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Comparison of Labour Induction between Intracervical PGE2 Gel and Intravaginal PGE1 Analogue Tablet among Patients with Intra Uterine Foetal Death- A Cross-Sectional Study

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Abstract **Original Research Article**

Introduction: In spite of modern medical advancement, there is some significant pregnancy loss during antepartum period. In majority of cases labour soon follows death of the foetus, but sometimes labour does not start for several weeks. So induction of labour is needed but the unfavourable cervix remains a well-recognized impediment to success of induction of labour in intrauterine foetal death. Prostaglandins in different Seems in different routes have been widely investigated to be used for induction of labour particularly when the cervix is unripe. Both Prostaglandin E1, and Prostaglandin E2 have been proved effective equally. Dinoprostone (PGE_2), has been widely used for cervical ripening and labour induction. Misoprostol, a methyl ester of prostaglandin analogue, has been shown to be effective for cervical ripening and labour induction. ***Aim of the study:*** The aim of this study was to compare the effectiveness of vaginal misoprostol (PGE_1 tablet) and prostaglandin (PGE_2 gel) in order to induce labour among patients with intrauterine foetal death. ***Methods:*** This was a cross-sectional study and was conducted in the Department of Obstetrics and Gynaecology of Dhaka Medical College Hospital, Dhaka, Bangladesh during the period from July, 2004 to June, 2005. In our study we included 70 patients who were given and during labour induction. Our patients were equally divided into two groups – i) Group A (Patients were given Per- vaginal prostaglandin tablet) & ii) Group B (Patients were given Intra-cervical prostaglandin gel). ***Result:*** In total 70 patients from both the groups completed the study. In our study we found the mean age was 23.94±4.19 and 24.46±2.44 years in group A and group B respectively and the mean induction to onset of labour time was less in prostaglandin E_2 group (5.97±3.75) hours, than in prostaglandin E_1 group (8.24±3.19) hour but induction to delivery interval time was not significantly different in most of the patients in both groups. With a smaller dose PGE_1, was effective for most of the deliveries even in earlier gestation. Risk of fever, post-partum haemorrhage and hyperstimulation did not differ significantly. Ono patient needed caesarian section in PGE_2 and two patients needed caesarian section with impending rupture and intrapartum haemorrhage in PGE_1 group. ***Conclusion:*** In our study, we found both the methods are suitable for successful induction of labour and delivery outcome in intra uterine foetal death. Induction to onset of labour time is less in PGE2 gel. But induction to delivery interval time is not significantly different in most of the patients in both groups. With a smaller dose PGE1 is effective for most of the deliveries even in earlier gestation.

Keywords: Labour induction, Intra Uterine Foetal Death, PGE_1, PGE_2.

INTRODUCTION

Labour is a natural process comprising of ripening of the cervix, followed by contraction of uterine musculature in order to delivery of the fetus from the uterus. In normal course of events, labour occurs at the end-term of pregnancy. However, in many pregnant patients, labour does not progress as expected. In these cases, it has to be induced by artificial means. Induction of labour i.e. artificially or prematurely stimulating childbirth may be done by the use of oxytocin to stimulate uterine contractions or via prostaglandins, when both cervical maturation & stimulation of contractions are needed [1].

Prostaglandins in general, are able to stimulate labour in a near-natural manner [2]. Whenever further continuation of pregnancy is considered hazardous, termination of pregnancy is sought for. The aim of induction being to achieve a safe vaginal delivery for the fetus without causing harm to mother. Failed induction may be associated with, besides a poor neonatal outcome, great physical and mental trauma to the mother. Failed induction is the failure to enter into active phase of labour after 12 hours of regular uterine contractions in a patient who has been induced [3].

Foetal death is defined as intrapartum death after the foetus has reached the age of viability. Stillbirth refers to the birth of child after 28th week of pregnancy that does not breathe or shows any sign of life after delivery from the mother. If the heart is beating after delivery, although there is no sign of respiration the death should not recorded as a stillbirth but as a neonatal death.[4] In some centre babies may live and even may survive following birth before 28 weeks although rarely even before 22-24 weeks [4]. The World Health Organization suggests a gestational age of greater than 24 weeks or a birth weight greater than 500gm. In many ways it is more practical as in many parts of the world accurate gestational age is not known for most woman while weighing the baby is a relatively easy and a more precise procedure [4]. According to WHO; fetal death is defined as "death prior to complete expulsion or extraction from its mother of a products of conception, irrespective of duration of pregnancy." The care should be multi-fold higher in the case of a woman with an IUFD. Retention of dead fetus in utero has its own ill effects on physical, psychological and social aspects [5]. Foetal death is high in extrem extremes of maternal reproductive age, (18-35 years) primi parity and para 5 and over and when interval between childbirths is less than 2 years. It rises to two folds with previous neonatal death. Maternal low pre-pregnant body weight (<45 kg), anaemia, early marriage and net weight gain in pregnancy (<8 kg) are some important factors.[6] Incidence of foetal death beyond 24 weeks in less than 1% of all pregnancies. Still birth rate in U.K. in 1991 was 5.7 per 1000 birth and 27.2 per 1000 in India [7]. Bangladesh has high still birth rate 29 per 1000 pregnancies [8]. It is estimated that about 7.3 million perinatal death occur annually in the world, most of these in developing countries especially in Asia. Though South Asia accounts for 50 percent of total birth, 70 percent of the perinatal death take place in this region. Here PMR is 87 per 1000 birthys. Bangladesh is having very high PMR-59 per 1000 births. The perinatal mortality rate varies from less than 10 (in Japan, Nordic countries, Germany) to as high as 80 or even 100 per 1000 birth in least developed countries. In developing countries, it is around 35-60 per 1000 birth (WHO, 1989) [6, 8].

In order to reduce the risk of maternal or neonatal morbidity and mortality, labour is often induced [9]. Approximately one in four or five women in Europe and USA is induced due to prolonged pregnancy, prelabour rupture of the membranes, and concerns about the well-being of the child or mother (e.g., poor growth, cholestasis, preeclampsia, etc.) [10]. Prostaglandins have been used for induction of labour since the 1960s [10, 11] and are widely used in clinical practice, but side-effects are reported including gastrointestinal symptoms (nausea, diarrhoea, and vomiting), uterine hyper stimulation, and fever [10, 12]. Various prostaglandin preparations are available, which have been used by various routes, including local (intracervical and intravaginal) and general administration (oral, intramuscular, and intravenous). For local administration, prostaglandin E2 (PGE2) is available in a gel in general 0.5 mg for intracervical use and 1 or 2 mg for intravaginal use. However, various other dosages and sustained-release pessary are also currently used [10, 11].

In spite of modern medical advancement, there is some significant pregnancy loss during antepartum period. This is a tragic event for mother, her family and the physicians who are providing the obstetric care [6]. In majority of cases labour soon follows death of the foetus, but sometimes labour does not start for several weeks. So induction of labour is needed but the unfavourable cervix remains a well-recognized impediment to success of induction of labour in intrauterine foetal death. A variety of methods have been used to effect cervical change. Prostaglandins in different Seems in different routes have been widely investigated to be used for induction of labour particularly when the cervix is unripe [13]. Both Prostaglandin E_1, and Prostaglandin E_2 have been proved effective equally. Dinoprostone (PGE_2), has been widely used for cervical ripening and labour induction. Misoprostol, a methyl ester of prostaglandin analogue, has been shown to be effective for cervical ripening and labour induction. However their preparations are expensive and need refrigeration for storage. Misoprostol a prostaglandin E, analogue has been shown to be effective for cervical ripening and labour induction. It is cheap and stable at room temperature [14, 15].

In this study we aimed to compare the effectiveness, safety and side effects between intravaginal misoprostol tab. (PGE) and intracervical prostaglandin gel (PGE) in the cervical repining and labour induction.

Objective of the study

The main objective of the study was to compare the effectiveness of vaginal misoprostol (PGE_1 tablet) and prostaglandin (PGE_2 gel) in order to induce labour among patients with intrauterine foetal death.

METHODOLOGY & MATERIALS

This was a cross-sectional study and was conducted in the Department of Obstetrics and Gynaecology of Dhaka Medical College Hospital, Dhaka, Bangladesh during the period from July, 2004 to June, 2005. In our study we included 70 patients who were given PGE_1 and PGE_2 during labour induction. Our patients were equally divided into two groups – i) Group A (Patients were given Per- vaginal prostaglandin tablet) & ii) Group B (Patients were given Intra-cervical prostaglandin gel).

These are the following criteria to be eligible for the enrollment as our study participants: a) Patients aged between 15 to 45 years; b) Patients with singleton pregnancy & gestational age 28-42weeks; c) Patients with intact membrane having no labour pain ; d) Patients with sonographic confirmation of intrauterine foetal death; e) Patients who were willing to participate in the study And a) Patients with uncontrolled DM, b) Patients with Coagulopathy; c) Patients with previous surgical history; d) Patients with known allergy to study drugs; e) Patients with any history acute illness (e.g., renal or pancreatic diseases, ischemic heart disease etc.) were excluded from our study.

Induction of labour by pervaginal prostaglandin tablet

Prostaglandin E analogue (1tab=200 µgm) was used for the study. In selected patients cervical scoring was done. The patients were treated by ½ tabs PGE1, applied in the posterior fornix with the patient in dorsal position. The doses were repeated every 4 hours for a total of 4 doses. Follow up were given at hourly interval or when the patient complained of any problem. Patient who was not responding, then oxytocin infusion (4 amp in 1000 cc) was started 6 hours after the last dose of tab PGE_1.

Induction of labour by intra-cervical prostaglandin

In a selected patient, cervical score was done, prostaglandin gel 500µgm was inserted intra-cervically, from a loaded syringe after exposing the uterine cervix by a speculum. Following insertions, the patient was kept in bed for half an hour. Then the patient was followed up with special attention to uterine contraction hourly and per vaginal examination was done when satisfactory uterine contraction was observed. Then per-vaginal examination was done at four hourly intervals.

Statistical Analysis

All data were recorded systematically in preformed data collection form and quantitative data was expressed as mean and standard deviation and qualitative data was expressed as frequency distribution and percentage. Statistical analysis was performed by using SPSS (Statistical Package for Social Sciences) for windows version 10. Chi-Square and unpaired students „t" test were performed to compare categorical variables between two groups. Probability value <0.05 was considered as level of significance. The study was approved by Ethical Review Committee of Dhaka Medical College Hospital.

RESULT

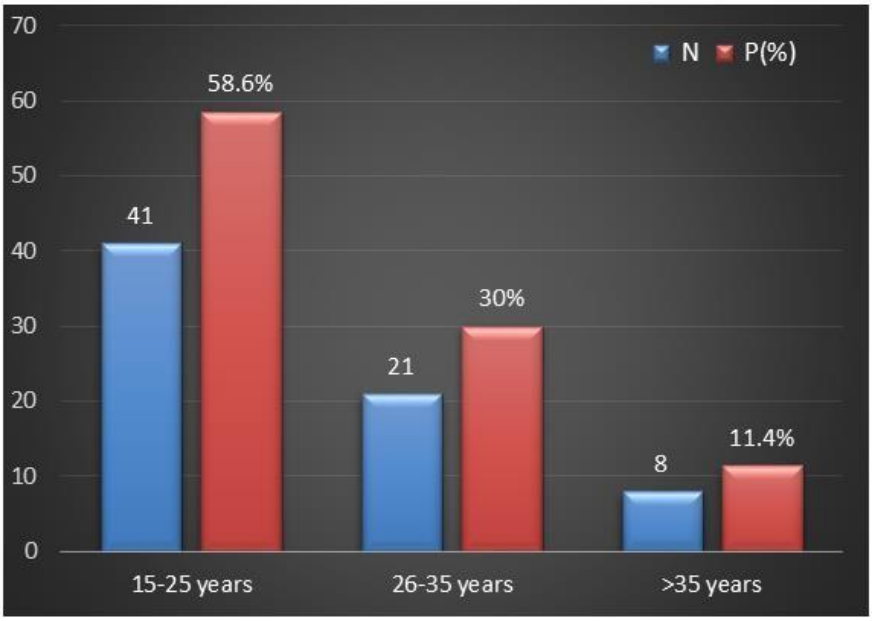

Figure 1: Age distribution among our study subjects

Table 1: Demographic characteristics of our study patients

Parameters	Group A(PGE_1)		Group B (PGE_2)		P-value
	(N=35)	P(%)	(N=35)	P(%)	
Age (Years)					
Mean±SD	23.94±4.19		24.46±2.44		0.121
Gravidity					
Primi	23	65.7%	18	51.4%	0.140
Multi	12	34.3%	17	48.6%	
Gestational age (weeks)	31.14± 3.52		33.51±4.04		0.001

Table 2: Doses of intra-vaginal PGE_1 and intra-cervical PGE_2

Dose (µgm)	Group A(PGE_1)		Group B (PGE_2)		P-value
	(N=35)	P(%)	(N=35)	P(%)	
1	2	5.7%	31	88.6%	
2	16	45.5%	4	11.4%	
3	10	24.6%	0	0	
4	7	20%	0	0	
Mean±SD	247.14± 102.14		542.86±142.01		**0.001**

Table 3: Requirement of oxytocin drip

Drip	Group A(PGE_1)		Group B (PGE_2)		P-value
	(N=35)	P(%)	(N=35)	P(%)	
Given	7	20%	5	14.2%	**1.010**
Not given	28	80%	30	84.5%	

Table 4: The time interval between induction to onset of labour(hour)

Induction to onset of labour (hours)	Group A(PGE_1)		Group B (PGE_2)		P-value
	(N=35)	P(%)	(N=35)	P(%)	
2-4	4	11.4%	17	48.6%	
>4-8	12	34.3%	9	25.7%	
>8	16	45.7%	7	20%	
Mean±SD	8.24± 3.19		5.97±3.75		**0.001**

Table 5: Induction to delivery interval in hours

Induction to delivery interval (hours)	Group A(PGE_1)		Group B (PGE_2)		P-value
	(N=35)	P(%)	(N=35)	P(%)	
6-12	12	34.3%	22	62.9%	
>12-24	20	57.1%	8	22.9%	
>24	2	5.7%	3	8.6%	
Mean±SD	8.24± 3.19		5.97±3.75		**0.001**

Table 6: Maternal complication after induction of labor

Complication	Group A(PGE_1)		Group B (PGE_2)	
	(N=35)	P(%)	(N=35)	P(%)
Fever ≥ 100°F	2	5.9%	3	8.6%
Gastro intestinal symptom	0	0	0	0
Postpartum hemorrhage	1	2.9%	2	5.7%
Hyperstimulation	2	5.7%	1	2.9%
No complication	30	85.7%	29	82.8%

Table 7: Outcome of induction measures and hospital stay

Parameters	Group A(PGE_1)		Group B (PGE_2)		P-value
	(N=35)	P(%)	(N=35)	P(%)	
Successful Induction	33	94.30%	34	97.4%	0.510
Failed Induction	2	5.7%	1	2.9%	
Hospital stay (Days)	2.17±1.98		2.56±1.32		0.121

In Figure 1 we showed the age distribution of our study patients. Majority (58.6%) of our patients were aged between 15-25 years old, followed by 30% & 11.4% patients were aged 26-35 years & above 35 years respectively. In table 1 we showed the demographic characteristics of our study patients. We found the mean age was 23.94±4.19 and 24.46±2.44 years in group A and group B respectively. Among all patients 65.7% & 51.4% had primi gravidity in group A & B respectively. Mean gestational age was found 31.14± 3.52 & 33.51±4.04 weeks in group A & B respectively.

Table 2 shows the dose requirement among study subjects. Most of the patients 16 (45.5%) in group A has got 2 doses and mean doses was 247.14±102.14 µgm and 31(88.6%) patients in group B got single dose and mean dose was 542.86±142.01 µgm. Result is statistically significant in favour of group A. Table 3 Shows that small number 7 (20%) patients needed oxytocin drip in group A and 5 (14.2%) patients needed oxytocin drip in group B, 80% patient in group A & 84.5% patient in group B delivered without oxytocin drip.

Table 4 Shows that mean induction to onset of labour time is less in prostaglandin E_2 group (5.97±3.75) hours, than in prostaglandin E_1 group (8.24±3.19) hour. Labour started with in 2 to 4 hours in 48.6% patients of PGE_2 group compared to 11.4% patients of PGE_1 group.

In table 5 we showed that mean induction to delivery interval time was not significantly different in both groups. In 22 (62.9%) patients in PGE_2 group compared to 12 (34.3%) in PGE_1 group delivered within 6-12 hours of induction. Among all respondents 20 (57.1%) patients in PGE_1 group compared to 8 (22.9%) in PGE_2 group delivered within 12-24 hours.

Table 6 shows that maternal complications were few and did not vary between the two groups. The most common complication among vaginal deliveries was elevated temperature (≥100°F). Risk of fever, postpartum hemorrhage, and hyperstimulation did not differ significantly. We found 85.7% & 82.8% patients in group A & B respectively with no complication.

Table 7 shows that most of the patients 94.30% in PGE_1 group and 97.4% in PGE_2 group delivered vaginally after induction in both groups. Among all patients, 2.9% needed caesarean section in PGE_2 group compared to 5.7% in PGE_1 group. Hospital stayed in both groups were almost similar.

DISCUSSION

Induction of labour is a standard obstetric approach in properly selected patients. Achievement of vaginal delivery for a woman who requires induction of labour in intra uterine foetal death should be simple, safe, effective and non invasive. Before prostaglandins become available, the methods used included estrogen administration, intraamniotic injection of hypertonic solutions and high doses of oxytocin. A number of maternal deaths attribute to hypersonic intrauterine instillation, effective doses of injection nearly always led to some degree of water retention [13].

In the present study we compared the efficacy between intracervical PGE2 Gel and intravaginal PGE1 analogue tablet for induction of labour in late intrauterine fetal death.

In our study we found the mean age was 23.94±4.19 and 24.46±2.44 years in group A and group B respectively. Mean gestational age was found 31.14± 3.52 & 33.51±4.04 weeks in group A & B respectively (Table 1). Biswas *et al*., found the mean age was 21.05 ± 2.52 & 22.00 ± 2.18 years in misoprostol group & dinoprostone gel group respectively [16]. Reinhard *et al*., found the mean gestational age was 39.6 ± 1.5 & 39.7 ± 1.1 in cervical & intravaginal group respectively [17].

Most of the patients 16 (45.5%) in group A has got 2 doses and mean doses was 247.14±102.14 µgm and 31(88.6%) patients in group B got single dose and mean dose was 542.86±142.01 µgm (Table 2). One study reported by Bartha JL, Comino-Drigado R. 2000 *et al*., showed that a single dose of 50mg vaginal misoprostol compared with 5mg of intra-cervical dinoprostone every 6 hours was more effective but with a higher risk of hyperstimulation (6% vs 2%) [18].

In our study the mean induction to onset of labour time was less in prostaglandin E_2 group (5.97±3.75) hours, than in prostaglandin E_1 group (8.24±3.19) hour. Labour started with in 2 to 4 hours in 48.6% patients of PGE_2 group compared to 11.4% patients of PGE_1 group (Table 4). Brattacharvya *et al*., found the mean of induction delivery was 15.3 ±11.27 & 14.35 ± 10.9 hrs among PGE2 gel & Oxytocin group respectively [19].

In our study the mean induction to delivery interval time was not significantly different in both groups (Table 5). Biswas *et al*., found mean induction to delivery interval was 8.13 ± 1.62 & 14.32 ± 2.46 in misoprostol group & dinoprostone gel group respectively [16].

The most common complication among vaginal deliveries was elevated temperature (≥100°F). Risk of fever, postpartum hemorrhage, and hyperstimulation did not differ significantly (Table 6).

Sadhana Singh *et al*., found that minor side effects of nausea, vomiting and diarrhoea were more common with misoprostol. Uterine hyperstimulation was noted in both groups resulting in short duration of labour. Neonatal deaths seen in both groups were due to maternal causes [20].

Various methods of induction of labour following IUFD have been tried and studied and most of the studies compared between combined method (mifepristone and misoprostol) and misoprostol only. No study undertaken to compare the role of dinoprostone gel vs. misoprostol in induction of labour in a case of IUFD. There are various randomized studies, which compared vaginal misoprostol with dinoprostone for induction of labour at term with living fetus. In those studies the incidence of vaginal delivery within 24 h of induction was found higher in the misoprostol group [21-25]. Pandis *et al*., findings regarding maternal side effects, dose requirement, oxytocin augmentation, hospital stay, PPH, analgesia requirement was almost similar to our findings [21]. Intrauterine foetal death is a devastating incident that affects the mother, her family, and the obstetrician. Labor induction should be straightforward, safe, and preferably non-invasive.

Limitations of the study

Our study was a single centre study. We could only study a few adverse effects between PGE_1 & PGE_2 because of our short study period and limited resources. There are more adverse effects like insomnia, fatigue, nausea, constipation needs to be evaluated. After evaluating once those patients we did not do follow-up for a long period and have not known other possible interference that may happen in the long term with these patients.

CONCLUSION AND RECOMMENDATIONS

In our study, we found both the methods are suitable for successful induction of labour and delivery outcome in intra uterine foetal death. Induction to onset of labour time is less in PGE_2 gel. But induction to delivery interval time is not significantly different in most of the patients in both groups. With a smaller dose PGE_1 is effective for most of the deliveries even in earlier gestation. It is cheap and easily available. So, it is suitable for poor patients and can be used safely. Therefore a further study with prospective and longitudinal study design including larger sample size needs to be done to identify more adverse effects and evaluate the efficacy between PGE_1 and PGE_2 gel to prevent foetal death.

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