A RANDOMISED STUDY OF LOW-DOSE ORAL MISOPROSTOL AND INTRACERVICAL PROSTAGLANDIN E2 GEL FOR CERVICAL RIPENING AND LABOUR INDUCTION IN TERM PREGNANCY

Sandhya Jain¹, Shikha Pasrija², Shilpa Sakure³, Nivedita Sarda⁴

¹CMO (NFSG), Department of Obstetrics and Gynaecology, Dr. Baba Saheb Ambedkar Hospital and Medical College, Delhi, India.

²Specialist, Department of Obstetrics and Gynaecology, Dr. Baba Saheb Ambedkar Hospital and Medical College, Delhi, India.

³Senior Resident, Department of Obstetrics and Gynaecology, Dr. Baba Saheb Ambedkar Hospital and Medical College, Delhi, India.

⁴Professor, Department of Obstetrics and Gynaecology, Dr. Baba Saheb Ambedkar Hospital and Medical College, Delhi, India.

ABSTRACT

BACKGROUND

Labour induction is one of the most frequent interventions all over the world in pregnant women. The rate of induction varies by location and in many centres, it is currently more than 20%. When the benefits of expeditious delivery are greater than the risks of continuing the pregnancy, inducing labour can be justified as a therapeutic intervention. The current study was done with the objective of comparing the efficacy, acceptability and safety of low-dose oral misoprostol tablet (25 µg PGE1) and intracervical dinoprostone (PGE2) for labour induction and cervical ripening in women at term. In developing countries with low resources, misoprostol could be the preferred drug because of low cost and easy storage; however, monitoring the induced labour is a challenge.

Aims and Objectives- To compare efficacy, acceptability and side effects of low-dose oral misoprostol with that of intracervical dinoprostone for cervical ripening and induction of labour.

MATERIALS AND METHODS

A prospective, randomised, controlled study wherein 100 pregnant women admitted to labour ward at 37 weeks or beyond with a single live foetus for induction of labour were included. The enrolled women were randomly divided into two equal Groups A and B. Group A women received oral tab Misoprostol 25 µg every 2 hours for a maximum of 6 doses. Group B women received 0.5 mg intracervical dinoprostone gel 6 hourly, for a maximum of 3 doses. Outcomes in terms of improvement in Bishop's score, induction to delivery interval, number of doses required, requirement of any other means of ripening, induction and/or augmentation and mode of delivery were noted. Side effects and complications were compared. Foetal outcomes in terms of Apgar score and need for NICU admission was compared. The results observed were subjected to statistical analysis by SPSS: Chi-square/ Fisher's Exact test and Unpaired t-test.

RESULTS

The two groups were comparable in terms of age, parity, gravidity, period of gestation at induction and reasons for induction of labour. Successful priming was achieved in 100% women in Group A and 86% women in Group B. The 'p' value was 0.003, which is statistically significant. The number of women with a favourable score (≥ 6) was significantly higher in Group A. Successful induction was achieved in 88% and 66% women in Groups A and B respectively. The mean induction to delivery interval was shorter in Group A. Vaginal delivery was the outcome in 92% women with misoprostol induction and 74% women with dinoprostone induction. Side effects of prostaglandin inductions when compared in two groups showed no statistically significant differences.

CONCLUSION

Low-dose oral misoprostol is more effective than dinoprostone gel for cervical priming and labour induction without compromising safety. It has an advantage of decreasing the need of additional measures to achieve vaginal delivery, lower cost and patient acceptability as shown by VAS score.

KEYWORDS

Cervical Ripening; Labour Induction; Misoprostol; Dinoprostone.

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BACKGROUND

Labour induction is one of the most frequent interventions all over the world in pregnant women. The rate of induction

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Corresponding Author:

Dr. Shikha Pasrija,

CA-16, Tagore Garden,

New Delhi-110027, India.

E-mail: shikhaspasrija@gmail.com

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varies by location and in many centres it is currently more than 20%.¹ The pros and cons of labour induction must be weighed against the potential maternal and foetal risks associated with this procedure. When the benefits of expeditious delivery are greater than the risks of continuing the pregnancy, inducing labour can be justified as a therapeutic intervention.² The aim of successful induction is to achieve vaginal delivery with good neonatal outcome in an acceptable timeframe and with minimum maternal discomfort or side effects. A ripened cervix and effective uterine contractions are two essential determinants for success in labour outcomes.³ Nulliparous women with a low

Bishop's score are particularly at a high risk of caesarean delivery when labour is induced, hence the need of a good cervical ripening agent.^{4,5}

Medications that ripen the cervix in a short period of time play a significant role in modern obstetrics. There have been many studies to evaluate the efficacy of misoprostol for labour induction in various doses, routes and intervals of administration, suggesting that misoprostol is effective, but there is still a concern that misoprostol may increase the rates of tachysystole and hyperstimulation and a search for ideal dose and mode is still on.⁶ Although, low-dose misoprostol is recommended by WHO,¹ FIGO⁷ and SOGC⁸ it is still not approved by FDA for this indication. The availability of low-dose misoprostol tablet is restricted to a few countries.

The current study was done with the objective of comparing the efficacy, acceptability and safety of low-dose oral misoprostol tablet (25 µgm PGE1) and intracervical dinoprostone (PGE2) for labour induction and cervical ripening in women at term. In developing countries with low resources, misoprostol could be the preferred drug because of low cost and easy storage; however, monitoring the induced labour is a challenge.

MATERIALS AND METHODS

A prospective, randomised, controlled study was conducted at a district hospital of New Delhi over a period of one year. Sample size was calculated based on assumptions that the two groups are of same size and the standard deviations are the same. Keeping the power of test as 90% and level of significance as 99%, a sample size of 50 in each group was obtained. 100 women admitted to labour ward with a single foetus in cephalic presentation and period of gestation 37 or more weeks with an indication for induction of labour were included in the study after an informed written consent. Exclusion criteria were contraindications for vaginal delivery, previous uterine surgery, malpresentation, grand multiparity, antepartum haemorrhage, abnormal foetal heart rate pattern, known allergy to prostaglandins, multiple pregnancies, medical illness in mother contraindicating the use of prostaglandins and women with Hb < 8 gm%. Detailed history including obstetric history, menstrual history, surgical and medical history was recorded. General physical and systemic examination was done. Abdominal examination assessed the fundal height, lie, presentation, amount of liquor and foetal heart sounds and vaginal examination confirmed presentation and assessed Bishop's score. Gestational age was confirmed by last menstrual period and/or Ultrasound.

The enrolled women were randomly assigned into two study groups using computer generated random numbers. In Group A (N= 50), women received Tab. Misoprostol 25 µgm orally repeated every 2 hours for a maximum of 6 doses. In Group B (N= 50), women received 0.5 mg intracervical dinoprostone gel repeated every 6 hours for a maximum of 3 doses. Partogram was maintained in all patients, foetal monitoring was done with CTG and modified Bishop's score was assessed at 0, 4, 6, 8, 10 and 12 hrs. Need for any additional method of induction or augmentation was noted.

Maternal outcomes in terms of improvement in the modified Bishop's score with time intervals, induction to

delivery interval, number of doses required, requirement of any other means of induction and/ or augmentation and mode of delivery was noted. Foetal outcomes in terms of Apgar score and need for NICU admission was recorded. Side effects and complications of two induction modes were recorded. Maternal experience and satisfaction was recorded using a VAS Likert scale of 1 - 5.

Following Definitions and Criteria were used to calculate the Results

- Successful Induction: If vaginal delivery was achieved within 24 hrs. of induction.
- Successful Priming: If cervix becomes favourable at 12 hrs. of induction.
- Failed Induction: When women does not go in labour even after 6 doses of misoprostol or 3 doses of dinoprostone.
- Partial Failure of Induction: Partial failure will be considered if women require any other means of augmentation for delivery.
- Uterine hyperstimulation include Tachysystole or Hypersystole with or without foetal heart rate changes.
 - Tachysystole: Defined as 5 or more uterine contractions in 10 mins for at least 20 mins period.
 - Hypersystole: Defined as single contraction lasting 2 mins or more in duration.

The results observed were subjected to statistical analysis by SPSS software: Chi-square/ Fisher's exact test and Unpaired 't' test.

RESULTS

The age of the patients ranged from 19 - 36 years, mean being 25.58 ± 2.87 in Group A and 25.04 ± 3.45 in Group B. Gravidity of women ranged from 1 - 6; 64% and 60% women in Group A and B respectively were primigravidae. Gestational age of women ranged from 37 + 2 wks to 41 + 6 wks. Mean gestational age was 39.62 ± 1.27 and 39.14 ± 1.37 in Group A and B respectively. The two groups were comparable in terms of age, parity, gravidity, period of gestation at induction and reasons for induction of labour (Table 1).

The most common indication for induction was post-dates (48%) followed by premature rupture of membranes (41%).

The mean modified Bishop's score at 0 hour was similar in two groups 3.16 ± 1.28 in Group A and 2.96 ± 1.52 in Group B; however, subsequent scores were higher for Group A and the difference was statistically significant (Table 2).

The number of women with a favourable score, that is ≥ 6 was significantly higher in Group A at 6, 8, 10 and 12 hours (Table 3). Successful priming that is a favourable score at 12 hrs. was achieved in 100% women in Group A and 86% women in Group B. The 'p' value was 0.003, which was statistically significant.

Oxytocin for augmentation was required in 28% and 40% women in Group A and B respectively. 'P' value was 0.032, which was statistically significant.

In Group A 28% women responded to 6 tablets, 24% responded to 2 tablets, 22% needed 3 tablets, 12% needed 4

tablets, 12% needed 5 tablets and 2% needed only one tablet. In Group B 42% each needed 1 and 3 gel insertions, while another 16% needed 2 gel insertions.

The mean induction to delivery interval in Group A and B was 10.4 ± 6.31 hrs. and 13.17 ± 7.34 hours respectively. The difference was statistically significant, 'p' value being 0.034 (Table 4). At 12 hours 67.4% women had delivered in Group A in contrast with 46% in Group B and when compared at 18 hours 91.3% women had delivered as against 75% in Group B. This is a big difference.

Successful induction was achieved in 88% and 66% women in Groups A and B respectively. Failed induction resulted in 12% and 34% women. Both differences were found to be statistically significant, 'p' value being 0.004 in each. Vaginal delivery was the outcome in 92% women with misoprostol induction and 74% women with dinoprostone induction which is significant (p value= 0.008).

Side effects of prostaglandin inductions when compared in two groups showed no statistically significant differences, vomiting being the most common followed by postpartum haemorrhage and tachysystole (Table 5).

There was a significant difference in the Apgar scores of babies in Group A and B with babies in Group A faring better (Table 6).

The mean VAS score in women of Group A was 4.20 ± 0.93 and in Group B was 3.3 ± 1.39 , 'p' value was 0.000 making it significant. Thus, maternal satisfaction was higher in Group A.

Characteristic	Group A Mean $\pm$ SD	Group B Mean $\pm$ SD	P value
Age in Years	25.58 ± 2.87	25.04 ± 3.45	0.20
Parity	01.16 ± 1.36	00.90 ± 0.97	
Primigravida (%)	64	60	0.34
Multigravida (%)	36	40	
Mean Gestational Age at Induction in Weeks	39.62 ± 1.26	39.14 ± 1.38	0.04
Indication of Induction			
Postdates (%)	44	28	0.05
PROM (%)	30	28	0.41
IUGR (%)	10	2	

Table 1. Clinical Profile

Number of Hrs. since Induction	Modified Bishop Score		P-value
	Group A	Group B	
	Mean $\pm$ SD	Mean $\pm$ SD	
0 hrs.	3.16 ± 1.28	2.96 ± 1.52	0.240
4 hrs.	5.40 ± 2.96	4.09 ± 2.68	0.014
6 hrs.	6.47 ± 2.83	5.07 ± 2.74	0.014
8 hrs.	7.45 ± 2.34	6.41 ± 2.74	0.049
10 hrs.	8.26 ± 2.05	6.88 ± 2.23	0.011
12 hrs.	9.17 ± 1.69	8.00 ± 2.68	0.049

Table 2. Improvement in Modified Bishop's Scores with Time

Number of Hrs. since Induction	Modified Bishop's Score ≥ 6				P-value
	Group A		Group B		
	N	%	N	%	
0 hrs.	0	0.00	0	0.00	-
4 hrs.	22	37.78	14	23.40	0.067
6 hrs.	32	52.63	23	35.71	0.041
8 hrs.	46	86.21	32	53.85	0.001
10 hrs.	49	95.65	36	58.82	0.001
12 hrs.	50	100.00	43	86.00	0.003
<i>Table 3. Women with Favourable Bishop's Score</i>					

Table 3. Women with Favourable Bishop's Score

Induction Delivery Interval (hrs.)	Group A		Group B		P-value
	N	%	N	%	
0-6	13	28.26	8	21.62	0.245
6-12	18	39.13	9	24.32	0.076
12-18	11	23.91	11	29.73	0.275
18-24	2	4.35	5	13.51	0.068
>24	2	4.35	4	10.81	0.129
Total	46	100	37	100	
Mean $\pm$ SD	10.40 ± 6.31		13.71 ± 7.34		0.034

Table 4. Comparison of Induction Delivery Interval

Side Effect	Group A		Group B		P-value
	N	%	N	%	
Diarrhoea	2	4	3	6	0.323
Fever	0	0	2	4	0.077
Vomiting	6	12	7	14	0.383
Hyperstimulation	3	6	2	4	0.323
Tachysystole	3	6	3	6	0.500
Postpartum Haemorrhage	3	6	3	6	0.500

Table 5. Maternal Side Effects

Apgar	Group A	Group B	P-value
	Mean $\pm$ SD	Mean $\pm$ SD	
1 min	5.94 ± 0.84	5.42 ± 1.44	0.015
5 mins	7.16 ± 0.87	6.54 ± 1.61	0.009
10 mins	8.84 ± 1.11	8.02 ± 1.88	0.005

Table 6. Apgar Score of Neonates

Figure 1. Improvement in Modified Bishop's Score with Time

Figure 2. Cumulative Cervical Favourability with Time

Figure 3. Cumulative Percentage of Women Delivered Vaginally

DISCUSSION

Labour induction at term gestation is the most common obstetric intervention of our times. Shorter induction to delivery time and quicker cervical priming is the need of hour in order to decrease the period of anxiety and discomfort for the patient and increased workload in hospitals. There is evidence that vaginal misoprostol is more efficacious than PGE2 gel and that oral misoprostol is more efficacious than vaginal route.^{6,9,10} There is limited good quality data on comparison of oral misoprostol with other inducing agents. Low dose oral misoprostol is the preferred mode, as it is easy and non-invasive. As we now have the 25 µgm tablet available that makes it even more convenient.

Innumerable regimes have been studied varying from single dose of 200 µg to various titrations of misoprostol solutions.¹¹⁻²⁶ The frequency of administration and the use of oxytocin once cervical ripening is achieved are other variations noted in the literature.

In most studies, Bishop's scoring was done at 6 hrs. or at 6 and 12 hrs. both. However, we studied the Bishop's score and thus cervical favourability every 2 hrs. starting from 4 hrs. till 12 hrs. and it was found to be higher in misoprostol group at 4, 6, 8, 10 and 12 hrs. The same mean Bishop's score was achieved about 2 hrs. earlier in the misoprostol group as compared to the dinoprostone group as depicted in Figure 1. Also 100% women achieved Bishop's more than 6, at 12 hrs. as contrast to 86% in dinoprostone group. In misoprost group 86% women already had a favourable score at 8 hrs.,

that is 4 hrs. earlier as can be seen in Figure 2. Thus, misoprostol was found to be more efficacious.

The mean induction to delivery interval in our study was about 3 hours shorter in Group A as compared to Group B (10.4 ± 6.31 hrs. and 13.17 ± 7.34 hrs. respectively). Mean induction to delivery interval in various studies ranged from 10.2 to 24.9 hours in misoprostol group versus 14.8 to 28.7 hours in dinoprostone group.¹⁹⁻²⁶ Though, most studies showed misoprostol give us a shorter induction interval compared to dinoprostone, the protocols used were different. As already discussed that cervical ripening occurred about 2 hours earlier, the moderate uterine contractions lasted about an hour less in the misoprostol group.

In our study vaginal delivery was achieved in 92% women in misoprostol group and 74% in dinoprostone group, which is similar to that observed by Gherman RB.²³ In the misoprostol group 84% women had delivered by 18 hrs., whereas only 56% delivered in the dinoprostone group (Figure 3). Studies done by Patil Kamal P²⁴ and A Rouzi¹¹ had also observed higher rate of vaginal delivery in misoprostol group. In literature, we found that vaginal delivery rate varied from 56 - 98.95% for misoprostol and 45 - 91% in various studies.

In various studies, the rate of successful induction varies from 31 - 98% with misoprostol and 32 - 98% with dinoprostol.¹⁹⁻²⁶ In present study successful induction, that is vaginal delivery within 24 hours was achieved in 88% women with misoprostol in contrast with 66% of women with dinoprostone gel. Failure of induction was 12% in misoprostol group and 34% in dinoprostone group, which is similar to that observed by Patil Kamal P²⁴ and A Rouzi.¹¹ Failed induction has been reported to be 12% - 68% with different misoprostol regimes and 28% - 67% with dinoprostone gel.¹⁹⁻²⁶

Caesarean section rate was significantly lower in misoprostol group as compared to dinoprostone group (8% vs. 26%). The caesarean delivery rate reported by various authors in literature ranges from 8 - 25% with misoprostol and 19 - 27% with dinoprostone. In a systematic review Kundodyiwa et al found lower caesarean rate with misoprostol compared with dinoprostone (20% vs. 26%).²⁷ In our study, we continued the use of misoprostol even after cervical ripening until the maximum 6 doses were used. The need of augmentation of labour with oxytocin in misoprostol group was lower (28% vs. 40%), thus avoiding inconvenience to the patients of continuous drip and also reduced cost to hospital.

If we compare the cost effectiveness, a total of 196 tablets of misoprostol were required and 100 dinoprostone gels were used. The cost of tablets was Rs. 794 compared to Rs. 25,000 for the gel which is a huge difference.

Maternal complications between the two groups were similar. Higher dose of misoprostol has been associated with higher side effects in literature.¹ In dinoprostone group 4% developed hyperstimulation and one woman developed severe bradycardia. Hyperstimulation developed in 6% in misoprostol group, but none developed foetal heart rate abnormalities. Kundodyiwa et al in their systematic review found no difference in hyperstimulation or further need of oxytocin.²⁷ Neonatal birth weight was comparable in both

groups. In misoprostol group no baby was affected with birth asphyxia, meconium aspiration and none needed NICU admission, while in dinoprostone group birth asphyxia (8%), meconium aspiration (6%) and NICU admission (6%) were observed.

CONCLUSION

We thus conclude that by using low-dose misoprostol, rate of modified Bishop's score improvement was faster by about 2 hours and thus cervical ripening occurred about 2 hours earlier. Also 14% more women reached cervical favourability with about 50% achieving so in 6 hrs. (contrast with 36%). In misoprostol group, induction to delivery interval was shorter by 3 hours with 18% higher vaginal delivery rate. Of those achieving vaginal delivery, 28% more women delivered at 18 hours. We saved about ₹24,200 and women reported better VAS scores. It also has an advantage of decreasing the need of additional measures to achieve vaginal delivery. We thus recommend low-dose misoprostol as preferred ripening and inducing agent without fearing its efficacy safety and acceptability.

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