Comparative study on safety and efficacy of cervical ripening agents misoprostol and dinoprostone in the induction of labour

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Abstract

Aim: To compare the safety and efficacy of two commercially available prostaglandin analogues, misoprostol and dinoprostone as cervical ripening agents.

Methods: Patients with a term, vertex, singleton pregnancy and a Bishop score of 4 or less were randomly assigned to receive misoprostol pessary (n = 35, 50 μg intravaginally, maximum dose of up to six pessary) or dinoprostone gel (n = 31, 0.5 mg intracervically; administered twice 6hrs apart). Patients were monitored throughout the period. If there was no progress in cervical dilatation or effective uterine contraction even after maximum dose of dinoprostone or misoprostol, patients were taken for cesarean section. Patients who were able to achieve Bishop's score more than 7 but the delivery was not progressing, were augmented with intravenous oxytocin infusion.

Result: Both drugs were found to be equally effective in improving Bishop's score. There was significant reduction in the need for oxytocin augmentation in misoprostol (37.1%) group than in dinoprostone (67.7%) group. However, abnormal fetal heart rate was observed in 3 (8.6%) cases in misoprostol group and 2 (6.5%) in dinoprostone group. There was no statistically significant difference in meconium passage in two groups. But there were no significant differences in the mean induction to delivery time in dinoprostone and misoprostol group. Cesarean sections in dinoprostone and misoprostol groups were 32.3% and 28.6% respectively. No uterine hyperstimulation was observed, Apgar score less than 7 at 1 minute was 6 (19.4%) and 11 (31.4%) neonates in dinoprostone and misoprostol group and Apgar score less than 7 at 5 minutes was found only in one neonate of dinoprostone group.

Conclusion: Vaginal misoprostol is an effective, safer and cheaper alternative to dinoprostone as a cervical ripening agent in underdeveloped countries with poor socioeconomic condition.

Key words: Dinoprostone, misoprostol, cervical ripening, Bishops score, Apgar score.

Introduction

Induction of labor refers to the process whereby uterine contractions are initiated by medical or surgical means before the onset of spontaneous labor. Induction of labor is common in obstetric practice. Labor induction in the presence of an unfavorable cervix may be prolonged, tedious and eventuate in a cesarean delivery. Induction of cervical ripening is critical to successful induction of labor in a pregnant patient whose cervix has not gone through the ripening process. Cervical ripening before induction with prostaglandin agents has been demonstrated to decrease induction time and need for oxytocin. Assessment of cervical ripening is accomplished by calculating Bishop Score (BS). When the BS is less than 6, it is recommended that a cervical ripening agent be used before labor induction.

When compared with placebo, use of vaginal prostaglandins increased the likelihood that a vaginal delivery would occur within 24 hours. The only

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drawback appears to be an increased rate of uterine hyperstimulation and accompanying FHR changes.

Dinoprostone has been the agent of choice for preinduction and cervical ripening for several decades.[1] Studies have claimed another synthetic prostaglandin (PG)E_1 analog, vaginal misoprostol more effective than placebo and oxytocin for unripe cervix.[2,3] This drug has been administered either by vaginal or oral route and its action has been compared with dinoprostone.[4-5]

The aim of this study was to compare safety and effectiveness of intravaginal misoprostol with our traditional protocol for cervical ripening and labor induction with repeated intracervical dinoprostone in women with unfavorable cervices and intact membranes.

Methods

This study was conducted at labor ward of Dhulikhel Hospital Kathmandu University Teaching Hospital (DH, KUTH) from March 2006 to July 2006. The study comprised 66 women, 31 received dinoprostone 0.5 mg intracervically at 6-hourly interval and 35 received misoprostol 50mcg vaginally at 6 hourly interval.

Approval was obtained from ethical and research committee of the hospital to conduct the study. Exclusion criteria were previous cesarean delivery, grand multiparity (>5), breech, contraindications to induction, BS of >4, contractions more than 3 per 10 minutes before drug administration and premature rupture of membranes (PROM). Inclusion criteria were >37 wks of gestation, indication for labor induction, BS <4, intact membrane and cephalic presentation.

Informed consent was taken and the women were randomly assigned to receive either misoprostol pessary 50 mcg per vagina or our hospital's standard induction protocol 0.5 mg of dinoprostone intracervically. BS was assessed just before insertion of these cervical ripening agents. FHR and uterine contractility was taken prior to drug administration. All patients underwent continuous FHR and uterine contraction monitoring every 15 minutes for first two hours then every 4 hours.

Tachysystole was defined as a contraction frequency of more than five within 10 minutes for two consecutive 10 minutes period. Uterine hyperstimulation was defined as exaggerated uterine response with late FHR decelerations or fetal tachycardia greater than 160 beats per minutes or other worrisome FHR changes. An abnormal FHR pattern was defined as the presence of fetal tachycardia, bradycardia, late decelerations, or a moderate to severe deceleration of FHR. Labor was

defined as regular painful uterine contractions with cervical change or spontaneous rupture of membranes. Failed induction occurred when painful, regular contractions with cervical change were not achieved and the patient was delivered by cesarean with failed induction as sole indication. Active phase was defined as complete cervical effacement and dilatation of at least 3 cm. Misoprostol pessary was administered every 6 hourly by the attending doctor in the posterior fornix with maximum dose of up to six. BS was reviewed continuously. In another group, dinoprostone gel was administered twice intracervically, 6hrs apart. A vaginal examination was performed before the administration of the second dose. If there is more than 3 contractions for more than 30 seconds in 10 minutes or labor has started or cervical score was 6 or more, the second dose of cervical ripening agent was not given.

Once in labor, women were cared for according to current obstetric practice. If there was no progress in cervical dilatation, effacement or effective contractions even after maximum dose of cervical ripening agents, patients were taken for cesarean section operation. Patients who achieved BS more than 7 but the delivery was not progressing for longer than 1 hour were augmented with oxytocin drip for maximum of 12 hours. After that, if women did not reach active phase, cesarean for failed induction was done.

The prespecified outcomes were interval from start of induction to vaginal delivery, vaginal delivery achieved within 24 hrs after randomization, change in BS, abnormalities of uterine contractility with and without FHR changes, mode of delivery, need of oxytocin augmentation, maternal morbidity and side effects (e.g., fever, chills, gastrointestinal symptoms) and short-term neonatal outcome (e.g. Apgar score, meconium passage, neonatal intensive care unit admission etc.

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) program version 11.5 using χ^2 test and Z test. For variables distributed normally, the results were presented as mean and standard deviation (SD). Quantitative variables are expressed as number and percentage.

Results

A total of 66 women were randomized. Baseline characters were similar between two groups in terms of patient's age, gestational time, parity and the preinduction BS.

Thirty one patients received dinoprostone gel 0.5mg intracervically up to 2 doses and remaining 35 patients received misoprostol pessary 50 mcg, intravaginally with maximum dose up to six, every six hourly.

The number of doses of dinoprostone required for preinduction was 1.65±0.48 (mean±S.D), and that of misoprostol was 2.14±1.2.

Although there was increase in the BS after treatment in both groups, there was statistically insignificant difference between two groups in terms of either the change in BS after drug administration or the BS measured pre treatment (Table 1).

There were no significant differences in the mode of delivery (P = 0.618). 10 (32.3%) patients out of 31 from dinoprostone group and 10 (28.6%) patients out of 35 from misoprostol group had cesarean delivery (Table 2).

Indications for cesarean section were similar: in misoprostol group, 4 (40%) cesarean sections were performed for failed induction and 5 (50%) were due to fetal distress. Remaining one was due to oligohydramnios. In dinoprostone group, 5 (50%) cesarean was due to failed induction and another 5 (50%) was due to fetal distress.

The difference in mean induction to delivery time was not statistically significant in two groups (17.19 hrs in dinoprostone versus 17.99 hrs in misoprostol group, P = 0.83).

Even though 19 (90.5%) out of 21 patients from dinoprostone group and 18 (72.0%) out of 25 patients from misoprostol group delivered within 24 hrs of initiation of induction, this difference was not found to be statistically significant (P = 0.42).

Augmentation of oxytocin was required in significantly greater number of patients in dinoprostone group than in misoprostol group (21 [67.7%] versus 13 [37.1%], P = 0.013). Women in the misoprostol group were much less likely to require oxytocin compared with dinoprostone group.

No cases of uterine hyperstimulation were observed in both groups. However abnormal FHR was observed in 2 (6.5%) cases in dinoprostone group and 3 (8.6%) cases in misoprostone group. Again there was no statistically significant difference between the two groups with regards to meconium passage (7 [22.6%] in dinoprostone group versus 8 [22.9%] in misoprostol group, P = 0.97). Our study indicates misoprostol 50 mcg 6 hourly to be an effective preinducing agent with no major maternal side effects, such as uterine hyperstimulation or uterine rupture (Table 3).

Minor maternal side effects reported were nausea, vomiting and diarrhea. 2 (6.5%) patient from dinoprostone group and 3 (8.6%) from misoprostol group experienced vomiting, whereas 3 (8.6%) patients from misoprostol group and another 1 (2.9%) patient from the same group experienced nausea and diarrhea respectively.

Birth weights of neonates were similar between groups. There was no statistically significant difference in Apgar score at 1 minute and 5 minute between two groups. One-minute Apgar score less than 7 (6 [19.4%] and 11 [31.4%] in dinoprostone and misoprostol group respectively) and Apgar score at 5 minutes less than 7 (1 [3.2%] in dinoprostone group) were not significantly

Table 1. Comparison of change in Bishop Score

Bishop score	Dinoprostone (n = 31)	Misoprostol (n = 35)	P value
Initial bishop score	3.35 ± 0.91	3.00 ± 0.90	.11
After 6 hours	5.48 ± 2.0	4.90 ±1.5	.22
After 12 hours	6.23 ± 2.2	6.38 ±1.9	.81
Change in 6 hours	2.17 ± 2.0	2.00±1.6	.72
Change in 12 hours	2.90 ± 2.1	.65±1.9	.23
(Mean ± S.D)			

Table 2. Comparison of mode of delivery

Mode of delivery	Dinoprostone (n =31)	Misoprostol (n=35)
Vaginal delivery	21 (67.7%)	24 (68.6%)
Assisted vaginal delivery	0(0%)	1 (2.9%)
Cesarean section	10 (32.3%)	10 (28.6%)

Table 3. Adverse effects

Adverse effects	Dinoprostone (n=31)	Misoprostol (n=35)	P value
Hyperstimulation	0 (0%)	0 (0%)	-
Abnormal fetal heart rate	2 (6.5%)	3 (8.6%)	0.74
Meconium passage	7 (22.6%)	8 (22.9%)	0.97

different between misoprostol and dinoprostone groups. Supplemental oxygen requirement was 10 (32.3%) in dinoprostone group and 11 (32.4%) in misoprostol group. None of the newborns required intubations, or admission to neonatal intensive care unit (Table 4).

Discussion

Labor induction is one of the most commonly performed obstetric procedures with up to 40% of all patients undergoing inpatients cervical ripening. Prostaglandins are highly efficacious cervical ripening agents used to shorten induction to delivery intervals, improve induction success, and reduce morbidities associated with prolonged labor induction.

In various studies, misoprostol and dinoprostone have been associated with favorable cervical changes with improvement on Bishops Score with slighter risk of uterine hyperstimulation or FHR changes.[5-7] Though one of the studies could not find significant difference in mean changes in BS between the comparative groups.[8]

Even our study did not show marked difference in the efficacy of the two drugs in terms of preinduction to delivery time. Number of deliveries within 12 hours of treatment initiation was also not significantly different between dinoprostol (29%) and misoprostol (28.6%) groups. More number of patients from dinoprostone (61.3%) group delivered within 24 hours of treatment initiation than misoprostol (51.4%) although this difference was found to be statistically insignificant. The preinduction to delivery time was found to be significantly shorter in misoprostol (11 vs. 18 hours) treated group in a study carried by Ramsey et. al.[9] However his study showed no significant difference in delivery within 24 hours between the two groups. Considerable variation as far as induction to delivery time is concerning as the ranges met were 9 to 17.9 hours.[1,2] Meta-analysis of misoprostol for cervical ripening and labor induction in 8 trials including nearly 1000 women revealed that misoprostol-treated subjects had a higher incidence of vaginal delivery within 24 hours of initially receiving misoprostol and a shorter time interval from start of medication to delivery when compared with control subjects by approximately 4.5 hours.[10]

There was no cases of hyperstimulation, uterine rupture or premature rupture of membrane. A Meta analysis has confirmed the safety of intravaginal misoprostol with similar incidences of uterine hyperstimulation in misoprostol and control group.[10]

The present study indicates that misoprostol was associated with less need of oxytocin augmentation. Cesarean section occurred in both groups were found to be comparable. Bartha et al found better result with oral misoprostol with less need for oxytocin augmentation and lesser cesarean section operations for failed induction.[11]

The Cochrane Pregnancy and Childbirth Group reviewed trials comparing misoprostol with placebo, oxytocin, or prostaglandin E$_2$ for cervical ripening.[2,12] The study showed that vaginal misoprostol (25 to 100 mcg) was more effective than dinoprostone for inducing vaginal delivery within 24 hours. However, uterine hyperstimulation with associated changes in the FHR was more common in women who received misoprostol than in women who received dinoprostone. No difference in the rates of cesarean delivery, serious neonatal or maternal morbidity or mortality was seen between women who received misoprostol and those who received dinoprostone.

Several studies have reported hyperstimulation and tachysystole with misoprostol. But we did not find any such cases. It may be due to the reason that others have used higher doses of misoprostol like 100 mcg and 200 mcg whereas we have used a lower dose of 50 mcg, which might explain absence of excessive uterine activity. There is less risk of hyperstimulation with lower dose of misoprostol but at the same time reducing the effectiveness of labor induction.[7,13] Incidence of hyperstimulation in a randomized double masked trial of 178 women found similar efficacy between 200 mcg oral and 50 mcg vaginal administration, but the oral route was associated with more frequent uterine contractility, including an unexpected high rate of hyperstimulation syndrome (44.1%).[14] To decrease hyperstimulation, lower oral doses of misoprostol was used in several other studies, but the effectiveness was also lowered.[15]

Regarding neonatal outcomes, perinatal results evaluated by means of Apgar score, birth weight,

meconium stain and admission to intensive care unit were comparable between two groups with similar perinatal outcome.It has been found that there is no difference in neonatal outcomes in both the groups. [16]

Although intravaginal dinoprostone is currently the drug of choice for labor induction, it is quite expensive and must be refrigerated to maintain its potency. When we did the comparison of cost we found that there is a significant price difference between misoprostol and dinoprostone for induction of labor. In our hospital dinoprostone is 7 times more expensive than misoprostol. The cost will be increased further if oxytocin augmentation is needed. They have found that misoprostol is more cost effective than the comparable commercial dinoprostone as an adjuvant to labor induction in women with unfavorable cervix.[9]

Various studies have proven effectiveness of misoprostol and dinoprostone for preinduction. Our study too found vaginal misoprostol and intracervical dinoprostone equally effective.

Conclusion

Misoprostol appears to be safe and beneficial for inducing labor in a woman with an unfavorable cervix. It is equally efficacious for cervical ripening and labor induction as dinoprostone in terms of improvement in Bishop Score.

Acknowledgement

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