

## Low-dose clonidine infusion during labour

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In this study, we have compared two different doses of clonidine (bolus of 25 µg and infusion of 19 µg h<sup>-1</sup>; bolus of 50 µg and infusion of 37 µg h<sup>-1</sup>, both added to 0.03% bupivacaine) with a control group of 0.03% bupivacaine alone. The study was performed in a randomized, double-blind manner, and a total of 45 patients were studied. Both clonidine regimens resulted in marked local anaesthetic sparing, with no change in the quality of analgesia. There was no difference in the severity of lower limb motor weakness and no difference in maternal sedation, although only a small number of patients were studied. No adverse maternal haemodynamic effects were observed. The newborn infants were not sedated on delivery. The number of fetal cardiotocographic traces judged to be of concern was higher in both clonidine groups. However, this just failed to reach statistical significance ( $P=0.055$ ).

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Analgesia for women in labour is achieved commonly by administration of local anaesthetic agents into the epidural space. Although the resulting pain relief is often excellent, the use of local anaesthetic agents alone is associated with side effects of motor weakness, numbness, increased duration of labour and possibly increased obstetric intervention. The potential of other analgesic agents warrants investigation.

The  $\alpha_2$  adrenergic agonist clonidine produces analgesia by a non-opioid mechanism.<sup>1</sup> Clonidine may be especially valuable in providing pain relief for women in the first stage of labour, as the pain is mainly a visceral stimulus. In a pregnant animal model, the pain threshold to both somatic and visceral stimuli increased in late pregnancy, a phenomenon termed 'pregnancy-induced analgesia'. Low-dose clonidine, insufficient to produce antinociception in early pregnancy, raises the threshold to visceral but not somatic stimuli in late pregnancy.<sup>2</sup> The safety of administration of clonidine into the epidural space, and to women in pregnancy, has been investigated previously. Administration of large doses of clonidine orally as an antihypertensive agent in late pregnancy was not associated with major problems.<sup>3,4</sup> In an animal model, no effects on uterine blood flow were seen.<sup>5</sup> Extensive animal investigations<sup>6</sup> and experimental administration of epidural clonidine to more than 2000 humans<sup>7</sup> have failed to demonstrate acute or chronic neurotoxicity.

In women in the first stage of labour, the analgesic effect of adding a bolus dose of clonidine to a local anaesthetic epidural bolus has been investigated. Addition of clonidine 120 µg to 0.125% bupivacaine improved both duration and quality of pain relief, but at the cost of increased maternal sedation.<sup>8</sup> Similar benefits and side effects were seen with addition of a bolus dose of clonidine 75 µg to 0.125% bupivacaine.<sup>9</sup> In a second study, a smaller bolus of 30 µg added to a mixture of 0.125% bupivacaine, epinephrine and sufentanil was not shown to provide any additional analgesic effect.<sup>10</sup>

The elimination half life of clonidine in cerebrospinal fluid after a single epidural dose is only 66 min.<sup>11</sup> This may suggest that administration of clonidine as a small initial bolus and subsequent infusion, rather than intermittent bolus alone, may be more useful clinically. Therefore, we have compared pain relief experienced by women throughout labour receiving a control infusion of low-dose local anaesthetic, with two groups receiving the same local anaesthetic infusion and one of two doses of epidural clonidine by bolus and subsequent infusion.

### Patients and methods

The Ethics Committee of the University of Newcastle-upon-Tyne approved the study. The Medicines Control Agency were informed of the study and allowed the supply of clonidine for the study without issuing a clinical trials

**Table 1** Treatment groups. Individual epidural bolus doses and infusions administered to each group (30 min after initial epidural block and when pain-free)

	Epidural bolus	Epidural infusion
Group 1	Saline 10 ml	0.03% bupivacaine at 12.5 ml h <sup>-1</sup>
Group 2	Saline 10 ml+clonidine 25 µg	0.03% bupivacaine at 12.5 ml h <sup>-1</sup> +clonidine 19 µg h <sup>-1</sup>
Group 3	Saline 10 ml+clonidine 50 µg	0.03% bupivacaine at 12.5 ml h <sup>-1</sup> +clonidine 37 µg h <sup>-1</sup>

certificate. We studied 45 subjects, all in established labour (experiencing regular painful contractions), requesting epidural analgesia as their primary method of analgesia. Only singleton pregnancies of vertex presentation were considered for inclusion. Patients were excluded if there was any significant maternal illness, onset of labour was before 37 weeks' gestation or the patient had previously received an opioid, tricyclic antidepressant or  $\alpha_2$  agonist.

All women received balanced saline solution 500 ml i.v. and an epidural catheter was sited using a standard technique at the L2–3 or L3–4 interspace. After a test dose of 0.5% bupivacaine 3 ml, analgesia was established with 0.125% bupivacaine 10 ml. Only when pain-free were subjects considered for entry into the study and written informed consent was obtained. Women were then allocated randomly by sealed envelope to one of the three infusion regimens (Table 1).

The saline–clonidine bolus and infusions were commenced in all patients 30 min after initial establishment of epidural block (time 0). All infusions were continued until delivery or obstetric intervention. When pain relief was felt by the patient to be inadequate, a bolus dose of bupivacaine 10 ml was administered and the time recorded. Boluses for the first two maternal requests were 0.125% bupivacaine and then 0.25% thereafter.

Patient, obstetrician and investigator were unaware of the treatment groups. Inadequate analgesia was defined as a request by the patient for improved analgesia. Pain was also assessed by a visual analogue scale (VAS), anchored at no pain (0 cm) and worst possible pain imaginable (10 cm), but its recorded value was not used as a trigger for the investigator to administer additional analgesia. Adequacy of analgesia was assessed by the number of top-ups required during labour. The VAS was recorded before siting the epidural catheter, when comfortable when the initial bolus of saline or clonidine was administered (time 0), 30 min after starting the infusion and hourly thereafter.

Sedation was assessed on a five point scale (1=wide awake, 2=drowsy, 3=dozing, 4=mostly sleeping, 5=awakening only when aroused). The height of sensory block was determined with an ethyl chloride spray, and degree of lower limb motor block by a modified Bromage scale (Table 2).

Arterial pressure, heart rate and oxygen saturation were measured non-invasively, and recorded at the time of administration of the epidural test dose, every 5 min for 20 min thereafter, at the time of administration of the saline or clonidine bolus, every 5 min for 20 min thereafter, and then hourly. Systolic arterial pressure of less than 100 mm

Hg was treated with ephedrine 5 mg i.v. Heart rate less than 45 beat min<sup>-1</sup> was treated with atropine 0.3 mg i.v. Cervical dilatation was noted at the time of request for epidural placement and at each time the midwife judged it necessary to examine.

Fetal well-being was assessed by continuous recording of heart rate on a cardiotocograph (Hewlett-Packard 8040A) connected to either an external electrode or an internal fetal scalp electrode. Fetal heart rate data were analysed retrospectively by a consultant in fetal medicine who was blinded to the treatment group. The technique of delivery was noted, and the baby's initial Apgar score, and cord arterial and venous pH values were measured. The effects of the medication received on the newborn baby were assessed by undertaking a neurobehavioural score (neurologic and adaptive capacity (NAC) score)<sup>12</sup> at 4 h of age.

Statistical analysis of continuous measurements (Tables 3, 4, 5, 6 and 8) was by one-way analysis of variance. Categorical data presented in Table 8 were analysed using a chi-square test.

## Results

All three groups were similar in patient characteristics (Table 3). Women in whom labour was induced for post-maturity made up the majority of patients in all three groups. Duration of epidural infusion until delivery or obstetric intervention was similar in all groups (Table 4). The number of boluses of local anaesthetic required to maintain acceptable pain relief however, was reduced in both clonidine groups. The control group (0.03% bupivacaine infusion alone) required a mean of 3.13 boluses of local anaesthetic to maintain adequate pain relief compared with 1.2 and 0.66 for the lower and higher dose clonidine groups ( $P<0.05$ ). The number of boluses required for the two clonidine groups was not significantly different. Mean duration from commencement of the infusions until request for the first additional local anaesthetic bolus to maintain adequate analgesia was 106.9 min for the bupivacaine control group compared with 182.9 and 234.4 min for the lower and higher dose clonidine groups, respectively. The increase in time to request for the first additional analgesia was statistically significant for the higher clonidine dose regimen compared with the control group. The resulting quality of analgesia (as reflected by pain scores) did not vary between groups, despite the difference in the amount of bupivacaine received (Table 5). The quality of analgesia was least acceptable in the control group, the value being significantly different at 30 and 60 min compared with time 0.

**Table 2** Modified Bromage scale. Scale used to assess degree of lower limb motor weakness

Degree of motor weakness	Description
1	Unable to flex at the knee or ankle joint
2	Unable to flex at the knee. Able to flex at the ankle
3	Partially able to flex at the knee
4	Unable to straight leg raise. Able to flex at knee and ankle joints
5	Able to straight leg raise but not against resistance
6	Able to straight leg raise against resistance

**Table 3** Patient characteristics in the three groups (mean (SD or range) or number). No significant differences

	Group 1	Group 2	Group 3
<i>n</i>	15	15	15
Age (yr)	25.1 (17–36)	28.2 (18–39)	27.5 (17–35)
Cervical dilation when epidural placed (cm)	2.5 (0.8)	2.6 (1.1)	3.0 (1.4)
Gestation (weeks)	40.5 (1.4)	40.5 (1.4)	40.2 (1.8)
Height (cm)	162.4 (7.4)	161.3 (8.2)	161.8 (9.4)
Weight (kg)	78.7 (15.6)	75.5 (12.6)	77.9 (15.4)
No. in whom labour was induced	11	11	9
No. of primiparous women	11	8	12

**Table 4** Bupivacaine requirements in the three groups (mean (SD)). \**P*<0.05, group 1 compared with groups 2 and 3; ††*P*<0.01, group 3 compared with group 1; ‡*P*<0.05, group 1 compared with groups 2 and 3

	Group 1	Group 2	Group 3
No. of top-ups	3.13 (1.12)*	1.2 (0.77)	0.66 (0.61)
Time to first top-up (min)	106.9 (64.5)	182.9 (108.1)	234.4 (106.9)††
Duration of infusion (min)	427.1 (194.6)	360.6 (145.8)	331.7 (98.4)
Total dose of bupivacaine received (mg)	17.5 (5.8)‡	12.1 (2.8)	10.4 (1.7)

**Table 5** VAS pain scores (mean (SD)). \**P*<0.05 compared with time 0

	Time (min)						
	-30	0	30	60	120	180	240
Group 1	75.9 (22.4)	8.6 (8.1)	17.4 (16.5)*	27.8 (22.1)*	13.7 (11.7)	21.8 (16.7)	26.8 (20.7)
Group 2	75.2 (18.5)	9.5 (9.6)	9.2 (7.9)	14.3 (21.3)	16.4 (19.2)	23.1 (26.9)	17.3 (28.8)
Group 3	75.3 (23.9)	7.1 (5.1)	8.6 (9.8)	8.3 (9.3)	10.2 (10.8)	9.4 (12.7)	17.9 (21.3)

**Table 6** Degree of maternal lower limb motor block (modified Bromage Score) (mean (SD)). No significant differences

	Time (min)					
	0	30	60	120	180	240
Group 1	4.80 (0.94)	4.87 (0.84)	4.93 (0.70)	4.60 (0.91)	4.46 (0.88)	4.38 (1.12)
Group 2	5.00 (0.68)	4.87 (0.74)	4.53 (0.99)	4.67 (0.72)	4.60 (0.74)	4.64 (0.81)
Group 3	4.47 (0.84)	4.43 (0.94)	4.47 (0.83)	4.40 (1.05)	4.27 (1.10)	4.29 (1.07)

**Table 7** Changes in maternal cardiovascular variables (heart rate (HR) and mean arterial pressure (MAP)) (mean (SD)). No significant differences

	HR at time 0 (beat min <sup>-1</sup> )	Lowest HR during infusion (beat min <sup>-1</sup> )	MAP (mm Hg)	Lowest MAP (mm Hg)
Group 1	86 (13)	81 (12)	91 (11.6)	90 (11.6)
Group 2	81 (6.8)	76 (6.1)	93 (6.9)	92 (7.1)
Group 3	79 (10.6)	70 (9.5)	89 (7.9)	88 (7.9)

The marked bupivacaine sparing effect of the clonidine groups did not lead to reduction in lower limb motor weakness (Table 6). Also, addition of clonidine did not result in major maternal cardiovascular changes (Table 7). In particular, there were no episodes of bradycardia or hypotension requiring treatment. Although patient numbers

**Table 8** Sedation scores (mean (SD)) in the three groups. No significant differences

	Time (min)					
	0	30	60	120	180	240
Group 1	1.47 (0.92)	1.6 (0.98)	1.80 (1.42)	1.60 (1.30)	1.46 (1.13)	1.46 (1.13)
Group 2	1.00 (0)	1.27 (0.59)	1.20 (0.56)	1.13 (0.35)	1.07 (0.26)	1.09 (0.30)
Group 3	1.4 (0.63)	1.73 (1.16)	1.40 (0.74)	1.13 (0.35)	1.47 (0.64)	1.73 (1.01)

**Table 9** Assessment of fetal traces

	Duration of epidural infusion (min)		
	0	30	180
No. of traces showing reduced variability			
Group 1	1	1	3
Group 2	1	2	5
Group 3	2	2	3
No. of possibly poorly reactive traces			
Group 1	2	2	0
Group 2	0	1	5
Group 3	0	0	4

**Table 10** NAC score, and cord venous and arterial pH values (mean (SD)). No significant differences

	Group 1	Group 2	Group 3
NAC score (4 h)	26.0 (1.47)	27.7 (2.24)	25.4 (1.71)
pH arterial	7.28 (0.08)	7.22 (0.11)	7.25 (0.06)
pH venous	7.33 (0.09)	7.29 (0.10)	7.34 (0.05)

were small, no increase in maternal sedation was seen in the clonidine groups (Table 8).

The number of fetal cardiocardiographic traces judged retrospectively by a consultant in fetal medicine to be of concern was higher in the clonidine groups (Table 9), but this just failed to reach statistical significance. There were no differences in the degree of sedation of the newborn infants (NAC score) or cord pH values (Table 10).

## Discussion

The population studied was predominantly primiparous women with labour induced for post-maturity. Clonidine, in small initial bolus doses with subsequent infusion added to an infusion of low-dose bupivacaine (0.03%), provided useful and adjunctive analgesia for this group of women throughout labour. This is in agreement with the study of O'Meara and Gin<sup>8</sup> who observed useful analgesia with larger bolus doses of epidural clonidine. Increased analgesia observed with the small doses in our study supports our initial hypothesis that clonidine may be a particularly appropriate agent for visceral-mediated pain in late pregnancy. Both low-dose regimens of clonidine provided similar analgesia and side effects. The relatively high-dose clonidine

regimen did not appear to confer any additional benefits over the low-dose regimen.

Although patient numbers were small, side effects of sedation and cardiovascular depression seen with larger bolus doses of clonidine<sup>8,9</sup> were not observed in this study. Despite marked reductions in the bupivacaine dose received, no reduction in lower limb motor block was seen. Intrathecal clonidine has been shown to prolong the duration of motor and sensory block after intrathecal injection of bupivacaine.<sup>13</sup> The mechanism is unclear. It may be that clonidine not only prolongs but enhances motor weakness caused by bupivacaine. The number of labours ending in obstetric intervention in the control and study groups was high but did not vary from the intervention rates observed in this high-risk obstetric population in this unit before the study.

There were no adverse effects on the newborn infants. During labour, no major concerns were expressed on the quality of fetal traces in subjects receiving clonidine. Subsequent blinded analysis by a specialist in fetal medicine highlighted a higher level of fetal traces showing reduced variability in the clonidine groups. While not statistically significant, this finding, in association with a high number of trace abnormalities reported by Chassard and colleagues<sup>14</sup> with bolus doses of clonidine 100 and 150 µg warrants further investigation. The lack of difference in umbilical blood pH values suggests that any effect is not caused by change in placental or fetal cardiac function. After delivery, there was no major sedation of infants, as judged by NAC scores. There was no report from postnatal nursing staff of any delay in the time to first request for feeding by the infants,

although this may be a more useful clinical marker for studying sedation in neonates in future studies.

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