COMPARATIVE EFFICACY OF MISOPROSTOL AND OXYTOCIN AS LABOR PREINDUCTION AGENTS: A PROSPECTIVE RANDOMIZED TRIAL

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Abstract- The purpose of this study was to compare the efficacy and safety of misoprostol and oxytocin for induction of labor. In this prospective and randomized controlled trial one hundred twenty women with an unfavorable cervix who underwent labor induction were assigned to receive either intravenous high dose oxytocin (6 mIu/min) or intravaginal misoprostol 50 µg every 6 hours for two doses. Twelve hours later if labor was not established oxytocin induction was initiated per standardized protocol (3 mIu/min). Mean Bishop Score change (± SD) over the initial 12 hours interval was significantly greater in the misoprostol group (11.98 ± 1.55) compared with the oxytocin group (8.83 ± 2.61). There were no statistically significant differences in the median duration of labor (449 ± 261.1 min, 514.5 ± 288.5 min, respectively; $P = 0.22$), the mode of delivery or the adverse maternal /neonatal out come among the two groups. Use of misoprostol as a labor preinduction / labor induction agent results in greater Bishop score changes compared with high dose oxytocin and both of them are comparable.

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INTRODUCTION

Induction of labor in the third trimester of pregnancy may be considered beneficial in many clinical circumstances (1). The main problems associated with induction of labor are ineffective labor and excessive uterine activity, which may cause fetal distress. Both problems may lead to an increased risk of cesarean section (2, 3).

Oxytocin and prostaglandins (PGs) are the pharmacologic agents most frequently used for induction of labor (4-6). Although oxytocin infusion is widely accepted as a safe and effective labor induction method, its success is highly dependent on the condition of the cervix at the beginning of the induction. Labor induction in the setting of an unfavorable cervix can result in prolonged induction, induction failure, increased operative delivery, longer hospitalization and increased medical costs (7). Hence, cervical ripening agents often are applied in women with unfavorable cervices before an oxytocin infusion is initiated (8). Prostaglandins, including a variety of classes, doses, and routs of administration, have been widely studied as alternatives to oxytocin (9-15). Induction of labor with PGs offers the advantage of promoting both cervical ripening and myometrial contractility (2, 10).

Recently, there has been considerable interest in the use of misoprostol a synthetic prostaglandin E1 (PGE1) analogue that has been marketed since 1988 for use in prevention and treatment of peptic ulcers. In addition misoprostol acts as an effective

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myometrial stimulant of the pregnant uterus, selectively binding to EP-2/EP-3 prostanoid receptors (16). The drug is inexpensive, easily stored at room temperature and have few systemic side effects but the optimal regimen that will initiate and maintain effective labor , without adversely affecting the fetus , has not been established (17, 18).

This study was undertaken to compare safety and efficacy of misoprostol with high dose oxytocin as cervical ripening agents for labor induction. We hypothesized that induction of labor with misoprostol would result to increase cervical Bishop Scores compared with high dose oxytocin and it's use would not be associated with adverse maternal or fetal outcomes.

MATERIALS AND METHODS

This study was a prospective randomized, blinded clinical trial that was designed to compare the efficacy of misoprostol and oxytocin as cervical ripening agents in women who underwent cervical ripening/ labor induction with an unfavorable cervix at the Shariati hospital from February 2004 through March 2005. All women with a medical or obstetric indication for labor induction were eligible for this investigation. Inclusion criteria were (1) an unfavorable cervical Bishop score of ≤5 (2) a singleton pregnancy with vertex presentation and no contraindication to vaginal delivery , (3) the absence of spontaneous uterine contractions (ie, <4 spontaneous contraction per hour) and (5) a reactive non stress test . Exclusion criteria included (1) a known hypersensitivity to prostaglandins allergy, sever asthma, (2) ruptured membranes , (3) suspected chorioamnionitis , (4) parity of >5 , (5) a previous cesarean delivery or a history of uterine surgical procedures, (6) pervious attempted induction of labor for this pregnancy, and (7) digital examination with lubricant immediately before induction. All women who met these requirements and gave medical inform consents were enrolled. The study was approved by Research Review Committee of Hormozgan University of Medical Science.

All study candidates were admitted to the labor and delivery unit before the scheduled induction of labor; cardiotocography was performed to rule out fetal distress and the presence of uterine contractions. A cervical Bishop score was assigned on admission by a single resident physician in a blinded manner for all patients who were enrolled in the study before the randomization. Randomization was done independently through our central hospital pharmacy using dynamic allocation with stratification by parity (primiparous vs multiparous) and initial Bishop score (≤ 2 vs. >2). Dynamic allocation was used to balance the enrolled patients within each of the prognostic strata previously mentioned. Women were assigned randomly to receive preinduction with either misoprostol (Cytotec, R. Pharmacia limited/ Davy Avenue, Milton Keynes, MK58PH/ UK) 50µg intravaginally in the posterior fornix initially, with one –time repeat dosing 6 hours later or oxytocin infusion at an initial rate of 6 mIU/min with 6 mIU/min incremental at 30- minutes intervals to a maximum 42 mIU/min. Because the 50µg tablet was not available commercially, a 200 µg tablet was cut into fourth by the hospital pharmacist. Preindution agents were administered by an on-call physician in the labor and delivery ward not by the physician who assigned the Bishop scores. Women with and established contraction pattern of >3 contractions in 10 minutes or with and abnormality of the fetal heart tracing did not undergo redosing of misoprostol or continuing of oxytocin. After 12 hours, a repeat Bishop score was assigned by the same initial examiner. patients who were not in and adequate labor pattern after the preinduction interval received standard oxytocin (pitocin, Parke-Davis Products, Morris Plains, NJ) infusion at an initial rate of 2mU/min, with 2mU/min incremental increases at 15- minutes intervals to a maximum of 42mU/min until an adequate labor activity (3 contractions in 10 minutes) was obtained. Patients in active- phase labor (≥4 cm dilation with regular uterine contractions) with arrest of dilation (no change in cervical dilation for ≥ 2 hours), despite adequate labor pattern contractions received oxytocin augmentation according to the above protocol. Continuous electronic fetal heart rate was use throughout labor. Standardized intrapartum treatment guidelines were used for all patients. Women in whom uterine hyperstimulation without

fetal heart rate changes [include uterine Tachysystole (> 5 contractions per 10 minutes for at least 20 minutes) and uterine hypertonus (a contraction lasting at least 2 minutes)] developed, received a single dose of intramuscular pethidine (25 mg) or promethazine (25 mg), along with a position change and oxygen administration. Patients who demonstrated no significant cervical change during the initial 24-hours period were retreated with the original cervical ripening regiment for an additional 12 hours before the oxytocin therapy was reinitiated. Demographic and outcome data were compiled.

We chose mean Bishop score changes of the cervix within the initial 12 hours of treatment as the primary outcome. Secondary outcome variables included, the route of delivery, mean duration of labor, fetal compromise such as the presence of meconium staining of the amniotic fluid, low Apgar scores and admission to the neonatal intensive care unit (NICU). Analysis was by intent to treat. statistical analysis included analysis with x^2 ANOVA and *t* test. Statistical significance was defined as probability value of < 0.05.

RESULTS

From 188 patients scheduled for induction of labor at the Shariati Hospital from February 2004 till March 2005 inclusion criteria were satisfied for 124 patients and they were enrolled.

Four participants were excluded from the analysis because of deviation from the protocol. One from misoprostol group didn't agree to continue protocol after one dose of misoprostol. One in each group had worsening hypertension and with impression of sever preeclampsia underwent immediate cesarean delivery, and one in the oxytocin group was excluded due to large baby. This left a total of 60 participants in each group.

No significant differences were noted among the two groups with respect to maternal age, body mass index, gestational age, initial bishop score or parity (Table 1). Similarly no significant difference was noted among groups with respect to the indication for induction, with postdates was the most common indication (Table 2).

Table 1. Demographic Charactristics

Demographics	Misoprostol (no 60)	Oxytocin (no 60)	*P value
Age(y)	25.65±5084	25.12±5.32	NS
BMI (kg/m2)	22.28±2.43	22.55±2.65	NS
Nullipara	42(70.56)	42(70.56)	NS
Multipara	18(28.34)	18(28.34)	NS
Gestational Age(day)	283.2±11.3	282.5±16.00	NS
Initial Bishop Score	2.57±1.48	2.52±1.35	NS

* t-test and x^2 ANOVA test

The mean Bishop score change (± SD) over the initial 12-hour interval was significantly greater in the misoprostol group (11.98 ± 1.55) compared with the oxytocin treatment group (8.83 ± 2.9, $P < 0.0069$).

As shown in Table 3, there was no statistically significant difference in vaginal delivery rates (47 or 78.13% in the misoprostol group and 46 or 76.4% in the oxytocin group). Of the patients who achieved successful vaginal delivery, there was no statistically significant difference in the interval between induction to active phase, active phase to delivery, or induction to delivery (Table 3). However stage one and two were shorter in the misoprostol group.

No adverse maternal effects were noted in either the misoprostol or oxytocin groups. Labor management was comparable among the two groups (Table 3). Uterine tachysystole was more common in women receiving misoprostol (5 or 17%) than in those receiving oxytocin (no case or 0%, *P* = ns) (Table 4).

Table 2. Indication for Induction of Labor

Indication	Misoprostol (n=60)	Oxytocin (n=60)	*P* Value
Preeclampsia	10(16.67)	21(35)	NS
Post term	32(35.69)	31(51.66)	NS
Diabetes Mellitus	9(15)	4(6.67)	NS
Oligohydramnios	7(11.66)	2(3.33)	NS
Fetal Growth Restriction	1(1.67)	1(1.67)	NS
Others	1(1.67)	1(1.67)	NS

* X^2 test
Data are given as number (percent)

Table 3. Obstetrics outcomes

Characteristic	Misoprostol (n=60)	Oxytocin (n=60)	*P Value
Change in bishop score Over initial 12hour	11.98±1.55	8.83±2.9	0.00001
Total vaginal delivery	47(78.33)	46(76.4)	NS
Total Cesarean Deliveries	13(21.67)	14(23.6)	NS
Nonreassuring FHR	5(38.4)	11(77)	NS
Dystotia	3(23)	0	
Meconium passage	5(38.4)	3(23)	NS
Median duration of labor(min)	449.9 ± 261.1(min)	514.5 ±288.5(min)	0.22
Uterine tachysystole	5(8.3%)	0	NS
Use of pethidine or promethazine	2(3.3%)	0	NS

*t-test and x^2test

Incidence of fetal heart decelerations was more common in the oxytocin group (12 or 55%, *P* = ns) than in misoprostol group (Table 4). No significant difference was noted in the rate of meconium-stained amniotic fluid or post partum bleeding. Neonatal outcomes (including birth weight, Apgar score, and rate of admission to the neonatal intensive care unit) were similar among two groups.

Mean hospital charge per patient and length of hospital stay was less in the misoprostol group compared with the oxytocin group.

DISCUSSION

The induction of labor with unfavorable cervix often results in a prolonged labor and increases the rate of cesarean delivery, both of which are associated with increased maternal and neonatal morbidity (1). Ripening of an unfavorable cervix has become an integral part of the labor induction process (2, 6, 10). The best method of cervical ripening remains controversial; no one method has proven to be superior (7, 12).

Table 4. Neonatal Outcomes

Outcome	Misoprostol (n=60)	Oxytocin (n=60)	*P* value†
Birth weight(g)	3159±454	3087±510	NS
Appgar score<7			
1 minute	5(8.33)	2(3.37)	NS
5 minute	1(1.67)	1(1.67)	NS
NICU admission	9(15)	12(20)	NS

†t-test and x^2 test

The development of standardized commercially available prostaglandin preparations has provided a reliable avenue for the treatment of patients with an unfavorable cervix who require labor induction (8, 9). Although these agents are efficacious, the relative costs vary greatly. So the identification of the most cost- effective preinduction agent to promote cervical ripening is of great clinical importance (11, 13, 14). Although misoprostol is effective and inexpensive, concern has been raised regarding the widespread use of this agent as a primary or adjuvant agent for labor induction (15-17). Our study compares the safety and efficacy of misoprostol directly with that of oxytocin. A dose of 50 µg misoprostol administered vaginally every 6 hours up to 4 doses, seemed to be an efficient means of inducing labor. The mean Bishop Score change over the initial 12-hour interval was significantly greater in the misoprostol group compared with the oxytocin treatment group. The cost and length of stay in hospital was less in the misoprostol group.

A concern in the use of misoprostol for induction of labor is uterine hyperstimulation or tachysystole (18, 19). It appears that the incidence of uterine tachysystole is dose related, as indicated by an incidence of 17% with the dose 25 µg dose (19), 37% with 50 µg (18), as used in our study, and72% with 100µg (20). But in our study the incidence of uterine tachysystole was about 17%. Contrary to some report (19), we did not find an increase in the incidence of meconium staining of amniotic fluid in the misoprostol group. It is important to note that 53.69% of women in the misoprostol group in our study underwent induction for post date pregnancy.

There were not significant differences between two groups with regard to the rate of cesarean section, meconium-stained amniotic fluid, post partum bleeding, neonatal outcomes (including birth weight, Apgar score, and rate of admission to the neonatal intensive care unit).

A large body evidence exists that shows the use of misoprostol for labor induction is highly efficacious and safe. Misoprostol dosing regimens that range from 25µg every 3 to 4 hours and 50µg every 4 to 6 hours have been shown to be safe and effective regimens for use in labor induction (1, 18-20). Sanchez-ramos *et al*. recently reported findings from a through review of literature on misoprostol use for cervical ripening and labor induction[21]. These authors systematically reviewed data from 44 prospective randomized studies (a total of 5735 women were enrolled in these trials, 2791 women were treated with misoprostol and 2944 women were treated with other active drugs or placebo). In spite of observation of more frequent events of tachysystole(odds ratio, 2.98; 95% CI, 2.43-3.66) and hyperstimulation syndrome(odds ratio, 1.73; 95% CI, 1.25-2.40), no significant differences were noted between the group of women who were treated with misoprostol and the other group of women who were treated with active drug/ placebo with regard to the incidence of cesarean delivery for fetal heart rate abnormalities nor the incidence of low 5-minute Apgar scores or neonatal intensive care unit admissions. These authors concluded that misoprostol is safe and effective for cervical ripening / labor induction when used at appropriate dosages intravaginally.

Conflict of interests

The authors declare that they have no competing interests.

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