Induction of labor using prostaglandin E_2 (PGE_2) vaginal gel in triacetin base

An efficacy study comparing two dosage regimens

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Summary: Objective: To compare two dosage regimens for the administration of vaginal prostaglandin gel in triacetin base for induction of labor.

Methods: Seventy subjects planned for elective induction of labor at term were randomized to treatment with PGE_2 vaginal gel every 6 or 12 hours. The 6-hourly group received an initial dose of 1 mg, followed by 2 mg at 6 hour intervals for a maximum of two additional doses if not in active labor. The 12-hourly group had an initial dose of 2 mg followed by two additional doses at 12 hour intervals if not in active labor.

Results: Successful induction rate was higher in the 12-hourly as compared to 6-hourly gel regimen (100% vs. 91%, $P>0.05$). Twelve hours after the initial dose, delivery occurred in 34% of the 12-hourly group as compared to 20% of the 6-hourly regimen ($P<0.05$) and by 18 hours delivery had occurred in 57% and 37% respectively ($P<0.01$). We found no difference in the induction-active labor interval ($P>0.05$), and the induction-delivery interval ($P>0.05$) between the two groups. Active labor followed a single dose of gel in 66% of the 12-hourly group compared to 40% of the 6-hourly group ($P<0.01$). Syntocinon augmentation was needed in 6% of subjects in the 12-hourly group as compared to 26% in the 6-hourly group ($P<0.01$). The cesarean section rate was similar in both groups. Uterine hyperstimulation occurred less frequently in the 12-hourly group ($P<0.05$). The perinatal outcome was similar in both groups.

Conclusions: The 12-hourly regimen was more effective than the 6-hourly regimen in initiating labor. The majority of the subjects in the 12 hourly group achieved labor following a single dose of gel. Induction delivery interval, however, was similar in both groups.

Key words: Prostaglandin; Induction; Labor; Vaginal gel.

INTRODUCTION

Elective induction of labor is a common obstetric practice. Some institutions have recorded increasing numbers of labor inductions in the early 70s ([1]). Over the past three decades, a variety of agents have been employed for induction of labor. Further research, however, is necessary in order to identify the ideal agent which is not only effective but is also free from serious adverse effects on the mother and fetus ([2]). The introduction of prostaglandin E_2 gel for induction of labor has shown good promise in this regard ([3-6]).

Prostaglandin E_2 in triacetin gel is a fairly stable compound which has a prolonged shelf life and allows a smooth release of Prostaglandin E_2 ([7]). Its vaginal and intracervical administration is markedly effective when compared to other

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treatment modalities ([2, 3, 6, 8, 9]). In a randomized controlled trial comparing outcomes of induction of labor using intracervical or intra-vaginal prostin gel, we noted that delivery achieved by 24 hours in the intracervical group was 50% as compared to 93.5% in the intra-vaginal group (unpublished observation). Based on this observation, it may be reasonable to assume that vaginal prostaglandin gel in triacetin base is an efficient method of induction of labor. A major limitation, however, is the lack of an ideal regimen of administration which would attain a high success rate in initiating labor without any untoward effects on the mother or baby.

This study aims at comparing two dosage regimens for the administration of vaginal prostaglanding gel in triacetin base for induction of labor.

MATERIAL AND METHODS

A preliminary project consisting of twenty-five suitable subjects was undertaken. Administration of a single dose of 2 mg vaginal prostaglandin in triacetin (Upjohn, Canada) for induction of labor revealed that 60% of participants were in active labor within 6 hours of administration and 88% by 12 hours. From this observation, it would appear that an interval of 12 hours prior to the next administration of gel might be suitable for the induction of labor.

From 1st of April to 30th of June 1993, seventy suitable patients undergoing elective induction of labor at the Royal University Hospital were enrolled in this study. The experimental protocol was approved by the Institutional Ethics Review Board. The study population included pregnant women at a gestational age of greater than 37 weeks, intact membranes, parity of 3 or less and a Bishop Score ([10]) of no greater than 8. Patients with previous cesarean section, surgery to the uterine corpus, conditions contra-indicating vaginal delivery, active liver disease, severe cardiac disease, glaucoma, severe asthma or allergy to prostaglandin were excluded.

Following informed written consent, participants were randomly assigned to receive one of the two dosage regimens utilizing sealed opaque envelopes. Thirty-five subjects received 6-hourly PGE_2 and 35 received 12-hourly PGE_2 administration. All initial cervical assessments, randomization and administration of first dose of prostaglandin gel were undertaken by a single investigator (RS). Subsequent assessment regarding progress of labor was undertaken by other physicians who were blinded to the treatment modality in the first 6 hours beyond which the allocated regimen became obvious.

In one treatment arm, we administered an initial dose of 1 mg of vaginal prostaglandin E_2 in triacetin gel (Upjohn, Canada) in the posterior fornix. The subjects received a further two doses of 2 mg each on a 6-hourly basis if they were not in labor. Participants in the second treatment arm received an initial dose of 2 mg of vaginal prostaglandin E_2 gel in triacetin (Upjohn, Canada) in the posterior fornix. This dose was repeated at 12 and 24 hours if the patients were not in active labor. During administration of gel, the examining glove was lubricated with sterile water in order to reduce the potential of a lubrificant interfering with the absorption of prostaglandin. A vaginal speculum was not used, so as to reduce vaginal loss of gel which sometimes occurs with the use of a speculum. Continuous electronic fetal and tocodynamometric monitoring was performed for one hour after gel administration. Subjects were re-assessed according to their experimental protocol or clinical response.

Active labor was defined for nulliparous women as at least two painful contractions every 15 minutes and confirmed by the presence of a fully effaced cervix and/or cervical dilatation of $\geq$ 2 cm, and for multiparous women as at least two painful contractions every 15 minutes and confirmed by a fully effaced cervix and/or cervical dilatation of $\geq$ 4 cm. At least two painful contractions every fifteen minutes associated with spontaneous rupture of the membranes after vaginal gel insertion irrespective of cervical dilatation or effacement also constituted a diagnosis of labor ([11]). Once labor had commenced, further management was undertaken by the attending physician. Induction of labor was deemed to have failed if the patient was not in active labor within 12 hours after administration of the third gel. Uterine hyperstimulation was defined as either a series of single uterine contractions lasting 2 minutes or longer or frequency of uterine contractions of five or more in ten minutes ([12]). Maternal systemic side-effects, fetal heart rate abnormalities and adverse neonatal outcomes were recorded.

STATISTICAL ANALYSES

Categoric data were summarized by proportions. Statistical significance of difference in proportions were based on Pearson's Chi-square test. Statistical significance of differences in arithmetic means between two treatment groups were assessed by the two-tailed T-Test.

All P values of less than 0.05 were considered to indicate statistical significance. Statistical calculations were made with the help of Minitab Computer Software, Release 7.1, 1989.

RESULTS

Table 1 shows the demographic features of the subjects enrolled. There were no significant differences between the two groups.

The outcome of labor is detailed in Table 2. The interval between Induction and Active Labor in the 6-hourly group was 11.7 ± 6.9 (mean $\pm$ SD) and 12.3 ± 7.7 hours in the 12-hourly group ($P > 0.05$). Similarly the Induction to Delivery interval was 20.8 ± 9.0 for the 6-hourly group and 18.7 ± 9.8 for the 12-hourly group ($P > 0.05$). Fourteen subjects were in active labour by 6 hours in the 6-hourly group compared to eight in the 12-hourly group. This disparity was related to the fact that participants in the 6-hourly group were all examined at 6 hours while those in the 12-hourly group were examined only when clinically indicated during the first 12 hours. The mean Bishop score was 6.0 (range 4 - 8) for these 14 subjects and 4.6 (range 2 - 7) for the 8 subjects respectively. The mean Bishop score for women who delivered after a single dose in the 12-hourly group was 5.0 (range 2 - 8). The relationship between Bishop score and frequency of gel administration is further detailed in Figure 1.

By 12 hours following the initial dose, 7 of 35 participants (20%) had delivered in the 6-hourly regimen compared to 12 of 35 (34%) in the 12-hourly group ($P < 0.05$). At 18 hours, this number had increased to 13 of 35 participants (37%) in the 6-hourly group and 20 of 35 subjects (57%) in the 12-hourly group respectively ($P < 0.01$). This result is demonstrated graphically in Figure 2. By the design of this study, failed induction in the 12-hourly group occurred at 36 hours after initial gel administration compared to 24 hours in the 6-hourly group. If we were to use 24 hours as our end point for the 12-hourly group, the failure rate in that group would have been 11%. This was not statistically different from

Table 1. – *Characteristics of subjects allocated to treatment groups.*

	6-hourly PGE_2 ($n=35$)	12-hourly PGE_2 ($n=35$)
Parity		
Nulliparous	21	21
Multiparous	14	14
Age	26.0±5.9	28.5±6.4
Gestational age	40.2±1.3	39.4±1.6
Initial Bishop score	4.6±2.2	4.3±2.1
Indications for induction:		
Post date	18	16
Gestational diabetes	2	4
Other	15	15

Data expressed as Mean±SD.
No significant differences for any category studied.

Table 2. – *Outcome of induction of labor.*

	Nulliparous		Multiparous	
	6-hourly ($n=21$)	12-hourly ($n=21$)	6-hourly ($n=14$)	12-hourly ($n=14$)
Ind-Active labor (hrs)	12.8±6.7	15.0±8.4	10.1±7.2	8.3±4.0
Ind-Delivery (hrs)	24.5±8.0	22.1±9.3	15.3±7.9	13.5±8.4
Failed induction	2	0	1	0
Syntocinon	8	1*	1	1

Data expressed as Mean±SD. (*) $P < 0.02$.
No significant differences noted for the other categories.

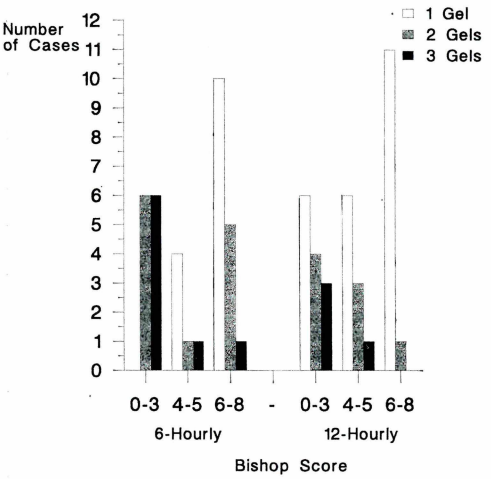

Fig. 1. — Relationship between Bishop score and number of gel(s) administered.

the results in the 6-hourly regimen and followed the use of two vaginal gel administrations only.

Fetal heart rate anomalies, defined as generation of a fetal monitoring strip of sufficient anomaly as to cause concern to the attending physician, occurred in 2 of 35 participants (6%) in the 6-hourly group and in 5 of 35 (14%) in the 12-hourly group ($p > 0.05$). Two cases of post-treatment fetal bradycardia occurred within half an hour of gel administration, one in each group. The episodes were transient, one lasting 3 minutes and the other 5 minutes. Both tracings improved with continuous monitoring and no adverse effect on the infants were observed. Three infants in the 6-hourly group and six in the 12-hourly group were admitted to the Neonatal Intensive Care Unit. Five infants in each group had an Apgar score of < 7 at one minute and one in the 6-hourly group had an Apgar Score of <7 at 5 minutes. All babies were discharged alive and well.

There were no significant differences ($P > 0.05$) between the two groups in the frequency of spontaneous vaginal delivery (20 of 35 in the 6-hourly group versus 23 of 35 in the 12-hourly group), operative vaginal delivery (10 of 35 in the 6-hourly group versus 7 of 35 in the 12-hourly group) and abdominal delivery (5 of 35 in each group) respectively. Analgesia requirements, maternal satisfaction and incidence of hyperstimulation are shown in Table 3.

Hyperstimulation occurred after the second dose in four participants and after the third dose in another four participants in the 6-hourly regimen. Three subjects had hyperstimulation after the first dose

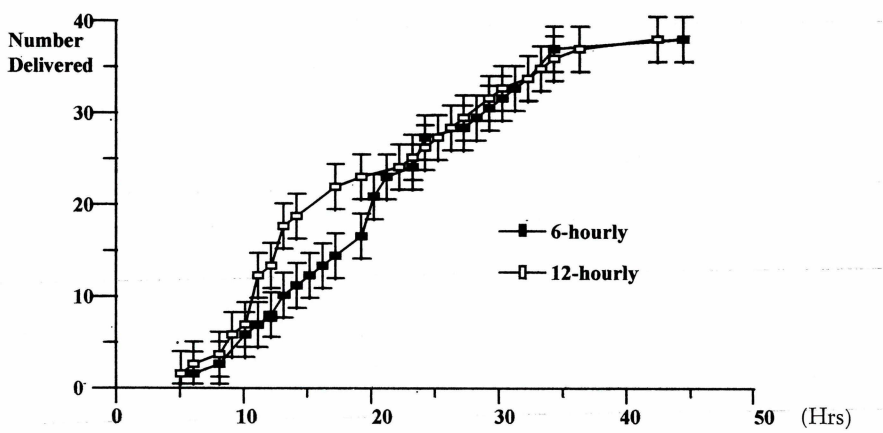

Fig. 2. — Relationship between number of deliveries and the time interval from initial gel administration.

Table 3. – *Maternal response to treatment.*

	6-hourly PGE_2 ($n=35$)	12-houryl PGE_2 ($n=35$)	P
Analgesia			
Epidural	24	24	N.S.
Demerol	16	8	<0.01
None	9	10	N.S.
Satisfaction			
Satisfied	28	31	N.S.
Dissatisfied	7	4	N.S.
Uterine hyperstimulation	10	6	<0.05
Emesis	4	5	N.S.

Level of significance $P<0.05$.

and three after the second dose in the 12-hourly group. No fetal effects were noted with hyperstimulation and vaginal swabbing with a saline soaked swab or use of tocolytics was not required in any of these cases. The participants were all discharged alive and well.

DISCUSSION

Vaginal PGE_2 in triacetin base has been studied more than any other preparation and its efficacy is well established ([2, 3, 9, 12, 13, 14, 15]). Our results demonstrated the superiority of the 12-hourly regimen based on the findings that sixty-six percent of subjects achieved labor with a single dose in the 12-hourly group and that the delivery rates at 12 and 18 hours were significantly higher in the 12-hourly group. This was achieved with less uterine hyperstimulation and less use of narcotic analgesic in the 12-hourly group as compared to the 6-hourly group. Furthermore, participants in the 12-hourly group required less syntocinon than those in the 6-hourly group and there were no failed inductions in the 12-hourly group.

We attributed the successful induction rate achieved in the 12-hourly group to the higher initial dose of prostaglandin used in that group. Greer *et al.* ([14]) demonstrated an upsurge in endogenous prostaglandin production following administration of vaginal prostaglandin. Thus, a higher initial dose might result in a higher level of endogenous prostaglandin and this may be of utmost importance in order to achieve successful induction. With regard to the technique of administration, Johnson *et al.* ([7]) noted in an in-vitro study that PGE_2 absorption varied with pH and was reduced by the use of a lubricant. We did not use any lubricant during administration of gel and this might also have contributed to better absorption of prostaglandin E_2 from the vaginal gel and higher endogenous prostaglandin production.

We observed that six of 13 (46%) participants with a Bishop score of 0-3 in the 12-hourly group achieved labor with a single dose. All participants with a Bishop score of 0-3 in the 6-hourly group, however, required more than one gel administration for induction of labor. Thus, the 12-hourly regimen may be more suitable for women with a very unfavourable cervix as it would reduce the discomfort of numerous gel administrations. However, strong conclusions could not be drawn as the sample size was small.

In cases of uterine hyperstimulation, good progress of labor was achieved despite low amplitude uterine contractions in some cases. This uterine irritability likely resulted from excessive endogenous production of prostaglandins presenting clinically as uterine hyperstimulation. Taylor *et al.* ([13]) demonstrated that salbutamol administration prior to vaginal prostaglandin insertion reduced the incidence of uterine activity during priming. Further research into the use of a tocolytic, for example salbutamol (8 mg), Indomethacin (25 mg) or Aspirin (80-160 mg) prior to administration of vaginal prostaglandin gel is required in order to evaluate the possibility of reducing uterine hyperstimulation during induction of labor with prostaglandin E_2 gel.

CONCLUSION

This study has demonstrated the superiority of the 12-hourly regimen in inducing labor in term pregnancies. The 12-hourly regimen with an initial dose of 2 mg was more effective and was associated with less uterine hyperstimulation compared to the 6-hourly regimen. Based on our findings, we would recommend a dosage regimen of 2 mg of vaginal prostaglandin gel on a twelve-hourly basis up to a maximum of 3 doses for induction of labor in patients with a Bishop score of up to 8.

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