COMPARATIVE STUDY ON SAFETY AND EFFICACY OF MISOPROSTOL AND DINOPROSTONE IN CERVICAL RIPENING AND LABOUR INDUCTION

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ABSTRACT

BACKGROUND

Induction of labour is the process of initiation of uterine contractions for the purpose of vaginal delivery. Use of prostaglandins in induction of labour improves the obstetric outcomes in complicated cases such as prolonged deliveries.
The aims and objectives of the study were to compare the effects of-

1. Prostaglandin E_1 (PGE_1) and prostaglandin E_2 (PGE_2) for prelabour ripening of unfavourable uterine cervix.
2. PGE_1 and PGE_2 on maternal complexities and neonatal outcomes.

MATERIALS AND METHODS

This was a prospective study conducted on 226 pregnant women with gestational age ≥37 weeks during one-year period in the Department of Obstetrics and Gynaecology of Government TD Medical College, Alappuzha, Kerala. All the 226 patients were divided into two groups. Group 1 contains 179 patients who received intravaginal PGE_1, (Tablet Misoprostol 25 µg or 50 µg) inserted in the posterior vaginal fornix under all aseptic precautions. Group 2 contains 47 patients who received intracervical PGE_2, (dinoprostone gel, 0.5 mg). Analysis and comparison of various parameters between the two groups such as Bishop score before and after administration of drug, mode of delivery, neonatal outcome and maternal complications were noted and analysed using Chi-square.

RESULTS

Majority of the patients in both the groups were in the age of 21-30 years. Maximum patients had a Bishop's score of 4 in both PGE_1 and PGE_2 groups. There was significant difference in age and parity of both groups. In our study, we found only 2 cases of postpartum haemorrhage among the entire sample (group I and group II). We found significant difference in the occurrence of hyperstimulation among PGE_1 and PGE_2; whereas, there was no significant difference in the occurrence of maternal pyrexia among two groups.

CONCLUSION

PGE_1 and PGE_2 drugs have similar efficacy in induction of labour, but PGE_1 is associated with more side effects. Cost wise PGE_1 is more cost effective than PGE_2.

KEYWORDS

PGE_1, PGE_2, Labour Induction, Cervical Ripening, Bishop Score.

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BACKGROUND

Induction of labour is defined as initiation of uterine contractions before spontaneous onset of labour. For majority of women, labour induction starts spontaneously and results in vaginal delivery at or near term. Due to medical or obstetric complications, labour induction in the presence of an unfavourable cervix maybe prolonged, tedious and eventuate in a caesarean delivery. Therefore, induction of cervical ripening is critical to successful induction of labour in a pregnant woman whose cervix has not gone through the ripening process.[1]

During pregnancy, the cervix remains firm and closed to ensure the integrity of the pregnancy. Towards the end of pregnancy, the cervix becomes softer and more distensible in a process known as cervical ripening. Ripening of cervix is normally a physiologic process that precedes uterine contractions and it includes a highly complex biochemical process. Cervical ripening may stimulate uterine activity and uterine contractions result in cervical ripening. Cervical ripening greatly facilitates labour and augments the chances of vaginal delivery.

The two categories of artificial means of cervical ripening prior to labour induction are mechanical and pharmacological means. Mechanical device dilates the cervix by accessing the foetal membrane and pharmacological preparation cause connective tissue softening, cervical effacement and uterine activity.[2,3] Despite the multiplicity of

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techniques, there is no universally accepted idea, thus the ideal method of labour induction remains elusive.[4]

Prostaglandins as pharmacological agents are used for induction of labour as well as cervical ripening. The commonly used prostaglandins in obstetrics are prostaglandin E_1 (PGE_1- Misoprostol) and prostaglandin E_2 (PGE_2- Dinoprostone). Cervical ripening induced by PGE_1 and PGE_2 is associated with an increase in inflammatory mediators in the cervix and remodelling of the cervical extracellular matrix through a decrease in collagen cross links and increase in cervical glycosaminoglycan.[5,6] Dinoprostone is the widely used PGE_2 analogue that has been approved by the FDA for cervical ripening in women. In many centers, misoprostol, the PGE_1 analogue has replaced the use of dinoprostone due to its lower cost, higher stability and probably higher efficacy.[7]

PGE_1 has an effect on cervix and myometrium, whereas oxytocin activity is limited to that of uterine muscle. PGE_2 softens the cervix by altering the extracellular ground substance of cervix. It increases the activity of collagenase and elastase. Exogenous PGE_2 also act on cervical smooth muscle, thus facilitating cervical dilatation. PGE_2 facilitates gap junction formation, thus sensitising uterus to oxytocin, thereby reducing its subsequent use.

Objectives- Following are the objectives of our study.

1. To compare the effects of PGE_1 and PGE_2 for prelabour ripening of unfavourable uterine cervix.
2. To compare the effects of PGE_1 and PGE_2 on maternal complexities and neonatal outcomes.

MATERIALS AND METHODS

Study Population- This study was an observation study conducted at the Department of Obstetrics and Gynaecology (OB and G), Government TD Medical College, Alappuzha. The study protocol was approved by the Regional Committee for Medical Research Ethics. The period of study was for one year. Information was collected from 226 pregnant women who were selected for induction of labour at MCH Alappuzha (O_I unit). All the participants were informed about this research and written consents were obtained from each participant.

Inclusion Criteria

The inclusion criteria selected for this study were Bishop's score <6, unscarred uterus, singleton pregnancy, cephalic presentation, intact membranes and no contraindication for vaginal delivery. Women admitted to the Department of OB and G who met the above inclusion criteria were selected for our study.

Exclusion Criteria

Pregnant women with previous scar on uterus (previous LSCS, previous myomectomy, etc.), active labour, i.e. more than 3 cm dilatation and/or having more uterine contraction lasting for more than 30 seconds in 10 minutes of observation, ruptured membranes, hypersensitivity to prostaglandins and any serious maternal disease or foetal conditions were excluded from our study.

General and systemic examination (cardiovascular system and respiratory system) was also performed. All biochemical investigations including blood and urine examinations were done. Baseline parameters were noted. Preinduction counselling was done. Patients were explained about the need for induction as well as use of the drugs, their safety and adverse effects.

Bishop's score was noted prior to induction (at zero hour). Detailed pelvic examination was done to judge the condition of cervix according to Bishop's score and adequacy of pelvis. An admission foetal non-stress test (NST) was carried out to examine foetal wellbeing. The patients with reactive NST were taken for the study. When NST was reactive, patient was induced with either of the two drugs. All pregnant women with Bishop score <6 were randomly allotted for induction of labour either with PGE_1 vaginal tablets or PGE_2 gel.

Dosage- All the 226 patients were divided into two groups. Group 1 consisted of 179 patients who received intravaginal PGE_1. The dosage of PGE_1 was 50 µg (4th hourly) or 25 µg (3rd hourly to a maximum of 250 µg) was instilled to the posterior vaginal fornix. ARM was done in active phase of labour.

Group 2 comprised of 47 patients who were received intracervical PGE_2 (0.5 mg). PGE_2 was instilled with all aseptic precautions to the cervical canal and repeated at the interval of 6 hours to a maximum of three doses. ARM was done once the patient entered the active phase of labour.

Vital parameters of all patients were recorded and per abdomen examination was done one hourly for uterine activity and hyperstimulation. Foetal heart rate was monitored. All patients were reassessed after 6 hours and if required re-induction was done with same method. Reassessment was also done to note improvement in Bishop's score and progression to active phase.

Important anthropometric details were recorded from the patients using a standard questionnaire. To avoid interobserver and instrumental bias, all measurements were taken by the same measuring instrument/scale and by same person.

Statistical Analysis

We calculated the descriptive statistics of the sample population and Chi-square test was carried out to study the association of PGE and pregnancy outcomes.

RESULTS

In the sample of 226 women, 179 women (Group I) were induced with PGE_1 and remaining 47 women (Group II) were induced with PGE_2 (Figure 1). In group I, 41.9% and 58.1% women were given 25 µg and 50 µg of PGE_1, respectively.

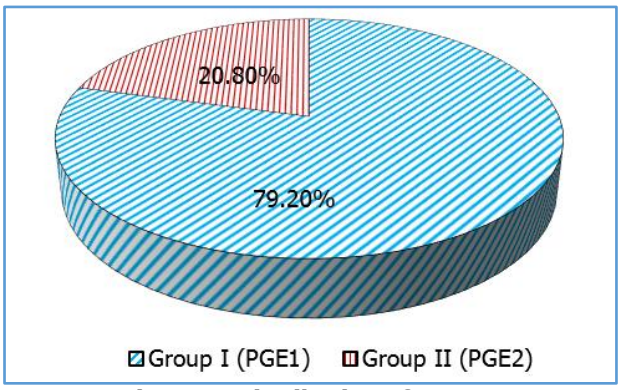

Figure 1. Distribution of Women According to the PGE Usage

Table 1 depicts the maternal demographic profile of the women included in the study. Both groups were comparable with respect to maternal age, parity and mean gestational age at the time of induction. In group I, 14.53% patients were below the age of 20 years. Maximum numbers of women belonged to the age group of 21 to 30 years in group I and minimum number was found in the age group between 31-40 years. Whereas in group II, women with age less than 20 years, between 21-30 and between 31-40 were 12.25%, 73.47% and 10.2%, respectively. As p value was less than 0.000, significant difference was found in the age of both groups. We found significant (p value 0.000) difference between the two groups in the case of parity, but we didn't find any significant (p value 0.461) difference between group I and group II in case of gestational age.

Indicators		PGE_1		PGE_2		P value
		Frequency	Percentage	Frequency	Percentage	
Age (Years)	<=20	26	14.56	6	12.77	0.000***
	21-30	145	81.01	36	76.60	
	31-40	8	4.47	5	10.64	
Parity	Primi	119	66.48	30	63.83	0.000***
	Para 1	51	28.49	15	31.91	
	Para 2	9	5.028	2	4.26	
Gestational Age	Preterm	13	7.26	2	4.26	0.461
	Term	166	92.74	45	95.74	

Table 1. Comparison of Demographic Variables in PGE_1 and PGE_2 Groups

***significant at 1%.

Table 2 portrays the oxytocin augmentation in group I and group II. There was no significant difference in oxytocin augmentation among two groups.

Pitocin	PGE_1 (%)	PGE_2 (%)	P value
Yes	38.55	42.55	0.617
No	61.45	57.45	

Table 2. Comparison of Oxytocin Augmentation in PGE_1 and PGE_2 Groups

Most of the women in both groups underwent normal delivery. Caesarean and instrumental delivery was more in group II when compared to group I (Table 3). Our study found significant difference in the mode of delivery among group I and group II.

Mode of Delivery	PGE_1 (%)	PGE_2 (%)	P value
Spontaneous	81.56	68.09	0.000***
Caesarean section	12.85	19.15	
Instrumental (forceps or ventouse)	5.59	12.77	

Table 3. Comparison of Mode of Delivery in PGE_1 and PGE_2 Groups

***significant at 1%.

In our study, we found only 2 cases of Postpartum Haemorrhage (PPH) among the entire sample (group I and group II). Two cases of PPH were found in patients who were induced with 25 µg of PGE_1 group. Table 4 depicts other maternal complications occurred among group I and group II. In our study, the maternal complications considered were hyperstimulation and maternal pyrexia. We found significant difference in the occurrence of hyperstimulation among PGE_1 and PGE_2; whereas, there was no significant difference in the occurrence of maternal pyrexia among two groups.

Maternal Complications		PGE_1 (%)	PGE_2 (%)	P value
Hyperstimulation	Yes	6.15	17.02	0.021**
	No	93.85	82.98	
Maternal pyrexia	Yes	3.35	0	0.073
	No	96.65	100	

Table 4. Comparison of Maternal Complications in PGE_1 and PGE_2 Groups

**significant at 5%.

Analysis of Apgar score was done for all newborn. All the babies born in PGE_2 group had a higher Apgar score (7-10). None of the babies of group II had Apgar score less than 6 at zero minute and after five minutes. Apgar scores are presented in Table 5.

Time	Apgar Score	PGE_1 (%)	PGE_2 (%)
At Zero Minute	0	1.68	0.00
	4	0.00	0.00
	6	0.00	0.00
	7	4.47	2.13
	8	5.03	6.38
	9	88.83	91.49
After 5 Minutes	0	1.68	0.00
	4	0.56	0.00
	6	0.00	0.00
	8	0.56	2.13
	9	97.21	97.87

Table 5. Apgar Scores of PGE_1 and PGE_2 Groups

The neonatal outcomes are depicted in Table 6. Meconium staining was found higher in PGE_2 group. There were no Fresh Stillbirths (FSB) in group II. There was no significant difference between two groups with regard to neonatal outcomes.

Neonatal Outcomes	PGE_1 (%)	PGE_2 (%)	P value
Meconium staining	47.62	50	0.659
Fresh stillbirths	9.52	0	
NICU admission	42.86	50	

Table 6. Comparison of Neonatal Outcome in PGE_1 and PGE_2 Groups

DISCUSSION

Labour induction is one of the most commonly performed obstetric procedures in patients undergoing inpatients cervical ripening. Recently, induction of labour by use of prostaglandins is very common due to a rise in indications for maternal and foetal reasons.[8] Prostaglandins are highly efficacious cervical ripening agents used to shorten induction to delivery intervals, improve induction success and reduce morbidities associated with prolonged labour induction. This study was done to compare the effects of intravaginal PGE_1 versus intracervical PGE_2 for prelabour ripening of unfavourable cervix in a pregnant woman.

In this study, a sample size of 226 cases were taken. Out of the total samples, 179 cases were induced with PGE_1 (group I) and rest 47 were induced with PGE_2 (group II). The baseline characteristics taken in the study were age, parity and gestational age. Among the three baseline characteristics, we found significant difference in age and parity among two groups. Total number of primigravidae were 149 and more number of the primigravidae were present in the age group of 21 to 30 years. Gestational age was found statistically insignificant.

The studies of Kelly and Tan[9] and Escudero and Contreras[10] conveyed that oxytocin is an effective method of labour induction. The present study indicates that PGE_1 was associated with less need of oxytocin augmentation. Caesarean section was also lower in group I. Bartha et al also indicated that PGE_1 is associated with less oxytocin augmentation and lesser caesarean section operations for failed induction.[11]

Several studies have stated that hyperstimulation and tachysystole were found more in patients induced with misoprostol. It may be due to the reason there is less risk of hyperstimulation with lower dose of misoprostol, but at the same time reducing the effectiveness of labour induction. But, our study found that hyperstimulation was higher in patients induced with PGE_2. Regarding neonatal outcomes, perinatal results evaluated by means of Apgar score, FSB, meconium stain and admission to intensive care unit were comparable between two groups with similar perinatal outcome. It has been found that there is no difference in neonatal outcomes in both the groups.

The efficacy of locally applied prostaglandins (vaginal or intracervical) for cervical ripening and labour induction have been demonstrated in a Cochrane review that involved more than 10,000 women. For instance, vaginal PGE_2 reduces the likelihood of vaginal delivery not being achieved within 24 hours, the risk of cervix remaining unfavourable or unchanged and the need for oxytocin. In addition, no difference was found between caesarean delivery rates, although there was a trade-off with PGE_2 use because the risk of uterine tachysystole with foetal heart rate changes was increased. Administration of misoprostol for labour induction and cervical ripening is considered as safe and effective off-label use by ACOG.[12]

CONCLUSION

Our study investigated the comparison between PGE_1 and PGE_2 in labour induction. We used Chi-square test to estimate the association of PGE_1 and PGE_2 with maternal complications and neonatal outcomes. Our study proved that PGE_1 and PGE_2 drugs had similar efficacy in induction of labour, but PGE_1 was associated with more side effects. Nevertheless, our study had limited number of patients and being a small-scale study, we recommend further studies involving large samples comparable to those done in Western countries. Precise use of induction agents with careful selection of patients can be a useful method to reduce the perinatal morbidity and mortality.

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