Induction of Labor: A Comparative Study of Intravaginal Misoprostol and Dinoprostone

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SUMMARY

Objective: To compare the efficacy and safety of intravaginal misoprostol and dinoprostone for elective induction of labor in nulliparous women with an unfavorable cervix.

Materials and Methods: A quasi-experimental study was conducted in Bahawal Victoria Hospital, Bahawalpur, Pakistan, from July 1, 2005 to August 31, 2006. A total of 120 primigravid women with gestational ages of > 40 weeks to < 42 weeks were divided into two groups. Group A ($n = 60$) was given 50 μg of misoprostol and Group B ($n = 60$) was given 3 mg of dinoprostone every 6 hours, for a maximum of three doses.

Results: The induction to onset of significant uterine contractions and delivery intervals were lower in Group A than in Group B (6.1 *vs*. 7.2 hours; $p = 0.16$; and 8.2 *vs*. 11.0 hours; $p = 0.007$, respectively). Group A had a lower cesarean section rate than Group B (7% *vs*. 30%; $p = 0.003$), but a higher rate of uterine hyperstimulation (10% *vs*. 3%; $p = 0.16$), tachysystole (17% *vs*. 3%; $p = 0.02$), and neonatal admissions to the intensive care unit within 24 hours of delivery (4 *vs*. 3; $p = 0.71$) and after 24 hours (2 *vs*. 1; $p = 0.56$) than Group B.

Conclusion: Vaginal misoprostol is more effective than dinoprostone for the elective induction of labor beyond 40 weeks of gestation, but is associated with more uterine hyperstimulation, tachysystole, and neonatal intensive care unit admissions. [*Taiwan J Obstet Gynecol* 2010;49(2):151–155]

Key Words: dinoprostone, induction, labor, misoprostol

Introduction

Prolonged pregnancy is a common indication for the induction of labor [1]. Gestational age exceeding 41 weeks is associated with higher maternal and perinatal morbidities, and termination of the pregnancy is preferred [2–6].

The rate of labor induction in America doubled from 1990 to 1998, from approximately 10% to 20% [7]. Prostaglandins can be administered at various doses and by different routes of administration. They have a twofold action that includes stimulation of myometrial contractility, as well as cervical ripening [8–10].

Several studies have demonstrated a higher efficacy of vaginally administered misoprostol compared with vaginal dinoprostone, in terms of both cervical ripening and labor induction [11–13]. A review of 45 randomized studies concluded that vaginal misoprostol (25–100 μg) was more effective than oxytocin or dinoprostone at the usual recommended doses used for induction, but was associated with increased rates of uterine hyperstimulation, both with and without associated fetal heart rate changes, as well as with meconium-stained fluid [14].

However, interpretation of most previous studies comparing misoprostol and dinoprostone for the

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induction of labor is complicated, because they have not been double-blinded [14] and have included both complicated and uncomplicated pregnancies, multiparous and nulliparous women, and a wide range of gestational ages (37–42 weeks). Moreover, the risk of side effects can be reduced by either decreasing the dose of the drug [12,13] or prolonging the dosage interval [15,16].

Dinoprostone (prostaglandin E_2 analogue) and misoprostol (prostaglandin E_1 analogue) are widely used in "induction of labor" practice for ripening the cervix and stimulating uterine contractions to achieve vaginal delivery. Misoprostol has the advantages of lower cost, no need for refrigeration, and potentially higher efficacy.

This study compared the efficacy and safety of vaginal misoprostol (50 μg) with vaginal dinoprostone (3 mg), both administered at 6-hourly intervals between repeated doses, in a homogeneous cohort of full-term pregnancies (nulliparous women with an unfavorable cervix, gestational age > 40 weeks and < 42 weeks, with no pregnancy complications). Obstetric and neonatal outcome measures were assessed. The primary outcome measures were time from induction to onset of uterine contractions, time from induction to delivery, and mode of delivery. The secondary outcomes were the cesarean section (CS) rate, and the incidences of meconium-stained amniotic fluid, uterine tachysystole, and fetal/neonatal complications.

Materials and Methods

This study was conducted between July 1, 2005 and August 31, 2006. A total of 120 women were selected for the study. All were recruited at Bahawal Victoria Hospital, Bahawalpur, Pakistan, a 1,300-bed tertiary referral center with an average annual delivery rate of 2,500. The hospital board of directors and research ethical committee approved the study, and all participants gave their written informed consent after the purpose of the study had been explained to them.

Inclusion criteria were age > 20 years, nulliparity, accurate dating of gestation, viable singleton pregnancy, gestational age > 40 weeks and < 42 weeks, cephalic presentation, unfavorable cervical status defined as a Bishop score < 6, intact membranes, and patient height > 150 cm. Exclusion criteria were known contraindications to receiving prostaglandins, placenta previa, previous uterine surgery, and any antenatal complications (medical/obstetric).

A detailed history was obtained for each subject, along with the results of general physical examinations, including vital signs and abdominal examination. Fetal cardiotocography was used to confirm fetal well-being. A digital examination was also performed. Baseline investigations included complete blood and urine examinations, blood grouping, and Rh factor determination.

Gestational age was estimated by ultrasound biometry (via crown-rump length measurements in the first trimester of pregnancy) in cases where there was more than 3 days' difference from the age obtained because of the last menstrual period [17]. Uterine tachysystole was defined as more than five contractions of moderate-to-severe intensity per 10 minutes, uterine hypertonus as one contraction lasting more than 2 minutes, and presence of fetal heart rate and hyperstimulation syndrome as the presence of a nonreassuring fetal heart rate tracing combined with either tachysystole or hypertonus [18].

Patients were randomly divided into two groups: Group A ($n = 60$) and Group B ($n = 60$). Group A were induced with misoprostol, and Group B with dinoprostone. The randomization procedure was done by opening sequentially numbered opaque envelopes containing cards stating the drug to be used. Bishop score was assessed prior to administration of either preparation; if it was < 6, then labor induction using either misoprostol or dinoprostone was planned.

Fifty micrograms of misoprostol (200-μg tablet, quartered; Group A) or 3 mg dinoprostone (Group B) was placed digitally high in the posterior vaginal fornix. This was repeated at 6-hourly intervals, up to a maximum of three doses (if needed). Doses were repeated if there was no uterine activity, or if the uterine contractions were less than two mild contractions in 10 minutes, with the patient being comfortable. Fetal cardiotocography was performed before each dose to confirm fetal well-being.

Vaginal assessment was performed when uterine activity suggested the onset of labor, and the woman was moved to the labor ward. Maternal vital signs were monitored at 4-hourly intervals throughout the procedure. The time when significant uterine contractions started was noted (significant uterine contractions: 3–5 contractions of moderate-to-severe intensity in 10 minutes). Adequate analgesia was given with pethidine. Continuous fetal and maternal monitoring was performed, and a detailed record of the labor was maintained on a partogram.

Failed induction of labor was defined as vaginal delivery not achieved within 24 hours of initiating induction [19]. The indications for CS were failed induction, uncontrolled hyperstimulation or fetal distress. Any complications occurring during the induction procedure were recorded and managed accordingly. At the time of delivery, a pediatrician was called to examine

and resuscitate the baby in the delivery room. Further management of neonates was carried out accordingly.

Data were analyzed using SPSS version 10 (SPSS Inc., Chicago, IL, USA) and subjected to descriptive analysis. Student *t* tests were applied to measured data (intervals between induction and significant uterine contractions and delivery). Categorical data were analyzed using χ^2 tests. A p value <0.05 was considered to be significant.

Results

Of the 120 study subjects, 78 (65%) were <25 years old and the remainder were >25 years old. The mean age in Group A was 23 years, while that in Group B was 25 years. In Group A, 18 (30%) subjects went into active labor after insertion of a single dose, compared with only eight (14%) in Group B. The obstetric outcomes of the subjects are presented in Table 1. The mean time from induction to onset of significant uterine contractions was 6.1 hours in Group A and 7.2 hours in Group B ($p=0.16$). Similarly, the mean time from induction to delivery was 8.2 hours in Group A and 11.0 hours in Group B ($p=0.007$). Induction failed in 18 subjects (30%) in Group B, but only failed in two (3%) in Group A ($p<0.001$). Group A had a lower cesarean section rate than Group B (7% *vs*. 30%; $p=0.003$) (Table 1).

Regarding the modes of delivery, 42 women (70%) in Group A had spontaneous vaginal deliveries, 14 (23%) had instrumental vaginal deliveries, and four (6%) required CS. In Group B, only 26 (43%) delivered vaginally, while 16 (27%) required instrumental vaginal deliveries and 18 (30%) required CS (overall $p=0.002$).

Table 2 presents the neonatal outcomes. There were more neonatal admissions to the intensive care unit in the misoprostol group than in the dinoprostone group within 24 hours of delivery (4 *vs*. 3; $p=0.71$) and after 24 hours (2 *vs*. 1; $p=0.56$; Table 2).

Discussion

Labor induction is increasingly common [20,21]. Recent studies have shown that this is mainly due to an increase in inductions performed for marginal or elective reasons. Elective induction and induction for postdate pregnancies, often applied to gestations of 40–41 weeks, are common indications [1,21]. Women may experience distress when labor has not started by the expected date [22], and obstetricians have to endure pressure from these patients, as well as the temptation to use prostaglandins earlier. Suitable evaluation of the pregnancy and consultation with the patient will identify those who can benefit from labor induction, thus eliminating the risk of postmaturity of the fetus, without inducing fetal distress during labor.

Table 1. Obstetric outcomes*

Variables	Group A (misoprostol; $n=60$)	Group B (dinoprostone; $n=60$)	p
Prostaglandin doses for active labor			
Single	18 (30)	8 (13)	0.049
Two	36 (60)	38 (63)	0.82
Three	6 (10)	14 (23)	0.07
Interval (hr)			
Induction to onset of SUC	6.1 ± 0.6	7.2 ± 0.5	0.16
Induction to delivery	8.2 ± 0.8	11.0 ± 0.7	0.007
Induction to delivery interval detail			
<6 hr	20 (33)	6 (10)	0.006
6–12 hr	32 (53)	30 (50)	0.80
>12 hr	8 (13)	24 (40)	0.005
Induction failure, *n* (%)	2 (3)	18 (30)	<0.001
Cesarean section rate, *n* (%)	4 (7)	18 (30)	0.003
Complications			
Uterine hyperstimulation	6 (10)	2 (3)	0.16
Uterine tachysystole	10 (17)	2 (3)	0.02
Allergic reaction	2 (3)	2 (3)	>0.99
Meconium-stained liquor	4 (7)	2 (3)	0.41

**Data are presented as n (%) or mean ± standard error. SUC = significant uterine contractions (3–5 moderate-to-severe contractions in 10 minutes).*

Table 2. Neonatal outcomes*

Variables	Group A (misoprostol; $n=60$)	Group B (dinoprostone; $n=60$)	p
Birth weight (g)	3,165 ± 430	3,273 ± 390	0.15
Perinatal death	0 (0)	1 (2)	0.32
Manual bag-valve-mask ventilation	7 (12)	6 (10)	0.78
Intubations in labor room	1 (2)	1 (2)	> 0.99
Apgar score < 7			
1 min	10 (17)	5 (8)	0.20
5 min	1 (2)	0	0.32
Birth trauma†	0 (0)	1 (2)	0.32
ICU admissions			
Within 24 hr	4 (7)	3 (5)	0.71
After 24 hr	2 (3)	1 (2)	0.56

**Data are presented as n (%) or mean ± standard deviation; †clavicle fractures. ICU = intensive care unit.*

The present study compared the use of misoprostol and dinoprostone for labor induction in a homogeneous cohort of nulliparous women with intact membranes, who were all at > 40 weeks' gestation, with no antenatal complications. Misoprostol was more effective than dinoprostone in these carefully selected patients at shortening not only the time between labor induction and onset of uterine contractions, but also that between induction and delivery. This positive result was achieved with a very low CS rate. This could have clinical implications in terms of patient health and cost effectiveness. Meta-analyses published by the Cochrane Library [12] and by Sanchez-Ramos et al [23] found lower rates of CS with misoprostol compared with dinoprostone.

Although misoprostol resulted in a higher rate of uterine hyperstimulation (10%) compared with dinoprostone (3%), the difference was not significant; however, there was a significantly higher incidence of tachysystole with misoprostol. The rate of meconium-stained liquor during induction with misoprostol use was low, but was still double that seen with dinoprostone (7% *vs*. 3%). The Cochrane meta-analysis [12] also found increased likelihoods of meconium staining of amniotic fluid and uterine tachysystole with misoprostol. Unfavorable neonatal outcomes such as low Apgar score in the first minute and entry to the neonatal unit within the first 24 hours were more frequent with misoprostol, although the differences were not significant. Thus, although the sample size in this study was too small to conclusively determine its safety, misoprostol use appears to be associated with a higher chance of admittance to the neonatal unit within 24 hours than dinoprostone, even in the absence of asphyxia. These results emphasize that early induction of childbirth is not necessarily advisable.

Based on the results of this and previous studies [13,24,25], the increase in clinically pertinent adverse effects with misoprostol appears to be dose and dose-interval dependent. These studies indicate that misoprostol not only acts more effectively on the myometrium than on the cervix, but that a higher dose is needed to ripen the cervix. This suggests that increasing the interval between repeated misoprostol doses should reduce the risk of asynchrony between a well- or even hyperstimulated uterus and a still not fully ripened cervix. Misoprostol may exhibit large interpatient variability in terms of its pharmacokinetics, but it is probable that a dose of 50 μg might induce asynchrony between effacement of the immature cervix and uterine contractions, resulting in a more rapid but also more stressful labor. Based on these findings, we propose that the misoprostol dose used in the current study should be slightly modified. An initial lower dose of misoprostol (20–25 μg) administered at longer intervals should be considered, with the aim of priming the cervix without inducing such high uterine contractility.

In conclusion, 50 μg misoprostol administered at 6-hourly intervals is more effective in promoting cervical ripening and inducing labor than dinoprostone. However, administration of this drug requires continuous monitoring because of the possibility of complications, and its effects on certain aspects of fetal well-being during labor induction remain to be clarified.

Future studies are needed to compare the efficacy and safety of different doses of vaginally inserted misoprostol tablets with those of controlled-release vaginal misoprostol inserts. Other studies to compare the efficacy and safety of different doses of controlled-release vaginal misoprostol inserts are also highly recommended [26].

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