Extradural clonidine combined with sufentanil and 0.0625% bupivacaine for analgesia in labour

D. CHASSARD, L. MATHON, F. DAILLER, F. GOLFIER, J. P. TOURNADRE AND P. BOULÉTREAU

Summary
We have studied the use of clonidine combined with low doses of sufentanil and bupivacaine in 45 parturients requiring extradural analgesia for the first stage of labour, in a double-blind, randomized study. We gave 0.0625% bupivacaine 10 ml containing 1:200 000 adrenaline and sufentanil 10 μg (1 ml) to which was added 0.9% saline, or clonidine 100 or 150 μg (1 ml). We compared the quality (VAS scores) and duration of analgesia, motor block, maternal haemodynamic state (mean arterial pressure and heart rate) and fetal and maternal side effects. Mean duration of anaesthesia was prolonged slightly: 105 (so 21) min without clonidine, 130 (26) min with clonidine 100 μg (P < 0.05 vs control) and 144 (40) min with clonidine 150 μg (P < 0.01 vs control, ns vs 100 μg). There were no differences in VAS scores, onset times, heart rate, ventilatory frequency, motor block, sedation, pruritus or bradycardia between the groups. Analgesia was associated with a reduction in mean arterial pressure with clonidine. However, these adverse side effects were of minor clinical importance regardless of the extradural clonidine dose, except for a high incidence of fetal heart tracing abnormalities when clonidine 150 μg was used. These effects associated with a limited effect on analgesia may curtail the widespread use of clonidine as an adjunct to extradural 0.0625% bupivacaine with sufentanil 10 μg during labour. (Br. J. Anaesth. 1996;77:458–462)

Key words

Opioids are commonly combined with local anaesthetics to enhance extradural anaesthesia during labour1, 2. Extradural clonidine, an alpha2-adrenergic receptor agonist, produces analgesia without the motor block associated with high doses or concentrations of local anaesthetics3 or side effects such as nausea, pruritus and risk of respiratory depression associated with the opioids4. Therefore, a combination of clonidine and opioids may be an attractive alternative for analgesia in labour but to date there have been no studies designed to assess the safety and efficacy of clonidine combined with low concentrations (<0.125%) of local anaesthetic during analgesia in labour.

The aim of this study was to evaluate the maternal, fetal and neonatal effects of clonidine 100 or 150 μg administered extradurally in combination with 0.0625% bupivacaine and adrenaline 1:200 000 with sufentanil 10 μg during the first stage of labour.

Patients and methods
The study was approved by the hospital Ethics Committee. After obtaining written consent, we studied 45 women, ASA I or II, with a singleton vertex pregnancy of at least 37 weeks’ gestation, who requested extradural analgesia in labour. A sample size calculation was performed using the Instat computer software package (GraphPad Instat, San Diego, CA, USA). Power analysis showed that a sample size of 15 patients per treatment group should provide 95% power (assuming α = 0.05) to detect a 30-min difference (sd) in duration of analgesia.

All patients had uncomplicated pregnancies and normal fetal heart tracings. We excluded patients receiving antihypertensive drugs, those with baseline heart rates <55 beat min−1 and patients who had already received opioid analgesia during this labour.

Each parturient received i.v. infusion of Ringer’s lactate 500 ml over 10 min before induction of extradural anaesthesia and was positioned in the sitting position. The extradural space was cannulated at L2–3 or L3–4 using loss of resistance to saline (5 ml) and 3 cm of catheter was left in place. The parturient was then repositioned to lie with a left lateral tilt.

A double-blind, randomized study design was used. Parturients were allocated randomly according to a list of random numbers into three groups (sealed opaque envelopes). All injectates were prepared by an anaesthetist not involved in data collection.

Each syringe of coded study solution was prepared freshly. Each parturient received a test dose of 2% lignocaine 2 ml with 1:200 000 adrenaline. Five minutes later, each received a 12 ml solution comprising 0.0625% bupivacaine 10 ml with sufentanil 10 μg (1 ml) to which was added clonidine 100 μg, clonidine
150 μg or 0.9% saline (1 ml). Bupivacaine 0.0625% solutions were prepared by diluting 0.25% solutions, without preservatives, with 0.9% saline and adrenaline was then added (1:200 000). Arterial pressure and heart rate were monitored with a non-invasive monitor (Cardiocap II, Datex, Helsinki) 5, 10, 20, 30, 40, 60, 80, 100 and 120 min after extradural injection, and then every 20 min until the need for an additional extradural anaesthetic injection. When additional analgesia was requested, the study was terminated. Subsequent top-up doses were not standardized, allowing the anaesthetist to use either 0.0625% or 0.125% bupivacaine as necessary.

Motor block (modified Bromage score: 0 = ability to move hips, ankles and knees; 1 = inability to raise extended leg; 2 = inability to flex knee; and 3 = inability to flex ankle, foot or knee), sedation (1 = wide awake, 2 = dozing, 3 = asleep, 4 = unrousable), cephalic dermalomal level of anaesthesia (cold test), ventilatory frequency and oxyhaemoglobin saturation (pulse oximeter, Cardiocap II, Datex, Helsinki) were recorded at the same times. Basal values were those obtained immediately before extradural injection.

Pain was assessed on a linear visual analogue scale (VAS). Each patient was presented with a line 100 mm long and was told that the left end represented no pain and the right end the worst pain imaginable. They were asked to make a mark on the line to indicate the intensity of pain at the peak of a contraction. Patients could request additional analgesia (0.25% bupivacaine via the extradural catheter) if pain relief was unsatisfactory by 15 min after injection of the study drug. At the end of the study, both the patient and nurse made an overall global rating of the treatment (poor, fair, good, very good, excellent).

The time from administration of study drug to request for additional analgesia was noted (duration of analgesia). Side effects such as pruritus, nausea and vomiting were recorded at completion of the study. Bradycardia was defined as the occurrence of a maternal heart rate > 60 beat min⁻¹ and treated with atropine i.v. Hypotension, defined as a decrease in systolic arterial pressure of at least 20% or a systolic arterial pressure < 100 mm Hg, was treated with i.v. ephedrine as necessary.

Continuous electronic cardiotocograph monitoring using an external transducer was used for all patients throughout labour (Hewlett Packard 80034 A). Tracings were analysed by an obstetrician who was unaware of patient group assignment.

A paediatrician who was unaware of patient group assignment.

STATISTICAL METHODS

For all calculations, the Instat computer software package (GraphPad Instat, San Diego, CA, USA) and Solo statistical software (BMDP, Los Angeles, CA, USA) were used. Intragroup comparisons for continuous variables and VAS scores were performed by analysis of variance (ANOVA) for repeated measures, followed by post hoc tests for comparison with baseline (Student–Newman–Keuls multiple comparison test). Significance of differences between groups was tested by analysis of variance for repeated measures (ANOVA). The Mann–Whitney U test was also used for comparison between groups when necessary (loss of subjects in group A after 100 min). To compare the duration of analgesia we used product limit survival analysis (Kaplan–Meier analysis) followed by Wilcoxon’s test. Where appropriate, Fisher’s exact test was performed. Results are expressed as mean (SD).

Results

The groups were comparable in age, weight at term, weeks of pregnancy, parity, VAS pain scores and stage of cervical dilatation at the time of entry into the study (table 1). All patients enrolled in the study were included in data analysis.

Onset times for analgesia did not differ between groups: 6 (2), 6 (2) and 7 (3) min, respectively, for the control and clonidine 100 μg and 150 μg groups. Mean duration of anaesthesia was 105 (21) min (range 70–140 min) for patients who did not receive clonidine, and 130 (26) min (range 100–185 min) (P < 0.05 vs control) and 144 (40) min (range 100–230 min; P < 0.01 vs control, ns vs clonidine 100 μg) for patients who received clonidine 100 μg and 150 μg, respectively. The percentage of patients not requesting additional analgesia was greater in the bupivacaine–clonidine 150 μg than in the other

Table 1  Patient data and details of labour (mean (SD or range) or number of patients)

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Clonidine 100 μg</th>
<th>Clonidine 150 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>28 (21–38)</td>
<td>25 (20–31)</td>
<td>26 (20–37)</td>
</tr>
<tr>
<td>Weight at term (kg)</td>
<td>73 (11)</td>
<td>72 (13)</td>
<td>69 (8)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164 (6)</td>
<td>165 (5)</td>
<td>163 (5)</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>10</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Cervical dilatation at time of study drug (cm)</td>
<td>3.4 (0.9)</td>
<td>3.2 (0.9)</td>
<td>3.2 (0.9)</td>
</tr>
<tr>
<td>VAS pain score at time of study drug (range)</td>
<td>6.14 (1.83)</td>
<td>6.53 (2.02)</td>
<td>6.83 (1.97)</td>
</tr>
<tr>
<td>Gestation (weeks)</td>
<td>39 (1.6)</td>
<td>39 (1)</td>
<td>39 (1.5)</td>
</tr>
<tr>
<td>Sensory level at 5 min (median)</td>
<td>T10 (6–12)</td>
<td>T10 (9–12)</td>
<td>T10 (6–12)</td>
</tr>
</tbody>
</table>

| Spontaneous delivery | 13 | 11 | 12 |
| Instrumental delivery | 2  | 2  | 1  |
| Caesarean section    | 0  | 2  | 2  |
groups when analysed by Kaplan–Meier survival analysis followed by Wilcoxon’s test (fig. 1). No patient failed to achieve analgesia throughout the study in both groups. Mean VAS scores decreased significantly within 5 min after administration of drug. By 80 min, although both clonidine groups had lower pain scores than the control group, this was not statistically significant until 100 min (table 2). At 100 and 120 min, pain scores between groups 100 and 150 μg were not significantly different. Overall, the degree of maternal and nurse satisfaction was high in all groups.

Maternal heart rates were comparable in all three groups before administration of the study drug: 85 (14) beat min⁻¹ for the control group, 82 (12) beat min⁻¹ for the clonidine 100 μg group and 86 (11) beat min⁻¹ for the clonidine 150 μg group. Atropine was administered for bradycardia in one patient in the clonidine 150 μg group.

Mean arterial pressure (MAP) was comparable in all groups at baseline: 87 (10), 90 (13) and 89 (10) mm Hg, respectively. From baseline to time 120 min, there were no significant changes in MAP in the control group, whereas it decreased significantly at 20 min in the clonidine 100 μg group (82 (14) mm Hg; \( P < 0.05 \)) (fig. 2). From 20 to 140 min this decrease remained significant, being highly significant at 40 min (79 (8) mm Hg; \( P < 0.001 \)). In the clonidine 150 μg group, MAP decreased more rapidly (at 5 min: 83 (6) mm Hg; \( P < 0.05 \)) and was highly significant at 20 min (73 (8) mm Hg; \( P < 0.001 \)). In all three groups, MAP was not different over the first 20 min (fig. 2).

One patient in the control group, two in the clonidine 100 μg group and one in the clonidine 150 μg group needed ephedrine for transient hypotension (ns).

There was no change in \( S_P_{O_2} \) at any time. Basal ventilatory frequency was comparable between groups and no significant change was noted throughout the study in the control and clonidine 100 μg group. In the clonidine 150 μg group, there was a significant decrease in ventilatory frequency in the first 80 min: 17 (5) bpm at 40 min vs 21 (3) bpm at baseline (\( P < 0.01 \)). However, inter-group comparisons showed no significant differences over the first 100 min.

In the control group, no patient had a Bromage score exceeding 1. Only one patient in each of the clonidine groups had a score of 2; no patient had Bromage score 3. Sedation scores were comparable between groups. No patient in the control group, one in the clonidine 100 μg group and two in the clonidine 150 μg group had a sedation score of 3.

Differences in FHR patterns were noted between groups. A decrease in long-term variability (\( P < 0.04 \)) and bradycardia (FHR < 120 beat min⁻¹) were more usual in the clonidine 150 μg group (\( P < 0.02 \)). The numbers of tracings with variable (\( P < 0.01 \)) and late decelerations (\( P < 0.04 \)) were significantly more frequent in the clonidine 150 μg group, while early decelerations were more frequent in the clonidine 100 μg group. For variable decelerations, five were moderate and two mild in the clonidine 150 μg group, four mild and one moderate in the clonidine 100 μg group and three moderate and one mild in the

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**Table 2** Mean (SD) VAS pain scores for the three groups. **P<0.001, ***P<0.001 vs control group

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>60</th>
<th>80</th>
<th>100</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group ( (n=15) )</td>
<td>6.14</td>
<td>1.6</td>
<td>0.46</td>
<td>0.23</td>
<td>0.16</td>
<td>0</td>
<td>0</td>
<td>1.27</td>
<td>3.85</td>
<td></td>
</tr>
<tr>
<td>Clonidine 100 μg ( (n=15) )</td>
<td>6.53</td>
<td>1.5</td>
<td>0.33</td>
<td>0.23</td>
<td>0.06</td>
<td>&lt;0.01</td>
<td>&lt;0.1</td>
<td>0.16</td>
<td>1.26</td>
<td>2.20</td>
</tr>
<tr>
<td>Clonidine 150 μg ( (n=15) )</td>
<td>6.83</td>
<td>1.9</td>
<td>0.8</td>
<td>0.13</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
<td>0.26</td>
<td>0.53</td>
<td>1.83</td>
</tr>
</tbody>
</table>
control group. However, no deceleration was classified as severe or needed emergency treatment.

The incidence of side effects was low (table 3). Thirteen patients in the control group had spontaneous vaginal delivery compared with 11 in the clonidine 100 µg group and 12 in the clonidine 150 µg group (table 1). Neonatal Apgar scores at 1 and 5 min did not differ between groups and neurological assessments were normal for all babies at 2 h.

Discussion

Local anaesthetics given extradurally are used widely for analgesia in labour. Fentanyl4 8 and sufentanil2 are frequently added to local anaesthetic solutions to potentiate their analgesic effects, allowing a reduced local anaesthetic concentration with less motor block10–12. However, the risk of delayed respiratory depression, pruritus and vomiting limits the use of opioids during labour7. These adverse effects have stimulated the search for alternative drugs13 or methods14 to provide analgesia during labour. We speculated that extradural clonidine, an alpha2 agonist, might provide effective analgesia when combined with sufentanil and low-dose bupivacaine. Extradurally administered clonidine may be ideally suited for obstetric use because it does not interfere with proprioception and does not induce motor block or respiratory depression15,16.

After extradural administration, clonidine 300 µg alone has been demonstrated to have no effect on fetal physiological indices in sheep14. Few studies have assessed the combination of clonidine and local anaesthetics in humans during labour. Brichant and colleagues found that clonidine 75 µg was added to fentanyl 100 µg–0.125% bupivacaine (177 vs 89 min). The mean duration of analgesia obtained in our study was approximately 150 min, longer than that observed with 0.125% bupivacaine and clonidine alone17,18. Our results showed that clonidine 100 and 150 µg with a sufentanil 10 µg–0.0625% bupivacaine–adrenaline solution significantly improved the duration of analgesia in the first stage of labour.

Analgesia in the control group was satisfactory without any significant change in MAP. Addition of clonidine 100 or 150 µg prolonged analgesia but caused significant haemodynamic changes. Comparisons between groups showed that this decrease was more important in the clonidine 150 µg group than in the clonidine 100 µg group. Extradural clonidine 700 µg alone decreased arterial pressure and heart rate in volunteers19 while minor changes in haemodynamic state were reported with extradural clonidine during pregnancy in a sheep model1. Doses of clonidine 30–150 µg did not alter haemodynamic state when combined with 0.125% bupivacaine during labour17,18 and the addition of sufentanil 10 µg19 or fentanyl 50 µg20 to clonidine (30 and 75 µg, respectively)–0.125% bupivacaine mixtures did not increase the need for ephedrine treatment during labour. Hypotension during extradural anaesthesia is greater after adrenaline–local anaesthetic solutions than after free adrenaline solution21. Extradurally administered clonidine has a U-shaped dose–response for arterial pressure15 and may explain the decrease in MAP in our study. Although we observed a decrease in MAP, the change in MAP was modest and the incidence of ephedrine treatment was similar in all groups.

While extradural administration of opioids is associated with respiratory depression4, extradural clonidine did not appear to have a marked effect on ventilation. It has been reported that clonidine does not potentiate morphine or alfentanil-induced respiratory depression22,23. In this study, although clonidine was combined with sufentanil, no episode of desaturation was noted and ventilatory frequencies did not differ between groups.

An additional side effect of extradural clonidine is sedation24. The incidence of sedation was similar between groups in our study. Other side effects were of minor importance.

Approximately 20% of normal gravidas develop fetal heart rate patterns which place the fetus “at risk” during labour. Most frequently, these patterns occur as a result of either umbilical, maternal or uteroplacental circulatory problems4. FHR abnormalities such as variable or late decelerations, bradycardia or change in baseline variability may occur. In this study we found that extradural clonidine, particularly clonidine 150 µg, was associated with such FHR abnormalities. It is unclear at present if these changes were caused by a direct effect of clonidine on the cardiovascular system of the fetus or an effect on oxygen supply. It has been reported that extradural clonidine 150 µg induced serum clonidine concentrations close to 1 ng ml–1 in postoperative patients24. In pregnant sheep, clonidine 1 ng ml–1 did not decrease uterine blood flow25 but a direct effect of such concentrations on fetal and uterine blood flow

### Table 3

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Control group (n = 15)</th>
<th>Clonidine 100 µg (n = 15)</th>
<th>Clonidine 150 µg (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patients requiring atropine</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Sedation score 1 (awake)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sedation score 2 (dozing)</td>
<td>15</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Sedation score 3 (asleep)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

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has not been evaluated in labouring parturients. In contrast, a decrease in long-term variability and bradycardia are expected responses after administration of tranquillizers, clonidine, opioids and extradural local anaesthetics\(^{25-26}\). In addition, our clinical study contrasts with those of Cellano and colleagues and O’Meara and Gin who showed no effect of clonidine 150 or 120 \(\mu\)g on FHR when given extradurally\(^{18}\). These differences could be attributed to the different time course of analgesia for the three groups which made intergroup comparisons difficult and to an additional effect of sufentanil on FHR.

**References**

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18. O’Meara ME, Gin T. Comparison of 0.125% bupivacaine with 0.125% bupivacaine and clonidine as extradural analgesia in the first stage of labour. *British Journal of Anaesthesia* 1993; 71: 651–656.