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A randomized prospective comparative study to evaluate the efficacy of prostaglandin E2 (Dinoprostone) controlled release vaginal insert versus sublingual prostaglandin E1(Misoprostol) in induction of labor in term gestation

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ABSTRACT

In modern obstetrics, one of the common challenges is induction of labour (IOL). WHO Global Survey reported that IOL accounted for 9.6% of all deliveries.

Prostaglandins have evolved and frequently used pharmacologic agents for IOL, owing to their dual action of cervical ripening and uterine contraction inducing effect.

Aim: 1. To compare the efficacy and induction to delivery interval (IDI) of PGE2 vaginal insert and Sublingual PGE1 in induction of labor in term pregnant women; 2. To study the maternal and fetal outcome in both groups.

Materials and Methods: This a randomized, prospective, comparative study of 100 term pregnant women for induction of labour. Group 1-(50 women) PGE2-10mg vaginal insert and group 2-(50 women) PE1 Sublingual tablets – maximum 200 mcg in 24 hrs, at Dr LH Hiranandani Hospital, Mumbai, India.

Results: In my study the mean induction to delivery interval in Dinoprostone group was 17.47 hours and 23.44 hours in Misoprostol group. So the mean IDI was shorter in Dinoprostone insert group than Misoprostol group by about 6 hours. There was no significant difference noted in terms of overall incidence of caesarean deliveries among the groups.

Conclusion: Our study concluded that Dinoprostone 10mg vaginal insert was more efficacious than sublingual Misoprostol in reducing induction to delivery interval without maternal and fetal complications. Our study suggests that the Dinoprostone vaginal insert can be used as both inducing as well as augmentating agent in labour. Dinoprostone vaginal insert maybe more effective in reducing the incidence of caesarean sections.

1. Introduction

Induction of labour (IOL) defined as the initiation of labour by artificial means prior to its spontaneous onset at a viable gestational age, with the aim of achieving vaginal delivery in a pregnant woman with intact membranes (WHO 1). A study by the WHO Global Survey reported that IOL accounted for 9.6% of all deliveries.[1]

An ideal inducing agent is one which achieves labour in the shortest possible time, with a low incidence of operative delivery, cost effective, good shelf life, easily stored, does not affect the feto-placental unit, with no increase in maternal or perinatal morbidity.[2–4]

Dinoprostone- PGE2 is currently available as a 10-mg sustained-release vaginal insert that releases dinoprostone at a rate of 0.3 mg/hour for 24 hours. The advantages of dinoprostone insert is that it is easy vaginal application and removed in the event of uterine hyperstimulation. But,

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PGE2 insert is more expensive and needs cold storage. Dinoprostone is administered intravaginally and its half-life is approximately 2.5-5 minutes.[5,6]

Misoprostol is a synthetic prostaglandins (PGE1) analogue; it is rapidly absorbed by gastrointestinal tract. Misoprostol is extensively used because it is effective, inexpensive, available in tablet form, and no need cold storage. It has minimal effect on cardiovascular system and bronchial smooth muscles and so can be safely used in hypertensive and asthmatic patient.

Misoprostol can be administered intravaginally, orally, or sublingually and is used for both cervical ripening and induction of labor. Total systemic bioactivity of vaginal misoprostol is three times greater than that of orally administered misoprostol. The use of sublingual misoprostol also offers high efficacy as it bypasses gastrointestinal and hepatic metabolism and also lowers hyperstimulation of uterus. The peak concentration is achieved about 30 minutes after sublingual and oral administration, whereas following vaginal administration, it takes 75 minutes.[3] It is available as 25mcg, 200mcg and 600 mcg tablet. Although misoprostol currently is approved by the U.S. FDA for the prevention of peptic ulcers, in 2002, they approved a new label on the use of misoprostol during pregnancy for cervical ripening and induction of labor.[4,7]

Very limited knowledge is available on the efficacy of sublingual PGE1 and intravaginal controlled slow release PGE2 insert. Hence, this study was designed to bridge this lacunae comparing effectiveness of sublingual PGE1 with intravaginal PGE2 insert for mean induction to delivery time, maternal and fetal outcome.

2. Aim and Objectives

1. To compare the efficacy of PGE2 vaginal insert and Sublingual PGE1 in induction of labor in term gestation.
2. To study the maternal and fetal outcome in both groups.

3. Review of Literature

S.Campbell Austin, et al[8] 2010**;** Labour induction with intravaginal Misoprostol compared with the Dinoprostone vaginal insert: meta analysis. Total 11studies and 1572 women were enrolled in those trials. In this study, women who received Misoprostol had a higher incidence of vaginal delivery within 12 and 24 hours of prostaglandin application, compared with Dinoprostone. No significant difference in neonatal outcomes was noted between 2 groups. The study concluded that vaginally administered misoprostol was more effective than Dinoprostone vaginal insert for cervical ripening and labour induction and the safety profiles of both drugs were similar.

Wing DA et al[9] 2013 conducted a randomized controlled trail on efficacy and safety of a 200mcg Misoprostol vaginal insert with a 10mg Dinoprostone vaginal insert in 1,358 women. Women receiving the misoprostol insert had a significantly shorter median time to vaginal delivery compared with patients receiving the dinoprostone insert and lower incidence of caesarean deliveries.

Rouzi AA, et al.[10] 2014 compared the efficacy and safety of oral misoprostol- 20mcg /hour for 2 doses with vaginal dinoprostone insert in 160 women with dinoprostone 10 mg vaginal insert. The proportion of women who achieved vaginal delivery within 24 hours was significantly greater for women in the misoprostol group compared with the dinoprostone group.

Wang L, et al[11] 2016, studied efficacy of intravaginal misoprostol compared with the dinoprostone insert for labor induction at term: a meta-analysis. Eight of 436 studies (1669 women) identified met the criteria for meta-analysis There was no difference in the risk of tachysystole, uterine hyperstimulation, vaginal delivery within 24 h, caesarean delivery, NICU admission, between misoprostol and dinoprostone.

Mayer R.B. et al[12] 2016 compared misoprostol vaginal insert with dinoprostone vaginal insert for inducing labor in Austria. This retrospective cohort study evaluated the reduction in time to vaginal delivery and delivery within 24 h, in routine clinical work, in 119 labor inductions using a 200-mg misoprostol vaginal insert in comparison with 124 inductions using a 10-mg dinoprostone insert. Vaginal delivery within 24 h occurred in 77.3% of the misoprostol cohort and 74.2% of the dinoprostone cohort. The groups thus had similar rates of vaginal delivery and foetal outcomes.

4. Materials and Methods

4.1. Study setting

Dr. L H Hiranandani hospital, Mumbai, India.

4.2. Study design

Randomized, prospective, comparative study.

4.3. Time frame

From November 2018 till May 2019.

4.4. Inclusion criteria

1. Singleton gestation with cephalic presentation
2. 37 and more gestational weeks
3. Bishop score< or = 4 at admission
4. Less than or 3 previous viable deliveries

4.5. Exclusion criteria

1. Previous uterine scar.
2. Unexplained vaginal bleeding and Ruptured membranes
3. Contraindications for PGs like as glaucoma or allergic reaction.

4.6. Methodology

100 women were randomly selected with the help of computer generated system and divided into two groups of 50 each.

Group 1: Dinoprostone (PGE2) insert (10mg) was administered intravaginally. The insert was held between the index and middle fingers and is positioned transversely, high in the posterior fornix, using only small amounts of water soluble lubricants to aid insertion. Once correctly inserted, the end of the tape kept extended 2-3 cm from the vagina to facilitate removal by gentle traction on the retrieval cord. Patients were asked to remain recumbent for 20-30minutes to allow the insert to hydrate and swell, but after this period they may be ambulatory.

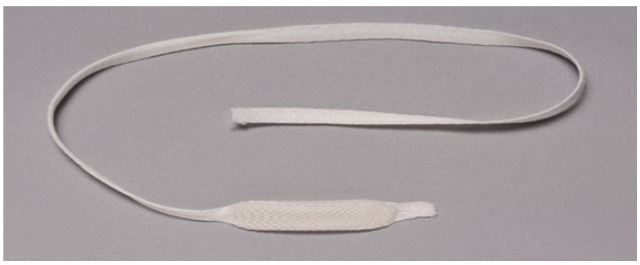

Fig. 1: PGE1- vaginal insert

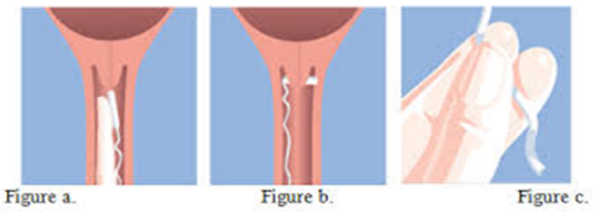

Fig. 2: Technique of insertion of PGE 2 insert **a:** Holding dinoprostone vaginal insert firmly between the index and middle fingers, the vaginal insert is introduced into the vagina and positioned behind the posterior vaginal fornix;**b:** Insert is positioned transversely to ensure it remains in situ;**c:** The retrieval cord should remain visible outside the vagina to permit removal

Group 2: Sublingual tablet Misoprostol(PGE1): Loading dose of 50 mcg PGE2 was given followed by 25mcg every 4hrly till patient goes into active phase of labor. Maximum 200mcg of PGE2 was given.

After admission, detailed physical examination was done for all women and a 20 minutes fetal heart cardiotocography was performed. The vital signs of the patient were monitored at hourly intervals for two hours and then at four hourly intervals thereafter. Uterine contractions and foetal heart rate were recorded every 15 minutes. If there was spontaneous rupture of membranes, the PGE2 insert was removed from the vagina. Patients who had non-progress of labor received intravenous oxytocin augmentation.

4.7. Primary outcomes

Induction to delivery time.

4.8. Secondary outcomes

1. Mode of delivery
2. Need for oxytocin augmentation
3. Foetal and maternal outcome.

4.9. Statistical analysis of the study

Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using unpaired t-test and Chi square test. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2013 and Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA version 21.

5. Results and Observations

The age of women included were <30yrs in group 1were 18 women and group 2 were 13 women. Age group of 30-35yrs in Group 1-27 women and group 2-31 women. Women of age >35yrs in group 1 – 5 and in group 2 were 6 women.

The Mean age of women in Group 1 was 30.80 yrs (SD-3.59) and of Group 2 was 31.70 yrs (SD- 3.41). P value (0.202) - not significant.

The Mean weeks of gestation in Group 1 was 38.82 (SD-0.91) and in Group 2 was 39.58 (SD-0.72). (P value (0 06 - not significant).

The total no of cases of Primigravida in Group 1 were 30 (60%) and multi-para were 20(40%) and in Group 2 primigravida were 33(66%) and multiparous were 17(34%).

The mean (S.D.) Pre-induction Bishop's score in Group 1-PGE2 was 2.38 (1.01) and in Group 2-PGE1 was 1.66 (0.80).

The mean (S.D.) post-induction Bishop's score in Group 1 was 7.12 (2.44) and in Group 2 was 5.44 (1.97). (P value (<0 01) is significant).

In Group 1, 18 (36%) cases needed oxytocin for augmentation while in Group 2, 28 (56%) cases needed

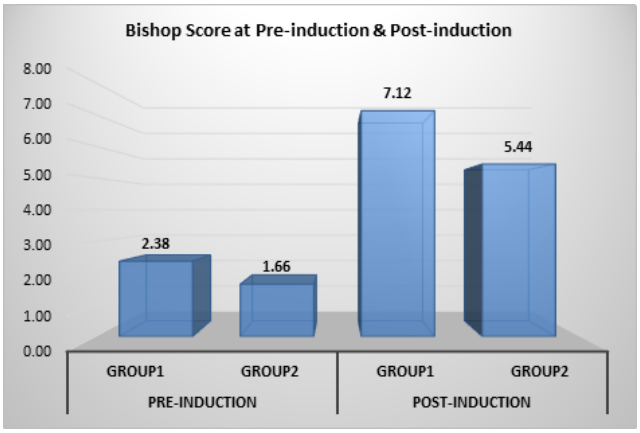

Fig. 3: Pre and post-induction bishop's score

Table 1: Need for oxytocin augmentation

Need for oxytocin	Group 1- PGE2	Group 2 PGE1	Total
Yes	18(36%)	28 (56%)	46
no	32(64%)	22(44%)	54
Total	50	50	100

P value of <0.01 is clinically significant.

oxytocin for augmentation.

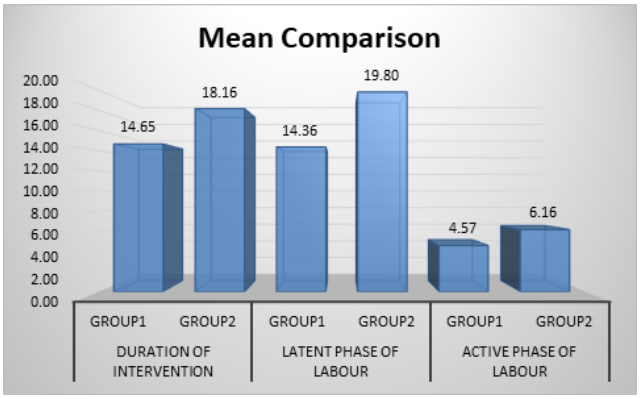

Fig. 4: Comparison of latent and active phase of labour

The mean duration of latent phase in Group 1 was 14.36 hours (7.84) and in Group 2 was 19.80 hours (9.28).

There was significant difference in mean duration of latent phase in both the groups. With the value of <0.01.

The mean (S.D.) duration of active phase for Group 1 was 4.57 (1.90) and in Group 2 was 6.16 (2.62).

There was significant difference in mean duration of active phase in both the groups. With the value of <0.01.

There was significant difference in mean induction to delivery interval in both groups. With P value of <0.01.

The mean (S.D.) induction to delivery interval in group 1 – PGE2 was 17 hours and 47 minutes (6.97) and in group 2 was 23 hours and 44 minutes (8.90).

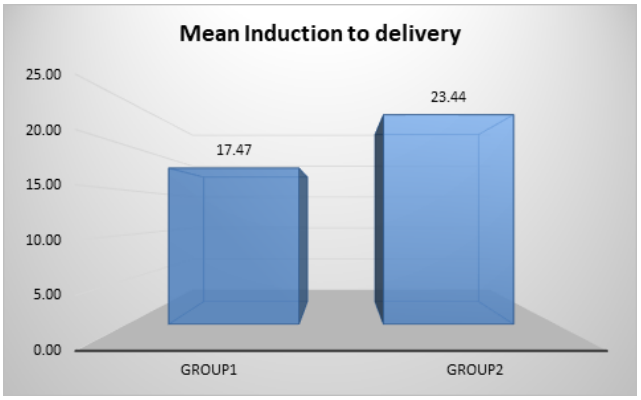

Fig. 5: Comparison of induction to delivery interval

Table 2: Mode of delivery

Mode of Delivery	Group		Total
	Group 1	Group 2	
Vaginal delivery	17	14	31
	34.0%	28.0%	31.0%
Assisted Vaginal delivery- vaccum/ forceps	17	14	31
	34.0%	28.0%	31.0%
LSCS	16	22	38
	32.0%	44.0%	38.0%
Total	50	50	100
	100.0%	100.0%	100.0%

p-value - 0.67- not statistically significant

Table 3: Indications of LSCS

Indications of LSCS	Group	
	Group 1	Group 2
Non Progress with Induction failure	7	10
Fetal Distress	2	1
Cephalo-pelvic disproportion	2	1
Meconium stained liquor	2	10
Opted Out of Induction	2	0
Placental Abruption with Fetal Distress	1	0
Total	16	22

p-value - 0.134- not significant

There was no significant difference in APGAR score at 5 minutes in both groups.

The 5 minute APGAR score was >7 in all the babies.

The mean (S.D.) birth weight in group 1 was3.06kg (0.35) and in group 2 was 3.17kg (0.37). (P value 0.129 –no significant difference

In Group 1, 3(6%) babies needed NICU admission while in Group 2, 8(16%) babies needed NICU admission.

There was no significant difference in need for NICU admission across both groups. (P value 0.199).

6. Discussion

In our study, there was no statistically significant difference in the age distribution and weeks of gestation across the groups. R.B. Mayer in 2016[12] and Wing et al. in 2008[9] showed similar results of age distribution and weeks of gestation across the groups.

In my study, the Bishop's score improved better in Dinoprostone group 1 than in Misoprostol group 2.

Braganza Veena et al.,[13] where they found there was statistically significant change in mean Bishop's score in pre-induction (3.32 vs 3.34) and post induction (8.59 vs 6.77) in both groups. So they concluded that the Bishop's score improved better in Misoprostol group than in Dinoprostone group.

In our study, in Dinoprostone insert group, 18 out of 50 (36%)cases needed oxytocin for augmentation. And in Misoprostol group, 28 out of 50 (56%) cases needed oxytocin for augmentation. So the Dinoprostone group required less oxytocin augmentation than the Misoprostol group.

Mayer et al,[12] found that requirement of oxytocin was almost similar in both PGE1 and PGE2 groups.

In Braganza et al.[13] about 46.3% cases needed oxytocin augmentation in Misoprostol group and 62.1% needed oxytocin augmentation in Dinoprostone group.

In our study, the mean(S.D.) duration of active phase for Misoprostol group was 6.16hours(2.62) while for Dinoprostone group was 4.57hours (1.90). There was statistically significant difference in duration of active phase between the two Groups. P value less than 0.01. So in my study active phase of labour was shorter in Dinoprostone group.

In Wing et al. 2008[11] study, active phase of labour was longer in Dinoprostone group than the Misoprostol group.

The induction to delivery interval mean (IDI) was shorter with Dinoprostone group of 17.47 hours (6.97) than in Misoprostol group 23.44 hours (8.90). In my study, there was significant difference in induction to delivery intervals in two groups.

Braganza et al,[13] reported no statistical significant difference in the mean induction to delivery interval in both groups. The mean IDI was 35.8 hours in misoprostol group and 32.4 hours in Dinoprostone group (P=0.106).

Study done by Mayer et al,[12] showed that the mean induction to delivery interval in Misoprostol group was761 minutes and in Dinoprostone group, it was 805.17 minutes, which was not statistical significant. In our study 44%(22 women out of 50) from Misoprostol group whereas 32% (16 women out of 50) from Dinoprostone group underwent caesarean section.

Though use of the Misoprostol was associated with an increased likelihood of caesarean delivery (RR.1.01), this difference did not achieve statistical significance.

Similar observations were noted in the study done by Mayer et al.[12] There was no significant difference in mode of delivery across two groups (Misoprostol vaginal insert 200mcg versus Dinoprostone vaginal insert 10mg).

In the meta analysis done by Austin et al.,[8] among the 1572 women who were assigned randomly to dinoprostone, the likelihood of vaginal deliveries was lower.(RR,0.65;95% CI,0.44-0.96;).

In our study there was no significant difference in indications of caesarean sections across both the groups. (P value-0.134). In the study done Braganza et al.[13] noted that 6.3%cases had foetal distress in Misoprostol group and 21.05% cases had foetal distress in Dinoprostone group.

There was no statistical significant difference in the Mean Birth weight of the babies, Apgar score and NICU across the two groups

7. Conclusion

In our study of 100 antenatal women, 50 participants were induced with Dinoprostone vaginal insert 10mg (PGE2) and 50 participants were induced with sublingual Misoprostol tablets (PGE1) maximum dose-200mcg in 24hours.

In my study the mean induction to delivery interval was 17.47 hours in Dinoprostone group and 23.44 hours in Misoprostol group. So the mean IDI was shorter in Dinoprostone insert group than Misoprostol group by about 6 hours.

There was no significant difference noted in terms of overall incidence of caesarean deliveries among the groups.

The incidence of meconium stained amniotic fluid was less in Dinoprostone group thus reducing the maternal and fetal morbidity.

Dinoprostone is comparatively expensive, requires refrigeration (-10 to -25C), and is not stable at room temperature.

Thus we came to a conclusion that Dinoprostone vaginal insert was more efficient than sublingual Misoprostol in terms of short induction to delivery interval without maternal and fetal complications.

8. Recommendations

Our study concluded that Dinoprostone 10mg vaginal insert was more efficacious than sublingual Misoprostol in reducing latent and active phases of labour and induction to delivery interval without maternal and fetal complications.

The study suggests that the Dinoprostone vaginal insert can be used as both inducing as well as augmentating agent in labour. Dinoprostone vaginal insert can be more effective in reducing the rate of caesarean sections.

We would suggest, need of more multicentric, randomized trials with large sample size comparing Dinoprostone vaginal insert with sublingual Misoprostol tablet to evaluate its efficacy and safety in induction of

labour.

9. Source of Funding

None.

10. Conflict of Interest

The authors declare no conflict of interest.

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