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Original Research Article

A comparative study between dinoprostone pessary and dinoprostone gel for induction of labor and neonatal outcome

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ABSTRACT

Aims and Objectives: This study compares the safety and efficacy of two dinoprostone formulations – a pessary and a gel.

Materials and Methods: A retrospective randomised observational study was conducted to compare Dinoprostone controlled release pessary and Dinoprostone gel for induction of labor at term in women with unfavourable cervix at Apollo Hospitals BGS, Mysuru during August 2018 – May 2020. Among study participants 50 expectant mothers received Dinoprostone pessary while 50 women received Dinoprostone gel for induction of labour. Both groups were compared and the outcomes were analysed. The primary outcomes of the study were induction to delivery interval, successful vaginal delivery, need for operative vaginal delivery and need for caesarean section. Secondary outcomes were observed for neonatal morbidity and uterine hyperstimulation.

Results: There was a significant (p=<0.001) improvement in Bishop scores after induction in both groups. When only the post-induction scores for the two formulations were compared, the pessary helped to improve the bishops score (or helps in cervical ripening) better than the gel formulation and therefore can help to improve the chances of vaginal delivery(because there is a significant change in post induction bishop score in pessary group). The mean interval from induction to delivery for the pessary group was 11.03±4.648 hours and for the gel it was 21.18±9.127 hours with a significant p value <0.005The pessary showed a significant improvement in the post-induction Bishop score and a shorter induction to delivery time compared to the gel. Differences in the mode of delivery were not significant. Fortunately, no serious side effects to the mother or fetus were observed with both products.

Conclusion: Both formulations of dinoprostone are safe for induction of labor at term. However, pessary achieves comparitively a higher rate of spontaneous vaginal delivery with a shorter labor induction time. Ease of administration, single application and thus decreased chance of infections are its additional benefits.

1. Introduction

Induction of labor is one of the most frequently performed obstetric procedures in delivery rooms around the globe. The rate of labor induction currently has an increasing trend (approx. 30% incidence). Induction of labor is indicated when outcomes for the fetus, mother, or both are better than expectant management, i.e., waiting for spontaneous onset of labor.[1]

Prostaglandins, a group of cyclic fatty acid compounds, are used since decades as agents for cervical ripening and labor induction.[2] Among the various prostaglandins used in obstetrics, Dinoprostone is the standard of care for cervical ripening in term pregnancies.[3] Various Dinoprostone preparations such as tablets, gel and pessary appeared to be equally effective.

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Dinoprostone vaginal pessary is a controlled -release hydrophilic matrix that provides sustained release of dinoprostone and was brought to light in 1995 by Ferring pharmaceuticals under the brand name PROPESS. It contains 10 mg of dinoprostone and has a sustained controlled release (0.3 mg/h) characteristic of a single application.[4] The need for repeated doses and thus the number of vaginal examinations is less when using a pessary due to its gradual release properties.[5] The pessary's knitted polyester pull-out system allows quick and easy removal when uterine tachysystole or non-reassuring FHR occurs. Slow and controlled release of the drug over 24 hours, less intervention, easy administration and removal, these are its other advantages over other dinoprostone formulations.[6]

Dinoprostone gel (CERVIPRIME) that is available as a semi-translucent viscous preparation, was used in the study. Both intravaginal and intracervical applications have been found to be safe and equally effective.[7] A pre-packaged 2.5 mL single-use syringe containing 0.5 mg dinoprostone gel is available to be used at an interval of every 6 hours for a maximum of 3 doses. Augmentation of labour by amniotomy or oxytocin can be done based on uterine contractions

This study was designed to compare the safety and efficacy of two controlled-release pessary (PROPESS) vs gel (CERVIPRIME) Dinoprostone formulations.

2. Materials and Methods

This study population consisted of 100 antenatal women admitted to the maternity ward at Apollo BGS Mysuru Hospitals during the study period from August 2018 to May 2020.

Ethical clearance was taken from Institutional Ethical Committee for the study. Informed written consent was taken from all participants and all the personal details of the patients were kept confidential.

2.1. Inclusion criteria

1. Gestational age of 37 weeks or more
2. Singleton pregnancy
3. Cephalic presentation
4. Age 18-40 years
5. Primigravida or multigravida
6. Adequate pelvis
7. Reactive non stress test
8. Unfavourable cervix

2.2. Exclusion criteria

1. Suspected cephalopelvic disproportion
2. Previous uterine surgery
3. Allergy to prostaglandins.
4. Malpresentations
5. Spontaneous labor onset
6. Unsatisfactory fetal condition.
7. Unexplained antenatal bleeding

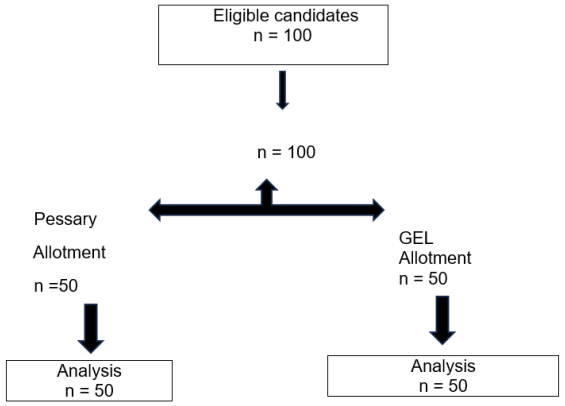

Figure 1: Coordinate diagram

As per the inclusion criteria, those patients who required pre-induction cervical ripening and induction of labour and received either of the two dinoprostone formulations that is pessary or gel were included in the study. Informed consent for induction and delivery was obtained as routine, after explaining the method to all recruited women in the delivery room. Entry CTG performed in both groups for fetal health.

Women in the pessary group were those who had received 10 mg PGE2 pessary (PROPESS), placed in the posterior fornix of the vagina. The pessary was removed as soon as adequate uterine contractions occurred, i.e., 4 contractions in 10 minutes, each lasting 40-50 seconds, or 24 hours after insertion.

The gel group had received PGE2 gel (CERVIPRIME) according to the institution's established protocol. 2 mg of gel intravaginally at 6-hour intervals for a maximum of 3 doses based on Bishop's score or until adequate uterine contractions have occurred.

In both groups, labor was augmented with oxytocin, when uterine contractions were not sufficient even after 24 hours. Fetal heart rate was monitored every 2 hours in both groups during the latent phase of labor.

Information regarding baseline parameters such as age and gestation period, indications for induction of labor were documented. The following details were noted using a pre-designed proforma.

1. Improvement in Bishop score over 24 hours
2. Interval between induction and delivery
3. Delivery method
4. The need for oxytocin for augmentation
5. Possible adverse consequences for the mother and the newborn.

The primary outcome measures were the safety and efficacy of the dosage forms.

Maternal and neonatal outcomes were the secondary outcomes studied. Maternal outcomes included any maternal health complications during delivery. Newborns were assessed using the APGAR score at birth.

The safety of the drug formulations was evaluated according to the occurrence of uterine hyperstimulation or neonatal morbidity.

The efficacy of drug formulations was evaluated from induction to delivery interval and successful vaginal birth with reduced oxytocin requirement and reduced operative interference.

At the end of study duration the data was collected and statistical analysis was performed using MS Excel and SPSS 16.0. Qualitative variables were compared using Chi-squared test/Fisher's exact test, with significant value taken as p <0.05.

3. Results

The results were comparable in terms of maternal age, parity, gestational age at induction, Bishop score at the time of induction in both pessary and gel groups.

IOL indications such as postdated pregnancy, medical comorbidities such as PE, GDM, FGR were also equally distributed in both groups.

Table 1: Breakdown of the age groups

Age in years	Pessary		Gel	
	Frequency	Percent	Frequency	Percent
20-25	1	2.0	2	4.0
25-30	36	72.0	46	92.0
>30	13	26.0	2	4.0
Total	50	100.0	50	100.0

Women were evaluated improvements in post-induction Bishop score, interval between induction and delivery, need for oxytocin augmentation, vaginal birth versus caesarean section and neonatal outcome were observed and compared between the two formulations. Adverse effects such as uterine hyperstimulation, fetal heart rate variability were carefully observed.

There was a significant (p=<0.001) improvement in Bishop scores after induction in both groups. The mean initial cervical bishop scores were 3.72±1.195 among pessary and 3.920±0.965 among gel group respectively, which increased to 10.18±2.4 and 5.94±1.51 among pessary and the gel groups, with significant (p=<0.001) improvement of bishop scores post induction in both the groups.When only the post-induction scores for the two formulations were compared, a lower Bishop score was noted in the majority of patients using the gel and the bishops score showed increased values in the majority of patients with the pessary, indicating that the pessary helped to improve the bishops score (or helps in cervical ripening) in comparison to the gel formulation and therefore can help to improve the chances of vaginal delivery.

The mean interval from induction to delivery for the pessary group was 11.03±4.648 hours and for the gel it was 21.18±9.127 hours with a significant p value <0.005. The induction interval to labor is significantly shorter in the pessary group compared to the gel, 72% of people gave birth within 12 hours and only 16% in the gel group. 26% and 52% of patients delivered between 12 and 24 hours in the pessary and gel group, respectively, and thus almost 98% in the pessary group delivered within 24 hours.

Table 2: Induction to delivery interval

Duration In hours	Pessary		Gel	
	Number of patients delivered	Percent	Number of patients delivered	Percent
<12	36	72.0	8	16.0
12-24	13	26.0	26	52.0
>24	1	2.0	16	32.0
Total	50	100.0	50	100.0

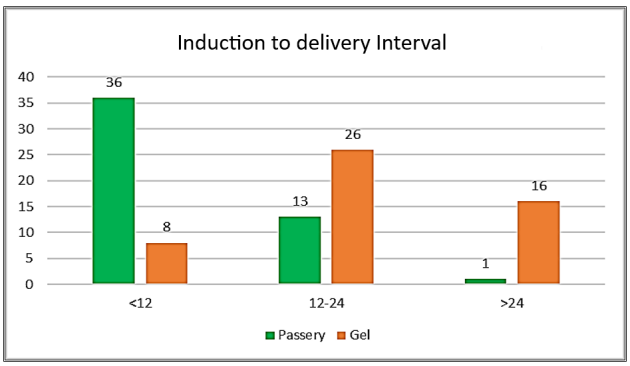

Figure 2: Graphs showing the interval between administration of inducing agent and delivery

In this study, more than 50% of patients required augmentation by oxytocin during labour in the gel group and 22% in the pessary group. Oxytocin was initiated at a minimum of 6 hours after instilling gel and 6 hours after pessary removal, depending on the Bishop score and fetal health assessed by CTG.

The incidence of vaginal delivery was 76% in the pessary group and 58% in the gel group. No significance, p=0.056, was observed in mode of delivery between the two groups.

No cases of uterine hyperstimulation or changes in fetal heart rate were observed in this study. None of the women complained of nausea and vomiting, fever, diarrhoea or any other side effect of the medications during the study. There was no incidence of postpartum haemorrhage in this study. No serious fetal complications were noted in either group during the study, with no low APGAR scores among both the comparison groups. No significant observation made in the colour of liquor(clear versus meconium stained)

between two group(p=0.461).

Disadvantages of dinoprostone gel are that when used intracervical in repeated doses, it causes discomfort to the patient, and also in case of hyperstimulation, the application cannot be reversed. However, the pessary formulation is a disposable, safe, controlled and gradual release, patient-friendly system that can be easily obtained at any time during labor, with a significant improvement in the Bishop score, shortening the induction to delivery interval, and thus may help in the higher chances of a vaginal birth.

4. Discussion

The aim behind labor induction is to end up with a successful vaginal birth by exciting uterine contractions before the spontaneous labor pains begin. The benefit of labor induction must be evaluated against the potential risks to the mother and fetus associated with the procedure as well as the risks of continuing the pregnancy.[8]

Prostaglandins have been used to induce labor since last 60 years, and Dinoprostone is the most common prostaglandin used to induce labor worldwide. PGE2 is thought to increase the chance of a vaginal birth within 24 hours. PGE2 tablets, gel, pessaries appear to be equally safe and effective with little difference between formulations.[5]

In our study both the formulations showed a significant improvement in Bishops score. However, post induction Bishop score was higher for the pessary group. A retrospective study showed an 81.5% success rate of labor induction by pessary in multigravida and 74.5% in nulliparous[9] and it is a safe and effective choice for labor induction. A published literature comparing the PGE2 controlled-release pessary versus placebo showed overall treatment success in terms of a higher rate of cervical ripening and onset of labor in the PGE2 pessary group.[10] A similar supporting evidence stated that cervical ripening within 24 h was achieved in the Propess (pessary) group in 80% as compared to 56% in the gel group.[11] Another study showed that the Dinoprostone vaginal pessary is a highly effective method of inducing labor at term. Its single application reduces the risk of ascending infections (as the need for per vaginal digital examinations are less). This not only adds to its safety but also reduces the anxiety of vaginal examination and labour induction among the expectant mothers.[12]

Regarding the fact that Dinoprostone pessary significantly reduces the induction to delivery interval compared to other prostaglandin formulations has been supported by several evidences.[13,14] One similar prospective comparative study showed (Mean IDI was 19.57 ± 5.46 (range, 10.60–32.40 hours) in gel group and 17.72 ± 6.81 (range, 9.4–42.5 hours) in pessary group.[13] This was of statistical significance with p = 0.043). Our study also showed a similar result (mean interval from induction to delivery for the pessary group being 11.03±4.648 hours and for the gel 21.18±9.127 hours with a significant p value <0.005). A retrospective analysis by Vollebregt A, Van't Hof DB et al. showed that the application-delivery interval was less for the pessary than gel. (29.8±22.0 h versus 62.0±78.8 h, P=0.039). In the Propess - pessary group 62% delivered within 24 h compared to 28% in the gel group.[11]

This study showed no significant difference in the mode of delivery between two groups. - The incidence of vaginal delivery was 76% in the pessary group and 58% in the gel group. This is similar to the success rate in other available similar studies (68% versus 64%).[13] However, a randomised controlled clinical trial involving 100 pregnant women at term with an indication for induction of labour conducted in UK revealed that there was no statistically significant difference in time to onset of labour, duration of labour, total time from induction to delivery, method of delivery, and analgesia requirements among these two formulations.[7]

A per a study reviewed, the need for labor augmentation with oxytocin was significantly low, and a low rate of LSCS was observed when the pessary was used.[6] Need for oxytocin was more for the gel group compared to the pessary group in our study.

A study in 2004, compared gel and pessary. This study gave the following results. The success of induction was comparable in the 2 groups: Propess pessary 67%, gel(Prepidil) 65%. The times needed to induce labour were on average longer with Propess (16 h 59 min) than with Prepidil (12 h 54 min), (p<0.05); nevertheless, the time needed to achieve delivery by the vaginal route within 24 hours was comparable (49% vs 48%). The number of patients requiring more than one application of prostaglandin was less in the Propess group (5.9%) than in the Prepidil group (55.8%) (p<0.001). Resort to caesarean section for fetal indication (cardiotocographic changes) was greater in inductions with Prepidil (8 cases) compared to Propess (2 cases), p<0. 0527. Also, Kho EM et al. in a retrospective cohort study involving 969 women in 2008, concluded that the use of a PGE2 pessary did not show a higher benefit compared to gel in terms of shorter labor time or any other labor outcome. In addition, there was significant hyperstimulation occurred clinically and more frequently after pessary use than gel.[15] To know if the slow release pessary a better induction agent than gel a comparative study done showed that more than one dose of prostaglandin was required to achieve amniotomy more often in the pessary group (53%) compared with the gel group (34%) (p =0·03). Propess was unable to demonstrate any advantage over gel in this study. Also, pessary was not cost-effective in this study.[16]

Although few studies demonstrate significant hyperstimulation with the dinoprostone vaginal pessary usage,[17,18] our study did not show such finding.

Multiple applications and vaginal examination are limitations of the gel compared to the pessary formulation. However, the gel is more affordable.

The limitation of our study was the small sample size for comparison of both preparations of PGE2. Future larger randomized controlled trials are necessary to justify these findings.

5. Conclusion

Induction of labour is routinely performed in most of the delivery rooms. Therefore, a good ripening and induction agent that is safe and effective is essential. This study may reflect the safety and efficacy of the two dinoprostone formulations - pessary and gel. Both formulations of Dinoprostone that are studied are safe for induction of labour at term. Although the gel is slightly more cost-effective, pessary has shown to achieve a higher rate of spontaneous vaginal delivery with a shorter labour induction time. Pessary also has added benefits such as easy administration and removal in case of hyperstimulation, single application thus decreasing chances of infections.

6. Ethical Approval

Institutional Ethics Committee(IEC) approval taken and the same enclosed.

7. List of Abbreviations

IOL: Induction of Labor; GDM: Gestational Diabetes Mellitus; PE: Pre-Eclampsia; PGE2: Prostaglandin E2; FGR: Fetal Growth Restriction; LSCS: Lower segment caesarean section.

8. Source of Funding

None.

9. Conflicts of Interest

None declared.

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