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Prostaglandin E_1 tablet versus prostaglandin E_2 gel for induction of labor in prelabor rupture of membranes at term

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ABSTRACT

Objective: To compare the efficacy of PGE_1 tablet and PGE_2 gel for induction of labour in PROM.

Material & Methods: A prospective study was conducted on 100 women with ≥ 6 hours of PROM at term; odd number women were given tablet PGE_1 (misoprostol) vaginally, 25mcg every 4 hours for maximum of 3 doses and even numbers were assigned PGE_2 gel (Dinoprostone) 0.5 mg vaginally every 6 hours for maximum of 2 doses or initiation of labor whichever was earlier. Primary outcome was measured as induction to delivery interval. Secondary outcome included mode of delivery, dosage, adverse effects, Apgar score of the neonate at 5 minute, NICU admission and neonatal sepsis.

Results: The mean duration of ruptured membranes to delivery interval (p=0.487) and induction to delivery interval (p=0.598) was similar in both groups. Both drugs were comparable in their efficacy for vaginal delivery within 24 hours, cesarean section rate, need for oxytocin, failed induction and neonatal outcome. The only significant difference observed was fetal heart abnormalities (p=0.014, RR 1.926, 95% CI1.049-2.204), tachysystole (p=0.002, RR 1.991, 95% CI 1.255-2.347) and dosage required (p=0.0001) which was higher in misoprostol group.

Conclusion: Both drugs are similar in efficacy for labor induction but PGE_2 gel is superior drug as compared to misoprostol as number of doses and adverse effects like tachysystole and fetal distress are less. Misoprostol being cheaper and stable at room temperature can be used in developing countries in centres where continuous fetal monitoring facilities are available.

Keywords: Prostaglandin E_2 gel, induction of labor, misoprostol, prelabor rupture of mambranes, Prostaglandin E_1 tablet.

INTRODUCTION

Premature rupture of membranes (PROM) is rupture of membranes before the onset of labor. At term, PROM complicates approximately 8% of pregnancies and generally is followed by the prompt onset of spontaneous labor and delivery [1]. Even with unfavorable cervix, spontaneous labor starts within 12 hours in most of cases, 50% of women will go in labor after 12 hours, 86% within 24 hours, 94% within 48-95 hours and 6% will not go in labor even within 96 hours of prelabor rupture of membranes [2-4].

Infection of the lower genital tract and/or amniotic cavity is one of the most important etiologies of PROM. The diagnosis is usually established by direct observation of pooling of amniotic fluid in the vagina. In problematic cases, the nitrazine and fern test can be used to confirm the diagnosis [5]. Term prelabor rupture of membranes is associated with maternal and neonatal infection, cord prolapse and fetal compromise which may result in operative delivery or low apgar score at five minute [4].

Prelabor rupture of membranes is also associated with chorioamnionitis in 6-10% of women at term and up to 40% in women with membranes ruptured for more than 24 hours. It occurs due to repeated vaginal examinations, longer duration of active labor and meconium staining of amniotic fluid [6]. The management of PROM is still a matter of debate and varies from centre to centre. Expectant management is one of the situations in which women with PROM wait for spontaneous onset of labor after rupture of membranes. In the absence of signs of infection, it seems to be a viable option, but the concern is the risk of infection to the mother and the fetus where as immediate induction can increase cesarean rate [7, 8]. Both oxytocin and prostaglandins are effective in inducing labor in women with PROM at term.

Dinoprostone is PGE_2 analogue. It acts by three different mechanisms 1) softens the cervix by altering extra cellular ground substance of cervix, 2) by acting on smooth muscle of cervix and uterus, 3) leads to gap junction formation which is necessary for coordinated uterine contractions of labor. It is costly and requires refrigeration due to thermal instability [9-11]. Although PGE_2 gel is the preferred pharmacologic method of induction of labor but due to its cost and storage requirement (2^0-8^0C), the search for an effective, easily stored, affordable labor inducing agent has led to the use of misoprostol as an inducing agent [11].

Misoprostol is synthetic PGE_1 analogue, administered through oral, sublingual, buccal, vaginal and rectal routes. Its mode of action is by binding to prostanoid receptors on myometrium. It is thermostable and cheaper than PGE_2 analogue (dinoprostone). Vaginal route is preferred due to longer half life as compared with oral. It is also associated with few adverse effects like uterine tachysystole and hyperstimulation [12,13].

The present study has been done to evaluate and compare the efficacy of vaginal prostaglandin E_1 tablet and prostaglandin E_2 gel for induction of labor in PROM at and beyond 37 weeks of gestation.

MATERIAL & METHODS

A prospective study was carried out on 100 women presenting in labor room with ≥ 6 hours of PROM, singleton pregnancy, cephalic presentation, at term (37-42 weeks of gestation) with modified Bishop's score <6, in a tertiary health care centre.

Exclusion Criteria : Women having uterine contraction, signs and symptoms of chorioamnionitis, fetal distress, grand multipara, scarred uterus, placenta previa, hypersensitivity to prostaglandins, renal, hepatic or cardiovasular disease and asthma. The study was approved by the institutional ethics committee. All women were subjected to detailed history including age, parity, gestational age and duration of ruptured membranes. Thorough general, systemic and obstetrical examination was carried out. Per speculum examination was done to confirm rupture of membranes. Informed written consent was taken. Women enrolled in the study were divided into two groups, odd number women were given tablet prostaglandin E_1 (misoprostol) 25 mcg vaginally every 4 hours for maximum of 3 doses (Group I) and even numbers were given 0.5mg vaginal prostaglandin E_2 gel (dinoprostone) every 6 hours for maximum of two doses or initiation of labor whichever was earlier (Group II).

Hemoglobin, total leukocyte count, differential leukocyte count, urine complete examination, urine and high vaginal swab for culture and sensitivity, was carried out in both the groups. Prophylactic antibiotic injection Ampicillin after sensitivity test was given to all subjects. The progress of labor was monitored by the Partogram. Bishop's score was assessed prior to every dose. If Bishop's score did not improve after 12 hours of induction, woman was subjected to caesarean section for failed induction. The adverse effects of PGE_1 and PGE_2 including nausea, vomiting, fever, tachysystole (uterine contraction more than five in 10 minutes duration averaged over period of 30 minutes) and hyperstimulation presence of tachysystole associated with fetal heart abnormalities) were noted. The post partum condition of mother and duration of hospital stay was recorded. Primary outcome was measured as induction to delivery interval. Secondary outcome was measured in terms of mode of delivery, number of doses of drug used, adverse effects, Apgar score of the neonate at 1 and 5 minute, NICU admission and neonatal sepsis. The data collected was subjected to statistical analysis by student's't' test and chi-square test. A p value < 0.05 was considered significant.

RESULTS

The demographic profile including age, parity, antenatal registration and gestational age was similar in both the groups as shown in Table 1. The maximum distribution of women in both the groups was observed in 20-24 years. Most women were nullipara as compared to parous women in both the groups. The duration of ruptured membranes and Bishop's score at the time of induction was also similar in both the groups as depicted in

Table 1: Demographic profile

Parameters		Group I (Prostaglandin E_1) (n=50)	Group II (Prostaglandin E_2) (n=50)	P value
Age(years) (mean±SD)		24.34±3.07	23.74±2.90	0.319
Parity	P_0	37 (74%)	38 (76%)	0.817
	P_1	11(22%)	8 (16%)	0.444
	P_2	2 (4%)	1 (2%)	0.558
	P_3	0	3 (6%)	
Antenatal Registration	B	21 (42%)	23 (46%)	
	UB	29 (58%)	27 (54%)	0.687
Gestational age (weeks) (mean±SD)		38.78±1.66	38.74±1.30	0.319

SD-Standard deviation, B-booked, UB-unbooked

Table 2 Seventy eight percent in dinoprostone group while 42% in misoprostol group required single dose of drug and the difference was statistically significant (p<0.0001).

Table 2: Labor outcome variables

Parameters (mean ± SD)		Group I Prostaglandin E_1 (n=50)	Group II Prostaglandin E_2 (n=50)	P value
Duration of ruptured membranes at time of induction (hours)		17.59±22.38	15.95±15.04	0.687
Bishop score		3.541±1.18	3.561±1.03	0.918
Ruptured membranes to delivery interval(hours)		30.02±22.92	26.95±18.07	0.487
Number of doses	1	21	39	<0.0001
	2	15	11	0.362
	3	14	0	
Need for oxytocin		13	8	0.220
Duration of 1st stage of labor (hours)	Nullipara <12	26(67%)	32(73%)	0.355
	Nullipara >12	2(5%)	0	
	Multipara <6	8(21%)	10(23%)	0.733
	Multipara >6	3(7%)	2(4%)	0.352

Table 3 shows induction to delivery interval and it was not significant statistically (p=0.444)in two groups. Out of 100 women, 39 delivered vaginally in group I and 44 in group II.

Table 3: Primary outcome variable

Induction to delivery interval (hours)	Group I (Prostaglandin E_1) (n=50-11*=39)		Group II (Prostaglandin E_2) (n=50-6*=44)		P value
	Number	Percentage	Number	Percentage	
<12	25	64	30	68	0.695
12-24	14	36	12	27	0.398
>24	0	0	2	5	-
Mean ± SD	11.18 ±6.02		10.51 ±5.48		0.598

* cesarean section

In group I, 100% women and 95 % in group II delivered vaginally within 24 hours of induction of labor, the difference was not statistically significant (P = 0.444). Failure of induction (failure to initiate uterine contractions or to improve Bishop's score ≥ 6 after 12 hours of induction) was present in three women (6%) in group I and four women (8%) in group II and was not significant (P = 0.695 RR 0.848, 95 % CI-0.227, 1.659). The mode of delivery is shown in table 4.

Table 4 : Mode of delivery

Mode of Delivery	Group I (Prostaglandin E_1) (n=50)		Group II (Prostaglandin E_2) (n=50)		P Value
	Number	Percentage	Number	Percentage	
Spontaneous Vaginal delivery	38	76	44	88	0.183
Operative vaginal delivery	1	2	0	0	--
Cesarean	11	22	6	12	0.183

Cesarean section was performed in 22% and 12% in group I and II respectively and was not significant (p=0.183, RR=1.377, 95% CI 0.778-1.956). The vomiting was present in 2% in group II. In group I, 2% women and 4% in group II had diarrhoea. The incidence of intrapartum fever was 4% in group I and 2% in group II, the difference was found not significant statistically (p = 0.558, RR 1.347, 95 % CI 0.034 -1.788). The temperature ranged from 99.4ºF to 100º F.

The incidence of hyperstimulation (presence of tachysystole associated with fetal heart rate abnormalities) was 4% in group I and 2% in group II women, the difference was found not significant statistically (P=0.558, RR 1.347, 95 % CI 0.034 - 1.788). The incidence of tachysystole (uterine contraction more than five in 10 minutes duration averaged over period of 30 minutes) was 26% in group I and 4% in group II women, the difference was found significant statistically (p=0.002 , RR 1.991, 95 % CI 1.255- 2.347).

The postpartum fever was encountered in 2% in group I and 4% in group II and was similar (p=0.558). In Group I, 16% cases developed fetal distress while in group II only 2% cases developed fetal distress and the difference was significant statistically (p=0.014, RR 1.926, ,95 % CI 1.049- 2.204). Only one case in group I had traumatic PPH, in which operative vaginal delivery was performed.

Table 5 depicts neonatal outcome. Seventy four percent of group I and 44% of group II had 1 minute Apgar score < 7 and was statistically significant (p = 0.002) but it did not exist at 5 minute. The indication for NICU admission was respiratory distress. All neonates were discharged in healthy condition from the hospital. There was no neonatal mortality in both the groups.

Table 5: Neonatal outcome

Neonatal Outcome		Group I PGE_1 (n=50)	Group II PGE_2 (n=50)	P Value
Birth weight (Kg)	Mean ± SD	2.67 ± 0.358	2.68 ± 0.392	0.926
APGAR score at 1min.	<4	0	0	
	4-6	37	22	0.002
	≥7	13	28	
APGAR score at 5min.	<4	0	0	
	4-6	0	0	
	≥7	50	50	
Admission to NICU		3	0	-
Neonatal sepsis		4	2	0.400
Neonatal antibiotics		38	32	0.190

The mean duration of hospital stay was 3.68 ±1.36 days in group I and 3.32 ±1.27 days in group II, and was comparable (p =0.175). Only 16% women in both the groups had ≥ 6 days of hospital stay, but it was not significant statistically between the two groups (p=0.623). The reason for longer hospital stay was due to neonatal sepsis and maternal complication.

DISCUSSION

There is no consensus as to what time interval between rupture of membranes and onset of contractions should be used. Immediate induction versus a policy of expectant management is one issue unresolved by clinical research to date [14-16]. Active management of term PROM with induction is associated with reduced maternal infective morbidity without increasing caesarean or operative vaginal birth [17].

Women who present with PROM and unfavourable cervix may have a higher chance of cesarean section if labor is induced by oxytocin. Induction of labor with prostaglandins offers the advantage of promoting both cervical ripening and myometrial contractility in this group of women [18].

Several investigators have compared immediate induction with 25mcg vaginal misoprostol and immediate or delayed induction with oxytocin in women with PROM at term [19,20]. Others have compared immediate induction with PGE_2 gel and delayed induction with oxytocin in women with PROM at term [21-23].

The present study was done as Misoprostol has not been compared extensively with PGE2 in study designed exclusively for women with term PROM. The mean age and parity is similar to other studies [24,25]but less than that of Abraham et al [26]. In studies done by Frohn et al, Abraham et aland Chaudhuri et al, nulliparous women were more than parous women [24-26]. Our study also had more nulliparous women. The mean duration of ruptured membranes to delivery interval in our study differs from the study of Chaudhuri et al[24] (16.97 ± 6.94 vs 16.77 ± 6.06 hours in group I and II respectively) as in our study induction was done after six hours of PROM but others have done immediate induction.

In the present study, mean induction to delivery interval was not statistically significant in two groups. The results are similar to the study of Chaudhuri et al[24] (10.75 ± 6.69 vs 9.37 ± 5.48 hours in PGE1 and PGE2 group respectively), but contrary to that of Abraham et al[26] (13.5 vs 21.5 hours as median, p=0.0003) and Frohn et al[25] (16.4 ± 10.2 vs 22.0 ± 12.9 hours, p=0.01), as the induction to delivery interval in these studies was significantly less in misoprostol group as compared to PGE_2 group. Women who delivered vaginally within 24 hours of induction of labor were comparable in both the groups and is similar to the study of Frohn et al[25] (81% vs 71%) and Abraham et al[26] (88.4% vs 58%). Women who delivered within 12 hours of induction of labor were similar in both the groups in our study but contrary to that of Frohn et al[25] (41% vs 16% p=0.005).

In the present study, significant difference was found in the dosage of drugs required for induction (P value = <0.0001). This is in agreement with the study of Chaudhuri et al[24] (21.9% vs 82.35%). The results are different from the study of Frohn et al[25] as 2nd dose required was more in PGE_2 group as compared to PGE_1 group (62% vs 22%, p <0.01). In our study, 26% women in group I and 16% in group II required oxytocin and was more as compared to study of Chaudhuri et al[24] in which no woman required oxytocin in misoprostol group and only 6% women needed oxytocin in PGE_2 group as five doses of misoprostol were used in their study. But the need for oxytocin was less as compared to Abraham et al[26] study (50% in misoprostol and 56% in dinoprostone group).

The duration of first stage of labor was comparable in the two groups in nullipara and parous women. Other studies have not compared this duration. Only one woman in misoprostol group and no woman in PGE_2 group had operative vaginal delivery. This is not in agreement with the study of Chaudhuri et al[24] (15.47% vs 3.7%, p=0.011). In the present study, caesarean delivery rate though higher in the misoprostol group but was not significant. This finding is in concordance with the results reported in literature [25,26]. Failure of induction is similar to the study of Abraham et al[26] (2% vs 2.08%) and Chaudhuri et al[24] (2.85% vs 2.94%).

Intrapartum and post partum complications were similar in both the groups. Incidence of intrapartum fever was more in study of Abraham et al[26] (21% vs 20% in group I, II). Post partum fever is comparable with the study of Chaudhuri et al[24] (0.95% vs 0.98 % in group I and group II). The only significant difference between two groups was present for tachysystole and fetal distress in our study. The fetal heart rate abnormalities are different from study of Frohn et al[25] (9% vs 11%, p=0.53), Chaudhuri et al[24] (2.85% vs 5.88 %, p=0.234), Abraham et al[26] (38% vs 39.58%) as in these studies no significant difference was noted between the groups. Occurrence of tachysystole is more with misoprostol and this is comparable with studies conducted by Frohn et al[25] (20% vs 6%, p=0.02), Sanchez-Ramos et al[27] (28.6% in PGE_1 group vs 14% in oxytocin group) and Moodley et al[28] (21% vs 9%, p=0.004).

In our study, higher number of babies born in group I had a low Apgar score (<7) than group II at 1minute, but this did not exist at 5 minute and is in agreement with the study of Chaudhuri et al[24] (11.42% vs 2.94%, p=0.036 at 1 min. and 0.95% vs 0.96%, p=0.743 at 5 min.). No neonate was born with Apgar score < 4 in both groups. NICU admission were less in our study (6% vs 0%) as compared to to other studies [24-26].

In the present study, neonatal sepsis is comparable with study of Frohn et al[25] (9% vs 7% p=0.70) and Chaudhuri et al[24] (2.85% vs 2.94%, p=0.644).

Neonatal antibiotics were given to 76% in group I and 64% in group II. Out of these only 8% and 4% had neonatal sepsis in group I and II respectively, remaining had received prophylactic antibiotic till 48 to 72 hours of births. These results are different from the study of Chaudhuri et al[24] (7.61%, 5.88% in PGE_1 and PGE_2 group) as in our hospital prophylactic antibiotics are given to neonates who are born after 18 hours duration of ruptured membranes. There is limitation in our study as the sample size was small and not blinded. Further large randomized controlled trials are required for comparing the efficacy and adverse effects of these two drugs in PROM.

Although both PGE_1 tablet and PGE_2 gel have been used for induction of labor in women with PROM, PGE_2 gel is better drug as compared to misoprostol as number of doses and adverse effects like tachysystole and fetal distress are less. However both the drugs are similar in efficacy for induction-delivery interval, caesarean section rate, need for oxytocin, failed induction and neonatal outcome. Misoprostol being cheaper and stable at room temperature can be a useful alternative in developing countries having low per capita income and tropical climate and where continuous fetal monitoring facilities are available.

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