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Intravaginal glyceryl trinitrate and dinoprostone for cervical ripening and induction of labor

Filomena P. Nunes, MD, Ana P. Campos, MD, Sónia R. Pedroso, MD, Cristina F. Leite, MD, Teresa P. Avillez, MD, Rosalinda D. Rodrigues, MD, Manuel Meirinho, PhD

Department of Obstetrics and Gynecology, Hospital Garcia de Orta, Almada, Portugal

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KEY WORDS
Labor induction
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Objective: This study was undertaken to evaluate the efficacy and safety of intravaginal administration of glyceryl trinitrate plus dinoprostone versus dinoprostone, for cervical ripening and induction of labor.

Study design: A prospective, double-blind, placebo-controlled, randomized clinical trial was conducted among 196 singleton low-risk nullipara women with term pregnancies and unfavorable cervices who were randomly assigned to receive intravaginal glyceryl trinitrate plus dinoprostone or placebo plus dinoprostone. The main outcome variables were time from application to active phase of labor and to delivery. Secondary outcomes were change in Bishop score, fetal and maternal morbidity, and incidence of cesarean deliveries.

Results: The interval from application of the initial dose to the beginning of active phase of labor was 868 $\pm$ 582 and 1136 $\pm$ 692 minutes ($P = .004$) and from initial dose to delivery was 1339 $\pm$ 826 and 1620 $\pm$ 975 minutes ($P = .03$) for the glyceryl trinitrate and placebo groups, respectively. There were no significant differences in Bishop score change, cesarean section rate, and in the incidence of hypersystole and hyperstimulation. The incidence of tachysystole was significantly lower in the glyceryl trinitrate group (4% vs 15%, $P \leq .02$). No maternal and neonatal adverse effects were noted.

Conclusion: The association of glyceryl trinitrate with dinoprostone is more effective than dinoprostone alone for labor induction in low-risk patients at term with unfavorable cervices.

Labor induction in the presence of cervical immaturity is a common indication for the use of prostaglandins, particularly intravaginal prostaglandin E_2.[1-3] However, in the last years, there has been a considerable interest in the use of misoprostol[4-11] and nitric oxide (NO) donors[12-15] for cervical ripening and labor induction. Previous studies, in both animals and humans, have shown that NO donors can induce cervical ripening after their local application,[16-18] but the results of a published trial suggest that glyceryl trinitrate (GT) is safe but less effective for labor induction than dinoprostone.[13] After analyzing this information, we thought that it was important to determine whether a combined therapy with NO donors and prostaglandins, for cervical ripening and labor induction at term, would

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result in improved clinical effectiveness and fewer side effects and this was the objective of this investigation.

Material and methods

This study was carried out in the Department of Obstetrics and Gynecology, Hospital Garcia de Orta, Almada, Portugal, a teaching community hospital. The study population consisted of 196 low-risk pregnant women at term who were admitted for induction of labor. The inclusion criteria were as follows: singleton term pregnancies, nulliparity, Bishop score 5 or greater, and a reassuring fetal heart rate (FHR) monitoring tracing. We excluded: patients with premature rupture of membranes, multiple pregnancy, polyhydramnios, noncephalic presentation, probable cephalopelvic disproportion, suspected intrauterine growth retardation (estimated fetal weight $<$10th percentile for the gestational age), previous uterine scar, uterine perforation, cone biopsy, or allergy to prostaglandins. The study was approved by the Hospital's Ethical Committee and written informed consent was obtained from all participants.

Before drug administration, the following data were collected: clinical history, clinical examination including evaluation of the Bishop score; maternal vital signs (blood pressure, axillary temperature, and pulse rate); and cardiotocography.

Subjects were assigned to GT or placebo by means of a computer-generated randomization table and their allocation kept in consecutively numbered, sealed, opaque envelopes. The hospital pharmacy dispensed GT or placebo tablets and neither the doctors nor the patients knew what medication was being administered. The placebo tablets were indistinguishable from the GT tablets.

An initial dose of GT 500 μg or placebo was applied in the posterior vaginal fornix, followed by dinoprostone 2 mg. In accordance with departmental protocol for induction of labor, FHR and uterine activity were monitored continuously for 3 hours after application of the medication, after the beginning of regular uterine contractions, and during all the active phase and second stage of labor. Maternal blood pressure and pulse rate were assessed every 15 minutes, during 2 hours after initiation of treatment. All maternal or fetal adverse effects were documented.

Six hours after the initial application patients were reevaluated and based on clinical response, no medication or a second dose of dinoprostone (1 mg) was given. Six hours after the second dose, all undelivered women who were not in active labor (regular contractions every 10 minutes lasting 1 minute, or a change in Bishop score of at least 4 points), were considered a treatment failure. In those cases, in the next day, labor induction continued with application of dinoprostone.

Table I Demographic characteristics

	Dinoprostone plus placebo (n = 97)	Dinoprostone plus GT (n = 99)	*P*
Age (y)*	27 ± 4.4	27.5 ± 4.7	NS
Race			
White	92	93	NS
Black	5	5	
Mass body index*	29.7 ± 4.1	29.8 ± 4.2	NS
Gestational age (wk)*	40.4 ± 0.8	40.3 ± 1.0	NS
Indication for induction			
Postterm	64	61	NS
Macrosomia	6	8	NS
Oligohydramnios	7	10	NS
Hypertensive disorders	5	6	NS
Diabetes	10	8	NS
Fetal growth restriction	3	2	NS
Others	2	2	NS
Initial Bishop score†	3 (0-5)	3 (0-5)	NS

* Mean ± SD.
† Median (range).

The efficacy of the medication was evaluated by predetermined outcome variables for cervical ripening and induction of labor and delivery. Cervical ripening was assessed by the change in Bishop score found 6 hours after the initial application. Labor induction was assessed by measuring the time interval from the initial dose to the beginning of the active phase of labor and by the number of subjects in active phase of labor, 12 and 24 hours after the first dose. The beginning of the active phase of labor was defined as the sudden increase in the slope of cervical dilatation that usually happens when the cervix reaches a dilatation of 3 to 4 cm. Other outcome variables were the time from initial application to delivery and the number of subjects that delivered vaginally 12 and 24 hours after the first dose of medication. Safety was evaluated by the occurrence of various adverse effects: hypersystole was defined as 1 uterine contraction with a duration of more than 90 seconds, tachysystole as 5 or more contractions in 10 minutes for 2 consecutive 10-minute periods without FHR abnormalities and hyperstimulation as tachysystole associated with an abnormal FHR pattern.

Epidural analgesia was given at the subjects' request. Intravenous oxytocin was used in women already in the active phase of labor with protraction or arrest disorders. There was no specific protocol for artificial rupture of the membranes that was performed at the discretion of the attending obstetrician.

Statistical analysis was performed by *t* test and χ^2 test as indicated. It was calculated that 92 patients were needed in each arm of the study to have a 90% power (1-beta) when testing at a level of significance of