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To Compare the Effect of Inducing Agents Dinoprostone Sustained Release Vaginal Pessary and Intracervical Gel on Labour and its Fetomaternal Outcome

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Abstract: ***Introduction: The use of dinoprostone is an effective method for cervical ripening and Induction of Labour. It is available as a gel, pessary, or tablet form. The pessary form has recently been introduced as a method for IOL with the advantage of 24 hours sustained release. Aim of study: A prospective randomized study to compare the effect of dinoprostone sustained release vaginal pessary and intracervical gel on labour and its fetomaternal outcome. Materials and Methods: Patients were randomly distributed into two groups, Group A (intravaginalpessary) and Group B (intracervical gel). Patients with successful induction in group A formed group C; and in the group, B formed group D respectively. The safety and efficacy of both agents were analyzed using a t-test and chi-square test of all the groups. Results: A higher rate of successful induction was seen in primigravidas who were induced with pessary as compared to multigravidas who responded better with gel preparation. The numbers of per vaginal examinations were significantly higher in those receiving the gel preparation. A higher level of patient satisfaction was noted in patients receiving the pessary. There was no statistical significance in the number of maternal and fetal adverse events in both groups. Conclusion: Both preparations of dinoprostone; gel and pessary were equally safe and efficacious for IOL.***

Keywords: prostaglandin E2, dinoprostone, IOL: induction of labour.

1. Introduction

Induction of labour is the artificial initiation of uterine contractions before the onset of spontaneous labour that leads to progressive dilatation and effacement of the cervix to achieve a vaginal delivery [1]. In developing countries, up to 25% of all pregnant women undergo induction of labour at term [2]. Induction of labor is carried out for various fetal and maternal conditions including post term pregnancy, maternal hypertension, gestational diabetes, oligohydramnios, and pre labour rupture of membranes, infections, chronic maternal conditions, bleeding, fetal growth restriction, and other conditions.

Various methods for induction of labour include traditional, mechanical, pharmacological, and surgical methods. Pharmacological methods include oxytocin and synthetic prostaglandins (PGE1 and PGE2). They promote a number of biochemical and biophysical changes that mimic the physiological sequence of cervical effacement and dilatation followed by uterine contractions that occurs during labour [3].

Aims & Objectives

To compare the effect of inducing agents dinoprostone sustained release vaginal pessary with intracervical gel on labour and its fetomaternal outcome.

2. Material and Methods

This is a prospective randomized study conducted in the Department of Obstetrics and Gynaecology, Dayanand Medical College and Hospital over a period of one year between1st January 2019 and 31st December2019.

Inclusion Criteria:

The study population consisted of both Booked/Un-Booked; primigravidas and multigravidas antenatal cases of gestation 37 weeks or more, with a singleton pregnancy, vertex presentation, with Bishops score <6.

Exclusion Criteria:

1) Subjects with multiple pregnancies
2) Gestational age less than 37 weeks
3) Fetal presentation other than vertex
4) scarred uterus (myomectomy, cesareansection)
5) Fetal distress
6) Patients with any contraindication to vaginal delivery or contraindication for labour induction by prostaglandin or oxytocin
7) Active vaginal bleeding

3. Method

A total of 100 patients were enrolled in the study after informed consent and approval from the ethical committee. A Detailed history, systemic and obstetric examination were done. Under all aseptic precautions per vaginal examination was done and the modified bishops score for each patient was calculated. Routine investigations were done. Patients with Modified bishops score less than 6 were selected for induction and those who fulfilled the inclusion and exclusion criteria were divided into two groups (group A and B). The patients were randomly distributed between the groups. Informed consent for induction of labor was taken. Non stress test was done before induction.

Group A: Patients in this group received a single dose of 10 mg slow release dinoprostone vaginal insert placed transversely in the posterior fornix of the vagina. After 24

hours, the modified bishops score was calculated, and the intravaginal insert was removed. It was removed earlier if the patient developed good intensity uterine contractions (5 contractions or less in 10 minutes averaged over a 30 minute window). Induction was considered successful if the MBS > 6 after 24 hours of its insertion.

Group B: Patients in this group received an instant release gel preparation containing 0.5 mg of dinoprostone, placed intra cervically. The patients were assessed every 6 hours, and a maximum of three doses was given, If a Bishops score was less than 6. Induction was considered successful if MBS > 6 after 24 hours of the start of induction. The patients in whom induction was successful, were further subdivided into two groups. The patients with successful induction in Group A formed Group C. The patients with successful induction in Group B formed Group D.

These patients were assessed for the need for oxytocin. Continuous electronic fetal heart monitoring was done for all patients. A partograph was plotted, the patients were followed till delivery and the maternal and neonatal outcomes were assessed. Adverse events were noted in both groups. In case of adverse events, pessary was removed and adequate measures were taken in patients induced with gel. Various Fetal and maternal parameters were studied.

Statistical Analysis

The data collected in respect of various variables were analyzed by using different statistical techniques which included T-test, Fischer's extract test, Chi-square test Statistical analysis included T-test and Chi-Square Test.

4. Observation and Results

In our study, a total of 100 pregnant patients for induction of labour were taken. Patients were randomly divided into two groups according to the preparation of the drug used. Those who received the intravaginal insert formed study group A, those who received intracervical gel formed group B.
Group A(n) = 56
Group B(n) = 44

Demographic Parameters
In our study the mean age in the group A and B was 28.75 years and
28.77 years respectively. A majority belonged to upper socioeconomic status in both the groups.

Maternal Parameters
The maternal parameters under study for all groups are:
1) Period of gestation at which labour was induced
2) Gravidity
3) Mode of delivery

1) Period of gestation at which labour was induced

Table 1: Distribution of patients according to the period of gestation at which labour was induced

		Drug Used				Total	Chi- square value	p-value
		Group A	Group A	Group B	Group B			
Gestation	37-37+6	19	34%	16	36%	35	0.064	0.8
	38-38+6	17	30%	12	27%	29	0.114	0.736
	39-39+6	11	20%	12	27%	23	0.81	0.368
	> 40	9	16%	4	9%	13	1.062	0.303
Total		56	100%	44	100%	100		

A majority were induced between 37 - 37+6 weeks period of gestation in both the groups. There was no statistically significant difference between the groups. (p-value was more than 0.005 in all groups)

2) Gravidity

Table 2: Distribution of women under study according to gravidity

		DRUG USED				Total	Chi- square value	p-value
		Group A	Group A	Group B	Group B			
GRAVIDA	Primi	48	72%	19	28%	67	20.16	0.001
	Multi	8	24%	25	76%	33		
Total		56	56%	44	44%	100		

In group A, 72% (n=48) women were primigravida and 24% (n=8) women were multigravida. In group B 28% (n=19) were primigravida and 76% (n=25) were multigravida. There was a statistically significant difference between the two groups (p-value was 0.001).

3) Mode of delivery
A majority of patients had vaginal delivery in both groups. The p-value in these groups was not statistically significant (p-value > 0.005).

4.1 Induction of Labour

Induction of labour is characterized under the following parameters

1) Modified bishops score and outcome of induction
a) Patients in group A were assessed for modified bishops score After 24 hours from the start of induction

Table 3: Distribution of patients in group A according to modified bishops score (MBS) and outcome after 24 hours of induction

Group A (n=56)		After 24 Hrs	
MBS	2	0	0%
	3	0	0%
	4	4	7%
	5	4	7%
	≥6	38	68%

After 24 hours, none of the patients in group A had an MBS of 3 or less; 7% (n=4) had an MBS of 4; 7% (n=4) patients had an MBS of 5; 68% (n=38) patients had an MBS of 6 or more. This indicates that patients with MBS 6 or more 68% (n=38). Out of the remaining patients 7% (n=4) patients underwent vaginal delivery and 11% (n=6) patients had a caesarean section. None of the patients underwent an instrumental delivery.

b) Patients in group B were assessed according to modified bishops score and outcome After eighteen hours from the start of induction

Table 4: Distribution of patients in Group B according to modified bishop's score and outcome after 18 hours from the start of induction

After Eighteen Hours	Group B	
MBS	n= 22	%
4	2	9%
5	8	36%
6	3	14%
Total	22	100%

A total of 22 patients were evaluated after 18 hours from the start of induction and were given a third dose of intracervical gel. Out of these, 9% (n=2) patients had an MBS of 4, 36% (n=8) patients had an MBS of 5, and 14% (n=3) patients had an MBS of 6 or more. Out of the remaining patients, 9% (n=2) patients underwent instrumental vaginal delivery; 27% (n=9) patients underwent non instrumental vaginal delivery and 5% (n=1) patients underwent a caesarean section.

2) Successful Induction

A total of 71 patients had successful induction the p-value is 0.320 which is not statistically significant. The patients with successful induction (n=71) were further divided into 2 groups; group C and group D. Forty-two patients in group A and 29 patients in group B who had successful induction formed group C and group D respectively.

3) Distribution of patients with successful induction according to gravidity

In group C, 81% (n=34) of women with successful induction were primigravida as compared to 19% (n=8) women in group D. 28 % (n=8) women in group C were multigravida as compared to 72% (21) women in group D. The p-value was 0.001 which was statistically significant.

Time taken between instillation of the drug to delivery

In Group A, the average time interval between instillation of drug and delivery was 17.87 hours and in Group B, the average time taken between instillation of drug and delivery was 16.16 hours. The p-value was 0.215, there was no statistically significant difference between the two groups.

4) Adverse events

a) Comparison of adverse events in group A and group B

The p-value was more than 0.005 indicating no statistical significance between groups. The majority of patients had MSL in group A and PPH in group B.

b) Comparison of adverse events between the two group C and group D

None of the patients reported spontaneous expulsion of pessary in group C. The p-value of all groups was more than 0.005 which was not statistically significant.

5) Number of per vaginal examinations

a) Number of per vaginal examinations between group A and group B

In group A, the average number of per vaginal examinations was 5.57 as compared to group B in which the number of per vaginal examination was 8.89. The p-value was 0.000 indicating a statistically significant difference between the two groups.

b) Number of per vaginal examinations between group C and group D

In group C, the average number of per vaginal examinations was 6.02 as compared to group D in which the number of per vaginal examinations was 8.14. The p-value was 0.000 indicating a statistically significant difference between the two groups.

6) Patient satisfaction score

a) Distribution of the patient according to patient satisfaction in group A and group B

This was a subjective assessment. In group A, the mean satisfaction was 8.14 as compared to group B where it was 7.25. The p-value was 0.000 which was statistically significant.

b) Distribution of the patient according to patient satisfaction in group C and group D

In group C, the mean satisfaction was 8.07 as compared to group D where it was 7.28. The p-value was 0.003 which was statistically significant.

7) Fetal Parameters

The fetal parameters under study are

1) Live birth
2) Fetal sex
3) Fetal birth weight
4) Agar Score
5) Admission to NICU
6) Indication of admission to NICU

Apgar score

Distribution of babies according to the mean Apgar score at 1 minute and 5 minute in group A and group B

The mean Apgar score at 5 minutes in group A was 8.93 +_0.26 and in Group B the mean Apgar score at 5 minutes was 8.93+_0.25. It was not of statistical significance (p value=0.950).

Distribution of babies according to the mean Apgar score at 1 minute and 5 minute in group A and group B
The mean Apgar score at 5 minutes in group C was 8.90 +_0.30 and in Group D the mean Apgar score at 5 minutes was 8.90+_0.31. It was not of statistical significance (p value=0.911).

Admission to NICU

Comparison of admission in NICU in group A and group B
The difference between the two groups was not statistically significant. (p value=0.106) The majority of the patients did not require NICU admission.

Comparison of admission NICU in group C and group D:
In group C, 17% (n=7) patients were admitted to NICU as compared to group D, in which 7% (n=2) patients were admitted in NICU. The p-value was 0.224 which was not statistically significant.

5. Discussion

Labour can be induced for various fetomaternal indications when the benefits of induction outweigh its risks. The different preparations of prostaglandins for induction of labour: gel, pessary, and tablet form are available. The intracervical gel form has been in use for many years, but it requires repeated vaginal examinations and repeated dosing. The dinoprostonepessary has been introduced as a better delivery system with the advantage of a 24 hour sustained release and rapid removal of the pessary when needed. This study has been conducted to compare the effect of both the agents on labour and its fetomaternal outcome.

Maternal Parameters
In our study, all the patients enrolled were beyond 37 weeks of gestation. In group A, the majority of 30%patients were induced at 38-38+6 weeks as compared to group B, in which the majority of patients,36%were induced at 37-37+6 weeks of gestation. In group C, 33% patients and 41% patients in group D in the gestation 37 to 37+6 weeks had successful induction. The gestational age for induction was similar between the groups.

In a study was conducted by Garg et al in 2018, they found that there was no statistically significant difference between the two groups in parity, gestational age, and indications for induction of labour and also in induction to the delivery interval [4]. This was comparable to our study.

Bassety et al, in June 2017 found that gestational age >41 weeks was associated with increased rates of failed induction [5]. However, he documented that there isa fewer number of studies comparing the effect of gestational age with the success of induction of labour. This is because induction of labour depends on many other factors interacting during labour that are not necessarily related to the induction process.

Multiparity is a known factor to predict successful induction. Cervical dilation rates are faster in multiparous as compared to nulliparous women. In our study in groups A and C, the majority of the patients were primigravida (72% versus 81%); in groups B and D, the majority of patients were multigravida (76% versus 72%). The p-value was 0.001, indicating a significant difference between the two groups. This can be explained by the fact that there was a random distribution of patients between the groups.

Out of the two groups, a higher rate of successful induction was seen in primigravida who was induced with pessary as compared to multigravidas who responded better with gel preparation. However, as the sample size of our study is small, the effect of parity on the success of induction of labour could not be determined.

Juhasova et al conducted a study in 2018 found that cervical dilation was faster in multiparous as compared with nulliparous women (p-value < 0.001) [6].

In contrast to the above studies, Garg et al, in 2018 found that there was an insignificant difference in terms of parity between the two groups (p-value = 0.229) [4].

In our study, out of a total 100 patients, 52% (n=29) patients in group A, 61% (n=27) patients in group B, 69 % (n=29) patients in group C and 83% (n=24) patients in group D had vaginal delivery. There was no statistically significant difference between the groups in the mode of delivery. In the study by Garg et al, in 2018 the difference in cesarean section rate among nulliparous and multiparous patients using vaginal pessary or intracervical gel was not statistically significant (p-value being 0.229) [4]. Kumari et al, in 2018 did a comparative study, there was a significant difference in the number of women requiring instrumental delivery, with those receiving gel more likely to need assisted vaginal delivery (RR 3.0, 95% CI 1.1–8.4, P = 0.04) [7].

Successful induction is defined by a Modified Bishop's score > 6. In our study, successful induction was considered by an MBS > 6. Out of a total of 100 patients in our study, 71 of them had successful induction. 75% patients in group A and 66% patients in group B had successful induction. This difference was not statistically significant (p-value 0.320). This suggests that both the pessary and gel forms did not differ in the rates of achieving successful induction.

Triglia et al, observed that successful induction was considered if active labour was established within 48 hours from the administration of the drug. Active labour was taken as at least four regular uterine contractions during 10 minutes, and the cervix was effaced and 3 cm dilated. The spontaneous vaginal delivery rate was 75% in the insert group and 50% in the gel group. [8]. They demonstrated that in women with a Bishop score < 4, a protocol of induction of labour with a vaginal dinoprostonepessary applied for 24 hours achieves a significantly higher rate of spontaneous vaginal delivery. This observation was in contrast to our study.

ACOG in 2009 defines good intensity contractions as five contractions or less in 10 minutes, averaged over a 30-minute window [9]. In our study, the average time interval

between induction of labour and onset of good contractions has been studied. It averaged about 12.07 hours in group A, as compared to 12.28 hours in group B. The average time interval between the start of induction and time of delivery was also evaluated. It averaged about 17.87 hours in group A, and 16.16 hours in group B. Both time intervals were comparable between the two groups. In our study, none of the preparations resulted in quicker delivery than the other.

Studies conducted by Garg et al in 2018, and Kalkat et al in 2008 had results that were comparable to our study [10, 4]. In contrast, our study, in a study by Kumari et al in 2018, the meantime to delivery for all women showed a statistically significant difference, with women receiving gel preparation delivering earlier on an average than those receiving the pessary preparation (21.1 versus 29.6 hours p = 0.018) [7]. This difference was seen irrespective of the mode of delivery.

The safety outcome of both the preparations of prostaglandins was assessed as the development of adverse events such as uterine hyperstimulation, postpartum hemorrhage, retained placenta, meconium-stained liquor, fetal distress, and uterine rupture. This shows that both the preparations were safe for use for induction of labour.

ACOG, 2009 defines uterine hyperstimulation (tachysystole) as more than five contractions in ten minutes, in a 30-minute window [9]. This is a known side effect of prostaglandin preparations used for induction of labour. In our study, none of the patients had uterine hyperstimulation. The incidence of adverse events such as meconium-stained liquor, postpartum hemorrhage, fetal distress, and retained placenta in our study were comparable between the two groups. There were no cases of uterine rupture. This shows that both the preparations were safe for use. Comparable to our study, Garg et al in 2018 observed no difference in the number of patients with adverse effects in the gel and pessary groups (p-value 00.866) [4]. None of the patients in our study reported spontaneous expulsion of the pessary. In contrast to our study, Facchinetti et al stated that the risk of hyperstimulation was statistically higher in nulliparous women using vaginal insert than the other ways of administration with RR = 2.17, 95% CI =1.08,4.33. [11]. Kho et al in 2008, documented that hyperstimulation (14 (2.9%) vs 2 (0.4%), RR 6.5 (1.5–28.9)) was more common in women who received the pessary versus gel. In the above studies, the use of pessary preparation was associated with a higher incidence of uterine hyper stimulation [12].

In our study, It was observed that the average number of per vaginal examinations were 5.57 in group A as compared to 8.89 in group B (p-value = 0.000); 6.02 in group C as compared to 8.14 in group D (p-value was 0.000). A statistically significant difference was noted between the groups with patients receiving the gel preparation requiring a higher number of per vaginal examinations as compared to pessary. This can be attributed to the 24 hours sustained release formulation of pessary as compared to repeated dosing of the gel form, necessitating the need for a vaginal examination.

Devdatt. L. Pitale in 2017 assessed the effectiveness of dinoprostone vaginal pessary in the induction of labour at term. He found that dinoprostone vaginal pessary was a highly effective method for induction of labour at term. It reduced consistently the number of internal examinations, reducing the risk of ascending infections and maternal anxiety during induction of labour [13]. This was comparable to our study.

In our study, patient satisfaction was subjectively assessed on a scale of 0 to 10, with 0 being the least level of satisfaction and 10 being the highest. The average score of patients in group A was 8.14 as compared to group B where it was 7.25 (p-value was 0.000); 8.07 in group C as compared to 7.28 in group D. (p-value was 0.003). This indicates a statistically significant difference between the groups, suggesting a higher level of patient satisfaction with the pessary form. This can be attributed to the fact that the use of pessary requires fewer vaginal examinations making it more comfortable and convenient for the patient. However, to the best of my knowledge, no studies are comparing prostaglandin preparations with the level of patient satisfaction.

Fetal Parameters

In our study, all women had live births, the mean fetal birth weight in group A was 3043.57 grams and group B was 2943.86 grams respectively. There was statistically no significant difference between the groups. The Apgar scores at 1 minute and 5 minutes were noted .84% (n=47) of neonates in group A had Apgar scores of more than 8 at one minute, 93% (n=52) had Apgar scores of 9 at 5 minutes. In group B, 93% (n=41) neonates had an Apgar score of 8 at 1 minute, and 93% (n=41) neonates had an Apgar score of 9 at 5 minutes. In groups C and D the Apgar scores were similar. Our study did not find any differences between the groups in terms of Apgar scores at 1 minute and 5 minutes.

This indicates that both the agents are safe for the fetus.

Comparable to our study, Triglia et al in 2010 conducted a study to compare 24-hour controlled-release vaginal dinoprostonepessary versus gel for induction of labour. They found that no cases of 5-minute Apgar scores <7 were present in either of the groups, indicating both methods to be safe for induction of labour [8]. Gulmezoglu et al in 2014 conducted a study on the induction of labour for improving birth outcomes for women at or beyond term. They observed that labour induction was associated with lesser perinatal deaths (risk ratio (RR) 0.31, 95% confidence interval (CI) 0.12 to 0.88). There was no significant difference between the rates of Apgar scores less than seven at five minutes (RR 0.72, 95% CI 0.44 to 1.18) [14]. These findings were similar to our study. This indicates that both formulations of the drug resulted in a good perinatal outcome indicating that both formulations are safe and effective inducing agents.

In our study, 16% (n=9) versus 5% (n=2) patients in groups A and B required NICU admission, whereas in groups C and D, 17% (n=7) and 7% (n=2) patients required it. There was no statistically significant difference in the number of NICU admissions in both groups. Various indications of admissions into NICU were assessed, such as perinatal

asphyxia, meconium aspiration, transient tachypnea, and others. They did not have a significant effect on induction. The results were comparable between the groups. In our study, none of the groups showed an increased rate of perinatal complications indicating that both formulations are safe-inducing agents.

Kandemir et al, in 2015 found that the number of admissions to NICU were similar in the multiparous and nulliparous groups receiving dinoprostone [15]. Cochrane review (2018) has shown that timely induction of labour lowers the rates of neonatal intensive care unit (NICU) admission, (RR 0.88, 95% CI 0.77 to 1.01) with fewer babies having Apgar scores less than seven at five minutes in the induction groups compared with expectant management (RR 0.70, 95% CI 0.50 to 0.98) [14]. This is comparable to our study where timely induction was planned for all the patients and the majority of the babies had good Apgar scores at birth.

6. Conclusion

We conclude that both the intravaginalpessary and intracervical gel are equally safe and efficacious for their use for induction of labour. The pessary form offers an advantage of a lesser number of vaginal examinations, thus reducing maternal anxiety and reducing the risk of ascending infections. It appears to be more comfortable for the patients. However, more studies are needed to evaluate the cost-effectiveness of the two preparations.

7. Limitations

There are many limitations to our study, the sample size is small. There is no blinding amongst the two drug preparations offered for induction of labour. The cost-effectiveness of the two preparations needs to be studied.

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