COMPARISON OF 0.125% BUPIVACAINE WITH 0.125% BUPIVACAINE AND CLONIDINE AS EXTRADURAL ANALGESIA IN THE FIRST STAGE OF LABOUR

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SUMMARY

We have studied 42 healthy patients with singleton vertex pregnancies, who were in the first stage of labour and requesting extradural analgesia. They were allocated randomly in a double-blind fashion to receive either 0.125% bupivacaine plain or 0.125% bupivacaine with clonidine 120 µg. Efficacy of analgesia was evaluated using linear visual analogue scoring (VAS), sensory block was assessed using bilateral pinprick in the midclavicular line and sedation scored on a five-point scale. Maternal and fetal cardiovascular variables were measured every 2 min for 20 min, at 30 min and subsequently at 15-min intervals. The reduction in VAS was greater at all times in the bupivacaine-clonidine group (P < 0.01). The median (range) duration of analgesia was greater in the bupivacaine-clonidine group (114.5 (30-243) min) compared with the bupivacaine group (53 (30-100) min) (P < 0.001). Analgesia was associated with a reduction in arterial pressure in both groups, but there were no between-group differences. Maternal heart rate was less than baseline values at 30-90 min in the bupivacaine-clonidine group only. Sedation was greater in the bupivacaine-clonidine group, especially from 15 to 45 min (P < 0.01). There were no differences in fetal heart rate, mode of delivery or Apgar scores between the two groups. (Br. J. Anaesth. 1993; 71: 651-656)

KEY WORDS


Bupivacaine is the standard agent for extradural analgesia in labour. Adrenaline and opioids are often added to improve analgesia, reduce the dose of bupivacaine and minimize side effects, but both additives have disadvantages. Adrenaline may contribute to fetal and maternal tachycardia and reduce spinal and uterine blood flow [1]. Fentanyl may cause pruritus, urinary retention, delayed gastric emptying [2], late respiratory depression [3] and reactivation of maternal herpes labialis [4].

Clonidine, an alpha2 agonist, may be a useful adjuvant [5-7]. It has analgesic properties when administered extradurally alone [8] and acts synergistically with extradural opioids [9] and local anaesthetics [10]. Clonidine does not interfere with proprioception and does not cause motor block, nausea or vomiting. Respiratory depression does not occur [11], although ventilatory changes have been observed secondary to sedation when large doses of clonidine have been used [12].

Eisenach and colleagues suggested that clonidine may offer advantages as an analgesic in pregnancy [13]. It modulates, but does not abolish, sympathetic responses and so may interfere less with maintenance of arterial pressure during aortocaval compression [14]. Intrathecal and extradural clonidine have been studied extensively in the pregnant ewe and there were only minor changes in maternal and fetal physiology and biochemistry at concentrations of clonidine anticipated to be effective in the human [13, 15]. Extradural clonidine has been used successfully for analgesia after Caesarean section [12, 16, 17]. Oral clonidine has been used in pregnancy for the treatment of hypertension, with no adverse effects on the fetus [18, 19].

The aim of this study was to evaluate the safety and efficacy of a bolus of 0.125% bupivacaine 8 ml and clonidine 120 µg compared with 0.125% bupivacaine 8 ml alone for extradural anaesthesia in the first stage of labour.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee. We studied 42 pregnant patients with a singleton vertex pregnancy of at least 36 weeks gestation. They were in established labour but of less than 5 cm cervical dilatation, complaining of pain, using Entonox and requesting additional analgesia. All patients gave informed consent. We excluded patients younger than 18 yr, those with comitant disease such as hypertension or diabetes, patients receiving antihypertensive drugs or tricyclic anti-
depressants, those with a baseline heart rate less than 55 beat min\(^{-1}\) and patients who had already received opioid analgesia during this labour.

All patients were receiving continuous cardio-
tocograph (CTG) monitoring using an external transducer while arterial pressure was measured using a Dinamap on the non-dependent arm. Patients were given Hartmann's solution 500 ml i.v.

over 10 min and positioned in the left lateral position. The extradural space was cannulated at L2-3 or L3-4 and 3 cm of catheter left in place. The patient was then repositioned to lie with a left lateral tilt. Baseline observations of maternal heart rate, arterial pressure, sedation, motor power and fetal heart rate were recorded. Pain was assessed by asking the patient to complete a 10-cm visual analogue scale (VAS) at the peak of a contraction. All patients received a test dose of 2\% lignocaine plain 3 ml and were allocated randomly to receive either 0.125\% bupivacaine 8 ml or 0.125\% bupivacaine 8 ml with clonidine 0.15 \(\mu\)g ml\(^{-1}\) (120 \(\mu\)g) 2 min after the test dose. One investigator prepared the extradural solution while the other blinded investigator assessed the patient.

Maternal heart rate, arterial pressure and fetal heart rate (FHR) were recorded at 2-min intervals for 20 min, at 30 min and thereafter at 15-min intervals. Hypotension was defined as a decrease in systolic arterial pressure of at least 20\%. It was treated by turning the patient to the left lateral position, administering 40\% oxygen by Hudson mask, giving Hartmann's solution 200 ml i.v. and ephedrine 6 mg, repeated as necessary.

The sensory level was assessed by response to bilateral pinprick at the mid clavicular line downwards every 2 min for 20 min, at 30 min and every 15 min thereafter. The patient was asked to complete a VAS at approximately 15-min intervals to coincide with the peak of a contraction. Onset of analgesia was assessed by the time to achieve sensory block of T12 and the time to reach the maximum decrease in VAS. Duration of analgesia was taken as the time from the initial dose to the time the patient requested additional analgesia. Unsatisfactory analgesia was defined as a request for further analgesia before 45 min or failure to achieve more than 50\% reduction in VAS.

Motor impairment was assessed at 15-min intervals using the Bromage scale. Sedation was assessed on a five-point scale (0 = wide awake; 1 = drowsy; 2 = dozing, eyes shut intermittently; 3 = asleep; 4 = unrousable) at 15-min intervals. Any episode of shivering during the first 30 min was noted.

The CTG was monitored continuously and analysed after delivery by an obstetrician who was blinded to the study drugs. Changes in the baseline FHR, beat-to-beat variability and the number of accelerations and decelerations were noted. The mode of delivery, neonatal birth weight and Apgar scores at 1 and 5 min were recorded. All patients were examined the next day.

Patient data were compared using Student's \(t\) test. Maternal arterial pressure, heart rate and FHR were analysed by repeated measures analysis of variance.

The Mann-Whitney test was used to compare the time to sensory block of T12, time to maximum decrease in VAS, height of block, duration of block, sedation and VAS between groups. The baseline comparison of VAS used the raw data. Subsequent VAS were compared after transformation of data. Each VAS was divided by the baseline VAS for that patient to give values representing pain score as a fraction of the initial pain score. The incidence of successful analgesia, sedation and other categorical data were compared using the chi square test. \(P < 0.05\) was considered significant.

**RESULTS**

There were 22 patients in the plain bupivacaine group and 20 in the bupivacaine–clonidine group. There were no differences between the groups in age, height, weight, parity or gestation (table 1). The management of labour, duration of labour, and cervical dilatation before insertion of extradural catheters were similar also (table 1).

| Table 1. Patient data and details of labour (mean (range or SD) or number of patients) |
|---------------------------------|-----------------|-----------------|
| **Bupivacaine + clonidine**     | **Bupivacaine** |
| Age (yr)                        | 26.2 (18–34)    | 28.0 (20–36)    |
| Height (cm)                     | 158 (5.2)       | 158 (4.4)       |
| Weight (kg)                     | 66.9 (11.4)     | 67.3 (6.7)      |
| Gestation (weeks)               | 38.8 (1.3)      | 40 (1.4)        |
| Parity = 0                      | 18              | 15              |
| Parity = 1                      | 2               | 7               |
| Artificial rupture of membranes | 9               | 10              |
| Oxytocin infusion               | 9               | 14              |
| Cervical dilatation (cm)        | 2.4 (0.9)       | 2.6 (1.0)       |

Duration of labour before extradural (h) 4.2 (3.3) 4.8 (3.1).

**FIG. 1.** Median and 25-75\% range for percentage reduction in visual analogue score (VAS) after extradural bupivacaine (\(O – O\)) or bupivacaine and clonidine (\(\bullet — \bullet\)). Sample size at each time denoted by \(n\). *\(P < 0.05\); **\(P < 0.01\) between groups.
EXTRADURAL CLONIDINE AND BUPIVACAINE DURING LABOUR

![Graph showing percentage of patients with at least 50% reduction in pain score after extradural bupivacaine or bupivacaine and clonidine.](image1)

**TABLE II. Quality and duration of analgesia (median (range) or number of patients)**

<table>
<thead>
<tr>
<th></th>
<th>Bupivacaine + clonidine</th>
<th>Bupivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unsatisfactory analgesia</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Sensory block to at least T12</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Onset to sensory block at T12 (min)</td>
<td>8 (4-30)</td>
<td>8 (2-18)</td>
</tr>
<tr>
<td>Maximum height of sensory block</td>
<td>T8 (T4-Nil)</td>
<td>T10 (T4-Nil)</td>
</tr>
<tr>
<td>Time to maximum analgesia (min)</td>
<td>15 (15-60)</td>
<td>15 (15-60)</td>
</tr>
<tr>
<td>Duration of analgesia (min)</td>
<td>114.5 (30-243)</td>
<td>53 (30-100)</td>
</tr>
</tbody>
</table>

![Graph showing mean systolic arterial pressure after extradural bupivacaine or bupivacaine and clonidine.](image2)

There were incomplete data in two patients: the Dinamap printer was faulty for one patient and another patient declined to complete the VAS.

Between-group comparisons of VAS and cardiovascular variables were made for the first 60 min only, because of the high exclusion rate in the bupivacaine group after that time, arising from requests for further analgesia.

There was no difference between groups in onset of sensory block to T12, maximal height of block, initial VAS or time to reach maximum reduction in VAS. The reduction in VAS from 15 to 60 min (fig. 1) and the maximal reduction in VAS were greater in the bupivacaine–clonidine group ($P < 0.01$). The number of patients with more than 50% reduction in VAS was greater in the bupivacaine–clonidine group at all times (fig. 2). The mean duration of analgesia was twice as long in the bupivacaine–clonidine group ($P < 0.001$) (table II). Overall, analgesia was unsatisfactory in three (15%) of the bupivacaine–clonidine group, compared with 12 (59%) in the bupivacaine group ($P < 0.01$). These patients with failed analgesia were given 0.125% bupivacaine 5-10 ml extradurally and this produced satisfactory analgesia in all of them.

There were no differences between groups in systolic (SAP), mean or diastolic arterial pressure initially or over the next 60 min. SAP in the bupivacaine group was less than baseline from 6 to 20 min ($P < 0.01$) (fig. 3). In the bupivacaine–clonidine group, SAP was less than baseline values from 16 to 90 min ($P < 0.01$). Hypotension occurred in three patients from the bupivacaine–clonidine group and two in the bupivacaine group. This was treated easily and ephedrine was effective in all patients. No patient required atropine.

Baseline heart rate was greater initially in the bupivacaine group but, after taking this into account, there were no differences between groups over the next 20 min (fig. 4). Heart rate was unchanged from baseline values in the bupivacaine group over the first 60 min. In the bupivacaine–clonidine group, heart rate was less than baseline values from 30 to 90 min ($P < 0.01$).
Sedation was greater in the bupivacaine–clonidine group from 15 to 60 min (table III). Fifty percent of these patients had a sedation score of 2 or greater at 30 min, but at no stage were patients unrousable. At 105 min, three of the 11 remaining patients had a score of 2.

Three patients in the bupivacaine–clonidine group and five in the bupivacaine group complained of shivering.

There were no differences in FHR between the groups and with respect to time. Detailed minute-by-minute analysis of the CTG was difficult because of the intermittently poor quality of many of the recordings as a result of movement and positioning of the external transducer. The different time course of analgesia for the two groups also made between-group comparisons difficult. Maternal hypotension was reflected usually by a transient decrease in the FHR. An overall impression of the significance of ways. It may have central effects which modulate the descending pathways involved with nociceptive transmission. When administered extradurally alone, it is believed to produce analgesia predominantly by a spinal mechanism [22] from stimulation of the alpha₂ receptors of the dorsal horn. Clonidine may potentiate the effect of bupivacaine by reducing spinal cord blood flow and prolonging the effective availability of bupivacaine [7]. However, clonidine has a greater analgesic effect than that produced by the most powerful vasoconstrictors. Studies with extradural lignocaine and clonidine have indicated potentiation of analgesia and increased plasma concentrations of lignocaine, suggesting that clonidine may reduce hepatic metabolism of lignocaine [23]. There is no corresponding information for bupivacaine.

During pregnancy, there are increased concentrations of endogenous opioids [24] and clonidine may have potentiated their effects. Studies in animals have shown that clonidine enhanced pregnancy-induced analgesia may be antagonized by naloxone [20]. Other animal work suggests there is a morphine–clonidine interaction which is synergistic for visceral antinociception [25].

Recent studies of the analgesic effect of extradural clonidine have examined acute postoperative pain. The results varied depending on the site of operation, dose of clonidine and use of adjuncts. Eisenach, Lysak and Viscomi used clonidine alone and found that the large dose requirement (400–800 µg) resulted in unacceptable sedative side effects [26]. Gordh considered clonidine 150 µg inadequate for post-thoracotomy pain [27]. Carabine, Milligan and Moore studied patients who had undergone total hip replacement and found that a bolus of extradural clonidine alone and in combination with 0.25% bupivacaine were superior to plain bupivacaine, and that combination therapy resulted in prolonged duration of action [10].

Some studies have shown that motor block is prolonged when clonidine is added to extradural lignocaine [22, 28] but not to bupivacaine [10]. We used a small dose of bupivacaine and few patients in each group developed motor block, so that possible potentiation of motor block could not be demonstrated.

The clonidine group were more sedated, but all could be roused to complete linear analogue scores. Sedation was of shorter duration than analgesia.

Discussion

The addition of clonidine to bupivacaine provided greater analgesia, but caused marked sedation. We used only 120 µg of clonidine (mean dose 1.84 µg kg⁻¹) in combination with a small dose of 0.125% bupivacaine (8 ml). We chose this dose of clonidine because we wished to minimize the potential for cardiovascular side effects. We expected that this dose would be effective in labour, because clonidine has been shown in animal studies to be more effective against visceral pain than somatic pain, with reduced analgesic dose requirements in late pregnancy [20]. The degree of analgesia with 0.125% bupivacaine 8 ml was comparable to that reported previously [21]. The duration of analgesia was relatively short, but an anaesthetist was present continually and the patient was able to request top-up administration at any time.

The improved quality of analgesia in the clonidine group at 15 min suggested the effect of clonidine was rapid. This has been noted previously [10]. Clonidine may have produced analgesia in a variety of ways. It may have central effects which modulate the descending pathways involved with nociceptive transmission. When administered extradurally alone, it is believed to produce analgesia predominantly by a spinal mechanism [22] from stimulation of the alpha₂ receptors of the dorsal horn. Clonidine may potentiate the effect of bupivacaine by reducing spinal cord blood flow and prolonging the effective availability of bupivacaine [7]. However, clonidine has a greater analgesic effect than that produced by the most powerful vasoconstrictors. Studies with extradural lignocaine and clonidine have indicated potentiation of analgesia and increased plasma concentrations of lignocaine, suggesting that clonidine may reduce hepatic metabolism of lignocaine [23]. There is no corresponding information for bupivacaine.

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The clonidine group were more sedated, but all could be roused to complete linear analogue scores. Sedation was of shorter duration than analgesia.
Clonidine is believed to act supraspinally, in particular at the locus coeruleus where there is a high concentration of alpha_2 receptors [29]. The onset of sedation was slower than the onset of analgesia, but more rapid than could be accounted for by cephalad spread in CSF. The systemic absorption of extradural clonidine is rapid, with peak plasma concentrations of clonidine occurring within 15 min of extradural administration [22, 30]. This is reflected in the relatively rapid onset of sedation in our patients. Some of the sedation may be a consequence of effective analgesia which allows the mother to rest. Neonatal sedation was not observed, but Apgar scores are insensitive measures of neonatal depression compared with neurobehavioural testing.

Five patients had significant hypotension which responded satisfactorily to ephedrine, while modest hypotension occurred with time in both groups. Although it appears that arterial pressure was decreased for a long time in the clonidine group, comparisons with the bupivacaine group should be restricted. Analgesia was more effective and longer lasting in the clonidine group, with the result that arterial pressure could be measured for a longer period. A decrease in arterial pressure may occur as a result of effective analgesia and all patients showed an increase in arterial pressure as pain returned.

The effects of extradural clonidine on cardiovascular variables are dose-related. It decreases arterial pressure and heart rate by enhancing parasympathetic nervous system activity and decreasing sympathetic nervous system activity at brainstem sites, and by inhibiting sympathetic outflow in the spinal cord. Clonidine has direct effects also on heart rate at the myocardium. With large doses, hypotension may occur secondary to stimulation of the alpha_2 postsynaptic vascular receptors.

There appeared to be no direct effects of clonidine on FHR and no episodes of maternal hypotension or bradycardia which could have resulted in an unfavorable outcome. FHR was measured continuously and the values at 2-min intervals analysed, but these values could be misleading as they gave no indication of beat-to-beat variability or other indicators of fetal distress. The CTG recordings were difficult to analyse subsequently and the use of fetal scalp electrodes and digital storage of FHR would have been preferable. Animal studies have shown a slowing of FHR with no evidence of fetal distress [13]. Reduced umbilical arterial flow occurred, but this was at concentrations of clonidine believed to induce hypoxaemia secondary to a platelet coagulation problem which is unique to sheep. Further studies in humans with Doppler measurement of umbilical artery flow would be valuable.

A single dose of clonidine was used and subsequent top-up doses were not standardized, so it is not possible to comment on the total dose requirements of bupivacaine. There were no differences between groups in the mode of delivery and the results were not inconsistent with obstetric practice in this hospital.

ACKNOWLEDGEMENT

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REFERENCES


