



An Open Label, Prospective Study to Evaluate the Efficacy of Misoprostol Versus Dinoprostone Gel For Induction of Labour

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Abstract

Objective: *This prospective study was conducted to compare the effect, efficacy & safety of intra-vaginal misoprostol (PGE1) & intra-cervical dinoprostone gel (PGE 2) for induction of labour.*

Methods: *60 women aged 18-35 years with single live fetus, cephalic presentation & term pregnancy, who were admitted for induction of labour were included in this study. 30 women received intravaginal 25 microgram Misoprostol (study group) & 30 women received 0.5mg of intracervical dinoprostone gel (control group). Comparison was done between the mean time taken for onset of labour, time taken for induction to delivery, mean duration of labour, requirement of Oxytocin augmentation, mode of delivery, side effects & the neonatal outcome in either of the groups.*

Results: *The mean time taken for onset of labour was less in the misoprostol group than in the dinoprostone group (58.22 min and 1 hr 55 min). Similarly duration from induction to active phase (1hr 57 min and 4hrs 25 min) and active phase to delivery (3 hrs 21 min and 5 hrs 9min) was less for misoprostol group and thus the induction to delivery interval (5 hrs 18 min and 9 hrs 34 min). Cesarean section rate was less in misoprostol group (10% v/s 24%). Maternal side effects were minimal in either group & the neonatal outcome was good in both the groups. The induction cost was much less in the misoprostol group.*

Conclusion: *Misoprostol is safe, efficacious, cheap and mother and fetus friendly drug for the induction of labour.*

Keywords: *Induction of labour, Misoprostol, Dinoprostone gel.*

Introduction

Labor induction is a method of artificially or prematurely stimulating childbirth in a woman.¹ Recently, elective inductions of labor at term have increased dramatically. Currently, two prostaglandin analogs are available for the purpose of cervical ripening –Misoprostol and Dinoprostone gel. Prostaglandin alter the extracellular ground substance of the cervix, ripen the cervix and also increases the activity of collagenase in the cervix. They also allow for an

increase in intracellular calcium levels, causing contraction of myometrial muscle.^{2,3}

Although dinoprostone gel is considered as the preferred method for labor induction, it is relatively expensive drug. The average maximum retail price is 230.50 per 0.5 mg dose of the endocervical gel (Cerviprime, AstraZeneca Pharma). Dinoprostone gel also requires refrigeration for storage which can cause significant problems for maternity units. There is a growing interest on misoprostol, a prostaglandin

E1 analogue for labor induction which is much cheaper and stable at room temperature. A single 100 µg tablet costs 8.60, thus a low dose of 25 µg dose costs approximately 2.15. Replacing dinoprostone with misoprostol would allow considerable cost savings. 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.^{4,5}

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.⁶ The FDA revised its labeling for misoprostol in April 2002 from "contraindicated in pregnancy" to "contraindicated in pregnancy for the treatment and prevention of NSAID-induced ulcers."⁷ Misoprostol (15-deoxy-16-hydroxy-16 methyl-PGE1) was the first synthetic prostaglandin analogue to be made available for the treatment of peptic ulcer. Impressed by its stimulant actions on the uterus, Sanchez Ramos in 1993 used it for the management of several obstetric conditions. Misoprostol is available as 25, 50, 100, 200 microgram tablets. Dinoprostone (PGE) is a synthetic preparation of naturally occurring prostaglandin E2. PGE 2 gel is available in 2.5 ml syringe for an intracervical application of 0.5mg of Dinoprostone.⁸

Material and Methods

After the approval of Institutional Ethics committee of Dr VPMC, Nashik, total 60 antenatal women admitted for induction of labour in Civil Hospital Nashik, were included in the present study randomly. 30 women received 25 microgram intrvaginal misoprostol and another 30 women received 0.5mg of intracervical dinoprostone gel. Misoprostol (50microgm) was kept in the posterior fornix after making it wet. Doses were repeated in both the groups, for a misoprostol group maximum of 5 doses 4-6 hourly and for dinoprostone gel maximum of 3 doses.

Inclusion criteria:

Pregnant women aged ≥ 18 to 35, 37 completed gestational weeks with normal antenatal screening test results, amniotic fluid index of five or more, Pregnant women willing to give conform consent form for the study, Singleton pregnancy, cephalic presentation, gestation confirmed by Ultrasonography

Exclusion criteria:

Multiple pregnancies, para three or more, abnormal presentation, pregnancy < 36 weeks, estimated fetal weight more than 4000 grams, or less than 2000 grams, previous caesarean section and myomectomy. Hypersensitivity to prostaglandins, renal, hepatic or cardiovascular disease and severe asthma.

Study group: Patients who received Misoprostol for induction of labour.

Control group: Patients who received Dinoprostone gel for induction of labour.

The patient was considered in the active phase when there was cervical dilatation of at least 3-4 cm. Women in labour were cared for, according to current obstetric practices. When they entered active phase, depending on the pattern of uterine contractility, oxytocin was used for augmentation. If women did not reach active phase within 24 hrs of induction, caesarean section was done for failed induction. No augmentation was done when uterine contractions reached a frequency of 3 in 10 minutes. The primary outcome measure was the interval from start of induction to active phase. Success of induction was defined as entry into active phase within 24 hours of the initial administration of the drug. Other measures studied were need for oxytocin augmentation, interval from active phase to delivery, mode of delivery, need for caesarean section, and side effects. The results were represented as mean & standard deviation & unpaired t test was applied to know the statistical significance. Qualitative variables were expressed as percentages. Neonatal outcome was measured according to the Apgar score.

Results

The baseline data of the study population included maternal age, gravidity and gestational age. They were comparable in the two groups. The mean

gestational age was identical i.e. 37 to 42 weeks. 70% in study group and 67% in control group were in 37-40 weeks of pregnancy as seen in Table No.1.

Table No.1 Gestational age

Gestational age (in wks)	Misoprostol	Dinoprostone
37-40	21 (70%)	20 (67%)
40.1-42	9 (30%)	10 (33%)

Table No.2 Indications for induction

Indication	Misoprostol	Dinoprostone
Post date Pregnancy	9 (30%)	10 (33.5%)
IUGR	9 (30%)	7 (23%)
PIH/Pre-eclampsia	11(37%)	11 (37%)
Eclampsia	1(3%)	2 (6.5%)

Table No.3 Mean time taken for onset of labour

	Misoprostol	Dinoprostone	Mean difference	S.D.(mean)	Standard error(mean)	t	P
In all patients	58.22 min	1 hr 55min	56.78 min	77.85	11.12	-3.3907	0.00069
In Primigravida	59.37 min	1 hour 41 min					
In Multigravida	58.25 min	1 hour 50.67min					

Table No. 4 Induction-delivery intervals

	Misoprostol	Dinoprostone	Mean difference	S.D. (mean)	Standard error (mean)	t	P
Induction to active phase	1 hr 57 min	4 hrs 25 min	2 hrs 28min	161.76	24.61	-2.71	0.006
Active phase to delivery	3 hrs 21 min	5 hrs 9 min	1hr 48 min	147.10	22.33	-2.599	0.01275
Induction to delivery	5 hrs 18 min	9 hrs 34 min	4 hrs 16 min	377.60	54.97	-3.8077	0.0004

In Misoprostol group the time taken for induction to active phase 1 hr 57 min & In Dinoprostone group 4 hrs 25 min. It states that in Misoprostol group time taken for induction to active phase was less which is statistically significant as $P=0.006$. Similarly active phase to delivery interval (3 hrs 21 min in Misoprostol group & in Dinoprostone group 5 hrs 9 min), was also less and was statistically significant with $P=0.01$. Overall there is less induction to delivery interval (5 hrs 18 min & 9 hrs 34 min) and this was statistically significant.

Table No. 5 Mean duration of labour

	Misoprostol	Dinoprostone	Mean difference	S.D. (mean)	Standard error (mean)	t	P
Duration of labour(mean)	4hrs 37 min	7hrs 51 min	3hrs 14min	212.61	32.5	-2.293	0.01519
Duration of labour in Primi (mean)	3hrs 25 min	7hrs 30 min	4hrs 5min	169.18	48.30	-2.872	0.02252
Duration of labour in multi (mean)	5hrs 08 min	8 hrs 06min	2hrs 58min	276.13	53.39	-1.501	0.10432

Mean duration of labour was much less in the misoprostol group (4 hrs 37 min) than in the Dinoprostone group (7 hrs 51 min) which is significantly less (P=0.015) as seen in Table No. 5

Even in Primigravida patients Misoprostol resulted in shorter duration of labour (3hrs 25 min) as compared to dinoprostone gel (7hrs 30 min) which is statistically significant as P=0.02

Table No. 6 Oxytocin augmentation

	Misoprostol	Dinoprostone Gel
	% of patients	% of patients
Oxytocin augmentation	10%	10 %

Oxytocin augmentation was required in 10% cases in both groups.

Table no.7 Mode of delivery

Type of delivery % of patients	No. Of patients		% of patients	
	Misoprostol	Dinoprostone		
Normal vaginal	26	21	86%	69%
Instrumental delivery	1	2	4%	7%
Cesarean section	3	7	10%	24%

86 % of patients in misoprostol group delivered normally as compared to 69 % in dinoprostone group as seen in Table No.7 .

Thus less rate of Cesarean section seen in the misoprostol group.

Table No. 8 Indication for Cesarean section

Indication for LSCS	Misoprostol	Dinoprostone
Failure of Induction	1	3
Meconium stained liquor	2	1
Fetal Distress	-	3
Total	3	7

Only 1 patient in study group had failure of induction whereas in control group 3 patients had failure of induction. The main indication of Cesarean section in control group was failure of induction as mentioned in Table No. 8. In the study group, Cesarean section was done mainly for meconium stained liquor which was also the second major indication for Cesarean section in the control group.

Table No. 9 Side effects

Side effects	%OF PATIENTS	
	Misoprostol	Dinoprostone
Nausea, Vomiting	8%	4%
Fever with chills	16%	-
GI symptoms	6%	4%
Hyperstimulation	8%	-
Meconium stained liquor	6%	3%

Although maternal complications like fever with chills, Hyperstimulation (Hypersystole & tachysystole) & Meconium stained liquor were

more in misoprostol group than in dinoprostone group as shown in Table No. 9. Significant side effect were not encountered.

Table No. 10 Neonatal outcome

APGAR SCORE < 7	Misoprostole	Dinoprostone
After 1 min	-	6%
After 5 min	-	3%
Need for NICU	-	3%

Apgar score <7 was seen in 2 cases of dinoprostone group out of which 1 have been admitted in NICU. None of the newborn in the study group had Apgar score <7.

The mean overall induction cost in Misoprostol group was much less in contrast to the high overall induction cost in dinoprostone group.

Discussion

The introduction of Prostaglandins to clinical practice, particularly their local use for cervical ripening, has decreased major difficulties of labour induction. Duration between induction and delivery has been decreased dramatically by introduction of Prostaglandins. Similarly it also decreased associated complication of amnionitis and fetal infection. The baseline data of our study population including maternal age, gravidity and gestational age were comparable with similar studies^{9,10,11}

In our study, indication for induction in Misoprostol group were post date pregnancy in 30% and Preeclampsia in 37% whereas in Dinoprostone group 33% and 37% respectively induced for postdated pregnancy and Pre-eclampsia. Thus majority of indication was due to these two conditions. Post dated pregnancy was

the main indication for induction in other studies^{9,10,11}.

The mean time taken for onset of labour was less in misoprost group (58.22 min v/s 1 hr 55 min). There was no significant difference between the primigravida and the multigravida in both the groups regarding the time taken for onset of labour.

In this study the mean induction to delivery interval was less in the misoprost group (5 hrs 18 min v/s 9 hrs 34 min), which is statistically significant ($P = <.001$). Similar results were seen in study in 2003 by Agarwal et al¹² where it was 12.8+/- 6.4 hrs v/s 18.53+/-8.5 hours. In 2003 D.Garry et al¹³ also concluded in his study that interval from start of induction to vaginal delivery was significantly shorter in the misoprostol group. Also in another study of Murthy Bhaskar Krishnamurthy in 2006, induction delivery interval was shorter in the misoprostol group. Other reported studies^{14,15} also had parallel observation. Thus misoprostol reduces the mean duration of labour which reduces the duration of suffering of a patient in labour and also provides fast delivery which is required in cases of Premature rupture of membranes, eclampsia and fetal distress.

The present study showed that Misoprostol was able to increase the vaginal deliveries compared to the control group as 86% patients delivered vaginally in study group compared to 69% in the control group. Thus Misoprostol had decrease rate of Cesarean section (10%) compared to Dinoprostone (24%). This was consistent with the study of Sahu Latika et al⁹ (8% v/s 20%) and also with the study of Patil Kamal et al¹⁰ and Murthy Bhaskar et al¹¹

In the present study, in the study group, out of 3 patients who underwent cesarean section only one was for failure of induction whereas in the control group 3 out of 7 patients operated for Cesarean section due to failure of induction. Thus the main indication of Cesarean section in the dinoprostone group was failure of induction which was consistent with the study by Patil Kamal et al¹⁰ and Murthy Bhaskar et al¹¹. In the Misoprostol group 2 out of 3 patients underwent Cesarean section due to meconium stained liquor though in the Dinoprostone group 2 patients had Cesarean section due to meconium stained liquor.

Maternal side effects were minimal in both the groups. In Misoprost group, 16% patients had fever with chills, 8% had nausea and vomiting and 6% had GI symptoms, 8% had hyper stimulation. Hypertonus was defined as one contraction with a duration of >2 minutes, tachysystole as >6 contractions in 10 minutes for two consecutive 10 minute periods¹⁷. Uterine hyperstimulation is when either of these condition (hypertonus or tachysystole) leads to a non reassuring fetal heart rate pattern¹⁸. Because of the frequency of tachysystole with vaginal administration of misoprostol, some researchers are studying oral and sublingual/buccal routes to determine if effectiveness can be maintained while decreasing the incidence of tachysystole.¹⁷⁻¹⁹. In 2000, G.D.Scarle & Company notified physicians that misoprostol is not approved for labour induction or abortion. Despite this American College of Obstetricians & Gynecologists (2000) quickly reaffirmed its recommendation for use of the drug because of proven safety & efficacy¹⁸

The neonatal outcome in both the groups was comparable. Birth weights were similar in both the groups. Apgar score < 7 at 1 min was seen in 3 cases of Dinoprostone group out of which one had to be admitted to NICU. Sahu Latika et al also had 12% newborns with Apgar < 7 at one minute in the dinoprostone group which is consistent with our study.

The mean overall induction cost in Misoprostol group was much less in contrast to dinoprostone group. As Misoprostol does not need refrigeration, its affordability as well as its availability in the peripheral areas is more than the Dinoprostone gel which requires refrigeration.

Conclusion

Our study results revealed that, Misoprostol is better inducing agent as compared to the Dinoprostone gel because it has short induction to delivery intervals and thus short duration of labour and advantage of rapid labour as required in cases of pre-eclampsia and eclampsia.

The need of Oxytocin augmentation was same with the Misoprostol and it results in more vaginal deliveries compared to Dinoprostone. Thus Misoprostol reduces the Cesarean section rate and also has less chances of failure of induction. Although hyper stimulation and meconium stained liquor was more in Misoprost group in few patients and did not had any effect on the neonatal outcome. Misoprostol also does not need cold chain storage and is cheaper. Thus Misoprostol can be considered as safe, efficacious, cheap drug for the induction of labour.

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