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MATERNO-FETAL MEDICINE

A comparison of misoprostol, controlled-release dinoprostone vaginal insert and oxytocin for cervical ripening

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Abstract
Objective We compared the safety and effectiveness of oxytocin, dinoprostone and misoprostol for cervical priming.
Study design A total of 218 patients were enrolled to receive between one and three treatments according to physicians' options. The end points were: (1) vaginal delivery or Bishop score ≥8 at the end of 12 h, (2) vaginal delivery by 12 h or difference ≥4 between the initial and 12th hour Bishop scores. Statistical analyses were performed with ANOVA, Krustal Wallis, Scheffe, χ^2, Fisher, Advanced χ^2, and Kolmogorov–Smirnov tests. Tukey's HSD was used as a post hoc test.
Results Misoprostol showed statistical significance for the rate of vaginal delivery <12 h, ≥8 Bishop score at the end of 12 h, and cervical change of ≥4 Bishop scores within 12 h ($p = 0.013$).
Conclusions Comparison between cases Bishop score <4 showed that misoprostol is more effective than dinoprostone and oxytocin. Considering Bishop score = 0 cases we calculated no statistical significance.

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Introduction

The purpose of cervical ripening and induction of labor is to achieve vaginal delivery and to avoid operative delivery by cesarean section. Induction of labor involves initiation of uterine contractions. Cervical ripening may stimulate uterine contractions and uterine contractions result in cervical ripening [1].

Between 20 and 30% of all pregnant women have labor induction and labor induction is becoming a frequent practice [2–4]. Labor induction can be preferred instead of operational intervention in situations such as post-term pregnancies, eclampsia–preeclampsia, diabetes, IUGR or fetal distress [5]. But induction may lead to uterine rupture, tachysystole or hyperstimulation of pregnant women [5, 6].

Oxytocin is the agent most frequently used for induction of labor [7, 8]. Oxytocin induction can be performed with low-dose or high-dose protocols with a maximum dose of 42 mu/min [1, 9].

Dinoprostone (either vaginally or intracervically), a prostaglandin E2 analog, used for preinduction cervical ripening [1, 10]. The major safety concern for dinoprostone use is uterine hyperstimulation and fetal tachysystole. This can be rapidly reversed by terbutaline administration, or by removal of the vaginal insert [11, 12].

Misoprostol, a synthetic prostaglandin E1 analog, can be used for first and second-trimester pregnancy termination and for cervical ripening and labor induction in the patients at term [13]. There are oral, intravaginal, rectal, sublingual and buccal misoprostol preparations available [14]. In many randomized studies, 25–100 mcg is misoprostol administered

[15]. Mostly 250 mcg doses is taken as a maximum dose [6]. Aim of this study is to compare effectiveness and safety of vaginal misoprostol, dinoprostone and intravenous oxytocin administration for cervical ripening.

Study design

This prospective study was conducted from September 2004 to January 2006.

The protocol was approved by the hospital ethics committee. A total of 218 patients were enrolled. Sample size for this investigation was calculated according to the end point: vaginal delivery or Bishop score ≥8 at the end of 12 h. With a power of 80%, 41 patients would be needed in each group. Criteria for eligibility were: 38 or greater weeks of gestation, reassuring fetal heart rate (FHR) pattern, unfavorable cervix (effacement < 50, dilatation ≤ 2 cm, retroposed positional cervix), cephalic presentation, and intact amniotic membranes. Exclusion criteria included: active labor, any contraindication to vaginal delivery, rupture of membranes, oxytoxic drug usage, previous cesarean delivery or uterine scar, previous cervical surgery, sonographically estimated fetal weight ≥4,500 g, multiple pregnancy, grand multiparity (parity is ≥5) [16], placenta previa or vaginal bleeding, any contraindication to prostaglandin use, suspected chorioamnionitis, and abnormal FHR pattern.

Women who participated in the study were assessed by vaginal examination (assessment of the cervix included an assessment of consistency, length, dilatation, position and station of the fetal presenting part as described by Bishop and modified by Calder) for Bishop scoring. Bishop score evaluation is made by gynecological specialist.

Written informed consent was obtained from each participant. The initial pelvic examination of each patient was done by the same physician but the treatment choice was done by other physicians who were blind to pelvic examination. They were just informed that the Bishop score was unfavorable. Participating women received between one and three treatments according to the second physician's option. The treatment for cervical ripening choice among these three arms was made by 40 gynecological specialists who worked in the labor and perinatology wards. There was no intervention to treatment selection or to cesarean indications.

The follow-up data was picked up by another physician who had no participation in patient and treatment choice.

Misoprostol was administered in many different ways [6, 17]. Instead of greater doses, we decided to use 25 mcg intravaginal misoprostol because of its safety. A 50 mcg misoprostol dose was associated with increased cesarean, uterine rupture, and hyperstimulation risk. The literature shows that there is no advantage in using more than eight doses and 200 mcg of misoprostol [18]. The first group received misoprostol (cytotec), 25 μg, administered into the posterior vaginal fornix; the dose was repeated every 4 h. A maximum of eight doses was administered. The second group received oxytocin (synpitan). The dosing regimen of oxytocin used a low-dose protocol (initial dose 2 mu/min, with increases of 2 mu/min as often as 20 min up to 36 mu/min) [19]. In case of uterine hyperstimulation, the oxytocin was stopped; left lying position, nasal oxygen, and intravenous hydration were provided. If hyperstimulation continued, tocolytic therapy was administered. The third group received dinoprostone (Propess ovul), 10 mg, which was inserted high into the vaginal fornix. It remained in the vagina for up to 12 h. Dinoprostone ovul is a controlled-release hydrogel pessary containing 10 mg prostaglandin E2. This sustained release pessary releases dinoprostone at a rate of 0.3 mg/h. It releases a total of 4–5 mg prostaglandin E2 in 12 h. The women with unfavorable cervix after 12 h administration of first dose received a second pessary. A maximum of two doses was administered. The pessary was removed when labor began (cervical dilatation of 3–5 cm or more, in the presence of uterine contractions, can be taken to reliably represent the threshold for active labor), amniotic membranes ruptured spontaneously or artificially, and 12 h elapsed.

All women included in the study were hospitalized. Patients were followed up with electronic fetal heart rate monitoring (EFM) and vaginal examination. Electronic fetal monitoring was mostly performed at left lying position. At other times the patients stood as they wanted. Artificial rupture of membranes was performed at Bishop score 8. EFM was used to assess fetal well being every 4 h antepartum and continuously during labor. Uterine tachysystole was defined as ≥6 contractions in a 10-min period; hypertonicity was defined as a single contraction that lasted longer than 2 min; uterine hyperstimulation syndrome was defined as the presence of either tachysystole or hypertonicity.

Postpartum hemorrhage is characterized by an estimated blood loss greater than 500 ml. The leading cause of postpartum hemorrhage is uterine atony, which is the failure of the uterus to contract after complete delivery of the placenta [20]. The uterine atony cases were managed by bimanual uterine compression, oxytocin infusion, and rectal misoprostol administration.

In this study we evaluated Bishop's score changes, total time of labor, duration of latent and active phase of labor, cases delivered by 12 h; vaginally or abdominally, maternal and fetal side effects and complications for each study group. Success of treatment was defined as: (1) vaginal delivery by 12 h or Bishop score ≥8 at the end of 12 h, (2) vaginal delivery by 12 h or difference ≥4 between the initial and 12th hour Bishop scores.

Table 1 Maternal and neonatal demographics

	Misoprostol $n = 43$	Oxytocin $n = 71$	Dinoprostone $n = 104$	p
Age				
Mean ± SD	25.00 ± 4.93	25.41 ± 4.95	25.35 ± 5.23	0.196
Min–max	(18–37)	(16–37)	(17–48)	
Gestational age (weeks)	39.76 ± 2.35	40.65 ± 1.45	40.5 ± 2.12	0.060
AFI				
mm	99.21 ± 45.45	91.18 ± 36.40	84.24 ± 28.89	0.059
Min–max	(36–257)	(20–240)	(15–178)	
Birth weight				
g	3,243 ± 605	3,246 ± 509	3,324 ± 516	0.550
Min–max	(1,710–4,250)	(2,100–4,750)	(1,860–4,850)	

Data are presented as mean ± standard deviation or n (%)

AFI amnion fluid index

Table 2 Initial Bishop score

0 (n)	18 (41%)	33 (46%)	79 (76%)	$\chi^2 = 28.02$
1	0	5	2	<0.001
2	24	32	23	
3	1	1	0	

Statistical analyses were performed with ANOVA, Krustal Wallis, Scheffe, χ^2, Fisher, Advanced χ^2, and Kolmogorov–Smirnov tests. Tukey's HSD was used as a post hoc test. A p value less than 0.05 was considered as statistically significant.

Results

The maternal and fetal characteristics of the study population are shown in Table 1. Maternal age, gestational age, amnion fluid index (AFI), and birth weight were not significantly different between the groups. The initial Bishop score between the groups showed statistical significance ($\chi^2 = 28.02$, $p < 0.001$). The number of patients with Bishop score 0 was higher in the dinoprostone group (Table 2).

There were no significant differences in the mode of delivery. Indications for cesarean section in 12 h and after 12 h were similar (Table 3).

Table 4 shows labor and delivery characteristics regardless of initial Bishop score. The duration of latent phase was significantly longer in the dinoprostone group (11.20 ± 11.67 h, 12.14 ± 11.12 h vs. 21.42 ± 15.69 h). However, the differences disappear when only initial Bishop score = 0 patients are considered for the dinoprostone and misoprostol group (Table 5).

There was no significant difference in the mean active phase duration. The induction to vaginal delivery interval was significantly longer in the dinoprostone group (17.89 ± 17.80 h, 17.26 ± 12.37 h vs. 24.72 ± 16.00 h), but the difference disappeared when nulliparas and multiparas were compared separately. Time to vaginal delivery was longer in nulliparas than in multiparas in the three treatment groups.

The rate of vaginal delivery <12 h was significantly higher in the misoprostol group; 60% of patients in the misoprostol group who did not have a cesarean delivery within 12 h of treatment delivered vaginally within 12 h or had ≥8 Bishop score at the end of 12 h. Between the three treatment groups, this success of misoprostol showed statistical significance ($p = 0.0014$). Misoprostol was also more effective in producing a cervical change of ≥4 Bishop scores within 12 h (75% as compared with oxytocin 68% and dinoprostone 51%, $p = 0.013$). Mean Bishop score changes within 12 h of treatment were similar in three groups.

Table 6 summarizes the labor and delivery outcomes of initial Bishop score = 0 patients. The rate of vaginal delivery before 12 h, rate of Bishop score ≥8 patients at the end of 12 h, rate of patients with cervical change of ≥4 Bishop scores within 12 h and mean Bishop score change within 12 h of treatment were not significantly different between the three treatment groups. The induction to vaginal delivery interval was significantly longer in the misoprostol

Table 3 Cesarean rates

	Misoprostol $n = 43$	Oxytocin $n = 71$	Dinoprostone $n = 104$	p
Spontaneous vaginal ($n = 138$)	28	48	62	$\chi^2 = 1.23$
Cesarean ($n = 80$)	15	23	42	$p = 0.539$

Table 4 Labor and delivery outcomes

	Misoprostol $n = 43$	Oxytocin $n = 71$	Dinoprostone $n = 104$	p
Time to vaginal delivery (h)				
Total	17.89 ± 17.80	17.26 ± 12.37	24.72 ± 16.00	**0.0016**
Nulliparas	22.31 ± 14.25	19.74 ± 13.52	27.00 ± 18.15	0.165
Multiparas	14.06 ± 20.07	12.74 ± 8.57	20.58 ± 10.23	0.151
Duration of latent phase				
h	11.20 ± 11.67	12.14 ± 11.12	21.42 ± 15.69	**<0.001**
Min–max	(0.67–48)	(1–60)	(1.58–72)	
Duration of active phase (h)	5.11 ± 5.55	6.71 ± 5.53	7.05 ± 6.11	0.0544
<12 h vaginal delivery *n* %	16 (48.5%)	22 (36.1%)	13 (13.3%)	**0.001**
>12 h vaginal delivery *n* %	12 (36.4%)	26 (42.6%)	49 (50%)	
>12 h Cesarean delivery *n* %	5 (15.2%)	13 (21.3%)	36 (36.7%)	
Cesarean delivery *n* (%)	15 (34.9%)	23 (32.4%)	42 (40.4%)	0.539
Bishop score at the time of cesarean delivery	5.07 ± 3.69	4.39 ± 2.43	3.79 ± 2.55	0.332
Time to vaginal delivery ≤12 h and 12th hour Bishop ≥8 *n* %	20 (60.6%)	28 (45.9%)	27 (27.6%)	**0.0014**
Time to vaginal delivery ≤ 12 h and 12th hour Bishop–initial Bishop ≥ 4 *n* %	25 (75.8%)	42 (68.9%)	50 (51%)	**0.013**
Bishop changes between 0 and 12 h	4.06 ± 3.05	3.72 ± 2.63	3,402.75	0.153

Data are presented as mean ± standard deviation or *n* (%)

Bold values are statistically significant

Table 5 Comparison of latency periods in Bishop score = 0 patients

	Mean (h)	SD	p
Misoprostol ($n = 18$)	17.62	14.72	MWU; $z = 1.59$ $p = 0.1118$
Dinoprostone ($n = 79$)	22.61	15.92	

MWU Mann–Whitney *U*

group compared with oxytocin and dinoprostone (34.58 ± 22.33 h, 16.60 ± 8.71 h, 24.36 ± 13.79, $p = 0.042$) (Table 6).

Maternal side effects to medication, including nausea, diarrhea, emesis, hypotension and maternal fever were uncommon (Table 7). There were no reports of maternal death and uterine rupture. The incidence of uterine atony did not differ among groups but was higher in the misoprostol group (20.9%). Uterine hyperstimulation rates were not significantly different between the three treatment groups (Table 8).

There was no significant difference in the rate of fetal tachycardia and 1 or 5 min APGAR scores. The rate of NICU admission was similar between groups but considering the route of delivery, NICU need for abdominally delivered cases showed statistical significance. The rate was higher in the misoprostol group. Meconium was more frequent in the misoprostol group with a rate of 37.2% compared with 20.3% in the oxytocin and 21.2% in the dinoprostone group, but this difference was not statistically significant. One case of intrauterine fetal death was reported in the dinoprostone group (Table 9).

Table 6 Outcomes of treatment among initial Bishop score = 0 patients

	Misoprostol $n = 12$	Oxytocin $n = 26$	Dinoprostone $n = 74$	p
Time to vaginal delivery (h)	34.58 ± 22.33	16.60 ± 8.71	24.36 ± 13.79	0.042
<12 h vaginal delivery	2 (16.7%)	6 (23.1%)	10 (13.5%)	0.399
Time to vaginal delivery ≤ 12 h and 12th hour Bishop ≥ 8				
n	4	8	20	0.867
%	33.3	30.8	27	
Time to vaginal delivery ≤12 h and 12th hour Bishop–initial Bishop ≥4				
n	6	18	36	0.187
%	50	69.2	48.6	
Bishop changes between 0 and 12 h	3.90 ± 3.67	4.45 ± 2.28	3.46 ± 2.89	0.173

Data are presented as mean ± standard deviation or *n* (%)

Table 7 Maternal side effect of treatments

	Misoprostol $n = 43$	Oxytocin $n = 71$	Dinoprostone $n = 104$	p
Nausea	0	0	2, 1.9%	0.330
Diarrhea	–	–	–	
Emesis	0	0	1, 1%	0.576
Hypotension	0	2, 2.8%	1, 1%	0.123
Maternal fever	1, 2.3%	7, 9.9%	12, 11.5%	0.206

Data are presented as *n* (%)

Table 8 Maternal complications

	Misoprostol $n = 43$	Oxytocin $n = 71$	Dinoprostone $n = 104$	p
Hyperstimulation				
Total ($n = 218$)	11, 25.6%	26, 36.6%	27, 26.3%	0.261
VB ($n = 138$)	4/28	18/48	16/62	0.084
C/S ($n = 80$)	7/15	8/23	11/42	0.334
Uterine atony	9, 20.9%	6, 8.5%	9, 8.7%	0.067
Uterine rupture	–	–	–	
Maternal death	–	–	–	

Data are presented as *n* (%), *n/n*

VB vaginal birth, *C/S* cesarean section

Table 9 Fetal and neonatal complications

	Misoprostol $n = 43$	Oxytocin $n = 71$	Dinoprostone $n = 104$	p
Fetal tachycardia	1, 2.3%	4, 5.6%	6, 5.8%	0.828
NICU admission				
Total ($n = 218$)	6, 14%	4, 5.6%	6, 5.8%	0.178
VB ($n = 138$)	2/28	4/48	2/62	0.494
C/S ($n = 80$)	4/15	0/23	4/42	0.027
Intrauterine fetal death	0	0	1%1.0	0.576
Meconium painted amnion	16, 37.2%	14, 20.3%	22, 21.2%	0.076
APGAR 1	7.23 ± 1.51	7.55 ± 0.69	7.38 ± 1.19	0.338
APGAR 5	8.44 ± 1.59	8.90 ± 0.48	8.81 ± 1.05	0.068

Data are presented as *n* (%). Data are presented as mean ± standard deviation, *n* (%), *n/n*

VB vaginal birth, *C/S* cesarean section

Discussion

Our study was designed to compare the three protocols: misoprostol, oxytocin and dinoprostone. Previous studies have compared the efficacy of oral or intravaginal misoprostol with placebo, with oxytocin and with dinoprostone [21–24].

The initial Bishop score between the groups showed statistical significance. The rate of patients with Bishop score 0 was higher in the dinoprostone group and this may explain the difference. In our study the patients with initial Bishop score = 0 were studied separately different from the previous reports.

The duration of latent phase was significantly longer in the dinoprostone group (11.20 ± 11.67 h, 12.14 ± 11.12 h vs. 21.42 ± 15.69 h). However the differences disappears when only initial Bishop score = 0 patients are considered for the dinoprostone and misoprostol group. In a randomized trial of 0.5 mg dinoprostone administered for every 6 h and single dose 200 μg oral misoprostol latent phase for dinoprostone was significantly longer [21].

The induction to vaginal delivery interval was significantly longer in the dinoprostone group in our study but the difference disappeared when parity was considered. A randomized prospective study showed that time from start of induction to delivery was significantly shorter after the application of misoprostol than dinoprostone in both primipara and multiparas [25]. Bolnick et al. [26] found no significant difference in vaginal delivery times even considering parity. Previous studies have reported shorter vaginal delivery time with misoprostol [21, 22, 27, 28]. We compared the vaginal delivery times of initial Bishop score = 0 patients and the induction to vaginal delivery interval was significantly longer in the misoprostol group compared with oxytocin and dinoprostone (34.58 ± 22.33 h, 16.60 ± 8.71 h, 24.36 ± 13.79, $p = 0.042$). We could not find out a previous report discussing the labor and delivery outcomes among Bishop score = 0 cases. In the light of literature, 25 mcg misoprostol, which is the smallest dose, is the safest as compared to other doses and usage modalities. Cesarean delivery rates were similar in reported studies comparing the dinoprostone and misoprostol groups [23, 25, 26, 29]. In a double-blind prospective randomized trial, the cesarean delivery rates showed no statistical significance between the misoprostol and the low-dose oxytocin groups [22]. In our study, there were no significant differences in the mode of delivery. Indications for cesarean section in 12 h and after 12 h were similar for the three groups.

In this study, uterine hyperstimulation rates were not significantly different between the three treatment groups. The misoprostol group with a rate of 25.6% compared with 36.6% in the oxytocin group and 26.3% in the dinoprostone group. In other studies, hyperstimulation rates for dinoprostone were reportedly higher than hyperstimulation rates for misoprostol [22, 26, 30]. Chang and Bartha found no statistical significance between hyperstimulation rates of the dinoprostone and the misoprostol groups.

The incidence of uterine atony did not differ among groups but was higher in the misoprostol group (20.9%).

Admission to NICU showed no statistical significance between groups but was higher for the misoprostol group. Considering the route of delivery, NICU need for abdominally delivered cases showed statistical significance for the misoprostol group. As far as we searched, we did not find out a reported paper comparing the NICU need with respect to the mode of delivery. Previous studies comparing misoprostol and dinoprostone reported similar NICU admission rates [21, 23, 26, 27, 30]. In a study comparing misoprostol and low-dose oxytocin, the NICU admission for the misoprostol group was statistically higher than the low-dose oxytocin group [30].

In our study one case of intrauterine fetal death was reported in the dinoprostone group. 28 years old, primipara woman with a gestational age of 40 weeks and 4 days. In the ultrasound examination, the AFI was reported as 48 mm (below fifth percentile for the gestational age). Antenatal reports showed that triple screening test has 1/195 trisomy 21 risk and genetic consultation was done. Amniocentesis was recommended but the family did not accept. After examination of the patient labor induction was planned because of oligohydramnios. Because of unfavorable cervix, dinoprostone was inserted vaginally and removed after 12 h. Cervical examination showed no Bishop score change. Second dose of dinoprostone was applied. After 8 h, the second dinoprostone ovul was removed because adequate uterine contractions with adequate Bishop score change occured. EFM reported persistent decreased variability pattern ($\leq$5 beasts/min for >60 min). 150 min after second ovul removal we found out that the fetus was dead in utero. In 5 h, the patient delivered a 3,410 g female fetus vaginally. Autopsy was not performed as the family refused approval.

Meconium was more frequent in the misoprostol group with a rate of 37.2%, but this difference was not statistically significant. Previous reports showed discrepant rates for meconium. Fetal distress is not only reason for meconium stained amniotic fluid. Bowel movements may be reason as well [31]. This could be the reason of insignificant difference of stained amniotic fluid rate between misoprostol and other groups instead of similar APGAR scores.

In some studies, the meconium rates were similar in the dinoprostone and the misoprostol group [21, 28–30]. Ferguson reported higher meconium staining rates in the low-dose oxytocin group than the misoprostol group [22].

It seems that first 12 h after the administration of therapy gives an idea about the prognose. In this study vaginal delivery within 12 h was 48% in the misoprostol group, 36.1% in the oxytocin and 13.3% in the dinoprostone group. This is statistically significant. But considering the initial Bishop score = 0 patients, the difference disappears.

Ferguson et al. reported higher vaginal birth rates in 24 h in the misoprostol group than in the low-dose oxytocin group. The other reports show no statistical significance in the rate of vaginal birth in 12 and 24 h between the dinoprostone and the misoprostol group [21, 23, 26, 29, 30].

In this study, comparison between all cases (cases Bishop score <4), shows that misoprostol is more effective than dinoprostone and oxytocin. But considering Bishop score = 0 cases we calculated no statistically significant difference.

Dinoprostone is an FDA approved drug; although it is not cost effective, the usage of dinoprostone versus misoprostol seems advisable. But in this study we want to conclude that oxytocin is an FDA approved drug, it is also cost effective and evaluating the maternal and fetal complications and outcomes it seems safe to use oxytocin.

Misoprostol is in the WHO list of necessary drugs even though it does not have FDA approval [32]. There are publications about misoprostol use approved by FIGO [33]. Misoprostol has wide indications for early miscarriage curettage and mid-trimester pregnancy terminations [34].

We also think that any of these protocols must be applied at hospital. Induction for cervical ripening needs close follow-up especially in post-term pregnancies. It is obvious that an unripe cervix at term needs time for ripening to begin labor.

A controlled trial in a group of nulliparous patients with a Bishop score = 0 can clarify the discrepancies about the labor induction and cervical ripening.

This study is not a randomized blind study. Treatment modality has been chosen by gynecological specialist. Therefore, this study reports a clinical observation. This is the negative point of our study.

Conflict of interest We declare that we have no conflict of interest.

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