vaginal delivery ≤ 24 hrs	34 (53.1 %)	34 (53.9 %)	1.000
Overall Cesarean delivery	21 (32.8 %)	27 (42.6 %)	0.304
Non-reassuring FHR	7 (10.9 %)	10 (15.9 %)	0.791
Failure to progress	2 (3.1 %)	6 (9.5 %)	0.247
Cephalopelvic disproportion	11 (17.1 %)	7 (11.1 %)	0.074
Failed induction after third dose	1 (1.6 %)	4 (6.3 %)	0.270

Values are presented as n (%), FHR; Fetal heart rate, * Two-sided difference test between two proportions, † Cesarean delivery except for cephalopelvic disproportion.

dinoprostone group achieved vaginal delivery by ≤ 24 hours (53.1%) was not statistically different (P=1.00) than those patients achieved vaginal delivery by ≤ 24 hours in the oxytocin group (53.9%). Overall cesarean delivery rate was 42.6% in the oxytocin group and 32.8% in the dinoprostone group (P>0.05).

Indications for cesarean section were as follows; non-reassuring FHR pattern (10.9% vs 15.9%), failure to progress (3.1% vs 9.5%), cephalopelvic disproportion (17.1% vs 11.1%) and failed induction after third dose (1.6 % vs 6.3%) in the dinoprostone and oxytocin groups, respectively but the differences were not statistically significant (Table 2).

Secondary delivery outcomes are shown in Table 3. The rate of hyperstimulation syndrome, time from active labor to complete dilation, time from complete dilation to delivery, overall time to delivery were similar between the groups (P>0.05); whereas time to hyperstimulation syndrome, time to membrane rupture, time to active labor were significantly shorter (P<0.05, P<0.01, P<0.05, respectively) and total time of drug application was significantly longer (P<0.01) in oxytocin group as compared with dinoprostone group.

Dose-response outcomes were compared between the two groups in Table 4. Seventeen patients in dinoprostone group (26.6 %) and 7 patients in oxytocin group (11.1 %) were still with unfavorable cervices or did not reach active labor at 12 hr after the start of first dose of drugs (P<0.05). Eight of the 17 patients entered active labor spontaneously at 1st rest in dinoprostone group; whereas did none of the 7 patients in oxytocin group (P<0.05). However there were no significant difference between the dinoprostone and oxytocin groups with

TABLE 3: Comparison of secondary outcome measures

Secondary outcome measures	Dinoprostone (n=64)	Oxytocin (n=63)	P value
Hyperstimulation syndrome (n)	5 (7.8 %)	7 (11.1 %)	0.642*
Time to hyperstimulation syndrome (hr)	2.7 ± 1.6	4.2 ± 2.7	0.021†
Time to membrane rupture (hr)	13.1 ± 14.3	7.0 ± 5.7	0.005†
Time to active labor (hr)	14.0 ± 14.4	8.8 ± 5.9	0.041†
Time from active labor to complete dilation (hr)	4.4 ± 3.2	4.0 ± 3.0	0.478†
Time from complete dilation to delivery (min)	26.7 ± 14.3	22.9 ± 23.6	0.375†
Time to delivery (hr)	18.9 ± 17.6	12.3 ± 6.6	0.186†
Total time of drug application (hr)	9.2 ± 6.2	12.9 ± 6.6	0.001†

Data are presented as mean ± S.D. and n (%), * Fisher exact test, † Mann-Whitney U test.

TABLE 4: Comparison of dose-response outcomes

Dose-response outcomes	Dinoprostone (n=64)	Oxytocin (n=63)	P value ‡
Remaining patient at 12 h*	17/64 (26.6 %)	7/63 (11.1 %)	0.046
Spontaneous active labor during 1st rest	8/17 (47.1 %)	0/7 (0 %)	0.036
Need for 2nd dose	9/64 (14.1 %)	7/63 (11.1 %)	0.485
Response† to 2nd dose	4/9 (44.4 %)	2/7 (28.5 %)	0.548
Spontaneous active labor during 2nd rest	0/5 (0 %)	0/5 (0 %)	1.000
Need for 3rd dose (Failed induction)	5/64 (7.8 %)	5/63 (7.9 %)	0.761
Response† to 3rd dose	2/5 (40 %)	0/5 (0 %)	0.152

* Those patients whose cervices were still unfavorable at 12 h, † Response means reaching to active labor while the drug was being applied, ‡ Two-sided difference test between two proportions.

TABLE 5: Comparison of adverse fetal outcomes

Adverse fetal outcomes	Dinoprostone (n=64)	Oxytocin (n=63)	P value *
Fetal weight > 4000 g	2 (3.1 %)	1 (1.6 %)	0.662
5-min Apgar score ≤ 7	5 (7.8 %)	4 (6.3 %)	0.746
Meconium-stained amniotic fluid	7 (10.9 %)	4 (6.3 %)	0.211
Admission to NICU	2 (3.1 %)	3 (4.8 %)	0.274

Values are presented as n (%), * Two-sided difference test between two proportions, NICU; Neonatal intensive care unit

respect to need for second dose (9/64 vs. 7/63), response to second dose (4/9 vs. 2/7), spontaneous active labor during second rest (0/5 vs. 0/5), need for third dose (failed induction; 5/64 vs. 5/63) and response to third dose (2/5 vs. 0/5).

Table 5 shows the adverse perinatal outcomes. There were no statistically significant differences between the dinoprostone and oxytocin groups regarding the rate of fetal weight > 4000 g (3.1 % vs. 1.6 %), 5-min Apgar score ≤ 7 (7.8 % vs. 6.3 %), meconium-stained amniotic fluid (10.9 % vs. 6.3 %) and admission to NICU (3.1 % vs. 4.8 %).

DISCUSSION

This randomized prospective clinical trial compared the efficacy and safety of two protocols, which were designed for the cervical ripening/labor induction in the presence of unfavorable cervix in patients with postterm pregnancy. To the best of our knowledge, this is the first study in the literature, where slow-release dinoprostone (PGE_2) vaginal insert was compared with low-dose intravenous oxytocin infusion. No statistically significant differences in efficacy (vaginal delivery rate within 24 hr and overall cesarean delivery rate) and safety (maternal and fetal outcomes) were found between the groups in the present study.

In the three recent randomized prospective studies,[11-13] in which effectiveness of dinoprostone vaginal insert was investigated in patients with an unfavorable cervix (Bishop's score, ≤ 6) as in our study. Stewart et al[12] compared the effectiveness of PGE_2 vaginal insert-subsequent oxytocin (n=73) with PGE_2 intracervical gel-immediate oxytocin (n=77) in patients at ≥ 37 weeks of gestation requiring labor induction. Of those pregnancies receiving the PGE_2 vaginal insert-subsequent oxytocin regimen, time to vaginal delivery was 21.6 ± 10.9 hrs. The vaginal delivery within 24 hrs and cesarean delivery rates were 67 % and 23 %, respectively.

Christensen et al[11] studied to determine if the concurrent administration of oxytocin with sustained-release dinoprostone (immediate group, 34 patients) results in shorter induction times when compared with oxytocin after the removal of the dinoprostone insert (delayed group, 37 patients) in pregnant women undergoing labor induction at ≥ 36 weeks. Authors reported the time from dinoprostone placement until delivery as 16.2 ± 7.1 and 25.3 ± 9.8 hrs, the proportion of deliveries within 24 hours as 90% and 53%, and cesarean delivery rates as 16% and 13% in the immediate and delayed groups, respectively.

Bolnick et al[13] compared the efficacy of two protocols [a single dose of sustained-release PGE_2 with concurrent low-dose oxytocin (dinoprostone, n=74) versus multidosing of misoprostol (25 mg every 4 hours) followed by high-dose oxytocin (misoprostol, n=77)] in labor induction at ≥ 37 weeks of gestation. Cesarean delivery rate was 21.6 % and 81 % of patients delivered within 24 hrs in dinoprostone group. Time to vaginal delivery was 15.7 ± 7.8 hrs in the same group of patients.

There were no statistically significant differences between the dinoprostone and oxytocin groups in our study with respect to time to vaginal delivery (18.9 ± 17.6 and 12.3 ± 6.6 hrs, respectively), vaginal delivery within 24 hrs (53.1 % and 53.9 %, respectively) and overall cesarean delivery rate (32.8 % and 42.6 %, respectively).

It does not seem to be feasible to compare our findings with the results of these three studies[11-13] because of the differences between our study and their studies with respect to indications for labor induction (only post-term pregnancy in ours versus postdates, preeclampsia, diabetes mellitus, oligohydramnios in theirs) and gestational age (≥ 41 week and 3 days in ours versus ≥ 37 weeks in theirs) and labor induction protocols (none of them compared dinoprostone vaginal insert with oxytocin).

Number of patients who did not reach active labor or not deliver at 12 hr after first dose, was significantly lower in the oxytocin group (n=7) when compared to dinoprostone group (n=17). While eight of 17 patients in dinoprostone group reached active labor spontaneously during the first rest period, none of the 7 patients in the oxytocin group reached active labor during this period ($P<0.05$). Consequently, number of patients requiring second dose of induction at

24 hr was not significantly different between the dinoprostone (n=9) and oxytocin groups (n=7). The most important finding here was that patients receiving dinoprostone vaginal insert could reach active labor spontaneously after removal of the insert. To our knowledge, this was not revealed in the previous literature. This might be due to the effect of dinoprostone on cervical enzymes including collagenases and other proteases which cause time-dependent collagen degradation and increase in hyaluronic acid and therefore results in softening of cervix.[14]

Overall delivery rate within 24 hrs in oxytocin group was significantly higher than that of dinoprostone group and the difference was primarily related to cesarean deliveries in this time period (33.3 % and 15.6 %, respectively; $P<0.05$). Therefore oxytocin seems to be more favorable in delivering within 24 hrs but most of deliveries were by cesarean section. This may be due to the differences between the two agents in cervical priming/labor induction mechanism that prostaglandins have effects in the myometrium and the cervix, whereas the activity of oxytocin is limited to the uterine muscle.[15] Therefore oxytocin causes uterine contractions earlier but as the cervix was not prepared for labor sufficiently, most of the patients delivered via cesarean section within 24 hrs.

Lack of clinician blinding as to therapy was the major limitation of this pilot study. It was not easy to blind physicians, who followed the patients on labor ward, as no placebo of the agents was used during the study.

It can be concluded from our small pilot study that dinoprostone vaginal insert and low-dose oxytocin infusion every 12 hrs for a maximum of three doses in postterm patients with unfavorable cervices were similar in efficacy for cervical priming/labor induction and safety for maternal and fetal outcomes. Moreover time to delivery in oxytocin group was more likely to be shorter; however, cesarean delivery rate in dinoprostone group was more likely to be lower.

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