"Comparison of Maternal and Fetal Complications Following Induction of Labour with Oral Prostaglandins and Oxytocin Infusion"

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Summary: Induction of labour and safe delivery of the newborn is of great concern to the practising obstetrician and a search is on to find a method which is not only effective and acceptable to the patient and staff, but is devoid of any serious maternal or fetal side effects either directly or indirectly attributable to the drug in question. In the present study, labour was induced in 50 cases with oral tablets of prostaglandins, PGE_2. To compare the maternal and fetal safety, 50 cases were studied as control in whom labour was induced with oxytocin infusion. Only term singleton pregnancies with vertex presentation and Bishop scores >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 over oxytocin in primigravidae (P=NS) and oxytocin over PGE_2 in multigravidae (P=NS). Both the agents were equally efficacious in inducing labour. The majority of side effects in the PGE_2 group were gastrointestinal (20%) (P=S). The incidence of gastrointestinal side effects was dose related. Most of the patients (34) required a total dosage of 5 or <5mg. All the side effects were limited to patients requiring >5mg. Primigravidae and women with lower Bishop scores (<7) showed the maximum incidence of gastrointestinal side effects. A higher incidence 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 mean Apgar at 1 minute and 5 minutes favoured the PGE_2 group (8.24 & 9.8) as compared to oxytocin (7.72 & 9.56) (P=NS). The mean birthweights were similar in both the groups (2.72 & 2.79) (P=NS).

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

Introduction

A healthy mother and a healthy baby are the central concepts of any obstetric management. Labour has to be induced in order to achieve this objective in certain cases, either for maternal or fetal interests, or both.

An ideal inducing agent should be devoid of any serious maternal or fetal side effects either directly or indirectly attributable to the drug in question. It should also be convenient for patients and staff and have a short induction – delivery interval. Oxytocin has been widely used for induction of labour 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.

After extensive premarketing 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 compare the maternal and fetal safety profiles of PGE_2 and oxytocin 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 age and parity. In all the cases, a detailed history was obtained and thorough general physical and obstetric examination was done. Only singleton, cephalic presentations, 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 a maximum of 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) Indications for induction
2) Induction – Delivery Interval
3) Mode of delivery as follows
   a) Vaginal delivery
   b) Caesarean delivery
   c) Instrumental delivery-defined as the application of Forceps or Vaccum 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) Total dosage used
6) 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
7) Neonatal side effects as follows
   Birth asphyxia
   Jaundice
   Cardiovascular abnormalities
8) Neonatal outcome as follows
   Birthweights
   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 inductions group do not suffer from any feto-maternal compromise that might contribute to any maternal or fetal complications following induction.

Results

Table I analyses the indications for induction in our study. The Elective inductions (Group I) 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.

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 II). In multigravidae the results were in the favour of oxytocin.

Vaginal delivery occurred in 41 (82%) cases in PGE_2 and in 37 (74%) cases in oxytocin group respectively (Table III). 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 I.
Indication for Induction. (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 II.
Induction – Delivery Interval. (n=87)

	PGE_2 group		Oxytocin group		Significance (t test)
Paity	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 caesarean section for developed indications. These cases were excluded from the analysis.

Table III
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 IV.
Success and Failure rates. (n=100)

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

(Table IV). 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 V). These side effects did not warrant stoppage of treatment and were controlled in cases where necessary, with antiemetics.

Table VI demonstrates the relationship of PGE_2 dosage and incidence of gastrointestinal side effects. The incidence of gastrointestinal side effects is dose related. Most of the patients (34) required a total dosage of 5 or <5 mg. All the side effects were limited to patients requiring >5

Table V.
Maternal 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 haemorrhage	2	4	6	12	NS
8) Puerperal pyrexia	3	6	4	8	NS

Table VI.
Relationship of Dose and Gastrointestinal Side Effects in the PGE_2 Group (n=50)

Range (1-12 mg)	No.	Nausea	Vomiting	Diarrhoea	Nausea & Vomiting	Total
1-5	34	-	-	-	-	-
5.5-10	15	7	1	-	1	9
>10	1	-	-	-	1	1
Total	50	7	1	-	2	10

Table VII.
Relationship of Parity and Gastrointestinal Side Effects in the PGE_2 Group. (n=50)

Gravidity	Bishop score	No.	Total dosage	Nausea	Vomiting	Diarrhoea	nau. & Vomit.	Total
Primi	4-7	20	6.625	6	-	-	2	8
	8-12	5	2.30	-	-	-	-	-
Multi	4-7	15	3.63	1	1	-	-	2
	8-12	10	1.35	-	-	-	-	-
Total		50		7	1	-	2	10

Table VIII.
Neonatal Side Effects. (n=100)

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

mg. Primigravidae and women with lower Bishop scores (<7) showed the maximum incidence of gastrointestinal side effects (Table VII).

The oxytocin group also showed side effects specific to the drug delivery system in the form of extravasation of infusion, thrombophlebitis and drip reaction (Table V). It also showed a significantly high incidence (16% versus 4% in PGE_2 group) of dysfunctional uterine action (hyperstimulation and incoordinate uterine action) (Table

Table IX.
Apgar at 1 minute. (n=100)

	PGE_2 group (n=50)	Oxytocin group (n=50)	Significance (t test)
<5	2	6	
6-8	28	26	
9-10	20	18	
Mean	8.24	7.72	NS

Table X.
Apgar at 5 minutes (n=100)

	PGE_2 group (n=50)	Oxytocin group (n=50)	Significance (t test)
<5	-	1	
6-8	5	7	
9-10	45	42	
Mean	9.8	9.56	NS

Table XI.
Birthweights. (n=100)

	PGE_2 group (n=50)	Oxytocin group (n=50)	Significance (t test)
<1.5	-	-	
1.5-2	4	3	
2-2.5	7	10	
>2.5	39	37	
Mean	2.72	2.79	NS

V). Fetal heart rate variations were more common in the oxytocin group (10%) as opposed to PGE_2 group (4%) (Table V). The incidence of postpartum hemorrhage was higher for oxytocin group (12%) as compared to PGE_2 group (4%) (Table V). The incidence of puerperal pyrexia was 6% and 8% for PGE_2 and oxytocin groups respectively. The cause of puerperal pyrexia was breast congestion in most cases (Table V).

Neonatal side effects were higher in oxytocin group; 2(4%) cases had severe birth asphyxia with Apgar of 2 at 1 minute (Table VIII). 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 Apgar scores at 1 minute (Table IX) and 5 minutes (Table X). The birthweights for the two groups were similar. (Table XI).

Discussion

Our study was conducted with the objective of establishing the safety 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.

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 study of Krishna et al (1990) closely correlates with the observations in our study (Table I). They observed an incidence of 26% for elective inductions. In the indicated induction group, the most common clinical conditions requiring induction were PIH, postmaturity and PROM in that order (Table I). Most studies have observed postmaturity (Craft, 1972; Karim & Sharma, 1971), while a few PROM (Sandhu et al, 1995) as the commonest condition. Krishna et al (1990) observed PIH followed by PROM and postmaturity in their study.

The induction to delivery (I-D) interval is the 'gold standard' for judging the efficacy of any inducing agent. 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 II) which is much less than most studies (Karim & Sharma, 1971; Agarwal et al, 1993; Dubay et al, 1994). This may be explained by the fact that the inductions in our study were more favourable. Only cases with score more than 3 were induced as contrast to other studies, which also included cased with score 0-3. In primigravidae, studies have either favoured PGE_2 (Dubay et al, 1994) or 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 II). Most studies have favoured PGE_2 (Krishna et al, 1990; Agarwal et al, 1993; Dubay 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).

Most 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 III). 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 the efficacy of oral PGE_2 for the induction of labour, most investigators reporting a rate of more than 85% (Karim & Sharma, 1971; Gabert et al, 1979; Kelly et al, 1973; Krishna et al, 1990; El-Qarmalawi et al, 1990). Most studies (Kelly et al, 1973; Krishna et al, 1990; El-Qarmalawi et al, 1990; Agarwal et al, 1993; Dubay 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 IV).

Gastrointestinal side effects are an undesirable feature of oral prostaglandin inductions. Nausea, vomiting and diarrhoea have been reported following oral administration of PGE_2 tablets (Karim & Sharma, 1971; Kelly et al, 1973; Friedman et al, 1975; Nelson & Bryans, 1976; Gabert et al, 1979; Ueland & Conrad, 1983; Krishna et al, 1990; Rajan, 1992; Agarwal et al, 1993), ranging from 13.3% (Krishna et al, 1990) to 36.7% (Kelly et al, 1973). A few studies have observed a lower incidence of side effects (El-Qarmalawi et al, 1990). In clinical practice these side effects rarely necessited the discontinuation of medication (Kelly et al, 1973). In our study, an incidence of 20% was observed. When compared to oxytocin, the gastrointestinal side effects were significantly high (Table V). A similar observation was made by other studies (Kelly et al, 1973; Nelson & Bryans, 1976; Agarwal et al, 1993). The side effects did not warrant discontinuation of medication in our study. They were self-limiting and promptly disappeared after delivery. In a few cases, they had to be controlled with anti-emetics.

The incidence of gastrointestinal side effects is dose related (Friedman et al, 1974; Rajan, 1992). A dose not exceeding 1 mg (2 tablets) can limit these side effects (Rajan, 1992). Friedman et al (1974) used 2 dosage regimens for inductions-0.5 mg (1 tablet) hourly for 10 doses and other 1 mg (2 tablets) hourly for 10 doses. The induction was discontinued once active labour was established or if severe side effects supervened. They observed an incidence of 13% for the lower dosage group and 16% for the higher dosage group. In our study, most of the patients (34) required a total dosage of 5 mg or less. All the side effects (20%) were limited to patients requiring more than 5 mg (10 tablets) (Table VI). Primigravidae and patients with unfavourable Bishop score show a higher incidence of gastrointestinal side effects when induced with oral PGE_2 (Karim and Sharma, 1971; Gabert et al, 1979). This is due to the fact that these patients require higher dosages for successful inductions. Our study confirms the above observations (Table VII). Primigravidae and women with lower Bishop scores (<7) showed the maximum incidence of gastrointestinal side effects.

Very few cases of uterine hypertonus have been reported in literature following administration of oral PGE_2 (Friedman et al, 1975; Ueland & Conrad, 1983; Krishna et al, 1990; El-Qarmalawi et al, 1990; Agarwal et al, 1993). Theoretically oral administration of prostaglandins would seem more difficult to filtrate and it would appear difficult to stop the effect of the drug, should hypertonicity occur. As a rule vomiting supervenes with overdoses, which seems to provide the oral route with a built in safety valve (Rajan, 1992). In our study, there were 2 (4%) cases with hypertonus following oral PGE_2 induction (Table V). One case had to be terminated by caesarean section as she developed fetal distress following the hypertonus. 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 intrave-

nous 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 in the oxytocin group (Table V).

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 group as compared to 6 (12%) cases in oxytocin group (Table V). 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.

Fetal heart rate variations were higher for oxytocin group in most studies (Krishna et al, 1990; Agarwal et al, 1993; El-Qarmlawi et al, 1990). In our study there were 2 (4%) cases in PGE_2 and 5 (10%) cases in oxytocin group with fetal heart rate variations (Table V). 2 (4%) cases had severe birth asphyxia with Apgar of 2 at 1 minute (Table VIII, IX, & X). One was a multigravida, induced for IUGR, developed intrapartum fetal distress and was delivered by caesarean section. The birth weight was 1.9 kg and the baby was severely asphyxiated at birth. The Apgar was 2 and 4 at 1 and 5 minutes respectively. It survived a stormy neonatal course of 21 days with exaggerated physiological jaundice, septicemia and necrotizing enterocolitis, which were successfully tackled. However, no follow up studies were available. The other was a primigravida induced for PIH with IUGR, developed fetal distress in 2nd stage and was delivered by forceps. Birth weight was 2.35 kg and Apgar 2 and 6 at 1 and 5 minutes respectively. It survived a difficult neonatal period. The above observations bring out the controversy whether it would be worthwhile to induce with oral prostaglandins rather than oxytocin, mothers with clinically compromised fetuses as these fetuses are less tolerant to the stress of labour. It has been observed by many investigators that PGE_2 induced contractions are of lower amplitude than those induced by oxytocin and simulate very closely normal spontaneous labour contractions (Ueland & Conrad, 1983).

One proven advantage of prostaglandins for labour induction is a reduced incidence of neonatal hyperbilirubinaemia (Conway et al, Beazly & Weekes, 1976; Chew, 1977) In our study the incidence of jaundice was higher for oxytocin group (12%) as compared with PGE_2 group (6%) (Table VIII). Most of the cases had physiological jaundice.

There was no difference in the Apgar scores at 1 and 5 minutes and birthweights for PGE_2 and oxytocin groups (Tables IX, X, XI) as has been observed by other studies (Kelly et al, 1973; Agarwal et al, 1993; Dubay et al, 1994).

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