Research Paper

A Comparative Study between Sublingual Misoprostol (PGE_1) versus Intracervical Dinoprostone Gel (PGE_2) in the Induction of Labor:- A Prospective Observational Study

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Abstract

Objective: To compare the efficacy of sublingual misoprostol tablet and intracervical dinoprostone gel for induction of labor and also to assess the maternal and fetal outcome after induction. **Methodology:** A prospective observational study was conducted over a period of 6 months. Of 200 cases, 100 received sublingual misoprostol tablet (Group 1) and remaining received intracervical dinoprostone gel (Group 2). The time required from induction to delivery interval (IDI), and maternal and fetal outcome were assessed by the mode of delivery, Apgar score, and need for neonatal intensive care unit (NICU) admission. Data were analyzed using descriptive statistics, Student's *t*-test, and Chi-square test. **Results:** Induction to delivery time was 14.1 h in Group 1, whereas 13.9 h in Group 2. Stage II of labor was 2.3 h and 3.1 h in Group 1 and 2 ($P < 0.05$) respectively. Normal vaginal delivery occurred in 66 cases in Group 1 and 56 cases in Group 2. Apgar score (≥7) at 1 min was observed in 91 and 93 cases of Group 1and Group 2, respectively. Augmentation of labor by artificial rupture of the membrane was needed in 17 cases in Group 1 and 39 cases in Group 2 ($P < 0.05$). The need of NICU admission was 20 in Group 1 and 19 in Group 2 ($P < 0.05$). **Conclusion:** The misoprostol group showed shorter IDI, more number of vaginal deliveries, and reduced need of cesarean section, compared to dinoprostone group. There was a significant difference in the post induction Bishop's score, Stage II process of labor and reduction in the requirement of augmentation (ARM) between the two groups. Misoprostol was found to be more efficacious when compared to dinoprostone.

Keywords: Prostaglandins, uterine stimulants, vaginal delivery

Introduction

Induction of labor is the process of artificially stimulating the uterus to initiate labor.[1] It constitutes about 25% of deliveries at term.[2] Cervical ripening facilitates labor and delivery.[3] Prostaglandins bring about cervical ripening and uterine contractions.[4] Normal vaginal delivery (NVD) occurs between 37and 42 weeks of pregnancy.[5]

Misoprostol (PGE_1) is used as an off-label drug for cervical ripening.[6] PGE_1 increases both the tone and amplitude of uterine contractions by increasing the calcium influx and modulation of cAMP.[4] In the WHO model list of essential medicines, misoprostol is indicated for labour induction at term in lower doses (25-50 μg).[7] Misoprostol is cost-effective, can be stored at room temperature, and can be administered by oral, sublingual, buccal, vaginal, or rectal routes.[8] The sublingual route of misoprostol has rapid action when compared to its oral administration.[9] Dinoprostone (PGE_2) is approved by the FDA in 1995 for cervical ripening and induction of labor. Dinoprostone is costlier and requires refrigeration for storage, as it is unstable at room temperature.[10] PGE_2 induces collagenase, metalloproteinase, and elastin activity, thus causing separation of collagen bundles and cervical ripening.[11]

An ideal inducing agent must be effective, non-invasive, economical, and safe to mother and fetus.[12] It must achieve labor in shortest possible time, with lower incidence of failure

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to achieve vaginal delivery and with no increase in perinatal morbidity.[13] A pregnant woman is in labor, when three or more uterine contractions occur in 10 min and dilatation of the cervix is more than 4 cm.[14]

The comparative studies of sublingual, oral, and vaginal misoprostol showed that the sublingual route of administration is better than oral and vaginal routes for cervical ripening. Majority of studies have shown that dinoprostone is preferred in gel formulation with intracervical route of administration.[15] This study was undertaken to compare the efficacy of sublingual misoprostol tablet and intracervical dinoprostone gel for induction of labor, as well as to assess the maternal and fetal outcome after induction.

Methodology

This study was a prospective observational study conducted from August 2018 to January 2019 at Mandya Institute of Medical Sciences, Mandya, after obtaining approval from the Institutional Ethics Committee: ethical committee permission letter number MIMS/IEC/RP/2018/223. Written informed consent was obtained prior to administration of medications.

Inclusion criteria were pregnant women at term, primigravida, singleton live gestation, cephalic presentation, and Bishop's score ≤6. Exclusion criteria were pregnant women having, previous uterine surgery, cephalo-pelvic disproportion, abnormal foetal lie, amniotic fluid index ≤5, preterm delivery, antepartum hemorrhage, history of bronchial asthma, and intrauterine death.

Sample size was calculated taking $\alpha = 0.05$ and $\beta = 80\%$. Using formula based on two means of previous studies, we found the sample size to be 100 in each of the two groups. A total of 200 cases were recruited and each group consisted of 100 cases. Group 1 were given sublingual misoprostol tablet 25 μg, maximum of four doses, which were repeated every 4th hourly and Group 2 received intracervical dinoprostone gel 0.5 mg, maximum of two doses, repeated every 6th hourly. A repeat dose was given if cervical dilatation was ≤4 cm and if uterine contractions were not present.

In Group 1, misoprostol tablet 25 μg was given sublingually and instructed, not to chew or swallow, but to be kept underneath the tongue for about 4-8 min. In Group 2, dinoprostone gel 0.5 mg was instilled intracervically under aseptic precaution and was made to lie down on the left lateral position for about 30 min.

Both the groups were carefully monitored for fetal heart rate and uterine activity. Augmentation with oxytocin was started 6 h after the last dose of inducing agent, if needed. The efficacy of the drugs was measured in terms of post-induction Bishop's score, induction to active phase (IAP) interval, induction to delivery interval (IDI), Stage II process of labor, number of doses required, and need for augmentation with artificial rupture of the membranes/oxytocin.

The maternal outcome was measured by the mode of delivery, incidence of cesarean section, and color of liquor. The neonatal outcome was measured as Apgar score at 1 and 5 min, birth weight, meconium aspiration, and need for neonatal intensive care admission.

Statistical analysis

Data were collected and entered into the Microsoft Excel and were analyzed using the Statistical Package for the Social Sciences version 21. The mean and standard deviation were calculated for continuous variables and unpaired Student's *t*-test was used to compare between the groups. For categorical variables, proportions were compared using Chi-square test. $P < 0.05$ was considered statistically significant.

Results

A total of 200 pregnant women were recruited and each group had 100 cases. All were primigravida, in the latent phase of labor, and having cephalic presentation. The mean age in Group 1 was 23.04 ± 3.57 years and in Group 2 was 22.10 ± 2.96 years. The minimum age was 18 years and the maximum age was 38 years in this study. Around 66% were in the age range of 21-30 years. Gestational age was in the range between 37 and 42 weeks. Rh+ve pregnancy was about 95.5% and Rh-ve pregnancy was 4.5%. The mean hemoglobin value in Group 1 was 10.98 ± 1.13 g %, and in Group 2, it was 10.97 ± 1.05 g %. Pre-induction Bishop's score of ≤6 was included in this study, which implied unfavorable cervix. Preinduction Bishop's score of 3 was present in 24.5% of the total cases [Table 1].

The mean IAP interval and the mean IDI was shorter in the misoprostol group than the dinoprostone group. The Stage II process of labor showed a significant difference between the groups ($P < 0.05$) [Table 2].

There were 42 cases in each group, which required oxytocin for augmentation of labor. Artificial rupture of the membrane was done in 17 cases of Group 1 and 39 cases of Group 2 ($P < 0.05$). With the use of single dose of inducing agents, 58 cases in misoprostol group and 47 cases in dinoprostone group delivered the baby normally, which constituted a total of 52.5%. The second dose was required in total for 33.5% of cases, whereas only in misoprostol group, third and fourth doses were required in 12.5% and 1.5% of the cases, respectively. Post induction Bishop's score of 10 was present in 22.5% of the total cases. The post-induction Bishop's score between the groups showed significance ($P < 0.05$) [Table 2].

In maternal outcome, the mode of delivery, by NVD was 66 and 56 cases whereas by LSCS, it was 26 and 35 cases in Group 1 and Group 2 respectively, there was no much difference in the vacuum-assisted deliveries between the groups, and forceps delivery was required only in Group 2. Meconium-stained liquor, was observed in 15 cases of Group 1 and 11 cases in Group 2.

There was a significant difference for the indication of LSCS in between the groups ($P < 0.05$). Indication for cesarean section

Table 1: Basic demographic data

Demographic data	Group 1 (*n*=100)	Group 2 (*n*=100)	Total	Percentage (%)	*P*
Age (years)					0.122
18-20	26	37	63	31.5	
21-30	70	62	132	66	
31-40	04	01	05	2.5	
Gestational age (weeks)					0.121
Term (37-40)	97	92	189	94.5	
Post term (≥41)	03	08	11	5.5	
Blood group					0.438
Rh+ve	97	94	191	95.5	
Rh –ve	03	06	09	4.5	
Haemoglobin (g %)	10.98±1.13	10.97±1.05			0.979
Preinduction Bishop's score					0.860
0	24	24	48	24	
1	10	15	25	12.5	
2	22	19	41	20.5	
3	24	25	49	24.5	
4	12	8	20	10	
5	5	7	12	6	
6	3	2	5	2.5	

Table 2: Comparison of parameters between the groups

Parameters	Mean±SD		*P*
	Group 1	Group 2	
Induction to active interval (h)	10.96±3.37	10.06±5.00	0.189
Induction to delivery interval (h)	14.16±3.62	13.93±5.69	0.732
Stage II of labor (h)	2.33±1.96	3.10±2.01	0.018*

Parameters	Group 1 (*n*=100)	Group 2 (*n*=100)	Total	Percentage (%)	*P*
Need for augmentation					
Oxytocin					1.000
Yes	42	42	84	42	
No	58	58	116	58	
Artificial rupture of membranes					0.001*
Yes	17	39	56	28	
No	83	61	144	72	
Number of doses of test drugs					0.000*
1	58	47	105	52.5	
2	14	53	67	33.5	
3	25	00	25	12.5	
4	03	00	03	1.5	
Postinduction Bishop's score					0.005*
1-5	8	15	23	11.5	
6-10	47	54	101	50.5	
11-15	45	31	76	38	

*Significant *P* value. SD=Standard deviation

in misoprostol group, was due to the failed induction in 12 cases and failure to progress in 3 cases. In the dinoprostone group, failed induction was in 6 cases and failure to progress was in 14 cases. LSCS done due to meconium-stained liquor was in 1 and 4 cases of Group 1 and Group 2 respectively [Table 3].

Delivery of babies ≥3.5 kg was seen in 4 cases of misoprostol group and 14 cases in dinoprostone group, which showed significant differences ($P < 0.05$). Most of the baby birth weight was in the range of 2.5-3.4 kg, which constituted 76.5%. Apgar score at 1 min with ≥7 score was 91 and 93 cases in Group 1 and Group 2, respectively, which was statistically significant ($P < 0.05$). Apgar score at 5 min of ≥7 score was 97 and 94 cases in Group 1 and Group 2, respectively. In total, 19.5% of the cases required neonatal intensive care unit (NICU) admissions, of which 20 cases were in Group 1 and 19 cases in

Table 3: Comparison of Maternal outcome between the groups

Maternal outcome	Group 1 (n=100)	Group 2 (n=100)	Total	Percentage (%)	*P*
Mode of delivery					0.239
Normal vaginal delivery	66	56	122	61	
Caesarean section	26	35	61	30.5	
Vacuum assisted delivery	8	7	15	7.5	
Forceps	0	2	2	1	
Colour of liquor					0.400
Meconium stained	15	11	26	13	
Clear	85	89	174	87	
Indication for caesarean section					0.006*
Failed induction	12	6	18	9	
Fetal distress	9	9	18	9	
Failure to progress	3	14	17	8.5	
Meconium-stained	1	4	5	2.5	
Face presentation	0	1	1	0.5	
Deep transverse arrest	1	1	2	1	

*Significant *P*

Table 4: Comparison of Neonatal outcome between the groups

Neonatal outcome	Group 1 (n=100)	Group 2 (n=100)	Total	Percentage (%)	*P*
Birth weight (Kg)					0.015*
≤2.4	19	10	29	14.5	
2.5-3.4	77	76	153	76.5	
≥3.5	04	14	18	9	
Apgar score 1 min					0.008*
7-10	91	93	184	92	
≤6	9	7	16	8	
Apgar score 5 min					0.168
7-10	97	94	191	95.5	
≤6	3	6	9	4.5	
Meconium aspiration					0.733
Yes	4	5	9	4.5	
No	96	95	191	95.5	
NICU admission					0.858
Yes	20	19	39	19.5	
No	80	81	161	80.5	

Significant *P*.* NICU=Neonatal intensive care unit

Group 2. The number of NICU admissions due to the meconium aspiration was 4 in Group 1 and 5 in Group 2 [Table 4].

Discussion

The inducing agents, misoprostol and dinoprostone, for cervical ripening and labor induction are available in different formulations, such as gel, tablets, inserts, and pessaries, and which can be administered by various routes such as intravaginal, intracervical, oral, and sublingual.

In our study, majority of pregnant women belonged to the age group of 21-30 years, which were comparable to the study done by Swaran *et al*.[16] Gestational age corresponded from 37 to 42 weeks of gestation, similar to a study done by Sophia *et al*.[17]

In our study, there was shorter IDI in the misoprostol group compared to the dinoprostone group, which was similar to the studies done by Chitrakar,[10] Veena *et al*.,[13] and Girija and Manjunath.[18] Saxena *et al*.'s study showed, that induction to vaginal delivery interval with misoprostol 25 μg was 16.44 ± 7.37 h, and in dinoprostone group (0.5 mg), it was 16.38 ± 7.49 h, whereas in our study, IDI was 14.16 ± 3.62 h and 13.93 ± 5.69 h, respectively.[19] In Radhika and Soundara study, shorter IDI in the dinoprostone group compared to misoprostol group was observed, which was in contrast to our study.[20]

Progression of labor in our study was complete with a single dose of misoprostol 25 μg in 58 cases and 48 cases in dinoprostone 0.5 mg, whereas in a study done by Saxena *et al*., a similar result was obtained for misoprostol group only.[19] In our study, 66 cases had NVD in Group 1 and 56 cases in Group 2. Though there was more number of vaginal deliveries in the misoprostol group compared to the dinoprostone group, it was not statistically significant. Veena *et al*.'s study showed

that NVD in PGE_1 group was significantly higher compared to PGE_2 group (76.8% and 61.1%). The rate of LSCS was lower in PGE_1 compared to PGE_2 (15.8% versus 32.6%) which was similar to our study.[13] Another study done by Leuva *et al*., showed that majority had NVD in both the groups (PGE_1 92% vs. PGE_2 88%).[21]

Failed induction refers to failed attempts at ripening an unfavorable cervix with repeated doses of a drug, leading to delivery by the cesarean section. Yehia *et al*.'s study showed that less number of NVD in dinoprostone group, was due to the failed induction (3.7%), whereas in our study, failed induction was 9%.[22]

In Lamichhane *et al*.'s study, most common indication for LSCS was failed induction (44%) and the second common was fetal distress (29%), whereas in our study, similar indications for LSCS were observed.[14] Yadav and Chandwaskar study showed that fetal distress observed in PGE_2 (16%) was more than PGE_1 (6%),[23] whereas in our study there was no difference between the two groups. Madaan *et al*.'s study showed that dinoprostone group had significant increased rate of the cesarean section due to the fetal distress,[24] whereas in our study, 9 cases in each group had similar rates of fetal distress. The study done by Hatel showed that dinoprostone had a lower cesarean rate, in contrast to our study.[25] In our study, indication for the cesarean section was due to the failed induction, fetal distress, failure to progress, and meconium-stained liquor [Figure 1].

There were fewer requirements for the augmentation of labor with oxytocin in misoprostol group in our study. Similar results were obtained by studies done by Ruchika *et al*.[26] and Kudagi *et al*.[27] In another study done by Saxena *et al*., the lesser requirement of oxytocin for augmentation was seen in misoprostol 50 μg group, compared to 25 μg misoprostol and 0.5 mg dinoprostone group.[19]

In the misoprostol group, it was easier to administer sublingually and reduced the need for repeated vaginal examination. The added advantage of the sublingual route of administration is no restriction on mobility of the pregnant women, with better maternal satisfaction which was similar to the study by Huang *et al*.[28] There has been a higher number of successful vaginal deliveries in tablet formulation compared to gel formulation of misoprostol (65% vs. 48%) in Nadine and Ghada study, whereas in our study, similar results were seen in tablet formulation of misoprostol (66%).[29]

In this study, there was no significant difference between the groups for NICU admission, whereas a study done by Radhika and Soundara showed an increase in NICU admission rates in misoprostol group (6%) compared to dinoprostone group (4.6%).[20] Indications for NICU admission in our study were due to the birth asphyxia (8%), meconium-stained liquor (2%), low birth weight (2.5%), meconium aspiration syndrome (3%), weak cry for observation (2.5%), and instrumental delivery (2%).

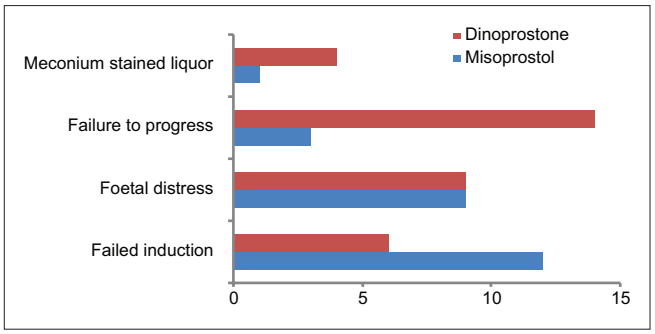

Figure 1: Indications for cesarean section between the groups

In our study, there was no statistical significance for meconium-stained liquor between the groups. In Group 1, cases with thin meconium-stained liquor, progressed to NVD and fewer NICU admissions compared to Group 2, with thick meconium-stained liquor requiring both LSCS and NICU admissions. A study done by Lamichhane *et al*. showed, 12.5% meconium-stained liquor among the total cases, which was similar to our study (13%).[14]

The limitations of the study were no blinding was made, as the routes of administration were different for both the prostaglandins and shorter duration of the study.

Further studies are required using different combinations of prostaglandins in a larger study population.

Conclusion

In this study, sublingual misoprostol 25 μg tablets have shown better cervical ripening, shorter IDI and reduction in Stage II process of labor, reducing need for augmentation of labor and increase in the successful vaginal deliveries with lower rate of cesarean section compared to intracervical dinoprostone gel 0.5 mg. Thus, sublingual misoprostol was more efficacious than intracervical dinoprostone. In dinoprostone group, babies having larger weight were delivered easily; Apgar score was better and showed lesser neonatal intensive care admission. The maternal outcome was better in the misoprostol group, whereas the fetal outcome was better in the dinoprostone group.

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Conflicts of interest

There are no conflicts of interest.

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