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A randomized clinical trial to compare the efficacy of different doses of intravaginal misoprostol with intracervical dinoprostone for cervical ripening and labor induction

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Abstract. – *Objectives:* **To compare the efficacy of 25 vs. 50 µg of intravaginal misoprostol vs. intracervical dinoprostone for cervical ripening and labor induction.**

Materials and Methods: **210 women with Bishop's score <6 were randomized into 3 groups of 70 each to receive 6 hourly doses of either 25 or 50 µg of intravaginal misoprostol or 0.5 mg intracervical dinoprostone to maximum of 3 doses and outcome parameters were compared.**

Results: **Induction to vaginal delivery interval was significantly lower (p<0. 05) for 50 µg (13.8±6.62 hours) as compared to 25 µg misoprostol (16.4±7.34 hours) or dinoprostone group (16.3±7.49 hours). Maximum improvement (p<0.05) in Bishop's score and minimum oxytocin requirement (p<0.05) was seen with misoprostol 50 µg. No significant difference was observed for women delivering vaginally within 24 hours (93.8 vs. 89.7 vs. 85.4%), patients delivering after one dose (24.3 vs. 21.4 vs. 20%), cesarean deliveries, fetal outcome, complications like hyperstimulation and fetal heart abnormalities for the 50 vs. 25 µg misoprostol vs. dinoprostone group.**

Conclusion: **Intravaginal misoprostol 50 µg administered 6 hourly appears to be most effective as it has least induction to delivery time, has maximum improvement in Bishop's score, least oxytocin requirement without any increase in complication rate.**

Key Words:

Misoprostol 50 µg, Misoprostol 25 µg, Dinoprostone, Cervical ripening, Labor induction.

Introduction

Induction of labour means initiation of uterine contractions after the period of viability by any method for the purpose of vaginal delivery. Induction of labor with an unfavorable cervix is often difficult. Use of prostaglandin preparations is recognized and accepted for induction of labour. The commonly used agents for induction of labor are dinoprostone gel and misoprostol tablets[1,2]. Dinoprostone is expensive, requires refrigeration, needs to be instilled in the cervix and many patients require additional oxytocin augmentation during induction of labor. Misoprostol is cheap, does not require refrigeration and can be given through vaginal, oral or sublingual routes. Numerous dosage schedules and time intervals have been described in literature[1-5] for inducing labor with misoprostol. Higher doses and short dosage intervals can lead to maternal and fetal complications while lower doses may not achieve the desired outcome. Therefore, in order to find the optimal regimen with minimal side effects, we compared the efficacy of 25 µg vs. 50 µg of intravaginal misoprostol vs. dinoprostone gel for cervical ripening and induction of labor.

Material and Methods

This prospective randomized clinical trial was conducted in the Department of Obstetrics and Gynecology of a tertiary level Hospital after obtaining Institutional ethical clearance. A total of 210 women with Bishop's score <6 were randomized into 3 groups of 70 each to receive 6 hourly either 25 µg or 50 µg of intravaginal misoprostol or 0.5 mg intracervical dinoprostone.

The inclusion criteria included women with singleton, term pregnancy with intact mem-

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branes, cephalic presentation, with an unfavorable cervix (Bishop's <6) and an amniotic fluid index (AFI) of >5. The exclusion criterion included women with premature rupture of membranes, multiple pregnancy, severe intrauterine growth retardation (IUGR), non cephalic presentation, cephalopelvic disproportion, previous uterine scar or history of uterine perforation, allergy to prostaglandin, Bishop's ≥6, severe oligoamnios or any medical disorder except gestational diabetes mellitus (GDM) controlled on diet and mild pregnancy induced hypertension (PIH).

All the recruited participants were fully informed about the nature, scope and the potential risks of the study which was followed by an informed consent. Randomization into 3 groups was performed by computer generated random numbers. Thorough general, systemic and obstetric examination was done. The Bishop's score was recorded. An ultrasound was done to verify the period of gestation, calculate AFI. Non stress test was done before instilling the allocated drug. Fetal heart rate tracings were taken for 30 min immediately after insertion and uterine contractions were monitored. Progress of labour was monitored by observing uterine contractions and descent of head. Fetal heart pattern was recorded by intermittent auscultation during the first stage and by continuous external electronic fetal heart monitoring in high risk patients. A repeat vaginal examination was done after 6 hr in each group and Bishop's score was reassessed. A repeat insertion was done if Bishop's score was ≤6 and a maximum of 3 doses were instilled for each group. Artificial rupture of membranes was performed if the cervix was >3 cm dilated. Intravenous oxytocin was administered only if active labor was not established despite maximum number of dosages. Oxytocin was administered 6 hours after instillation of the last dose of dinoprostone or misoprostol if required. Fetal heart rate (FHR) was assessed for any bradycardia [fetal heart sound (FHS) <110/min], tachycardia (>150/min), late deceleration, or variable deceleration pattern. Uterine activity was evaluated for tachysystole, hypertonicity, or hyperstimulation. Tachysystole was defined as at least six contractions in 10 min for 20 min, and hypertonus was considered if a single contraction was felt lasting for >2 min. Hyperstimulation was diagnosed if there was associated abnormal FHR pattern. Any patient with hyperstimulation was treated by discontinuing oxytocin if it was on flow, positioning the patient to left lateral, starting oxygen inhalation, Ringer lactate infusion and removing any remnants of the drug.

Once the patient went into active phase of labor, routine intra-partum management was performed without regard to treatment allocation. Development of potential adverse events was assessed at every 6 hours by using a standardized symptom questionnaire which included symptoms like continuous lower abdominal pain, nausea, vomiting, hyperthermia, dizziness, fatigue, diarrhea, headache and palpitation.

Outcome parameters evaluated were induction to delivery interval, change in Bishop's score after first instillation, number of patients delivering vaginally within 24 hours of induction or after first dose of drug, requirement of oxytocin for augmentation of labour, occurrence of tachysystole and hypersystole, mode of delivery along with indications for cesarean section. For fetal outcome, fetal heart rate abnormalities, passage of meconium and Apgar score at 5 minutes were evaluated.

Power analysis was performed on the basis of previous studies. Considering a between groups difference[6] of 20% for the percentage of patients delivering within 24 hours after 50 μg misoprostol and dinoprostone gel instillation, a sample size of 55 in each group was calculated with 95% power at $\alpha = 0.05$. We recruited 70 patients in each group.

Statistical Analysis

The statistical analysis was performed on the Statistical Package for the Social Sciences (SPSS version 10) software (SPSS Inc., Chicago, IL, USA) with the use of chi square test for categorical variables and Anova to compare between groups for continuous variables.

Results

Two hundred and ten women were recruited and divided into 3 groups of 70 each to receive intravaginal misoprost 25 μg (Group 1) or 50 μg (Group 2) or intracervical dinoprostone (Group 3). Number of nulliparous women was 47 (67.1%), 39 (55.7%) and 44 (62.8%) in group 1, 2 and 3 respectively. The average period of gestation was 39.8±1.0 weeks, 39.05±2.5 weeks and 39.8±1.2 weeks in group 1, 2 and 3 respectively. Indications for induction of labor for each group were comparable as shown in Table I.

Table I. Indications for induction of labor.

Indication	Misoprostol 25 µg n = 70 (Gr. 1)	Misoprostol 50 µg n = 70 (Gr. 2)	Dinoprostone n = 70 (Gr. 3)
> 40 weeks	54	59	56
PIH	7	4	6
Gestational diabetes mellitus	1	1	Nil
Cholestasis	2	2	1
IUGR	3	1	3
Oligoamnios	Nil	1	3
Decreased fetal movements	3	2	1

Labor outcome parameters are depicted in Table II. Number of vaginal deliveries within 24 hours occurred in 44/49 (89.7%) patients of group 1, 46/49 (93.8%) of group 2 and in 41/48 (85.4%) of group 3. Induction to vaginal delivery interval was significantly lower (p<0. 05) for group 2 (13.8±6.62 hrs) as compared to group 1 (16.4±7.34 hrs) and group 3 (16.3±7.49 hrs). The difference in induction to vaginal delivery interval between group 1 and 3 was statistically not-significant. The number of patients delivering after one dose in group 1, 2 and 3 were 15 (21.4%), 17 (24.2%) and 14 (20%) respectively (p=NS). The rate of cesarean sections was 21 (30%) in group 1 and 2 and was 22 (31.4%) in group 3 (p=NS).The indications of cesarean sections were fetal distress (10 vs. 8 vs. 8), meconium staining (5 vs. 7 vs. 7), failed induction which was considered when patients did not go into active stage of labor after 3 doses of misoprostol/dinoprostone and oxytocin stimulation (2 vs. 3 vs. 4), non progress (3 vs. 1 vs. 1) and cephalopelvic disproportion (1 vs. 2 vs. 2) in group 1, 2 and 3 respectively. Hyperstimulation was noted in 1 patient each of groups 1 and 3 and in 2 patients of group 2. This difference was not statistically significant. One patient each in group 2 and 3 had to undergo emergency cesarean for fetal heart abnormalities during the ripening process, but neonatal outcome was normal. Apgar score of <7 was present in 2 babies of 50 µg misoprostol group, 2 of 25 µg misoprostol group and in 1 baby of the dinoprostone group.

Significantly lower oxytocin requirement was seen in group 2 as compared to group 1 or 3 (14.2 vs. 21.4 vs. 30%) respectively. The difference in the Apgar scores and meconium passage was not significantly different between the three groups.

Comparison of Bishop's score before and after first application of drug is shown in Table III. Initial mean Bishop's score of group 1 was 2.20±1.33 which improved significantly to 3.46±2.69 (p<0.000) after first application of misoprostol 25 µg. Mean Bishop's score of group 2 improved from 2.38±1.4 to 4.64±2.8 (p<0.000) and of group 3 improved from 2.9±1.2 to 4.35±1.15 (p<0.000) after 6 hours. The increase in Bishop Score was significantly more for group 2 vs. group 1 (p<0.05) and group 3 (p<0.05). Potential adverse effects of misoprostol like nausea, vomiting, hyperthermia, dizziness, fatigue, diarrhea, headache and palpitation were not observed in any patient.

Discussion

Multiple regimens have been described for the two most commonly used agents, misoprostol and dinoprostone for cervical priming and labor induction in varying doses and time intervals but comparative efficacy of different doses of misoprostol and dinoprostone are yet to be evaluated in a single study. In this study we compared the efficacy of misoprostol in two dosage schedules, 25 µg and 50 µg along with 0.5 mg dinoprostone at a time interval of 6 hours to find the optimal agent for induction of labor.

Although more women delivered within 24 hours in the misoprost 50 µg group as compared to 25 µg or dinoprostone group, this difference did not achieve statistical significance. More women delivered after a single dose of 50 µg of misoprostol, but the difference between the three groups was not significant statistically (24.3%, 21.4%, 20% for 50 µg, 25 µg and dinoprostone respectively).

Table II. Comparison of labor outcome parameters.

Parameter	Misoprostol 25 µg n = 70 (Gr. 1)	Misoprostol 50 µg n = 70 (Gr. 2)	Dinoprostone n = 70 (Gr. 3)	*P* value
Induction to vaginal delivery interval (hours)	16.44 ± 7.37	13.88 ± 6.62	16.38 ± 7.49	Gr. 1 vs Gr. 2, Gr. 2 vs. c Gr. 3 (p<0.05) Gr. 1 vs. Gr. 3 (p = NS)
Vaginal delivery within 24 hours	44/49 (89.7%)	46/49 (93.8%)	41/48 (85.4%)	Gr. 1 vs. Gr. 2, Gr. 2 vs. Gr. 3, Gr. 1 vs. Gr. 3 (p = NS)
Delivery after one dose	15 (21.4%)	17 (24.3%)	14 (20%)	Gr.1 vs. Gr. 2 , Gr. 2 vs. c Gr. 3, Gr. 1 vs. Gr. 3 (p = NS)
Cesarean section	21 (30%)	21 (30%)	22 (31.4%)	Gr. 1 vs. Gr. 2, Gr. 2 vs. Gr. 3, Gr. 1 vs. Gr. 3 (p = NS)
Oxytocin augmentation	15 (21.4%)	10 (14.2%)	21 (30%)	Gr. 1 vs. Gr. 2, Gr. 1 vs. Gr. 3 (p<0.01), Gr. 2 vs. Gr. 3 (p<0.001)
Hyperstimulation	1 (0.01%)	2 (0.03%)	1 (0.01%)	Gr. 1 vs. Gr. 2, Gr. 2 vs. Gr. 3, Gr. 1 vs. Gr. 3 (p = NS)

The induction to vaginal delivery interval was 13.88±6.62 hours for the misoprostol 50 µg group vs. 16.44±7.37 hours for 25 µg group vs. 16.38±7.49 hours for dinoprostone group. Thus misoprostol 50 µg shortens the induction to vaginal delivery interval significantly by about three hours as compared to the other two groups. Oxytocin augmentation was least required for the misoprost 50 µg group as compared to 25 µg misoprostol or dinoprostone groups. These findings are in accordance with previous studies where the use of 50 µg of misoprostol was found to reduce the induction to vaginal delivery interval, reduced the need for repeat insertion and oxytocin augmentation[1-8].

All three agents significantly improved the initial Bishop's score while maximum improvement was seen in the misoprostol 50 µg group. It was seen that delivery occurred within 6 hours in 5 vs. 2 vs. 3 (p=NS) patients of misoprostol 50 µg, 25 µg and dinoprostone group. Of these, one patient each from misoprostol 50 µg and dinoprostone group underwent cesarean delivery due to fetal distress which did not settle with conservative management. There was no case of tachysystole while there were a total of 4 (1 vs. 2 vs. 1 in groups 1, 2 and 3) patients with hyperstimulation in this study. Higher rates of hyperstimulation and tachysystoles have been reported in previous studies where 50 µg misoprost had been used at 2-4 hourly intervals[9,10].

The difference in the rate of hyperstimulation, cesarean sections, Apgar score and meconium passage was not significantly different between

Table III. Comparison of Bishop's Score before and after first dose.

Parameter	Misoprostol 25 µg n = 70 (Gr. 1)	Misoprostol 50 µg n = 70 (Gr. 2)	Dinoprostone n = 70 (Gr. 3)	*P* value
Initial Bishop's Score	2.20 ± 1.33	2.38 ± 1.4	2.9 ± 1.25	
Bishop's score after 6 hours	3.46 ± 2.69	4.64 ± 2.8	4.35 ± 1.45	
Difference between 2 Bishop's	1.16 ± 2.23	2.11 ± 2.6	1.26 ± 2.30	
Significance	0.000	0.000	0.000	Gr. 1 vs. Gr. 2 , Gr. 2 vs. Gr. 3 (p<0.05) Gr. 1 vs. Gr. 3 (p=NS)

the three groups. This is similar to the findings of Austin et al[8] who have compared misoprostol with dinoprostone. They reported no significant difference in the rate of cesarean delivery, uterine hyperstimulation, tachysystole and neonatal outcomes between the 2 groups.

Misoprostol 50 µg 6 hourly had the shortest induction to vaginal delivery interval. It caused maximum improvement in Bishop's score and least oxytocin requirement for labor augmentation .The rate of cesarean delivery, hypersystole, tachysystole and fetal outcome was comparable to 25 µg and dinoprostone groups. Therefore, misoprostol 50 µg 6 hourly appears to be most suitable agent for cervical ripening and labor induction as compared to 25 µg misoprostol or dinoprostone.

References

1) Elhassan E, Mirghani O, Adam I. Intravaginal misoprostol versus dinoprostone as cervical ripening and labor-inducing agents. Int J Gynaecol Obstet 2004; 85: 285-286.

2) Sanchez-Ramos L, Kaunitz AM. Misoprostol for cervical ripening and labour induction: a systematic review of literature. Clin J Obstet Gynecol 2000; 43: 475-488.

3) Mackey P, Lang G, Bonertz L. Induction of labour in third trimester: review of outcomes with intravaginal misoprostol compared with dinoprostone gel at a rural hospital in British Columbia: Can J Rural Med 2002; 7: 259-264.

4) Rowlands S, Bell R, Donath S, Morrow S, Trudinger BJ. Misoprostol versus dinoprostone for cervical priming prior to induction of labour in term pregnancy: a randomised controlled trial. Aust N Z J Obstet Gynaecol 2001; 41: 145-152.

5) Langenegger EJ, Odendaal HJ, Grové D. Oral misoprostol versus intracervical dinoprostone for induction of labor. J Gynaecol Obstet 2005; 88: 242-248.

6) Lokugamage AU, Forsyth SF, Sullivan KR, El Refaey H, Rodeck CH. Dinoprostone versus misoprostol: a randomized study of nulliparous women undergoing induction of labor. Acta Obstet Gynecol Scand 2003; 82: 133-137.

7) Austin SC, Sanchez-Ramos L, Adair CD. Labor induction with intravaginal misoprostol compared with the dinoprostone vaginal insert: a systematic review and metaanalysis. Obstet Gynecol 2002; 99: 145-151.

8) Austin SC, Sanchez-Ramos L, Adair CD. Labor induction with intravaginal misoprostol compared with the dinoprostone vaginal insert: a systematic review and metaanalysis. Am J Obstet Gynecol. 2010 Apr 27. [Epub ahead of print]

9) Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin E2 gel for pre-induction cervical ripening and labor induction. Am J Obstet Gynecol 1995; 192: 1804-1810.

10) Sanchez-Ramos L, Kaunitz AM, Del Valle GO, Deke I, Schroeder PA, Briones DK. Labor induction with prostaglandin E1 methyle analogue misoprostol versus oxytocin: a randomized trial. Obstet Gynecol 1993; 81: 332-336.