Evaluation of the Role of Oral Prostaglandins in the Induction of Labour

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Summary: Labour was induced in 50 cases with oral tablets of prostaglandins, PGE_2. To compare the efficacy, safety, advantage and disadvantages of oral prostaglandins (PGE_2), 50 cases were studied as control in whom labour was induced with oxytocin infusion. Only term singleton cases with vertex presentation and Bishop score >3 were selected and matched with respect to their age and parity. The commonest clinical condition requiring induction was PIH. The induction-delivery interval favoured PGE_2(mean 9.44 hrs) over oxytocin (mean 10.31 hrs)in primigravidae (P=NS) and oxytocin (mean 6.12 hrs) over PGE_2 (mean 6.34 hrs) in multigravidae (P=NS). Caesarean section was performed for 4 cases in PGE_2 group and 6 cases in oxytocin group (P=NS). Induction was successful in 92% cases in PGE_2 and 94% cases in oxytocin group (P=NS). The majority of side effects in the PGE_2 group were gastrointestinal (20%)(P=S), whereas higher incidences of dysfunctional uterine action (16%)(P=S), fetal heart rate variations (10%). PPH (12%) and neonatal side effects (16%) were observed in oxytocin group. The neonatal outcome was similar in both the groups.

It was concluded that oral PGE_2 is a safe and effective alternative to oxytocin for induction of labour.

Introduction

Oxytocin has been widely used for induction since 1840's. This method is effective, but it has its disadvantages. The availability of prostaglandins has sparked a renewed wave of interest in the search of an ideal oxytocic agent. Its different mechanisms of action, various routes of administration and its usefulness in terminating pregnancy at all stages of gestation, have motivated many investigators to carry out clinical trials to determine if its use may be an improvement over the already available oxytocics.

After extensive premarking trials, prostaglandins were introduced in India for use in the oral form in the year 1991. The present study was undertaken at Goa Medical College, to assess the effectiveness of oral prostaglandins for the induction of labour.

Materials and Methods

All patients included in this study were taken from Goa Medical College over a study period of 2 years from January 1993 to January 1995. This study includes 50 cases of induction of labour by oral tablets of prostaglandins PGE_2. To compare the efficacy, safety, advantages and disadvantages of oral prostaglandins (PGE_2), 50 cases were studied as control in whom labour was induced with oxytocin infusion. The distribution of cases was matched with respect to their age and parity. In all the cases, a detailed history was obtained and thorough general physical and obstetric examination was done. Only singleton cases, in cephalic presentation, over 37 week's gestation, with a Bishop's score of more than 3 and no cephalopelvic disproportion were chosen for induction.

Labour was induced by oral PGE_2 in the study group and intravenous oxytocin in the control group. In the PGE_2 group induction was begun with a dose of 0.5 mg (1 tablet) PGE_2 per-oral at 0 hours increased by one tablet hourly till adequate contractions were established. The maximum dose allowed at one time was 1.5 mg (3 tablets) per hour. The quality of labour was evaluated every hour. Once adequate contractions of 3 per 10 min lasting for 45 seconds were established with a particular dose, the dose was gradually decreased to a minimum required for maintenance and this was continued till delivery. In the

oxytocin group induction was begun at the dose of oxytocin of 2 milliunits/minute by intravenous infusion and increased, if necessary, every half hourly by 2 milliunits / minute till a maximum of 20 milliunits/minute.

Clinical monitoring of induction was done as follows :-

1) hourly blood pressure and pulse.
2) Hourly temperature.
3) Fetal heart rate every 15 minutes in 1st stage and every 5 minutes in 2nd stage.
4) Uterine contractions-intensity, frequency and duration by external palpation only.
5) pervaginal examination every 2 hrs.
6) blood loss postpartum assessed hourly for the first 4 hours by taking estimates of quantum of soakage of vaginal pads and surgical linen.

The following observations were made :

1) preinduction Bishop score
2) induction-delivery interval
3) mode of delivery
   a) vaginal delivery
   b) caesarean delivery
   c) instrumental delivery-defined as the application of forceps or vacuum extractor for aiding vaginal delivery.
4) success and failure rates
   a) a successful induction was defined by onset of active labour within 8 hrs of induction and the uterine contractions simulating normal labour pattern.
   b) a failed induction was defined as follows
   1) induction stopped after a trial period of 8 hours.
   2) induction stopped because of the side effects directly attributable to the drug in question.
5) side effects as follows
   gastrointestinal – nausea, vomiting, diarrhoea
   extravasation of infusion
   thrombophlebitis
   drip reaction
   dysfunctional uterine action which includes hyperstimulation and incoordinate uterine action
   fetal heart rate variations
   postpartum hemorrhage
   puerperal pyrexia
6) neonatal side effects
   birth asphyxia
   jaundice
   cardiovascular abnormalities
7) neonatal outcome –
   birthweight
   Apgar scores at 1 and 5 minutes.

The cases in each group were studied as Elective Inductions (Group I) and Indicated Inductions (Group II). This was done because the cases in the elective induction group do not suffer from any associated complicating factors that might influence the outcome of the induction. Hence it is possible to judge the efficacy of the inducing agent without bias.

Results

Maximum cases from both groups were in the age group 20 – 30 years i.e 30 (60%) and 28 (56%) respectively (Table I). Of the total 100 cases 25 (50%) in each group were primigravidae (Table II). Both the groups were matched with age and parity.

Table I.

Age Distribution in Both Groups (n=100)

Age (Years)	PGE_2 group (n=50)		Oxytocin group (n=50)	
	No	%	No.	%
< 20	1	2	2	4
20 – 30	30	60	28	56
> 30	19	38	20	40

Table II.

Parity Distribution In Both Groups (n=100)

Gravida	PGE_2 group (n=50)		Oxytocin group (n=50)	
	No	%	No.	%
1	25	50	25	50
2	18	36	16	32
> 3	7	14	9	18

Table III.

Indications for Inductions (n=100)

Group Indications	Total	PGE_2 group		Oxytocin group	
		No	%	No.	%
I) Elective	30	14	28	16	32
II) Indicated	70	36	72	34	68
a) PIH		15	37.5	12	30.0
b) Postdatism		11	27.5	10	25.0
c) PROM		7	17.5	8	20.0
d) IUGR		6	15.0	7	17.5
e) Diabetes		1	2.5	2	5.0
f) Rh-isoimmunization		-	-	1	2.5
	100	54*		56*	

* some cases had more than one indication

Table IV.

Pre-Inducibility Score (n=100)

	PGE_2 group (n=50)		Oxytocin group (n=50)		Significance (t test)
Parity	No.	Mean	No.	Mean	
Primigravidae	25	5.36	25	5.64	NS
Multigravidae	25	6.56	25	6.64	NS

Table V.

Induction-Delivery Interval (n=87)

	PGE_2 group		Oxytocin group		Significance (t test)
Parity	No.	Mean	No.	Mean	
Primigravidae	21	9.44 hrs	19	10.31 hrs	NS
Multigravidae	23	6.34 hrs	24	6.12 hrs	NS
	44*		43*		

*There were 6 cases in PGE_2 group and 7 in oxytocin group in whom either the induction failed or who had to be subjected to emergency cesarean section for developed indications. These cases were excluded from the analysis.

Table VI.

Mode of Delivery (n=100)

Mode of Delivery	PGE_2 group (n=50)		Oxytocin group (n=50)		Significance (z test)
	No.	%	No.	%	
Vaginal	41	82	37	74	NS
Caesarean section	4	8	6	12	NS
Instrumental	5	10	7	14	NS

Table VII.

Success and Failure Rates (n=100)

	PGE_2 group (n=50)	Oxytocin group (n=50)	Significance (z test)
Success rate	92%	94%	NS
Failure rate	8%	6%	NS

Table VIII.

Material Side Effects (n=100)

Side effects	PGE_2 group (n=50)		Oxytocin group (n=50)		Significance (z test)
	No.	%	No.	%	
1) Gastrointestinal	10	20	1	2	S
2) Extravasation	-	-	8	16	-
3) Thrombophlebitis	-	-	2	4	-
4) Drip reaction	-	-	1	2	-
5) Dysfunctional uterine action	2	4	8	16	S
a) Hyperstimulation	2	4	5	10	-
b) Incoordinate uterine action	-	-	3	6	-
6) Fetal heart rate variations	1	2	5	10	NS
7) Postpartum hemorrhage	2	4	6	12	NS
8) Puerperal pyrexia	3	6	4	8	NS

Table IX.

Neonatal Side Effects (n=100)

Side effects	PGE_2 group (n=50)		Oxytocin group (n=50)		Significance (z test)
	No.	%	No.	%	
1) Asphyxia	-	-	2	4	
2) Jaundice	3	6	6	12	NS
3) Cardiovascular	-	-	-	-	

Table X.

Neonatal Outcome (n=100)

	PGE_2 group (n=50)	Oxytocin group (n=50)	Significance (t test)
Mean Apgar at 1 min	8.24	7.72	NS
Mean Apgar at 5 min	9.80	9.56	NS
Mean Birth weight	2.72	2.79	

Table III analyses the indications for induction in our study. The elective inductions Group comprised of 1/3rd and the indicated inductions (Group II) comprised of 2/3rd of the total cases. In the indicated group, the most common clinical condition requiring induction was PIH followed by postdatism and PROM.

Our study was undertaken in cases with inducibility score of cervix ranging from 4 to 12 (Table IV). The PGE_2 group had lower mean preinduction scores in both primigravidae and multigravidae. The difference was not significant.

The induction – delivery interval was shorter in the PGE_2 group for primigravidae (mean 9.44 hours) as compared to oxytocin (mean 10.31 hours) group (Table V). In multigravidae the results were in favour of oxytocin.

Vaginal delivery occurred in 41 (82%) cases in PGE_2 and in 37 (74%) cases in oxytocin group respectively (Table VI). There were 4 (8%) caesarean sections in PGE_2 and 6 (12%) in oxytocin groups respectively.

In the PGE_2 group induction was successful in 46 cases and failed in 4 cases whereas in the oxytocin group, induction was successful in 47 cases and failed in 3 cases (Table VII).

The PGE_2 group showed significantly higher incidence of gastrointestinal side effects (20% in PGE_2 as opposed to 2% in oxytocin group). However most of the cases (7 cases) were limited to mild nausea (Table VIII). These side effects did not warrant stoppage of treatment and were controlled in cases where necessary with antiemetics. The oxytocin group showed a significantly high incidence of dysfunctional uterine action (hyperstimulation and incoordinate uterine action). The oxytocin group also showed side effects specific to the drug delivery system in the form of extravasation of infusion, thrombophlebitis and drip reaction.

Neonatal side effects were higher in oxytocin group; 2(4%) cases had severe birth asphyxia with Apgar of 2 at 1 minute (Table IX). They survived stormy neonatal courses. There was a higher incidence of jaundice in the oxytocin group. Most of the cases had physiological jaundice. There was no significant difference in the neonatal outcomes for the 2 groups (Table X).

Discussion

Our study was conducted with the objective of establishing the efficacy of oral prostaglandins (PGE_2) as agents for induction of labour and to find out the comparative superiority, if any, over the widely used oxytocin infusion.

An attempt was made for symmetrical distribution of cases with respect to their age and parity in both the PGE_2 and oxytocin groups (Tables I & II). The maximum cases in both the groups were between 20 to 30 yrs. Many other studies had similar distribution (Elder, 1975; Friedman et al, 1975; Jina et al, 1994). Both the groups were evenly matched for parity, 25 cases in each group being primigravidae and 25 multigravidae. A similar distribution was seen in other studies (Lauersen & Wilson, 1974, Krishna et al, 1990).

Elective induction is still practiced in many centers especially for convenience of the hospital and/or patients. Literature provides a range of 5% (Karim & Sharma, 1971) to 42% (Craft, 1972) for elective inductions. The Krishna et al (1990) 26% incidence is similar to 30% in our study (Table III).

In the indicated induction group, the most common inductions were PIH, postmaturity and PROM in that order (Table III). Most studies have observed postmaturity (Craft, 1972; Karim & Sharma, 1971), while a few PROM (Sandhu et al, 1995) as the commonest indication. Krishna et al (1990) has PIH followed by PROM and postmaturity as most common indications in their study.

Induced labours are shorter than spontaneous labours

Sandhu et al, 1995). Whether this interference with the natural process is harmful or beneficial has not been conclusively proved. The induction to delivery (I-D) interval is the 'gold standard' for judging the efficacy of any inducing agent. In this respect, prostaglandins have demonstrated ample superiority over oxytocin (Friedman et al, 1975; Jina et al, 1994), especially in inductions with poor preinduction cervical score (Nelson & Bryans, 1976). In our study, for the PGE_2 group, the I-D interval was 9.44 hours for primigravidae and 6.34 hours for multigravidae (Table V) which is much less than most studies (Karim & Sharma, 1971; Agarwal et al, 1993; Dubey et al, 1994; Mackenzie, 1990) and comparable to a few others (Lauerson & Wilson, 1974; Gabert et al, 1979). This may be explained by the fact that the inductions in our study were more favourable (mean preinduction scores were 5.36 for primigravidae and 6.56 for multigravidae) than other studies (Table IV). Only cases with score more than 3 were induced in contrast to other studies which also included cases with score 0-3 (Lauerson & Wilson, 1974; Agarwal et al, 1993; Dubay et al, 1994; Mackenzie, 1990). The study, which used the same selection criteria for Bishop score as our study, was that of Krishna et al (1990). However, in that study, PGE_2 had a higher mean I-D interval for primigravidae (11.1 hours) and lower mean I-D interval for multigravidae (4.70 hours) than present study. Besides, they studied induction of labour in only 30 patients as opposed to 100 patients in our study. In primigravidae, some studies have favoured PGE_2 (Dubey et al, 1994; Jina et al, 1994) and some oxytocin (Krishna et al, 1990; Agarwal et al, 1993; Sandhu et al, 1995). In our study, primigravidae delivered faster in the PGE_2 group (Table V). Most studies have favoured PGE_2 (Krishna et al, 1990; Agarwal et al, 1993; Dubay et al, 1994; Jina et al, 1994) as efficient labour inducers in multigravidae. In our study multigravidae delivered faster with oxytocin than with PGE_2. A similar observation was made by Sandhu et al (1995).

Literature reports caesarean section rate as low as 0% (Krishna et al, 1990) to as high as 18.2% (Squires & Mason, 1980) for induction of labour with oral PGE_2. Many studies (Nelson & Bryans, 1976; El-Qarmalawi et al, 1990; Sandhu et al, 1995) have observed similar caesarean section rate for PGE_2 group (8%) as our study (Table VI). There are studies which have observed a lower caesarean rate (Ueland & Conrad, 1983; Kelly et al, 1973; Krishna et al, 1990) which may be due to the influence of early amniotomy on labour (Kelly et al, 1973) or because they studied very low number of cases (Krishna et al, 1990).

Since 1971, a large number of studies have appeared in literature evaluating of oral PGE_2 for the induction of labour. The success rate has ranged from a low of 68% (Elder, 1975) to a high of 100% (Craft, 1972; Murnaghan et al, 1974; Dubay et al, 1994), most investigators reporting a rate of more than 85% (Karim & Sharma, 1971; Lauersen & Wilson, 1974; Gabert et al, 1979; Kelly et al, 1973; Krishna et al, 1990; El-Qarmalawi et al, 1990). There has been no uniformity in defining success and this has reflected in the wide variability of success rate. In our study, establishment of labour within 8 hours was used as criterion for defining success of an induction. Nelson & Bryans (1976) used the same criterion for defining success. They, however, observed a success rate of 82% and a failure rate of 18%, which are not in accordance with our study. Most of their failures were limited to lower Bishop scores (≤5) whereas, our study included patients whose Bishop Scores was >3. Most studies (Kelly et al, 1973; Krishna et al, 1990; El-Qarmalawi et al, 1990; Agarwal et al, 1993; Dubay et al, 1994; Jina et al, 1994) have failed to show any advantage for either PGE_2 or oxytocin over the other as agents for the induction of labour. In our study, both agents were almost equally efficacious in inducing labour (Table VII).

The high incidence of gastrointestinal side effects in the prostaglandin group (Kelly et al, 1973; Nelson & Bryans, 1976; Krishna et al, 1990; Agarwal et al, 1993), ranging from 13.3% (Krishna et al, 1990) to 36.7% (Kelly et al, 1973) is an undesirable feature. A few studies have observed a lower incidence of side effects (El-Qarmalawi et al, 1990). In our study, an incidence of 20% was

observed. When compared to oxytocin, the gastrointestinal side effects were significantly high ($p<0.05$) (Table VIII). A similar observation was made by other studies (Kelly et al, 1973; Nelson & Bryans, 1976; Agarwal et al, 1993).

Hyperstimulation and incoordinate uterine action have been observed to be higher for oxytocin as compared to PGE$_2$ group (Kelly et al, 1973; Nelson & Bryans, 1976). This may be due to the fact that it is difficult to titrate accurately the oxytocin dosage by the conventional intravenous drip as it is affected by the hand positioning of the patient, venous caliber and drip system used. In our study, the incidence of dysfunctional uterine action (hyperstimulation and incoordinate uterine action) was significantly higher ($p<0.05$) in the oxytocin group (Table VIII).

Fetal heart rate variations were higher for oxytocin group in most studies (Krishna et al, 1990; Agarwal et al, 1993; El Qarmalawi et al, 1990). This could be because oxytocin induced contractions are more tumultuous and of a higher amplitude than PGE$_2$ (Ueland & Conrad, 1983). In our study there wee 2 (4%) cases in PGE$_2$ and 5 (10%) cases in oxytocin group with fetal heart rate variations (Table VIII).

Very few investigators have studied the incidence of PPH following induction with oral prostaglandins. Krishna et al (1990) observed an incidence of 6.6% whereas, Dubay et al, (1994) found no case of PPH in PGE$_2$ induced labours. In our study there were 2 (4%) cases of PPH in the PGE$_2$ group as compared to 6 (12%) cases in oxytocin group (Table VIII). Krishna et al (1990) found a higher incidence of PPH in the PGE$_2$ group (6.6% and 0% respectively) as opposed to the study of Dubay et al (1994) (0% and 4.25% respectively). Krishna et al (1990) studied only 30 cases, 15 in each group whereas Dubay et al (1994) studied 100 cases, 50 in each group.

Dubay et al (1994) observed neonatal complications in 2 (4.7%) cases in PGE$_2$ and 4 (9.5%) cases in oxytocin group. In our study the neonatal side effects were higher for the oxytocin group when compared with PGE$_2$ group (Table IX). There was no difference in the neonatal outcomes in PGE$_2$ and oxytocin groups (Table X) as it is been observed by other studies (Kelly et al, 1973; Agarwal et al, 1993; Dubay et al, 1994, Jina et al, 1994).

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