Thai Journal of Obstetrics and Gynaecology
March 2000, Vol. 12, pp. 21-25

OBSTETRICS

A Randomized Comparison Between 25 Microgram Misoprostol Gel and 50 Microgram Misoprostol Vaginal Tablet for Induction of Labour

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ABSTRACT

Objective To compare the safety and effectiveness of intravaginal administered misoprostol at doses of 25 microgram gel and 50 microgram tablet for labor induction in patients with an unfavorable cervix.

Design Prospective study.

Setting Department of Obstetrics and Gynaecology, Srisangwal Hospital.

Subjects Using a randomized method. 166 uncomplicated patients received either 25 microgram gel or 50 microgram tablet of misoprostol, placed intravaginally in the posterior fornix. The dose was repeated every 6 hours until adequate labor was achieved (at least three contractions in 10 minutes).

Main outcome measures Mode of delivery, time taken from initial application of PGE2 to the full cervical dilatation and to the delivery,total dosage, uterine hyperstimulation, Apgar score and immediate newborn status at birth.

Results Among uncomplicated 166 patients evaluated, 83 patients were allocated to the 25 microgram group and 83 patients to the 50 micrograms group. The patients' characteristics were not different between two groups. (Maternal age, parity, height, weight, gestational age, initial bischop score, new born birth weight) The start-to-fully dilated cervix and start-to-delivery interval were equal between the 25 microgram and 50 microgram group. (846.132 minutes vs 910.324 minutes ($p = 0.561$) and 873.361 minutes vs 959.325 minutes ($p = 0.471$) respectively). The mean total dosage of misoprostol tablet group (106.625 micrograms) was more than that of misoprostol gel group(80.12 micrograms, $p = 0.043$). Patients required oxytocin augmentation were not different in the two groups ($p = 0.141$). There was no different in the cesarean section rate or other operative delivery rate among patients in the two treatment groups. ($p = 0.169$) The apgar score at 1 minutes in the 25 microgram group was greater than 50 micrograms group (9.506 vs 8.313 $p = 0.003$). The incidence of birth asphyxia in 50 micrograms group was more than in 25 microgram group ($p = 0.015$). The apgar scores at 5,10 minutes of both newborn groups were not different ($p = 0.473, 0.319$). The incidence of uterine hyperstimulation in 50 micrograms group was more than in 25 microgram group ($p = 0.0315$).

Conclusion The 25 microgram misoprostol vaginal gel is more effective and safe than 50 microgram vaginal tablet. Because it is not associated with a lower incidence of low apgar score, it is recommended for labor induction in the cases associated with risks of fetal asphysia or distress.

Key words : misoprostol,vaginal administration, induction of labour

Medical control of labour is often necessary in modern obstetrics. The status of the cervix may dictate the method of induction and influences its success. Amniotomy and intravenous oxytocin has been used as a standard method for induction of labour in some institutes. However, patients with unfavourable cervix are likely to have prolonged labour with all inevitable sequelae. Locally applied prostaglandin E_2(dinoprostone) has been widely used, not only to ripen the cervix but also to induce labour.[1] Many published data confirm the safety, efficacy of intravaginal misoprostol (prostaglandin E_1) as an agent for cervical ripening and labor induction.[2] Compared with oxytocin for labor induction, misoprostol results in a shorter induction-to-delivery interval, a reduction in the rate of cesarean delivery for dystocia, and a decreased use of epidural analgesia.[3] Compared with prostaglandin E_2(dinoprostone), it is cheaper and stable at room temperature.[4] Intravaginal administration of misoprostol is a safe and effective alternative for cervical ripening and labor induction. Maternal and neonatal complications did not increase significantly.[5,6] Vaginal misoprostol administation is as effective as dinoprostone for cervical ripening and the induction of labor. Mean time intervals to delivery, needs for oxytocin augmentation, and routes of delivery were similar between the two groups.[7] Although a usual dose of misoprostol is 50 microgram from dividing 200 micrograms misoprostol tablet into four is associated with a shorter start-to-delivery interval and a higher incidence of vaginal delivery after one dose but there is a higher incidence of tachysystole and cord pH values < 7.16 when it was compared with the lower dose.[8,9] Nevertheless, the question remains as to what is the pregnancy outcome in different doses and in what preparation form of misoprostol. This prospective study is to compare the outcome (safety and effectiveness) between patients with 25 microgram misoprostol gel and 50 microgram misoprostol vaginal tablet for induction of labour.

Materials and Methods

This prospective randomized study was carried out at the Department of Obstetrics and Gynaecology, Srisangwal Hospital, Following the approval by Public health ministry, one hundred and sixty-six patients received either 25 microgram gel or 50 microgram tablet of misoprostol, placed intravaginally in the posterior fornix. The dose was repeated every 6 hours until adequate labor was achieved (at least three contractions in 10 minutes). Inclusion criteria before informed consent were singleton pregnancy, 38 to 41 week gestational age, vertex presentation, intact membranes, reactive nonstress test and no evidence of fetal distress. Patients with abnormal lie or presentation, premature rupture of membranes, oligohydramnios, previous uterine scars, uterine contraction, obstetrical complication, history of allergy to prostaglandins or severe medical diseases such as asthma, heart diseases were excluded from the study. The gestational age was estimated by confirmed last menstrual period during early antenatal care or ultrasonic findings that were compatible with the patients' menstrual dates. All procedures were performed in the labour room. Each patient was checked for cervical score and monitored over a period of 30 minutes to ensure that the fetal heart rates (FHR) were normal and there were few or no uterine contractions (fewer than three in 30 minutes). After an evaluation period, the patient was chosen randomly to use 25 microgram PGE_1 gel or 50 micrograms PGE_1 vaginal tablet. It was placed in the posterior fornix then the patients were asked to remain in prone position for at least 1 hour. In the first 2 hours, the patients were closely monitored for abnormal FHR and uterine hyperstimulation. The cervical score was assessed by the same obstetrician until delivery. After the first 2 hours, the patients received the standard Thai Public health ministry labor care. The dose was repeated every 6 hours until adequate labor was achieved (at least three contractions in 10 minutes). Amniotomy was performed when cervical dilatation reached 3-4 cm and other conditions for amniotomy were fulfilled, unless membranes ruptured spontaneously. Augmentation with oxytocin was done as indicated, using arithmetic-progression method. Route and method of

delivery were performed under obstetric indication.

The following indices are used to measure outcomes : time from initial application of prostaglandins unitil fully dilated cervix and delivery, the number of drug repeating, the total dose used, incidence of uterine hyperstimulation, mode of delivery, apgar score and immediate newborn status at birth. Birth asphyxia is defined as having apgar score at 1 minutes equal or less than 7. Averaged data were reported as means and standard deviations and compared by unpaired t-test and chi-square test. $P<0.05$ was considered significant.

Results

Among 166 patients evaluated, 83 patients were allocated to the 25 microgram group and 83 patients to the 50 microgram group. The patients' characteristics of the two groups were similar (Table 1). The pregnancy outcomes of patients with 25 microgram Prostaglandin E_1 gel and 50 microgram Prostaglandin E_1 Vaginal tablet are demonstrated in Table 2-4.

Table 1. Patients' characteristics

Characteristics	Group 1(n=83)	Group 2(n=83)	P-value
- Age(yr)	24.867	24.723	0.871 (NS)
- Parity	2.072	2.205	0.57 (NS)
- Height(cm)	153.48	154.009	0.523 (NS)
- Weight(kg)	59.761	61.552	0.17 (NS)
Gestational age(wk)	39.687	39.711	0.886 (NS)
Initial Bischop score			
- Dilatation	0.964	0.831	0.17 (NS)
- Effacement	0.651	0.566	0.417 (NS)
- Station	0.723	0.807	0.324 (NS)
- Consistency	1.386	1.361	0.772 (NS)
- Position	1.398	1.373	0.786 (NS)

Group 1 = Patient with 25 microgram misoprostol gel group

Group 2 = Patient with 50 microgram misoprostol tablet group

Table 2. Mean time from application of prostaglandin E1 vaginal suppository to delivery, in cases of successful vaginal delivery (in minutes)

	Group 1 (N =81)	Group 2 (N =74)	P-value
1. Application to full-dilatation	910.325 (mins)	846.132 (mins)	0.561(NS)
2. Application to delivery	959.325 (mins)	873.361 (mins)	0.471(NS)

Table 3. Pregnancy outcomes

	Group 1(n=83)	Group 2(n=83)	P-value
Mother			p=0.169
1. Route of dilivery	72	64	
- Normal dilivery	2	9	
- Cesarian section	9	10	
-F/E or V/E			
2. Aumentation with Oxytocin	12.05%	20.48%,	p = 0.141
3. Vaginal delivery after one dose insertion	38.5%	46.9%	p = 0.003
Newborn (Mean)			
1. Birthweight(gm.)	3106.506	3128.494	p = 0.763(NS)
2. Apgar score at 1 minute	9.506	8.313	p = 0.003
3. Apgar score at 5 minutes	9.952	9.880	p = 0.473
4. Apgar score at 10 minutes	10	9.940	p = 0.319
5. Apgar score at 1 minute equal or less than 7 (% of cases)	0.1%	5.9%	p = 0.015
6. Hyperstimulation (% of cases)	2.4%	7.2%	p = 0.0315
7. Mean total dosage of prostaglandin (Microgram)	80.12	106.625	p = 0.043

The start-to-fully-dialtation and start-to-delivery interval in Group 1 ,the 25 microgram gel, equaled to group 2, 50 micrograms tablet (p = 0.561, 0.471). The incidence of vaginal delivery after one dose was higher in the 50 microgram group (46.9% vs 38.5%, p = 0.003). Patients receiving 25 microgram required oxytocin augmentation were not different with those receiving 50 microgram (12.05% vs 20.48%, p = 0.141). The cesarean section and other operative delivery are shown in table 3. They were no different between patients in the two treatment groups. The apgar score at 1 minutes in the 25 microgram group was greater than in the 50 microgram group (9.506 vs 8.313 p = 0.003). The incidence of newborns with birth asphyxia (apgar score at 1 minutes equal or less than 7) was greater in the 50 microgram group(5.9% vs 0.1%, p = 0.015). The incidence of hyperstimulation between the two groups were different(p=0.0315). One in 50 microgram group was more than in 25 microgram group(2.4% Vs 7.2 % P = 0.0315). The mean amount of 50 microgram misoprostol tablet group was 106.625 micrograms and the 25 microgram misoprostol gel group was 80.12 micrograms. There were no side effects of misoprostol in both groups.

Discussion

In this study, for excluding the confounder, the cases's characteristics were not different statistical significantly as the table 1. We compared pregnacy outcomes between the two groups using 25 microgram misoprostol gel (group1) and 50 microgram misoprostol intravaginal tablet(group2). It was found that although the incidence of vaginal delivery after one dose in group 2 was more than that in group 1 but the start-to-fully-dilated and to delivery interval were not different between the two groups. Their effectiveness was considered by the total dosage and the time taken for full dilatation of cervix. When the cases in both groups had prolonged the progression of labour such as, in active phase, second stage, they were managed by

oxytocin augmentation or other obstetric maneuver as mentioned in methodology. In table 3 the routes of delivery were not different statistically, this inferred that there was not the difference of cephalo-pelvic disproportion between two groups. The application to full-dilate and to delivery time were not different between two groups significantly as table 2. But the total dosage of misoprostol in group 1 was fewer than group 2 (p=0.043 as table 3). Therefore, we could imply that the 25 microgram misoprostol gel was more effective than the 50 microgram misoprostol tablet. The incidence of low apgar score at 1 minute and birth asphyxia in 25 microgram misoprostol gel were fewer than 50 microgram misoprostol tablet (table 3). The cause of low apgar score and birth asphyxia could be the uterine hyperstimulation, induced by 50 microgram misoprostol ,which was more than by 25 microgram misoprostol. Therefore, the incidence of birth asphyxia and low apgar score at 1 minute in group 2 were more than in group 1 .9,10 So,fetal cardiotocographic monitor should be used with 50 microgram misoprostol induction. In one study there was a slightly higher prevalence of tachysystole (six or more uterine contractions in a 10-minute window for two consecutive 10-minute periods) in the 3-hour interval vaginal misoprosol administration group (14.6%) than in the 6-hour group (11.2%), but this difference was not statistically different.12 The side effects of misoprostol ,in general are shaking chills, abdominal and extremity cramping, emesis, confusion hyperthermia and hypotension but fortunately, they did not occur in this study.[13,14] Other route of misoprostol administration is in the oral form but it is less effective than vaginal route for induction of labor at term.[15]

In conclusions, the 25 microgram misoprostol vaginal gel is more effective and safe than 50 microgram vaginal tablet (In term of using less dosage and time taken for full dilatation of cervix). As this is not associated with a lower incidence of low apgar score, it is recommended for labor induction in the cases associated with risks of fetal asphysia or distress.

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