

Of the 214 patients, 192 (90%) had ischaemic heart disease, and 159 (74%) had had an acute myocardial infarction. Primary ventricular fibrillation occurred in 139 (65%).

Many factors affect the success of defibrillation, and one of the most important is the duration of ventricular fibrillation before attempted conversion. Increased oxygen consumption is associated with the asynchronous and very rapid rate of contraction of the fibres of the fibrillating heart.^{7,8} Even a brief interruption of coronary flow might be expected to increase myocardial injury and thus increase the difficulty in removing ventricular fibrillation.

Although external cardiac massage and ventilation will maintain the viability of the cerebrum for 20 minutes or longer,⁹ it is important to recognise the limitations of cardiopulmonary resuscitation. The report of Kouwenhoven *et al*¹⁰ showed that the arterial pressure obtained during chest compression is about 80 mm Hg, while between compressions it is some 20 mm Hg. Thus the mean coronary perfusion pressure is usually less than 70 mm Hg. A mean pressure below 70 mm is unlikely to be associated with perfusion of ischaemic areas of the myocardium. Progression of myocardial injury may explain the inverse relation between the duration of cardiopulmonary resuscitation and the chance of survival. In this study ventricular fibrillation was present for two minutes or less in 74% of the episodes. Tacker *et al*¹ did not indicate the duration of ventricular fibrillation in their study.

Tacker *et al*¹ did not record details of the defibrillation technique or indicate the training and experience of the personnel concerned. It has become clear that paddle positions^{10,11} and their application,¹² electrode paste, and paddle size¹³ influence the amount of stored energy required for the successful removal of ventricular fibrillation. In our prospective study the personnel were medically qualified, and all had experience of coronary care and had received intensive training in resuscitation techniques. The paddles used were 8.5 cm in diameter. One was placed to the right of the sternum, below the clavicle, and the other in the fifth left intercostal space in the anterior axillary line. The electrode paste was chosen to give maximum reduction in transthoracic impedance.

The concept of weight-related energy dose proposed by Tacker and Geddes¹⁴ advocated the use of 4-6 J/kg body weight. They also said that for patients over 100 kg the initial shock should exceed 500 W s (delivered energy)¹⁵ and that if the initial shock fails the energy should be increased by increments of 100-200 W s.¹⁶ Our experience indicates that a second shock of identical energy often succeeds when the initial shock has failed.

This was also the experience of Mackay and Leeds.¹⁷ That heavy patients require high-energy shocks does not accord with the experience of others. Curry and Quintana¹⁸ reported the success of a single shock of 300 W s in a case of ventricular fibrillation that occurred after acute myocardial infarction in a woman weighing 108 kg. Lappin¹⁹ corrected ventricular fibrillation in a man weighing 145 kg with one 400 W s shock (stored energy). In this study there were three episodes of ventricular fibrillation in two patients who weighed 102 kg. A single shock of 200 W s (stored) was successful in two of these episodes; in the other, shocks of 400 W s (stored) succeeded.

Our findings do not support the proposition of Ewy and Tacker²⁰ that defibrillators capable of delivering 500-1000 W s should be developed. Indeed, it seems more logical to develop small, cheap, and more readily available machines, whose stored energy need not exceed 400 W s.

References

- Green, H L, Hieb, G E, and Schatz, I J, *Circulation*, 1971, **43**, A101.
- Dunning, A J, in *Textbook of Coronary Care*, ed L E Meltzer and A J Dunning, p 376. Amsterdam, Excerpta Medica, 1972.
- Hopps, J A, *Canadian Medical Association Journal*, 1964, **90**, 123.
- Tacker, W A, *et al*, *New England Journal of Medicine*, 1974, **290**, 214.
- Pantridge, J F, *et al*, *British Medical Journal*, 1975, **2**, 313.
- Tacker, W A, Cole, J S, and Geddes, L A, *Journal of Electrocardiology*, 1976, **9**, 274.
- Berglund, E, Monroe, R G, and Schreiner, G L, *Acta Physiologica Scandinavica*, 1957, **41**, 261.
- McKeever, W P, Gregg, D E, and Canney, P C, *Circulation Research*, 1958, **6**, 612.
- Kouwenhoven, W B, Jude, J R, and Knickerbocker, G G, *Journal of the American Medical Association*, 1960, **173**, 1064.
- Detmer, R A, *et al*, *Surgical Forum*, 1964, **15**, 251.
- Moore, T W, *et al*, *Bulletin of the School of Medicine, University of Maryland*, 1967, **52**, 3.
- Rivkin, L M, Roc, B B, and Gardner, R E, *American Journal of Surgery*, 1962, **104**, 286.
- Connell, P N, *et al*, *Journal of Electrocardiology*, 1973, **6**, 313.
- Tacker, W A, and Geddes, L A, *British Journal of Clinical Equipment*, 1977, **2**, 13.
- Geddes, L A, in *Proceedings of the Purdue Defibrillation Conference*, p 59. Purdue University, Indiana, 1975.
- Tacker, W A, in *Proceedings of the Purdue Defibrillation Conference*, p 124. Purdue University, Indiana, 1975.
- Mackay, R S, and Leeds, S E, *Journal of Applied Physiology*, 1953, **6**, 67.
- Curry, J J, and Quintana, F J, *Chest*, 1970, **58**, 82.
- Lappin, H A, *New England Journal of Medicine*, 1974, **291**, 153.
- Ewy, G A, and Tacker, W A, *American Heart Journal*, 1976, **91**, 403.

(Accepted 28 September 1977)

Cervical ripening with intravaginal prostaglandin E₂ gel

I Z MACKENZIE, M P EMBREY

British Medical Journal, 1977, **2**, 1381-1384

Summary

We describe a technique of administering prostaglandin E₂ (PGE₂) in a viscous cellulose gel into the vagina to ripen the unfavourable cervix in patients requiring induc-

tion of labour. A total of 168 primigravidae were studied, of whom 102 received 2 mg PGE₂ in 2% gel and 66 received 5 mg PGE₂ in 4% gel. In the latter group, the state of the cervix was significantly improved in 58 patients (87.9%), while 32 (48.5%) had started labour before planned induction. There were no maternal or fetal side effects or complications.

Introduction

The state of the uterine cervix has an important influence on the outcome of induced labour—particularly affecting the duration of labour, the incidence of maternal and fetal complications, and the need for caesarean section. For routine use in

Nuffield Department of Obstetrics and Gynaecology, John Radcliffe Hospital, Headington, Oxford OX3 9DU

I Z MACKENZIE, MRCOG, clinical lecturer
M P EMBREY, FRCOG, clinical reader

inducing labour, prostaglandins by intravenous infusion do not seem to offer any special advantages over intravenous oxytocin.¹ Nevertheless, when the cervix is uneffaced and tightly closed and amniotomy would be technically difficult, prostaglandin E₂ (PGE₂) given by extra-amniotic infusion considerably improves the labour prospects.² A similar effect can be achieved and the cervix "ripened" by instilling a single dose of PGE₂ in a viscous gel into the extra-amniotic space before formal induction.³ Using the same principle of prelabour "ripening" of the cervix with a prostaglandin E₂ gel, we developed a considerably simplified technique of vaginal administration, and report here the results.

Patients and methods

We studied a total of 168 patients with viable pregnancies. All were primigravidae with cephalic fetal presentations and unfavourable labour prospects as denoted by a modified Bishop score 0-3.³ The gestational ages of the pregnancies ranged from 35-42 weeks. All patients had obstetric or medical indications for induction of labour, and gave informed consent to the procedure. After an initial pilot study in which the effects of prostaglandin administration were observed by various means including tocography, we designed a double-blind trial. We subsequently investigated a larger cohort of patients.

PREPARATION OF PROSTAGLANDIN GEL

Prostaglandin E₂ in aqueous alcohol (Prostin E2, Upjohn) was used for all studies, and was administered in a highly viscous gel. This was prepared by adding either 2 mg PGE₂ diluted in 10 ml sterile water to 0.2 g powdered sodium carboxymethylcellulose (ICI England) to make a 2% solution, or by adding 5 mg PGE₂ in 10 ml sterile water to 0.4 g of the cellulose base to make a 4% solution. The cellulose granules had been autoclaved at 112°C for 15 minutes. The prostaglandin solution was mixed with the powdered cellulose in a standard plastic 20-ml syringe 1-28 days before intended use, and stored at 4°C.

MANAGEMENT OF PATIENTS

With few exceptions patients were initially assessed and treated by a single observer throughout the study; in most cases the subsequent cervical assessment and amniotomy were performed by the same person. Treatment was instituted in the antenatal ward with the patient in the dorsal position, and after clinical assessment of the cervix and pelvis, vaginal instillation was performed using a Nélaton catheter (size 16, French scale). The catheter tip was directed into the posterior vaginal fornix. Prostaglandin gel was administered the evening before planned induction; immediately after instillation the patient remained recumbent for 15 minutes, and subsequently no specific restrictions were imposed.

With the onset of uterine activity experienced by the patient, regular half-hourly observations of maternal pulse, blood pressure, temperature, and uterine activity and fetal heart rate were recorded. The next morning, 16-18 hours later, a formal induction was performed in the delivery unit in patients not already established in labour; after low amniotomy a rising regimen of intravenous oxytocin was started. Labour was subsequently managed by the duty obstetric staff. If the cervical state had not improved the following morning beyond a score of 4, a formal induction was performed or a second vaginal instillation of prostaglandin gel was given, and induction delayed a further 24 hours. Initially 24 patients were managed in a double-blind trial; each was randomly assigned to receive either the prostaglandin gel or a similar volume of gel without prostaglandins. The following morning labour was induced irrespective of the state of the cervix.

Results

Of the 168 patients treated, 102 received 2 mg PGE₂ in 2% gel and 66 received 5 mg PGE₂ in 4% gel. Within two hours of instillation of PGE₂ gel patients usually experienced backache and uterine

contractions of variable intensity and frequency, but not requiring analgesia. These contractions either persisted for three to four hours and then waned (fig 1), or progressed to established labour and delivery (fig 2). We observed no difference in uterine activity between the two dosage schedules.



FIG 1—External tocographic recording showing stimulated uterine activity after intravaginal administration of PGE₂ gel. Activity decreased after 5 hours.

Table I summarises the results of the double-blind trial. All 24 patients were delivered vaginally; there were no perinatal deaths. Four of the 12 patients who received PGE₂ became established in labour without further treatment, three being delivered before the time of planned induction the following morning; in none of the 12 patients in the control group did labour occur. In the former group only two patients had an induction-delivery interval of more than 15 hours, compared with five patients in the latter group.

Table II shows the results for all 168 patients managed by prelabour cervical ripening. No patient experienced side effects. There were no episodes of nausea, vomiting, or diarrhoea as an immediate result of the prostaglandin gel instillations. No patient had fever during the treatment phase; three patients had fever during subsequent labour, one of whom was given antibiotics, and all had an uneventful

TABLE I—Results of double-blind trial of vaginal instillation of PGE₂ in 2% gel and placebo (2% gel only) in 24 primigravidae with cervical scores 0-3.* Values are means \pm SD

Variable	PGE ₂	Placebo	P value
No of patients	12	12	
Pretreatment cervical score	2.4 \pm 0.7	2.5 \pm 0.7	NS
Post-treatment cervical score	7.6 \pm 4.1	3.6 \pm 1.3	P < 0.005
No established in labour†	4	0	
Length of labour (hours)	10.7 \pm 4.7	14.9 \pm 5.3	P < 0.05
Maximum dose of oxytocin infused (mU/min)	15.8 \pm 16.4	42.1 \pm 20.3	P < 0.0025
Apgar score at 1 min	9.1 \pm 0.7	7.2 \pm 2.8	P < 0.025

*Modified Bishop score.

†That is, without further treatment.

NS = not significant.



FIG 2—Intrauterine pressure recording showing stimulated uterine activity leading to established labour after intravaginal administration of PGE₂ gel. Note initial low amplitude (30–40 mm Hg) and frequent contractions.

TABLE II—Results of prelabour cervical ripening with either 2 mg PGE₂ in 2% gel or 5 mg PGE₂ in 4% gel in 168 primigravidae with cervical scores 0–3

Variable	PGE ₂ in 2% gel	PGE ₂ in 4% gel
No of patients	102	66
Pretreatment cervical score*	2.4 ± 0.7	2.5 ± 0.6
Post-treatment cervical score*	5.6 ± 2.3	6.1 ± 2.0
No (%) established in labour†	24 (23.5%)	32 (48.5%)
No (%) with post-treatment cervical score <5	29 (28.4%)	8 (12.1%)
Length of labour (hours)*	10.5 ± 4.4	10.6 ± 4.8
No (%) having caesarean section	14 (13.7%)	7 (10.6%)
Apgar score at one minute*	8.1 ± 2.0	7.9 ± 2.0

*Values are means ± SD.

†That is, without further treatment.

puerperal recovery. Four hours after treatment episodes of fetal bradycardia were noted on routine auscultation in one patient, but subsequent continuous external fetal heart monitoring showed no evidence of fetal distress, and after amniotomy the next morning a spontaneous vertex delivery occurred without complication. Two of the 168 patients had meconium-stained liquor at the time of amniotomy or spontaneous rupture of the membranes.

In the 56 patients in whom labour started as a result of the prostaglandin treatment, labour started within 0.75–12.75 h after instillation (mean time 6.7 ± SD 5.0 h); in only two of these 56 patients was caesarean section performed, in one for suspected but unconfirmed fetal distress and in the other for cephalopelvic disproportion. Two of the patients who ultimately delivered vaginally laboured for longer than 24 hours. Among the 168 patients, 66 had spontaneous vaginal deliveries and 81 forceps deliveries; 112 patients were managed with epidural analgesia. There were no perinatal deaths in the study; 128 neonates had a one-minute Apgar score of 8 or more, 25 had a score of 5–7, and 15 a score of 4 or less.

Twenty-one (12.5%) caesarean sections were performed; 12 were for cephalopelvic disproportion, four for fetal distress, and five for failure to progress. In 29 patients treated with 2 mg PGE₂ and eight given 5 mg PGE₂ the cervical state did not improve beyond a score of 4. Labour was induced as planned in 16 of these 37 patients the next morning, and 21 were given a further treatment, formal induction being delayed a further 24 hours. Of the former, six required delivery by caesarean section, compared with four of the latter. In three

patients given a second treatment, "spontaneous" labour resulted without recourse to formal induction. Only eight patients who received a second treatment remained unfavourable, making amniotomy technically difficult. There was, however, no difference in the mean length of labour in these two groups.

Discussion

The principle of priming or ripening the cervix with prostaglandins before planned induction of labour was first proposed and investigated by Calder *et al.*³ Their method entailed the extra-amniotic administration of a small dose of PGE₂, 250–400 µg in a viscous gel, using a self-retained Foley catheter inserted through the cervical canal. It resulted in a considerable reduction in the duration of labour, less need to resort to caesarean section, and improvement in the condition of the neonate. We have achieved essentially similar results using a much simpler technique of vaginal administration.

The intrauterine method needs a self-retaining catheter, and the influence that the catheter may have upon cervical state has been in question; the effect of the catheter alone upon cervical ripening is slow,⁴ and can only be contributory. Shepherd *et al.*⁵ have recently shown that the effect of the extra-amniotic method is not simply mechanical. Using a similar extra-amniotic technique to Calder *et al.*,³ they found that instillation of a viscous medium alone had little effect upon the cervical state compared with the medium containing prostaglandins. The influence of the prostaglandin gel on the state of the cervix and subsequent labour compared with the gel alone in the double-blind trial in the present study is convincing evidence of a prostaglandin effect. There is concern about the possible introduction of infection after the extra-amniotic administration of prostaglandins. Clinical experience, however, suggests that such anxiety is ill-founded. The technique described by us limits the theoretical risk of intrauterine sepsis by obviating the need to introduce any foreign material into the extra-amniotic space.

A further advantage of the method is the ease with which the PGE₂ gel can be removed from the vagina if hypertonic uterine

activity occurs; this would not be possible with extra-amniotic or oral administration. It should be emphasised, however, that hypertonic uterine activity did not occur in any patient in the present series.

Nearly 24% of patients receiving 2 mg PGE₂ compared with 48.5% receiving 5 mg PGE₂ went into "spontaneous" labour as a result of the treatment alone, while 28.4% and 12.1% respectively showed little significant improvement in cervical score. The last group is especially important. The results suggest that the second prostaglandin treatment was of possible benefit to patients who had failed to respond to the first application, as it reduced the incidence of caesarean section and made amniotomy technically simpler. Numbers are small, however, so the findings may still be considered as inconclusive. Deviations in uterine response cannot be explained simply. In addition to the difficulty of precise cervical assessment there may be as yet unexplained variations in the rate of absorption of the prostaglandins from the vagina. The concentration of circulating steroid hormones may be important, for evidence has been presented that oestrogens can provoke an endogenous release of prostaglandins.⁶ Increased experience and a further adjustment in the dosage of prostaglandins or in the viscosity and volume of the gel vehicle might enhance the results. Larger doses should be used with caution, however, to ensure that overstimulation of the uterus does not occur.

Our results suggest that this method of cervical ripening produces no adverse effects on the fetus. Nevertheless, patients with suspected placental insufficiency should be monitored for the first few hours after treatment in case of possible fetal compromise.

We thank the medical staff at the John Radcliffe Hospital for referring patients to the study, and Sisters Fran McIntosh and Sue Bradley for their expert nursing care. Part of this work was supported by a grant from the Oxford Regional Health Authority.

References

- ¹ Hillier, K, MacKenzie, I Z, *Proceedings of the First International Congress of the Asian Federation of Obstetrics and Gynaecology*, p 83. Lancaster MTP Publications, 1976.
- ² Calder, A A, Embrey, M P, and Hillier, K, *British Journal of Obstetrics and Gynaecology*, 1974, **81**, 39.
- ³ Calder, A A, Embrey, M P, and Tait T, *British Journal of Obstetrics and Gynaecology*, 1977, **84**, 264.
- ⁴ Embrey, M P, and Mollison, B G, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1967, **74**, 44.
- ⁵ Shepherd, V, Sims, C, and Craft, I, *Lancet*, 1976, **2**, 709.
- ⁶ Liggins, G C, *et al*, *Recent Progress in Hormone Research*, 1973, **29**, 134.

(Accepted 26 September 1977)

Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam

J E HEGARTY, J W DUNDEE

British Medical Journal, 1977, **2**, 1384-1385

Summary

The occurrence of thrombosis and phlebitis after intravenous injection of 10 mg diazepam, 4 mg lorazepam, or 1-2 mg flunitrazepam was studied on the second or third and the seventh to 10th days. A significantly higher incidence occurred with all drugs on days 7 to 10 than on days 2 and 3. Painless thrombosis occurred much more often with diazepam than with the other two benzodiazepines. Its incidence was greater in small hand or arm veins than in large antecubital vessels.

Lorazepam and flunitrazepam therefore have clear advantages over diazepam.

Introduction

Opinions vary about the incidence and severity of venous sequelae after the injection of benzodiazepines. The ever-increasing popularity of these drugs as parenteral sedatives warranted a detailed study of their effects. We report here the findings of a study in which patients were given roughly

equivalent sedative doses of undiluted preparations of diazepam, lorazepam, and flunitrazepam and then followed up for 10 days.

Method

Unselected patients were given either 10 mg diazepam, 4 mg lorazepam, or 1-2 mg flunitrazepam intravenously into the largest available vein for sedation or preanaesthetic medication. There was no selection as to which drug was given. No other drug was given through the same needle (size 21 or 23 swg). Once the drug had been injected the needle was withdrawn immediately and a sterile swab was strapped to the injection site. A vein was not included when there was evidence of extravenous leakage or haematoma, or if it was used subsequently for venepuncture, or if an intravenous infusion was erected in that arm.

Each patient was seen by one of us on the second or third day after injection and again at seven to 10 days. The site of injection was examined for the presence of tenderness on palpation of the vein or venous thrombosis. Positive findings were classified as phlebitis (tenderness without thrombosis), thrombosis (painless hardening), or thrombophlebitis (combination of the above.) Thrombosis and thrombophlebitis were graded as localised (less than one inch) or extended.^{1 2}

Results

At seven to 10 days there was a significantly higher incidence of venous sequelae among patients who had received diazepam than among those who had received lorazepam ($\chi^2=5.89$; $P<0.02$) or flunitrazepam ($\chi^2=14.71$; $P<0.0005$). The incidences of sequelae after lorazepam and flunitrazepam did not differ significantly (table 1). In each series more patients had some form of venous damage after 7-10 days than after two or three, the total incidence being significantly different at the two observations times ($\chi^2=4.48$; $P<0.05$).

Department of Anaesthetics, Queen's University of Belfast, Northern Ireland

J E HEGARTY, MB, FFARCS, senior tutor

J W DUNDEE, MD, FFARCS, professor of anaesthetics