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Original Article

Pre-induction cervical ripening using two different dinoprostone vaginal preparations: A randomized clinical trial of tablets and slow release retrievable insert

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ABSTRACT

Objective: The current study compared the safety and efficacy of two different dinoprostone preparations (dinoprostone vaginal tablets & dinoprostone slow release retrievable vaginal insert) to ripen the cervix at term.

Materials and methods: Women admitted for pre-induction cervical ripening were included in a randomized controlled trial. Eligible women were randomly assigned to receive Dinoprostone either in the form of vaginal tablets or slow release retrievable vaginal insert. Study outcomes included time to vaginal delivery and time to onset of labor intervals and vaginal delivery rate.

Results: No statistically significant difference was found between the two groups regarding the main outcome measures, however, the probability of successful vaginal delivery was independently related to the type of dinoprostone preparation used to ripen the cervix (proportional hazard, 1.366; 95% CI, 1.010−1.847; P, 0.043) and the parity (proportional hazard, 1.412; 95% CI, 1.041−1.915; P, 0.026).

Conclusion: Both dinoprostone preparations were effective and potentially safe. The probability of successful vaginal delivery was higher with dinoprostone vaginal tablets while use of dinoprostone vaginal insert was associated with better patients' acceptability.

clinicaltrials.gov: NCT01635439.

Introduction

The ideal cervical ripening agent has to be effective, safe, easy to be administered and acceptable to the pregnant woman. Utilizing prostaglandins (PG) for cervical ripening during induction of labor (IOL) was first described in the 1960s [1]. Since that time various types of prostaglandins including $PGF_{2\alpha}$, PGE_2 (Dinoprostone) and PGE_1 (Misoprostol) were extensively studied to elicit the best prostaglandin pharmacological agent for pre-induction cervical ripening.

Dinoprostone was found to be superior to the others, as it increases the rates of successful vaginal delivery within 24 h without increasing the operative delivery rates. Vaginal route was found to be a safe and effective approach of bringing on labor. However, the best vehicle for delivering vaginal prostaglandins still needs further research [1].

There are several dosage forms of dinoprostone including tablet, gel and sustained release insert. Dinoprostone sustained release preparations have been developed to reduce the number of applications needed during IOL and subsequently decreasing the number of vaginal examinations. These preparations are easily retrievable in case of uterine tachysystole and/or abnormal fetal heart rate tracing [2]. On the other hand, the tablet form is designed to dissolve in the vaginal cavity and release PGE_2 for several hours; it has the advantage of easy manufacture and application [3].

Only two old studies [4,5] have compared between these two vehicles: the first study [5] was conducted in 1998 and included a very small number of patients with high degree of cross over, it reported a higher vaginal delivery rate and better fetal outcomes with dinoprostone vaginal insert; on the contrary, the second study [4] did not report any difference in the studied maternal and fetal outcomes. Due to the limitations in the previous studies, the current trial was conducted to reevaluate the safety and efficacy of

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dinoprostone vaginal tablets and dinoprostone slow release retrievable vaginal insert in pre-induction cervical ripening at term.

Patients and methods

This randomized controlled trial was conducted in the labor and delivery unit of a tertiary care governmental maternity hospital, after being approved by the local institutional ethics and research committee. This trial has been registered at clinicaltrials.gov (identification number NCT01635439). Women admitted for pre-induction cervical ripening, as per the institutional protocol, were initially enrolled to participate in the study. A written informed consent was obtained from all participants.

Inclusion criteria included the presence of a singleton gestation at ≥37 weeks with unfavorable cervix (Bishop Score < 7), vertex presentation, absence of labor and presence of reassuring fetal heart rate (FHR) pattern. Gestational age was calculated at the time of enrolment according to Naegele's rule and confirmed by reviewing the early pregnancy ultrasound report(s). Women with antepartum hemorrhage, placenta previa, uterine scar, suspected cephalopelvic disproportion, previous use of labor inducing agent during the current pregnancy, contraindications for vaginal delivery and/or known hypersensitivity or contraindication to dinoprostone or any of the other constituents of dinoprostone vaginal tablets or inserts were excluded from the study.

Eligible participants were randomly assigned to have pre-induction cervical ripening using dinoprostone either in the form of vaginal tablets or slow release retrievable vaginal insert, randomization was performed using a computer generated random numbers, and participants were assigned to their groups using sealed envelopes that were opened just before starting the intervention. Women assigned to the vaginal tablets arm, received 3 mg dinoprostone vaginal tablets (Prostin E_2, Pfizer, Sanico NV, Turnhout, Belgium). The tablets were inserted in the posterior vaginal fornix every 6 h with a maximum of four doses. Women assigned to the vaginal insert arm, received the 10 mg dinoprostone slow release retrievable vaginal insert (Propess, Ferring Pharmaceuticals, Copenhagen, DK) as a single dose: the insert is a hydrogel reservoir strip that releases PGE_2 with a controlled and constant rate of 0.3/hour over 24 h.

Pre-induction assessment of Bishop score (BS) [6] was done by the attending physician, presence of normal FHR pattern and absence of uterine activity were assured using cardiotocography (CTG) for 90 min (30 min before dinoprostone insertion and 60 min after), the same assessments were repeated with each new dose of dinoprostone (in dinoprostone vaginal tablets arm) or if labor onset was suspected (in both groups).

Discontinuation of dinoprostone (i.e. no further doses of dinoprostone vaginal tablets versus immediate removal of dinoprostone vaginal insert, according to the assigned group) was done if one of the following events occurred: 1) labor onset, presence of regular uterine contractions occurring every 2–3 min; 2) non-reassuring fetal heart rate pattern; 3) reaching the maximum dose of dinoprostone; or 4) improvement of Bishop score to be ≥ 7. Four hours after the last dose of dinoprostone vaginal tablets or 2 h after the removal of the dinoprostone insert; artificial rupture of fetal membranes (ROM) was considered if there was: 1) no evidence of active labor despite reaching the maximum dinoprostone dose; or 2) poor progress of labor despite the presence of regular uterine contractions. Oxytocin, if needed, was begun 2 h after artificial ROM, using a low dose titration approach with starting dose of 2 mU/minute, increments of 2 mU/minute every 15 min till achieving adequate uterine contractions or reaching the maximum dose (32 mU/minute).

Interpretation of intrapartum fetal heart rate pattern was done according to ACOG guidelines [7]. Failure of IOL was only defined as inability to achieve an active labor within at least 6 h of oxytocin maximum dose administration. Uterine tachysystole was diagnosed when more than five contractions were present in 10 min for at least 20 min [8].

Patient acceptability was assessed via the general questionnaire that is distributed to all patients at the time of discharge from the hospital and recollected during the first postnatal visit. Among the items of this questionnaire four items were added to evaluate pre-induction cervical ripening pharmaceutical preparation; each item was rated as either strongly agree, agree, disagree, or strongly disagree; a total score of ≤50 was categorized as unsatisfactory. The four items were: 1) you are satisfied with the pharmaceutical preparation used in pre-induction cervical ripening; 2) if you need to have pre-induction cervical ripening in the future, you do not mind using the same pharmaceutical preparation again; 3) you are fully satisfied about the frequency of application of the used pharmaceutical preparation; 4) you did not experience any discomfort during the insertion or application of the used pharmaceutical preparation.

The required sample size was estimated using G*Power© v.3.1.0 (Institut für Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany). The primary outcome measure was time to vaginal delivery interval. Based on this outcome, and data from previous study [4], it was estimated that a sample size of 100 women in each arm would have a power of 80% to detect an effect size (Cohen's d = 0.4). The test statistic used was the two-samples t test and significance was targeted at an α-error of 0.05. The secondary outcomes included vagina delivery rate, time to labor onset interval, patient's acceptability to the used dinoprostone preparation, uterine tachysystole, adverse maternal outcomes, low APGAR score at 5 min, delivery related neonatal intensive care admission rate and low cord pH.

Whenever possible outcome assessors were kept blinded to the intervention done especially when assessing a subjective outcome (i.e. patient's satisfaction), Additionally, data analysts and the persons in charge of reporting the results of the trial were kept unaware of the identity of the study groups.

Statistical analysis was done on a personal computer using IBM® SPSS® Statistics version 19 (IBM® Corporation, Armonk, NY, USA). Normally distributed numerical data were presented as mean (SD) and the independent-samples t test was used to compare differences between group means. Nominal data were presented as number (%) and differences between the two groups were compared with the chi square test or Fisher's exact test if > 20% of the cells in a contingency table had an expected count of <5. A two-tailed P value of <0.05 was considered statistically significant. Cox proportional hazard regression was used to evaluate the impact of parity, initial Bishop score and type of dinoprostone used in pre-induction cervical ripening on the probability of successful vaginal delivery at all time to vaginal delivery intervals. The simultaneous (enter) method was used for regression to avoid automatic elimination of pertinent predictors from the model.

Results

217 Women were found to be eligible for randomization, 109 were assigned to dinoprostone vaginal tablets arm and 108 were assigned to dinoprostone vaginal insert arm; by the end of the study 200 women were included in the final statistical analysis (Fig. 1).

As shown in Table 1, there were no statistically significant differences as regards the studied maternal and labor data of both groups. The rate of caesarean section was 11% in dinoprostone