CONTROLLED TRIAL OF EXTRADURAL BUPIVACAINE WITH FENTANYL, MORPHINE OR PLACEBO FOR PAIN RELIEF IN LABOUR

J. D. LIRZIN, P. JACQUINOT, P. DAILLAND, J. C. JORROT, J. JASSON, M. L. TALAFRE AND C. CONSEILLER

The use of extradural opioids for pain relief in labour has been shown to be inefficient and hazardous [1–9]. It has been demonstrated, however, that the combination of an opioid and a local anaesthetic may improve both the onset and the duration of analgesia produced by the latter, and provide better quality of analgesia [10–13].

Niv and co-workers concluded that the concomitant use of extradural morphine 2 mg augmented the analgesic effect of 0.25% bupivacaine [12], but Cohen and colleagues found that the addition of extradural fentanyl 50 or 100 µg to 0.25% bupivacaine 9 ml did not result in significant improvement in analgesia compared with the local anaesthetic alone [14]. The majority of clinical trials have been limited to small numbers of parturients, and none has compared fentanyl with morphine in combination with extradural bupivacaine. This study has been carried out in a prospective, randomized double-blind manner to compare, in a large study, the efficacy of extradural combinations of fentanyl with bupivacaine, morphine with bupivacaine and placebo with bupivacaine for control of labour pain.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all participating patients—255 healthy pregnant women with uncomplicated full-term gestation (> 38 week) who elected to have extradural analgesia for labour and delivery. All patients were in labour with a healthy singleton fetus in a cephalic presentation. Previous opioid administration excluded the patient from the study.

When a patient requested pain relief, an extradural catheter was inserted at the L2/3 or L3/4 space via a 17-gauge Tuohy needle. A 4-ml test dose of 0.25% plain bupivacaine was injected. Patients were allocated randomly to one of the three groups. The ampoules of extradural solution had been coded randomly and prepared by the hospital pharmacy. Each ampoule contained 8 ml of 5% dextrose alone or in combination with either fentanyl 80 µg or 4 mg of preservative-free morphine hydrochloride. The pH values of the three solutions were, respectively, 4.46 (placebo), 4.83 (fentanyl) and 4.60 (morphine). The contents of the coded ampoule were administered extradurally 7 min after the test dose. Twelve minutes after the test dose, each parturient was given 0.25% plain bupivacaine 8 ml. This timing was chosen to avoid dilution of bupivacaine. The

SUMMARY

In a prospective, randomized double-blind study carried out on 255 parturients, fentanyl 80 µg (n = 81), morphine 4 mg (n = 83) or placebo (n = 85) was added to 0.25% bupivacaine administered extradurally for pain relief during labour. Fentanyl increased the mean duration of bupivacaine analgesia by 30% and did not reduce the rate of inadequate pain relief. Morphine did not increase the mean duration of bupivacaine analgesia significantly, but increased the rate of inadequate pain relief. It was concluded that morphine 4 mg added to extradural 0.25% bupivacaine was of no value.
duration of analgesia was defined as the time between administration of the test dose and the first request for re-injection.

The patients were asked to rate the efficacy of the extradural block. Analgesia was considered successful and adequate when contractions were painless. Inadequate pain relief was assessed as decreased but persistent painful contractions, persisting painful area or lateralized analgesia. When a further injection was needed within 35 min, patients were excluded from data analysis. Subsequently, 0.25% bupivacaine was administered extradurally at the patient’s request. Throughout labour, fetal status was assessed by continuous fetal heart rate monitoring. The presence of adverse side-effects was also recorded, including pruritus, nausea and vomiting, drowsiness, hypotension (decrease in systolic arterial pressure of more than 20%), respiratory depression (ventilatory rate less than 10 b.p.m.). The study was terminated at the first reinjection.

All the results are presented as mean (SEM). Statistical analysis was performed using one-way analysis of variance, unpaired Student’s *t* test and Chi-square test, as appropriate. Statistical significance was assumed when *P* < 0.05.

### RESULTS

Two hundred and fifty-five women entered the study, but six coded ampoules were opened and not used. Thus data were obtained in 249 parturients allocated randomly to one of the three groups: placebo (n = 85), fentanyl (n = 81) and morphine (n = 83). The three groups were comparable with regard to age, weight, height, parity, term and cervical dilatation at the time of the test dose (table I).

**Duration of analgesia.** The mean duration of pain relief induced by bupivacaine was significantly greater in the group given fentanyl 80 μg than after placebo (table II). In addition, significantly more parturients were delivered vaginally without an additional dose of bupivacaine (table III). The time elapsed between test dose and delivery was not significantly different in these two groups (115 min v. 102 min). In the group given morphine the mean duration of pain relief induced by bupivacaine was not significantly longer than that in the placebo group. The number of parturients delivered vaginally without additional bupivacaine was not different in the morphine and placebo groups (table III). For the

### Table I. Maternal characteristics and state of cervical dilatation at the onset of the study (mean (SEM)).

No significant differences

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 85)</th>
<th>Fentanyl group (n = 81)</th>
<th>Morphine group (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>29.3 (0.6)</td>
<td>29.7 (0.6)</td>
<td>28.8 (0.7)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>Before pregnancy</td>
<td>55.9 (0.9)</td>
<td>57.1 (1.0)</td>
</tr>
<tr>
<td></td>
<td>At term</td>
<td>69.6 (1.3)</td>
<td>69.2 (1.7)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td></td>
<td>163.0 (0.7)</td>
<td>164.0 (0.8)</td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td>Primiparous</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Multiparous</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td><strong>Term (week)</strong></td>
<td>39.6 (0.1)</td>
<td>39.7 (0.1)</td>
<td>39.7 (0.1)</td>
</tr>
<tr>
<td><strong>Cervical</strong></td>
<td>dilatation (cm)</td>
<td>3.3 (0.1)</td>
<td>3.4 (0.1)</td>
</tr>
</tbody>
</table>

### Table II. Mean duration of analgesia assessed as the interval between the test dose and first increment (mean (SEM)).

*P* < 0.05 compared with placebo. No other significant differences

<table>
<thead>
<tr>
<th></th>
<th>Placebo group (n = 85)</th>
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<th>Morphine group (n = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parturients who required an increment</strong></td>
<td>68 (80%)</td>
<td>48 (54.2%)</td>
<td>67 (80.7%)</td>
</tr>
<tr>
<td><strong>Duration of analgesia (min)</strong></td>
<td>97.2 (3.7)</td>
<td>132.5 (5.0)*</td>
<td>109.6 (6.4)</td>
</tr>
</tbody>
</table>
parturients who were delivered without additional bupivacaine, the time elapsed between the test dose and delivery was not significantly different (92 min v. 102 min). There was no significant difference in duration of pain relief in the morphine and fentanyl groups (table II).

Efficacy of analgesia. There was an equal rate of inadequate pain relief (persisting painful contraction or painful area) in the fentanyl and placebo groups (table IV). However, there was a greater rate of inadequate pain relief in the morphine group, compared with the fentanyl and placebo groups (table IV).

Side effects. There was a higher rate of side effects in the fentanyl and morphine groups than in the placebo group (table V). In both opioid groups the frequency of pruritus and drowsiness was greater than in the placebo group (table V). One patient with drowsiness in the morphine group required repeated administration of naloxone.

Mode of delivery and Apgar scores. Sixty-eight percent of patients had a normal vaginal delivery, 8% had Caesarean section and 24% had forceps delivery; there was no significant difference between the three groups. No changes in fetal heart pattern occurred in association with the extradural blocks. Apgar scores > 7 at 1 min and > 9 at 5 min were achieved in 94.8% and 98.4% of neonates, respectively, with no significant difference between the three groups.

DISCUSSION

In non-pregnant patients, extradural fentanyl produces a short lasting analgesic effect of rapid onset [15]. In pregnant patients, extradural fentanyl has been shown to be effective only in achieving pain relief in the first stage of labour [4, 16, 17]. Several investigators [4, 10, 11, 13] reported that the combination of fentanyl with small doses of bupivacaine increased the duration
of analgesia provided by bupivacaine alone administered extradurally. However, in a recent study [14] the addition of fentanyl 50 or 100 μg to 9 ml of 0.25% extradural bupivacaine following a test dose of 1% lignocaine 3 ml was not found to prolong analgesia. In our study, the addition of fentanyl 80 μg to 0.25% bupivacaine 8 ml after a test dose of 0.25% bupivacaine 4 ml was found to increase significantly the duration of analgesia produced by bupivacaine. Our study confirmed the observations of Cohen [14] that the combination did not increase the success rate of complete analgesia produced by bupivacaine. In addition, no clinical respiratory depression was reported with the fentanyl combination.

In non-pregnant women, extradural morphine alone provides a long-lasting analgesia of slow onset. In pregnant women, extradural morphine alone, in a dose of 5 mg or less, is ineffective in providing satisfactory pain relief throughout labour [1,3,5–9], probably because the extradural vascular congestion of pregnancy enhances vascular absorption of morphine [18–24]. Several investigators have reported that extradural bupivacaine improves the quality of analgesia when administered after [9] or simultaneously with [12] extradural morphine during the first stage of labour. However, in our double-blind study we could not demonstrate any improvement in analgesia by combining morphine with bupivacaine.

REFERENCES