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ORIGINAL ARTICLE

Sublingual Misoprostol (PGE1) Versus Intracervical Dinoprostone (PGE2) Gel for Induction of Labour: A Randomized Control Trail

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This study was conducted at Bangalore Baptist Hospital, Bellary Road, Hebbal, Bangalore, 560024 (Phone: 080-22024700).

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Abstract

Background Prostaglandins are popular agents for induction of labour, owing to their dual action of cervical ripening and inducing uterine contractions. Sublingual misoprostol offers high efficacy as it bypasses first-pass metabolism. Researchers have proved that intracervical PGE1 is as effective as PGE2 except for increased caesarean rate and hyperstimulation. Limited knowledge is available on the efficacy of sublingual PGE1 and intracervical PGE2. This study was designed to compare the effectiveness of sublingual PGE1 with intracervical PGE2.

Methods A randomized control trial was conducted in Bangalore Baptist Hospital, Bangalore. One hundred and ninety women with singleton, term pregnancy were equally divided into PGE1 and PGE2 groups, and primary outcome was measured.

Results Post-induction mean Bishop's score in PGE1 group was statistically significant ($t = 6.57$, $p < 0.05$).

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Failed induction rate (1 vs 13.6 %) and need for augmentation (46.3 vs 62.1 %) were lower with PGE1 than those with PGE2 ($p < 0.05$). Significant ($p < 0.05$) maternal and foetal outcomes like higher rate of NVD (35.8 vs 26 %), lower LSCS rate (15.8 vs 32.6 %), lower incidence of foetal complications (7.3 vs 21 %) were noted with PGE1. APGAR scores at 1 and 5 min were not significant. Mean cost of induction with PGE1 was 12.55+/4.15 INR and with PGE2 470.65+/126.5.

Conclusion Sublingual PGE1 is a better cervical ripening agent, faster and more effective, with a shorter induction-to-delivery interval as compared to intracervical PGE2. We also noted lower incidence of caesarean section and foetal distress with sublingual PGE1 compared to oral or vaginally administered PGE1.

Keywords IOL · Sublingual misoprostol · Cerviprime gel · Hyperstimulation · Safe inducing agent

Introduction

Induction of labour (IOL) is a common procedure in obstetrics. WHO defines IOL 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. In developed countries, IOL accounts for about 25 % of all deliveries. In developing countries, the rates vary [1]. A study by the WHO Global Survey on Maternal and Perinatal Health in 24 countries reported that IOL accounted for 9.6 % of all deliveries. The incidence of IOL was also noted to be on the increase [2].

There is a wide range of mechanical and pharmacological inducing agents which have been tried over the years. An ideal inducing agent is one which achieves labour in the shortest possible time, with a low incidence of failure to achieve vaginal delivery, with no increase in perinatal morbidity compared to spontaneous labour. Prostaglandins have evolved as the most popular and frequently used pharmacologic agents for IOL, owing to their dual action of cervical ripening and uterine contraction inducing effect. Prostaglandin E_2 (cerviprime gel), a registered inducing agent in many countries is expensive and needs to be refrigerated due to its sensitivity to temperature changes. It is instilled intracervically or placed high in the posterior fornix of the vagina and may need to be re-instilled after 6 h if required. Another alternative is misoprostol (15-deoxy-16-hydroxy-16-methyl prostoglandin E1) which is used in various dosages. It is stable at room temperature, comparatively cheaper and can be given via several routes (oral, vaginal, sublingual, buccal and rectal).

The use of sublingual misoprostol also offers high efficacy as it bypasses gastrointestinal and hepatic metabolism and also lowers hyperstimulation of uterus by avoiding direct effect on the cervix. Moreover sublingual route, having the added advantage of easier administration, is less invasive and therefore obviates the need for repeated per vaginal examinations. However, prostaglandins being powerful uterotonics can lead to adverse maternal and perinatal outcomes. Researchers in the past have compared efficacy of vaginal and oral PGE1 with intracervical PGE2 and proved that PGE1 is as effective as PGE2 except for increased incidence of caesarean rate and hyperstimulation [3, 4]. Very limited knowledge is available on the efficacy of sublingual PGE1 and intracervical PGE2. Hence, this study was designed to bridge this lacunae comparing effectiveness of sublingual PGE1 with intracervical PGE2 in terms of the maternal and foetal outcomes.

Methodology

A parallel randomized controlled trial was conducted with allocation ratio of 1:1 to compare effectiveness of sublingual misoprostol (PGE1) and intracervical dinoprostone (PGE2). To detect the mean difference of 2.0, with an estimated standard deviation of mean post-induction Bishop's score in misoprostol group as 3.5 and PGE2 group as 5.5 with power of 80 % at 95 % confidence interval, the sample size was calculated as 168 (84 in each arm). However, 190 samples were included to account for dropout of 10–15 %.

The study was conducted in the labour room of Bangalore Baptist Hospital (BBH) at Bangalore which is a multispeciality teaching hospital in Bangalore. The data were collected over a span of 16 months between April 2013 and August 2014. Women with term gestation with a single live intrauterine foetus with cephalic presentation and unripe cervix (Bishop's score <6) with no other complications were enrolled. A total of 190 women participated in this study. Women with obstetric complications such as uterine scar due to previous LSCS, antepartum haemorrhage, foetal anomalies, and systemic diseases were excluded from the study.

All participants fulfilling the inclusion criteria were considered for the study after an informed consent and were assessed using the modified Bishop's score. Patients were randomized and allotted their respective groups—A (sublingual misoprostol group) or B (intracervical PGE2 gel group) (95 in each arm) by the block randomization method. A computer-generated sequence was obtained and kept in sequentially numbered sealed opaque envelopes by the investigator in an agreed location in the labour ward. Participants were randomized at the time of admission to the labour ward into control or intervention group.

Group A

Participants were administered 50 mcg of misoprostol sublingually, and repeat doses of 25 mcg was given in the absence of uterine activity (maximum of four doses repeated at intervals of 4 h until uterine activity or favourable score was attained). Participant was reassessed using the modified Bishop's score after 6 h and charted by the labour room doctor. With the onset of active labour, the routine hospital protocol was followed.

Group B

Under aseptic conditions, 0.5 mg of PGE2 gel was instilled intracervically by the labour room doctor and reassessed after 6 h. If Bishop's score remained less than 6, a second gel of PGE2 was instilled. With the onset of good contractions and Bishop's score >5, hospital protocol was followed.

In both groups, if the Bishop's score remained <5 after the maximum doses of PGE1 or PGE2, the hospital protocol was followed. Progress and outcome of labour were recorded by the labour room doctor.

Statistical Analysis

Data obtained were coded and entered into Microsoft Excel 97–2003, and the analysis was carried out using SPSS (Statistical Package for Social Sciences) 16.0. The primary outcome was to measure the change in Bishop's score following induction, and three secondary outcomes were studied: namely interval between IOL and onset of active labour, interval from IOL to delivery and cost effectiveness of the two methods of IOL.

Pre- and post-induction mean Bishop's scores among each group were compared by paired t test. The change in mean Bishop's score between PGE1 and PGE2 groups was compared by z test. Outcomes such as induction-to-active labour interval, induction-to-delivery interval, requirement of augmentation and cost of induction were tested between two groups using Chi-square test. p value less than or equal to 0.05 was considered as significant.

Ethical Standards

The drugs used in the study have been approved by WHO as methods of induction which are time tested and proven to be safe. Misoprostol is a cheaper alternative to the routinely used PGE2 gel or Foley catheters. Sublingual route of administration is also less invasive than the routinely practised methods, namely intracervical Foley or PGE2 gel. The study was approved by the institutional review board which consists of ethics and scientific committee. A signed informed consent was obtained from all the voluntary participants before the admission to labour room, and they were assured of the option to withdraw from the study at any moment.

Results

One hundred and ninety antenatal women were equally randomized into PGE1 and PGE2 groups. Fifty-four percentage in PGE1 and 50.5 % in PGE2 belong to age groups between 20 and 25 years (Table 1). Majority of them were primigravida in both groups (PGE1—71.6 %, PGE2—53.7 %). Most of the women were nulliparous constituting 78.9 and 62.1 % in the two groups, respectively. The mean gestational age at admission was 39.2 (SD—1.002) weeks among PGE1 group and 39.15 (SD—1.041) among PGE2 group. The most common indication for induction was post-dates in both groups (PGE1—38.9 %, PGE2—36.8 %) followed by PROM (12.6 %) in PGE1 group and GHTN (14.7 %) in PGE2 group. Maximum number of women in the study group had a Bishop's score of 3–4, constituting 56.9 (PGE1) and 51.6 % (PGE2), respectively, and this was not statistically significant ($p = 0.179$). The baseline characteristics were comparable in both the groups ($p > 0.05$).

Though there was significant ($p < 0.05$) 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 (Table 2), mean Bishop's score in PGE1 group was statistically significant ($t = 6.57$, $p < 0.05$) as compared to PGE2 group (Table 3). Majority of the women entered active labour within 12 h in both groups. Only 1 % of failed induction was noted in PGE1 group as against 13.6 % in PGE2 group. Most of the women required augmentation with either oxytocin or ARM in both the groups comprising 62.1 % in the PGE2 group as against 46.3 % in PGE1 group, and this difference was statistically significant. Approximately more than three quarter of women delivered within 24 h. Among those delivered within 12 h, majority of them belonged to PGE1 group [35.8 % (34/95)] as compared to PGE2 group [26 % (27.4/95)] (Table 4).

Foetal distress and hyperstimulation were two foetal complications noted in both groups (Table 5). Overall, 27 mothers had foetal related complications out of which 7.3 % (7/95) were from PGE1 group and 21 % (20/95) were from PGE2 group. There was no statistical significance of the APGAR score at 1 and 5 min. Most of the women had clear amniotic fluid, and 4.21 % (4/95) women in PGE2 group had Grade III meconium-stained amniotic fluid (MSAF). Most of the women in both groups delivered vaginally. 32.6 % (31/95) in the PGE2 group underwent LSCS as compared to 15.8 % (15/95) in PGE1 group, and

Table 1 Demographic profile

Characters	Variables	PGE1 group ($N = 95$)		PGE2 group ($N = 95$)		Chi-square	p value
		Number	Percentage	Number	Percentage		
Age (in years)	<20	10	10.5	4	4.2	6.06	0.195
	20–25	52	54.7	48	50.5		
	26–30	27	28.4	32	33.7		
	31–35	4	4.2	10	10.5		
	>35	2	2.1	1	1.1		
Gravida	1	68	71.6	51	53.7	7.14	0.129
	2	14	14.7	21	22.1		
	3	7	7.4	15	15.8		
	4	4	4.2	6	6.3		
	5	2	2.1	2	2.1		
Parity	0	75	78.9	59	62.1	11.1	0.01*
	1	18	18.9	27	28.4		
	2	1	1.1	9	9.5		
	3	1	1.1	0	0		
Pre-induction Bishop's score	0	1	1.1	2	2.1	7.61	0.179
	1	10	10.5	5	5.3		
	2	13	13.7	13	13.7		
	3	22	23.2	29	30.5		
	4	32	33.7	20	21.1		
	5	17	17.9	26	27.4		

* Significant p value

Table 2 Comparison of pre- and post-induction mean Bishop's score

Group	Intervention	Mean Bishop's score	Standard deviation	Standard error	T statistics	p value
PGE1	Pre-induction	3.32	1.274	0.131	28.635	<0.005*
	Post-induction	8.59	1.595	0.164		
PGE2	Pre-induction	3.45	1.286	0.132	16.641	<0.005*
	Post-induction	6.77	2.195	0.225		

* Significant p value

Table 3 Comparison of post-induction mean Bishop's score between two groups

Group	Post-induction mean Bishop's score	Standard deviation	Standard error of difference	T statistics	p value
PGE1	8.95	1.595	0.278	6.578	<0.005*
PGE2	6.76	2.196			

* Significant p value

this difference was statistically significant. Failed induction was a most common indication for LSCS in PGE2 group [48.3 % (15/31)], whereas cephalopelvic disproportion was most common indication in PGE1 group [53.3 % (8/15)]. Majority of the women in PGE1 group [85 % (6/7) had instrumental delivery for poor maternal efforts, whereas in the PGE1 group it was foetal distress [66.6 % (4/6)]. The mean cost of induction in PGE1 group was 12.55+/4.15 INR as against 470.65+/126.5 in PGE2 group.

Discussion

Foetal death was the only indication for IOL centuries ago, taken over by prolonged pregnancy and hypertensive disorders in the past 50–60 years. Safety, success and patient satisfactions are the main concerns with economical factor now being a significant factor in search of an ideal inducing agent. PGE1 has been widely used for second-trimester termination pregnancy. The effectiveness of vaginal PGE1

Table 4 Comparison of obstetric outcome between PGE1 and PGE2 groups

Characteristics	Variables	PGE1 group ($N = 95$)		PGE2 group ($N = 95$)		Chi-square	p value
		Number	Percentage	Number	Percentage		
Induction-to-active labour interval (in h)	<6	31	32.6	28	29.4	65.5	<0.05*
	8	32	33.6	1	1		
	12	20	21	53	55.7		
	>12	11	11.5	0	0		
	Failed	1	1	14	13.6		
Augmentation with oxytocin and ARM	Yes	44	46.3	59	62.1	4.7	<0.05*
	No	51	53.7	36	37.9		
Induction-to-delivery interval (in h)	<12	34	35.8	26	27.4	1.57	0.45
	12–14	49	51.6	55	57.9		
	>24	12	12.6	14	14.7		
Colour of liquor	Clear	88	92.6	81	85.2	7.62	0.106
	Grade I	3	3.1	1	1.05		
	Grade II	4	4.2	8	8.4		
	Grade III	0	0	4	4.21		
	Blood stained	0	0	1	1.05		
Mode of delivery	LSCS	15	15.8	31	32.6	7.36	<0.05*
	Instrumental	7	7.4	6	6.3		
	Vaginal	7.3	76.8	58	61.1		

* Significant p value

Table 5 Comparison of foetal outcome between PGE1 and PGE2 groups

Complications	PGE1 group ($N = 95$)		PGE2 group ($N = 95$)	
	Number	Percentage	Number	Percentage
Hyperstimulation	1	1	0	0
Maternal infection	0	0	0	0
Foetal distress	6	6.3	20	21.05

over PGE2 has been extensively studied, and it is proven that PGE1 is a cheaper and effective alternative over PGE2 and is not affected by heat [3].

The most common indication for induction in our study population was post-dates, and this corresponds to existing evidence that the common indication for induction in Indian setting is post-dates [5]. Though more than two-thirds of the women both groups progressed to labour within 6 h of induction, significant proportion of women in PGE2 group progressed to labour only after 6 h as compared to PGE1 group. Correspondingly, shorter induction-to-labour time has been noted when vaginal misoprostol was compared with cerviprime gel for induction at term [3, 6]. A research from India has also found significant difference in the post-induction mean Bishop's score when PGE1 was administered vaginally, and our finding is in concordance with this observation [7]. Significantly less proportion of patients required augmentation of labour with oxytocin or ARM (46.3 vs 62.1 %), and this correlates with evidence from Pakistan where oral PGE1 was compared with intracervical PGE2 [4] and by Niveditha et al. [8] in PPROM. Our study has showed significant proportion of mothers had shorter induction-to-delivery time in PGE1 group than PGE2 group. Similar observation has been found by Niveditha et al. [8] when sublingual PGE1 was induced for PPROM after 34 weeks, and it has been shown to be more effective than intracervical PGE2. This finding is also in concordance with observation from Chaudhuri et al. [9] when vaginal misoprostol was compared with PGE2.

The proportion of women who had normal vaginal delivery was significantly high in PGE1 group (76.8 and 61.1 %), and notably less proportion underwent LSCS (15.8 vs 32.6 %). This observation contradicts few other existing evidences in which misoprostol was shown to increase the rate of caesarean section when oral misoprostol was compared to PGE2 (28 vs 24 %) [3]. Similarly, Parmar et al. [3]

also have found significant higher caesarean rate in PGE1 group when administered vaginally. However, Faucett et al. [10] have concluded that there is no significant difference in caesarean rate between oral misoprostol and vaginal PGE2. Similar finding was also observed by Niveditha et al. [8]. A study from Ludhiana which compared oral PGE1 and vaginal PGE2 found an increased incidence of caesarean rate in oral PGE1 group [11]. This could be explained by shorter duration of action (3 h) of sublingually administered PGE1 compared to vaginally administered PGE1 (4 h). The sublingual route theoretically combines the higher efficacy of vaginal route by avoiding gastrointestinal and hepatic metabolism and the lower hyperstimulation rates by avoiding a direct effect on the cervix. This finding also can be supported by lower incidence (<1 %) of hyperstimulation and foetal distress noted in our study. Similarly, our study also showed less proportion of women had meconium-stained liquor in the PGE1 group as against PGE2 group (Grade III—4.2 %). Recently published study revealed that when compared to oral and vaginal route, sublingual misoprostol achieved its peak serum concentration in an interval similar to that achieved by the oral route [12]. Our findings contradict the existing evidences which compared vaginal PGE1 and PGE2 and showed increased incidence of hyperstimulation and foetal distress [7, 13].

Our study had adequate sample size and followed prescribed randomization and allocation concealment; there was no violation of protocol, and it was analysed based on intention to treat.

Conclusion

Our study has shown sublingual PGE1 as a better cervical ripening agent, faster inducing agent by shortening induction-to-active labour interval, more effective inducing agent by reducing the need for either oxytocin or ARM and shortening induction-to-delivery interval as compared to intracervical PGE2. We also noted lower incidence of caesarean section and foetal distress with sublingual PGE1 as against the existing evidences when PGE1 administered orally or vaginally.

Misoprostol is an excellent labour-inducing agent and can be used liberally for labour induction, as long as proper patient selection and vigilant labour monitoring are done. Sublingual misoprostol significantly reduces the induction-to-delivery interval and has fewer induction failures; thus, it could contribute towards reducing the morbidity caused by prolonged labours. Misoprostol (PGE1), unlike PGE2 gel, is comparatively cheaper and is stable at room temperature; thus, it could be an ideal inducing agent in poor resource settings. Strict adherence to asepsis and minimal use of invasive procedures are essential steps to avoid infections, and the sublingual misoprostol obviates the need for repeated internal examinations. As such it could be a preferred option in cases where repeated internal examinations are best avoided as in PROM. Multicentre trails with large sample size comparing sublingual PGE1 and vaginal PGE2 will throw more light on findings from our trail. The use of PGE2 gel for labour induction cannot be totally brushed aside as it continues to be the agent of choice in patients with severe oligohydramnios and with evidence of early foetal compromise.

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Authors' contribution

	Veena	Rajinish	Leeberk	Carolin
Concepts	Yes	Yes	No	Yes
Design	Yes	Yes	No	Yes
Definition of intellectual content	Yes	Yes	Yes	Yes
Literature search	Yes	Yes	Yes	Yes
Clinical studies				
Experimental studies	Yes	Yes	Yes	Yes
Data acquisition	Yes	No	No	No
Data analysis	No	No	Yes	Yes
Statistical analysis	No	No	Yes	Yes
Manuscript preparation	No	No	Yes	No
Manuscript review	Yes	Yes	Yes	Yes
Guarantor	No	Yes	No	No

Compliance with Ethical Standards

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest Veena B, Rajinish S, Leeberk R and Carolin E declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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