A COMPARATIVE STUDY OF LOW DOSE INTRAVAGINAL MISOPROSTOL (PGE_1) WITH INTRACERVICAL DINOPROSTONE (PGE_2) GEL FOR CERVICAL RIPENING AND LABOUR INDUCTION

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ABSTRACT: OBJECTIVES: (1) To compare the efficacy of low dose PGE_1 with PGE_2 for induction of labour at term. (2) To compare the safety of PGE_1 with PGE_2 in terms of labour and neonatal outcome. **METHODOLOGY:** It was an open label randomized controlled trial conducted in the Department of Obstetrics & Gynecology, Mysore Medical College Hospital. Total 200 patients satisfying the inclusion criteria were included in the study. One hundred of them received PGE_1 (25 µg repeated 4th hourly to a maximum of six doses) and remaining one hundred received PGE_2 (0.5 mg gel repeated 6th hourly to a maximum of three doses). Analysis was done with respect to age, parity, gestational age, indication for induction, number of doses required, oxytocin requirement, mode of delivery, indication if LSCS done, induction delivery interval, complications and neonatal outcome with respect to 5 minutes APGAR score, meconium stained liquor and NICU admission. **RESULTS:** Both groups were comparable to age, parity and gestational age. Oxytocin requirement was more for PGE_2 group (63%) than PGE_1 group (35%). LSCS rate was 26% for PGE_1 group compared to 23% in PGE_2 group. The major indication for LSCS was fetal distress in 79.6% of PGE_1 group whereas it was failed induction or failure to progress in 60% of PGE_2 group. Incidence of traumatic PPH was 11% in PGE_1 group compared to 6% in PGE_2 group. Incidence of atonic PPH was 3% in PGE_2 group which was 2% in PGE_1 group. Other complications and induction to delivery interval were comparable in both groups. Neonatal outcome in terms of 5 minutes APGAR < 7, NICU admission rates and meconium staining of liquor were all less with PGE_2 group. **CONCLUSION:** Dinoprostone appears to be a safer inducing agent in view of fewer complications with respect to labour and neonatal outcome with induction delivery interval almost equal in both drugs. Misoprostol is efficacious and low cost agent for cervical ripening and labour induction. But even with low dose regimens (25 µg repeated 4th hourly to a maximum of 6 doses), it is associated with increased uterine contraction abnormalities, Fetal HR irregularities; NICU admission rates and low APGAR scores. Although it is efficacious, it requires extensive trials to determine the appropriate dose and route of administration.

KEY WORDS: Labour Induction; Cervical Ripening; Misoprostol; Dinoprostone

INTRODUCTION: Induction of labour is performed in about 20% of pregnancies.[1] Although in the majority of cases there is successful vaginal delivery, in about 20% of cases there is failure of

induction necessitating caesarean section.[2,3] Another important complication of induction is hyperstimulation, which is associated with both maternal and perinatal mortality and morbidity[4]. The success of induction is primarily dependent on the preinduction condition of the cervix. When the cervix is favourable the usual method of induction is amniotomy and oxytocin, whereas with an unfavourable cervix vaginal prostaglandins are commonly used. Although prostaglandins licensed for obstetric applications have been used extensively, they are expensive and unstable, requiring refrigerator storage. Recent interest in inducing agents has focused on misoprostol, a synthetic prostaglandin PGE_1 which was first introduced for the treatment of gastric and duodenal ulcers. Misoprostol is about 100 times cheaper than PGE_2 preparations and is stable at room temperature. Several randomized studies have demonstrated that misoprostol may be more effective than other inducing agents, with a higher rate of vaginal delivery within 24 h of induction. However, the use of vaginal misoprostol has been associated with increased uterine hyper contractility, although there is no apparent increase in operative delivery rates or neonatal morbidity[5]A large body of data exists on misoprostol for use in cervical ripening and labor induction. Vaginal application of misoprostol has been reported in over 9000 women worldwide and seems to have safety profile similar to that of dinoprostone[6,7].The initial trials have used much higher dose of drug. But the American College of Obstetricians and Gynecologists (ACOG) recommends the use of low dose of 25 μg vaginal misoprostol every 3 to 6 hours[8]. At present, there is only limited information available on low dose regimens (25 μg) of misoprostol for labour induction. With this background information the current trial was designed to compare the efficacy and safety of low dose of vaginal misoprostol with routinely used dinoprostone gel for induction of labor.

MATERIAL AND METHODS: This study was undertaken at Government medical college Hospital, Mysore between October 2005 to March 2007 after obtaining ethical committee clearance from the hospital authorities. All eligible women with obstetrical or medical indication for labour induction with no contraindication for vaginal delivery were enrolled in the study. The inclusion criteria were; singleton pregnancy, more than 37 weeks, cephalic presentation, Bishop score of five or less, amniotic fluid index of five or more, reactive fetal heart rate pattern, membranes intact or ruptured. Women with following criteria were excluded from the study; para three or more, prior uterine scar (previous cesarean section and myomectomy), multiple pregnancy, abnormal fetal heart rate (FHR) tracings on non stress test (NST), placenta previa, hypersensitivity to prostaglandins, renal, hepatic or cardiovascular disease and severe asthma. Prior to induction vaginal examination will be done to assign the Bishop's score and a NST will be routinely performed to evaluate the fetal wellbeing. After written informed consent, women were randomized to receive either 25 μg of misoprostol tablets every 4th hourly (maximum of six doses) in the posterior fornix of vagina or 0.5 mg of dinoprostone gel intracervically. The dose was repeated if necessary every six hourly to a maximum of three doses in 24 hours. Artificial rupture of membranes done once cervix is 80% effaced and 3 cm dilated. Intravenous oxytocin augmentation given if active labour gets arrested for > 2 hours. Oxytocin was started 2 hours after last dose of misoprostol or 4 hours after last dose of dinoprostone gel. Labour induction was considered successful if vaginal delivery occurred within 24 hours of induction. A primary outcome measure was the interval from first dose of drug to vaginal delivery. Secondary outcome variables included; mode and route of delivery, indications for cesarean delivery, number of emergency cesareans performed for abnormal FHR pattern, number of doses of drugs used, oxytocin augmentation, incidence of

adverse effects; uterine contraction abnormalities . Specific prostaglandin side effects such as hyperpyrexia, vomiting and diarrhoea, incidence of postpartum hemorrhage, cervical tears, and vaginal tears were recorded. The variables in neonatal outcome included birth weight, APGAR score at 5 min, incidence of meconium stained amniotic fluid, admission to neonatal intensive care unit. Statistical analysis of data was performed using SPSS version 16. Variables were analyzed with chi-square test, Fisher exact t test, and student *t*-test. The *P* value < 0.05 was considered as significant.

RESULTS: Two-hundred patients requiring induction of labour were studied who satisfied the inclusion criteria of which 100 were randomly assigned to receive PGE_1 (Misoprostol) for induction and other 100 received PGE_2 (Dinoprostone) for induction.

Both the groups were statistically similar in terms of age, parity & gestational age. Majority of the patients (81% in the Misoprostol and 83% in the Dinoprostone group) were in the age group 17 to 24 years. Majority of PGE_1 induction group were multiparous (51%) and PGE_2 induction group were primiparous (58%) .Maximum number of patients (56% in the Misoprostol group and 58% in the Dinoprostone group) were of the gestational age between 40-41 weeks. The age group of38 to 40 weeks formed the next largest group(36% in the misoprostol and 35% in the Dinoprostone group).The mean Gestational age in both groups did not differ statistically.

Table 1: Indication for induction

Groups	PIH	Postdatism	Rh –ve + postdatism	PIH + postdatism	Eclampsia
PGE_1(n=100)	40	34	19	0	7
PGE_2(n=100)	45	39	8	4	4

The most common indication for induction in both groups was PIH followed by postdatism. More of Rh –ve post-term pregnancy and eclampsia were induced with PGE_1 than PGE_2.

Table 2: Bishop's score at the time of induction

Groups	Bishop's Score				
	1	2	3	4	5
PGE_1(n=100)	1	30	22	31	16
PGE_2(n=100)	0	12	34	37	17

34% of cases induced had Bishop's score – 4 at time of induction. 28% had a score of 3 and 21% had a score of 2.

Table 3: Number of doses required

Groups	Doses					
	1	2	3	4	5	6
PGE_1(n=100)	4	30	43	15	5	3
PGE_2(n=100)	37	44	19	0	0	0

43% of patients in PGE_1 group required 3 doses and 30% required 2 doses. 44% of PGE_2 group required 2 doses and 37% required 1 dose. The mean dosage required for PGE_1 is 2.96 and that of PGE_2 is 1.82.

Table 4: Delivery method and fetal outcome

	PGE_1 (n=100)	PGE_2 (n=100)	RR (95% CI)
Spontaneous	68	70	0.97(0.81 to 1.17)
Instrumental(forceps or ventouse)	6	7	0.86 (0.3 to 2.46)
Cesarean section	26	23	1.13 (0.69 to 1.84)
Requiring oxytocin augmentation	35	63	p=0.0002
Apgar score below 7 at 5 minutes	33	19	p=0.02
Meconium-stained amniotic fluid	36	30	0.91((0.75 to 1.1)
Admission to neonatal unit	4	2	0.98 (0.93 to 1.12)

74% delivered vaginally in PGE_1 group compared to 77% in PGE_2 group. Caesarean section rate was 26% in PGE_1 group compared to 23% in PGE_2 group.6.5% required instrumental delivery. Six of PGE_1 group required instrumental delivery of which five required ventouse. Seven of PGE_2 group required instrumental delivery. About 63% of PGE_2 group required oxytocin acceleration compared to only 35% of PGE_1 group. This was statistically very significant.33% of PGE_1 group had APGAR score <7 at 5 minutes compared to 19% of PGE_2 group.(p=0.02)Meconium staining was found in 36% of PGE_1 group compared to only 30% in PGE_2 group which is not statistically significant.

Table 5: Indications for LSCS

Groups	**Indications for LSCS**			**Total**
	Fetal distress	**Failed induction**	**Failure to progress**	
PGE_1	22	3	1	26
PGE_2	17	4	2	23

Most LSCS were done for fetal distress. The incidence of fetal distress was comparatively more inPGE_1 (85%) group than PGE_2(74%) group, whereas the incidence of failed induction and failure to progress was more in PGE_2 group.

Table 6: Induction to delivery interval

Groups	Interval			Mean	Standard deviation	Total
	<12	12-24	24+			
PGE_1	46	53	1	12.33	3.95	100
PGE_2	43	54	3	12.89	5.54	100

The mean induction to delivery interval was almost same in both groups 12.33 in PGE_1 and 12.89 in PGE_2. In both groups most delivered around 12-24 hours.

Table 7: Complications

Groups	Complications						Total
	Vomiting	Diarrhoea	Vaginal wall	Cervical tear	PPH	Hyper stimulation	
PGE_1	5	3	7	4	2	4	25
PGE_2	4	3	4	2	3	2	18

Cervical tear, vaginal wall tear accounted for 11 cases in PGE_1 group and 6 cases in PGE_2 group. Hyper stimulation was more common in PGE_1 than PGE_2. Other complications were found to be almost equal in both groups.

DISCUSSION: In this study, two hundred (200) women were studied who satisfied the inclusion criteria. Out of which, 100 received PGE_1 25 µg repeated 4th hourly (maximum six doses).100 received PGE_2 for induction 0.5 mg intracervical gel repeated 6th hourly (maximum three doses).

The two groups were matched for age, parity, gestational age, and Bishop's score at time of induction. In our present study, administration of the two prostaglandins resulted in a similar induction delivery intervals confirming the results of previous investigators.[9,10] But there was conflicting reports by other investigators. Gemund van et al[17] in their study concluded that the median induction-to-vaginal delivery interval was approximately 6 hours longer in the misoprostol group (25 versus 19 hours, p = 0.008). Where as in an Indian study by Nanda et al[11] demonstrated that the mean induction to delivery interval is five hours shorter in misoprostol group(13.30+78.74 vs. 18.53+11.33 p=0.011). Since Gemund van et al[17] has used pulverised misoprostol with cellulose ina capsule, it is possible, that the efficacy of the misoprostol may have been reduced.

The requirement of oxytocin acceleration was significantly more for PGE_2 group than PGE_1 group in this study and this correlates with Howard A Blanchetteet al.[12] and Gupta Nirmal et al.[15] studies. The mean induction to delivery interval was almost same in both groups 12.33 in PGE_1 and 12.89 in PGE_2. Most patients delivered in < 24 hours especially in PGE_1 group was consistent with Gupta Nirmalet al.[15] study. 74% delivered vaginally in PGE_1group compared to 77% in PGE_2 group. Caesarean section rate was 26% in PGE_1 group compared to 23% in PGE_2

group. The result of the present study correlates with Howard A Blanchetteet al.[12] and Gregron S et al.[10] studies with the number delivering vaginally more with PGE_2 group. This was because PGE_1 group showed more of fetal distress requiring termination by LSCS. However, a meta analysis conducted by Sanchez Ramos et al.[18] comparing misoprostol with other regimen for labour induction noted a significant reduction in LSCS rate in women receiving PGE_1.In our study most LSCS were done for fetal distress. The incidence of fetal distress was comparatively more in PGE_1 (85%) group than PGE_2 (74%) group, whereas the incidence of failed induction and failure to progress was more in PGE_2 group.

The LSCS rate being higher in PGE_1 group correlated with the study of Howard A Blanchette et al.[12] The percentage of LSCS done for fetal distress was more for PGE_1 group correlating with the study of Krishnamurthy MB et al.[16] This finding is also consistent with the result of the meta analysis reported by Sanchez-Ramos et al.[18]

The incidence of failed induction was more with PGE_2 group correlating with the other two studies done by Howard A Blanchette et al.[12] and Krishnamurthy MB et al.[16] The incidence of failure to progress correlated with the study of Gupta Nirmal et al.[15] and Krishnamurthy MB et al.[16] in that the incidence being higher with PGE_2 group. Cervical tear, vaginal wall tear accounted for 11 cases in PGE_1 group and 6 cases in PGE_2 group. Hyper stimulation was more common in PGE_1 than PGE_2. The incidence of hyperstimulation being higher with PGE_1 group correlates well with the study of Gupta Nirmalet al.[15] and Krishnamurthy MB et al.[16]In contrast to the study by Van Gemund N et al.[17] the incidence of Postpartum haemorrhage was more for PGE_1 group than PGE_2 induction group. The more number of PPH in PGE_1 group was due to traumatic aetiology (cervical and vaginal wall tear) rather than atonicity. Incidence being 11% in PGE_1 group and 6% in PGE_2 group. Other complications like vomiting, diarrhea were not significant statistically correlating with the study of Wing DA et al.[13]

33% of PGE_1 group had APGAR score <7 at 5 minutes compared to 19% of PGE_2 group. In contrast to other studies wherein the incidence of low APGAR were equal in both groups, the incidence in this study was little unfavourable towards PGE_1 group. This was statistically significant (p-value 0.02) Meconium staining of liquor was more common in PGE_1 group according to the present study and the study by Van Gemund N et al.[17]NICU admission rate was higher among PGE_1 group. This was correlating with the study by Wing DA et al[13] and Peter Danielien et al.[14]Misoprostol is efficacious and low cost agent for cervical ripening and labour induction. But even with low dose regimens (25 μg repeated 4th hourly to a maximum of 6 doses), it is associated with increased uterine contraction abnormalities, Fetal HR irregularities; NICU admission rates and low APGAR scores. So Dinoprostone appears to be a safer inducing agent in view of fewer complications with respect to labour and neonatal outcome with induction delivery interval almost equal in both drugs.

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REFERENCES:

1. RCOG. Induction of labour. Evidence-based Clinical Guideline Number 9. London: RCOG Clinical Support Unit, 2001
2. Arulkumaran S, Gibb DM, Tambyraja RL, Heng SH, Ratnam SS. Failed induction of labour. Aust NZ J ObstetGynaecol1985; 25:190–3

3. Crowley P. Interventions for preventing or improving the outcome of delivery at or beyond term. (Cochrane Review). The Cochrane Library. Oxford: Update Software, 2001: Issue 3
4. Graves G, Baskett T, Gray JH, Luther ER. The effect of vaginal administration of various doses of prostaglandin E2 gel on cervical ripening and induction of labor.Am J ObstetGynecol 1985; 151:178–81
5. Hofmeyr GJ, Gulmezoglou AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review. Br J ObstetGynaecol1999; 106: 798–803
6. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. The Cochrane Database Syst Rev. 2003;CD000941. DOI:10.1002/14651858.CD000941
7. Sanchez-Ramos L, Kaunitz AM. Misoprostol for cervical ripening and labor induction: a systematic review of the literature. ClinObstet Gynecol. 2000; 43:475– 488.
8. ACOG committee opinion. New US Food and drug administration labeling of cytotec (misoprostol) use in pregnancy Int J GynecolObstet 2003;82:137-138.
9. Prager M, Eneroth-Grimfors E, Edlund M et al. A randomised controlled trial of intravaginaldinoprostone, intravaginal misoprostol and transcervical balloon catheter for labour induction. BJOG 2008;115: 1443-50.
10. Gregson S, Waterstone M, Norman I, Murrells T. A randomised controlled trial comparing low dose vaginalmisoprostol and dinoprostone vaginal gel for inducing labour at term. BJOG 2005;112:438–44
11. Nanda S, Singhal SR, Papneja A. Induction of labour with intravaginal misoprostol and prostaglandin E2 gel:a comparative study. Trop Doct 2007;37:21–4.
12. Howard A Blanchette, SandhyaNayak, Sapna Erasmus. Comparison of the safety and efficacy of intravaginal PGE_1 with PGE_2 for cervical ripening and induction of labor in a community hospital. Am J ObstetGynecol 1999; 180(6):1551-9.
13. Deborah A Wing, Margaret M Jones, Ann Rahall, Murphy Goodwin, Richard H Paul. Comparison of misoprostol and prostaglandin E_2 gel for preinduction cervical ripening and labor induction. Am J ObstetGynecol 1995; 172(6):1804-10.
14. PeterDanielian, Belinda Porter, Natalia Ferre. Misoprostol for induction of labor at term.A more effective agent than dinoprostone vaginal gel. British Journal of Obstetrics and Gynecology 1999 August; 106:793-7.
15. Gupta N, Mishra SC, Jain Shradha. A randomized clinical trial comparing misoprostol and dinoprostone for cervical ripening and labour induction. J ObstetGynecol India 2006 March/April; 56(2):149-51.
16. MurthyBhaskar Krishnamurthy, ArkalgudMangalaSrikantaiah. Misoprostol alone versus a combination of dinoprostone and oxytocin for induction of labour.J ObstetGynecol India 2006 September/October; 56(5).
17. VanGemund N, Scherjon S, Schagen JH. A randomized trial comparing low dose vaginal misoprostol and dinoprostone for labor induction. British Journal of Obstetrics and Gynecology 2004 January; 111:42-9.
18. Sanchez Ramos L, Kaunitz AM, Wears RL. Misoprostol for cervical ripening and labor induction: a meta analysis. ObstetGynecol 1997; 89:633-42.