PROSTAGLANDIN E_2 GEL AND PLACEBO FOR CERVICAL RIPENING

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SUMMARY

A double blind randomised clinical trial with prostaglandin E_2 Gel and Placebo Gel by intracervical instillation was carried out in 445 women. Uterine contractions were stimulated and labour was established in 70% of women who received PGE_2 Gel instillation, out of which 37.6% had delivered within 12 hours of administration of drug in contrast to 11.6% of women who delivered within 12 hours of 40% in whom uterine contractions were stimulated in the Placebo Gel group. Succss rate for cervical ripening was found to be significantly higher in PGE_2 Gel group, the rates of vaginal and operative deliveries were similar in both the groups.

Introduction

Oxytocin for induction of labour in the presence of unripe cervix has led to a caesarean section rate for failed induction of approximately 50 per cent Prins *et tl* (1983) Shepherd *et al* 1983). Various methods have been proposed to prime the cervix including mechanical stretching with an extra-amniotic balloon, use of laminaria Tehow *et al* (1979) and relaxin gel Maclenan *et al* (1980). In recent reports prostaglanding E_2 has been used for cervical ripening. The Indian Council of Medical Research, therefore initiated a comparative clinical trial with Prostaglandin E_2 Gel and Placebo Gel for cervical ripening and its impact on onset of labour.

Material and Methods

The trial was carried out at 13 Medical Colleges. A double blind randomized clinical trial using 0.5 mg of PGE_2 gel in 2 ml of gel and 2 ml of plain gel for placebo was carried out in total of 445

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subjects in whom labour was to be induced for a variety of medical and/or obstetric reasons. Women enrolled were primiparous, had gestational age of 34-42 weeks with intact membranes, a single foetus presenting by vertex, not in labour and had a modified Bishop score of 0-3. The trial was considered successful if modified Bishop score at 12 hours after administration of Gel was 6 or more or women had delivered spontaneously before this cut-off point.

Observations

A total of 445 women of which 221 had been administered PGE_2 Gel and 224 Placebo Gel were enrolled for the study.

Status at 12 hours

Effect of PGE_2 gel application on cervix was successful in 154 (69.7%) cases including 83 (37.6%) who had delivered within 12 hours of drug administration and in 71 Bishop score was 6 or more. The trial was successful in 76 (33.9%) cases of placebo group, including 26 (11.6%) who had delivered within 12 hours and 50 with Bishop score 6 or more. Success rate was found to be significantly high with PGE_2 gel in comparison to placebo gel ($P < .05$). Trial was interrupted in 10 and 3 cases and there was no response to gel in 57 and 145 cases in PGE_2 and placebo group, respectively (Table I).

TABLE I
Status at 12 Hours

Status	PGE_2 GEL		PLACEBO GEL	
	No.	%	No.	%
Delivered	83	37.6	26	11.6
Bishop Score >6	71	32.1	50	22.3
Total Successful:	154	69.7	76	33.9
Trial interruption	10	4.5	3	1.3
No response	57	25.8	145	64.8
Total failures:	67	30.3	148	66.1
Total:	221	100.0	224	100.0

TABLE II
Trial Interruptions—Reasons and Management

Reasons for trial interruption	PGE_2 GEL		PLACEBO GEL	
	LSCS	Synto-cinon	Spont. Del.	LSCS
Foetal distress	6	—	—	2
PROM	1	1	—	—
Hypertonic ut. cont.	1	—	—	—
Hypersensitivity to drug	—	—	1	—
Deep transverse arrest	—	—	—	1
Total:	8	1	1	3

Trial interruptions and their management

There were 13 women, 10 in PGE_2 group and 3 in Placebo group in whom the trial was interrupted. Caesarean section was performed and baby was delivered in all 3 cases of placebo group.

In the prostaglandin group trial was interrupted due to foetal distress, premature rupture of membranes, post dated pregnancy, hypertonic uterine contractions and hypersensitivity to drug. Caesarean section had to be performed in 8 cases. The drug was wiped in case of hypersensitivity 15 minutes after administration (Table II).

Failures and their management

The application of gel had no significant effect on status of cervix or labour in 57 women (25.8%) in PGE_2 group and 145 (64.8%) in placebo group. Caesarean section was performed in 22 (40.0% including 9 cases of failed induction), women in drug group and in 30 (21.2%, including 15 cases of induction failure) in the placebo group. The rate of caesarean section among the failure cases was significantly higher in the drug group ($P < .05$) as compared to placebo. Remaining women had vaginal delivery (Table III).

TABLE III
Management of Failure Cases

	PGE_2 GEL		PLACEBO GEL	
	No.	%	No.	%
LSCS	22	40.0	30	21.2
Induction	23	41.8	54	38.3
Spontaneous delivery	10	18.2	57	40.5
LAMA	2	—	4	—
Total:	57	100.0	145	100.0

Side effects and complications during labour

Minor side effects like nausea, vomiting, diarrhoea, fever, etc. occurred in 18 women (9.1%) in drug group and in 7 women (3.1%) in placebo group. Foetal distress was the commonest side effect occurring in 27 women (12.2%) in prostaglandin group and in 19 women (8.5%) in the placebo group. Other side effects included uterine hypertonicity (6 and 1 cases), uterine inertia (2 cases in each group) transverse arrest (1 and 2 cases), APH (1 and 2 cases), PPH (2 cases in each group), maternal distress (one case in each group) and intrapartum sepsis (one case in placebo group) hypersensitivity to drug (one case in PGE_2 group). No side effects were observed in 73.8 per cent women in PGE_2 group and 83.5 per cent women in placebo group.

Mode of delivery and outcome of pregnancy

In PGE_2 group 178 women (81.7%) had vaginal delivery as compared to 184 women (83.6%) in the pacebo group. Caesarean section had to be performed in a total of 40 (18.3%) women in drug group and in 36 (16.4%) in the placebo group.

There were 29 women, 12 in prostaglandin group and 17 in placebo group in whom indication for induction was intrauterine death. There was one more still birth in PGE_2 group. Outcome was live birth in all remaining cases.

Neonatal morbidity and mortality

There were 13 sick neonates, 6 in the PGE_2 gel group and 7 in the placebo group. Neonatal morbidity in PGE_2 group included 3 cases of asphyxia, one

case of respiratory distress, and 2 cases of congenital malformation. In the placebo group 2 babies had asphyxia and one case each had jaundice, meconeum aspiration, hypoglycaemia, septicaemia and congenital malformations. Four neonates in drug group and 3 in placebo group expired.

Maternal Mortality

There was no maternal death in PGE_2 group. One woman in placebo group who had postpartum haemorrhage and was given blood transfusion died within 2 days. Cause of death was attributed to blood transfusion reaction.

Discussion

There is recent evidence of prostaglandin E_2 being used in different dosages for cervical ripening. In this study 0.5 mg of PGE_2 gel stimulated the uterine activity in 69.7 per cent of which 37.6 per cent delivered vaginally before cut-off point of 12 hours, similar findings have been reported by William, Wilkerson, *et al* (1985) where 87.5 per cent showed successful cervical ripening and 37.5 per cent went into labour. Lorenz, *et al* (1984) compared 2 mg of PGE_2 gel with a placebo gel and reported no difference in cervical score, induction delivery interval. However Buchanan, *et al* (1984) found 3 mg PGE_2 vaginal suppository more effective than placebo gel. A study carried out by Robert, *et al* (1986) on 800 subjects, who were administered PGE_2 gel 6 hourly until a Bishop Score of 7 or more was obtained showed that sequential application has no added advantage for cervical ripening than single application over a similar period of observation.

In conclusion the intracervical administration of PGE_2 gel in a small dose of 0.5 mg prior to induction has been found successful, safe and effective non-invasive technique for cervical ripening and shortening induction delivery interval. However our study did not show any difference in rate of operative deliveries.

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