The Analgesic Effect of Epidural Clonidine After Spinal Surgery: A Randomized Placebo-Controlled Trial

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BACKGROUND: Clonidine is an α_2 adrenoreceptor and imidazoline receptor agonist, which has analgesic, sedative, and minimum alveolar anesthetic concentration-sparing effects. It has been used orally, IV, and epidurally. In spinal surgery, there is a reluctance to use local anesthetic-based epidural analgesia postoperatively because of fears of masking important signs of nerve root or spinal cord injury.
METHODS: We randomized 66 patients undergoing uncomplicated decompressive spinal surgery to receive an epidural infusion of either clonidine (Group C) or saline placebo (Group P) postoperatively. Morphine consumption by patient-controlled analgesia device was recorded for 36 h.
RESULTS: Morphine consumption was significantly lower in Group C. The mean consumption at 36 h was 35 mg (95% confidence interval 21–50 mg) in Group C, compared with 61 mg (95% confidence interval 48–74 mg) in the control group. Nausea was significantly reduced in Group C (6.5%), when compared with placebo (38.2%).
CONCLUSION: Low-dose epidural clonidine significantly reduced the demand for morphine and reduced postoperative nausea with few side effects.
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Clonidine is an α_2 adrenoreceptor and imidazoline receptor agonist which has analgesic, sedative, and minimum alveolar anesthetic concentration-sparing effects. It has been used orally, IV,[1,2] and epidurally.[1,3–5] In spinal surgery, there is a reluctance to use local anesthetic-based epidural analgesia postoperatively because of fears of masking important signs of nerve root or spinal cord injury. This pilot study examines the analgesic efficacy of low-dose epidural clonidine after simple spinal surgery.

METHODS

After local Research Ethics Committee approval, 66 consenting patients scheduled for elective lumbar decompression or discectomy surgery were randomized at the time of treatment using a computer-generated random number, to receive an infusion of epidural clonidine (Group C) or saline placebo (Group P) for 36 h as part of their postoperative analgesia regime. Patients whose preadmission analgesic requirements included strong opioids or who had complicated chronic pain histories were excluded. The CONSORT-style patient flow diagram is shown in

Figure 1. All patients received identical general anesthesia and intraoperative analgesia as follows:

> Premedication: paracetamol 1 g, ibuprofen 600 mg, and ranitidine 150 mg PO.
> Induction: propofol 1–3 mg/kg as required, fentanyl 1 μg/kg, and atracurium 0.5 mg/kg.
> Maintenance: oxygen 33%, nitrous oxide 66%, and isoflurane 0.5%–1% end-tidal. Intraoperative analgesia: fentanyl 0.7 μg/kg at 30 min intervals.

Just before closure of the wound, an epidural catheter was sited under direct vision by a single surgeon. A bolus dose of study drug (1.5 μg/kg clonidine in 5 mL solution for Group C or an equivalent volume of saline for Group P) was administered via the catheter at this time.

In the recovery ward, Group C received 5 mL/h of a solution containing 5 μg/mL of clonidine. Group P received an equivalent infusion of saline. A standard patient-controlled analgesia (PCA) device was connected and programmed to deliver a 3-mg initial bolus of morphine on first actuation and 1-mg bolus doses thereafter. The anesthetic, surgical, and recovery teams were blinded to the identity of the epidural infusion. All patients received oral paracetamol (1 g, QDS, PO) postoperatively. Data were recorded up to 36 h by the patients' named nurse. The principal end point was analgesia requirement via the PCA device, analyzed as the cumulative morphine consumption at 36 h. The secondary end points were 1) pain scores, 2) heart rate and arterial blood pressure, 3) sedation score (4-point scale: 0 = awake and alert, 1 = drowsy, 2 = mostly sleeping, and 3 = difficult
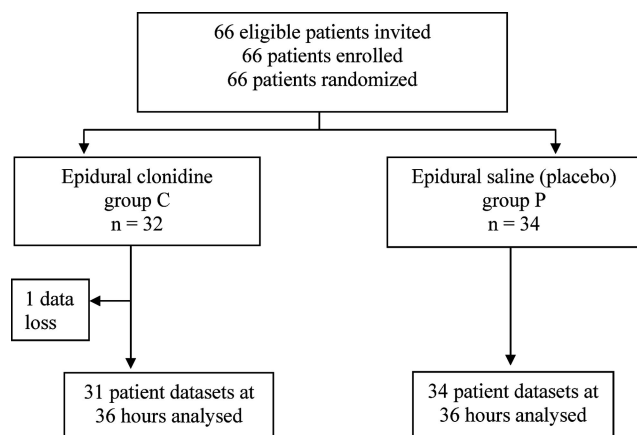
Figure 1. Flow of patients through the trial.

Figure 1 flowchart content:

66 eligible patients invited
66 patients enrolled
66 patients randomized

Epidural clonidine group C n = 32

Epidural saline (placebo) group P n = 34

1 data loss

31 patient datasets at 36 hours analysed

34 patient datasets at 36 hours analysed

Table 1. Distribution of Case and Patients Details Between Groups

Group	Placebo	Clonidine	Statistical significance
Number of cases	34	31	$P = 0.71$, NS[a]
Of which discectomies	9	8	
Of which single level decompressions	18	14	
Of which two level decompressions	7	9	$P = 0.94$, NS[b]
Mean age (SD), yr	53.5 (15.0)	56.9 (18.9)	$P = 0.50$, NS[c]
Male/female	14/20	14/17	$P = 0.75$, NS[b]
Duration of surgery (SD), min	69 (16)	73 (15)	$P = 0.73$, NS[c]
Median operative blood loss (range), mL	55 (0–508)	0 (0–605)	$P = 0.42$, NS[d]

NS = not significant.
[a] Normal approximation to the binomial distribution.
[b] χ^2.
[c] t-test for independent means.
[d] Mann–Whitney.

or impossible to awaken), 4) incidence of urinary retention, and 5) incidence of nausea and vomiting.

Pain scores were recorded every 15 min in the first hour, with the frequency reducing to every 30 min (2–8 h), every hour (8–16 h), and every 4 h thereafter. Scores were representative of typical clinical activity and included movement in the bed. The worst pain score in the time period recorded was used for analysis.

Pain scores, morphine consumption rate, heart rate, and arterial blood pressure were treated as normal data and analyzed with a general linear model for repeated measures (SPSS, v13, SPSS Inc, Chicago, IL) Cumulative morphine consumption by 36 h was analyzed by unpaired t-test. Differences in the incidence of nausea and vomiting and urinary retention were analyzed with the χ^2 test.

Power analysis: To show a reduction in morphine consumption at 36 h by one-third, with a power of 0.8 at the 5% level of significance, we estimated that approximately 60 participants would be required.

RESULTS

The age, sex, case distribution, duration of surgery, and operative blood loss were similar in both Group C and Group P and are shown in Table 1. The data from one patient were lost from the study.

Morphine Consumption

Figure 2 (right panel) shows the cumulative morphine consumption in the postoperative period at 36 h. The cumulative dose in Group P was significantly higher than in Group C (61 mg vs 35 mg, $P = 0.011$). Figure 2 (left panel) shows the rates of morphine consumption versus time up to 36 h. Using a general linear model (SPSS v13), morphine consumption rate is seen to vary significantly between groups ($P = 0.004$), and there is a significant interaction between time and treatment group ($P = 0.0004$), i.e., the treatment difference is time dependent.

Pain Scores

Pain scores were generally low in both groups throughout the study. Although the study was designed to minimize differences in pain perception, small but statistically significant differences in pain scores were observed between groups, Group P scoring higher than Group C ($P = 0.002$). These differences were significantly time dependent ($P = 0.004$) and appear most marked in the first 6 postoperative hours. Within the first 2 h, these differences are probably clinically significant but are not so thereafter. These data are shown in Figure 3.

Arterial Blood Pressure and Heart Rate

Figure 4 shows the heart rate and arterial blood pressure data for the two groups. There was a small but significant difference in heart rate and systolic blood pressure between Group C and Group P; mean values for Group C were 11%–17% (heart rate) and 8%–12% (arterial blood pressure) lower than Group P.

For arterial blood pressure, these differences have a significant treatment effect ($P = 0.005$), but there is no significant interaction between time and treatment group ($P = 0.087$), i.e., the treatment difference is not time dependent. Similarly for heart rate, the differences have a significant treatment effect ($P = 0.00$), but there is no significant interaction between time and treatment group ($P = 0.063$).

Sedation

In no patient was the sedation score more than 2, and there was no significant difference in score between groups.

Nausea and Vomiting

At least one episode of nausea and/or vomiting occurred in two patients in Group C (6.5%) and 13 patients in Group P (38.2%). This difference was significant ($P = 0.0023$, χ^2).

Urinary Retention

Three patients (9.7%) in Group C and five patients (14.7%) in Group P required urinary catheterization. The differences were not statistically significant ($P = 0.54$, χ^2).
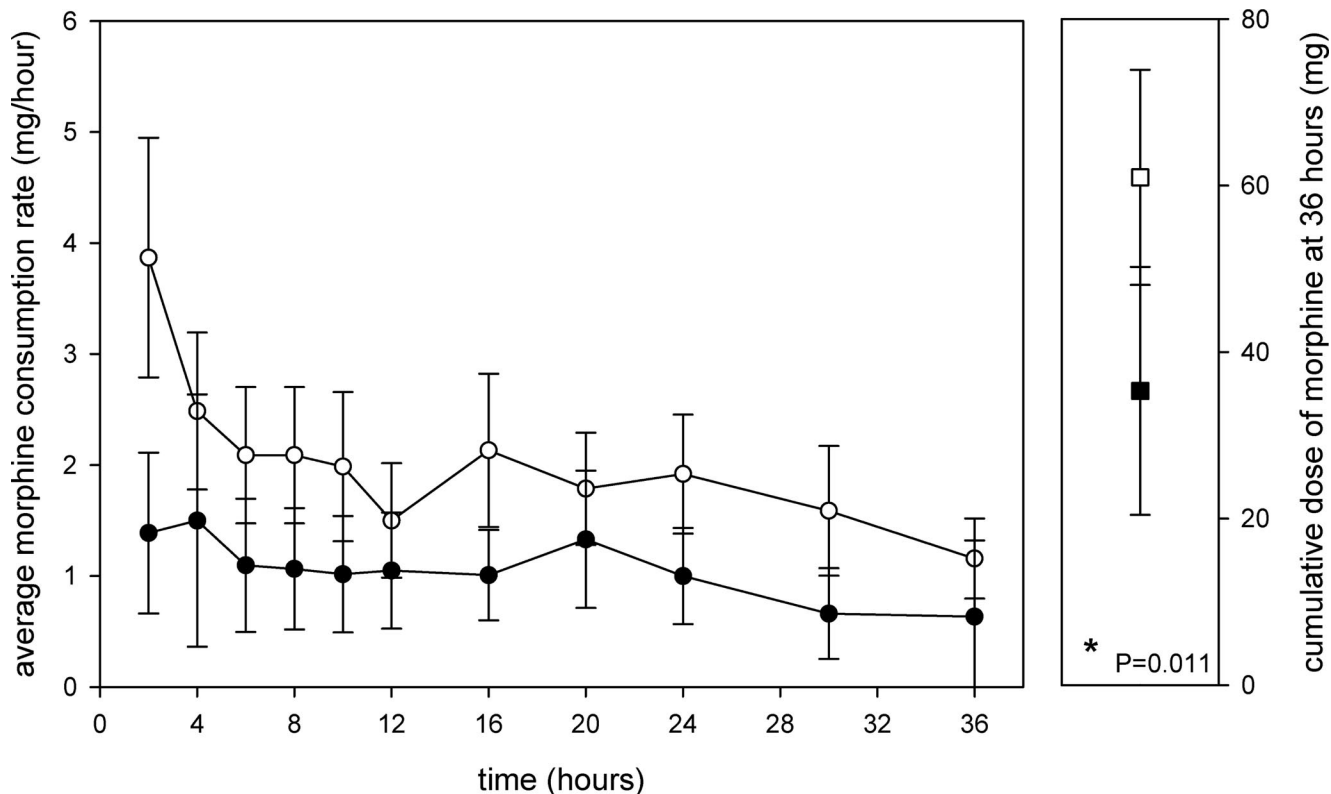
Figure 2. Left panel: morphine consumption rate via patient-controlled analgesia (PCA) device in mg/h averaged over the time bin indicated versus time postoperatively (means ± 2 SE). Open circles (○) control group, filled circles (●) clonidine group. Morphine consumption varies significantly between groups ($P = 0.004$), and there is a significant interaction between time and treatment group ($P = 0.0004$), i.e., the treatment difference is time dependent. Right panel: cumulative (total) morphine consumption at 36 h postoperatively (means ± 2 SE). Open squares = control group, filled square = clonidine group, $P = 0.011$.
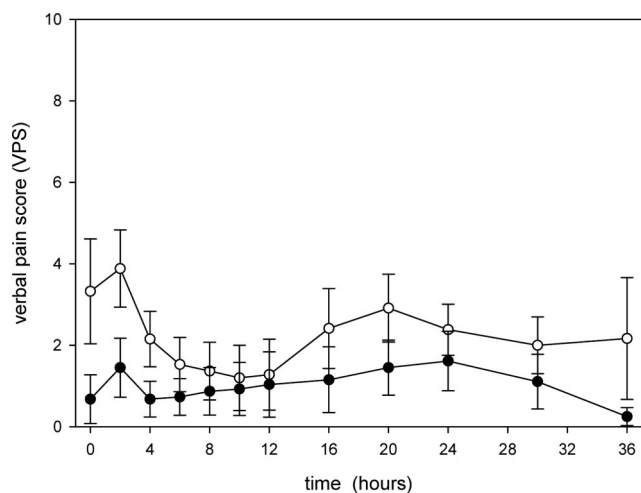

Figure 3. Subjective verbal pain scores (VPS) versus time postoperatively (means ± 2 SE). Open circles are control group, and filled circles are clonidine group. VPS varies significantly between groups ($P = 0.004$), and there is a significant interaction between time and treatment group ($P = 0.004$), i.e., the treatment difference is time dependent.

DISCUSSION

This study has demonstrated that clonidine infused epidurally reduces postoperative analgesic requirement and, despite the intentions of the study, reduces pain intensity in the early postoperative period. Pain scores were acceptably low in both groups but significantly lower in Group C.
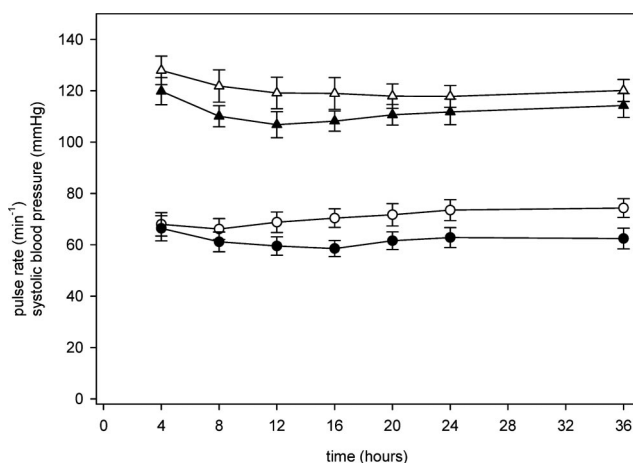

Figure 4. Pulse rate (circles) and systolic blood pressure (triangles) versus time (means, 95% confidence intervals). Open symbols = control group; closed symbols = clonidine group. Data plotted at time t represent the values averaged over the preceding time epoch bounded by the preceding time point. Systolic blood pressure varies significantly between groups ($P = 0.005$), and there is no significant interaction between time and treatment group ($P = 0.087$), i.e., the treatment difference is not time dependent. Pulse rate varies significantly between groups ($P = 0.001$), and there is no significant interaction between time and treatment group ($P = 0.063$).

Mean-morphine consumption at 36 h in Group C was about 43% less than that in Group P, but there was considerable interindividual variation of data in

both groups. There is evidence that a significant part, if not all, of clonidine's analgesic effects is mediated by effects at the spinal level. Indirect support of this assertion comes from Bernard et al.,[3] who demonstrated in patients receiving PCA clonidine via the epidural or IV route, that for equianalgesia both the required doses and plasma concentrations of clonidine were markedly lower in the epidural group. Marinangeli et al.,[1] in a dose-ranging study of IV clonidine for pain relief after laminectomy, found it to have an opiate-sparing effect. However, the doses used epidurally in our study were lower than their least effective dose used IV, suggesting a spinal site of action. More recently, clonidine has been shown to have an effect on action potential generation in tonic firing neurones in the dorsal horn; i.e., to have a "local-anesthetic type" effect.[6] Unlike local anesthetics, it does not block voltage-gated Na^+ channels at the typically low doses used clinically, but it does reduce tonic firing frequency at low doses and shift the steady-state Na^+ current inactivation curve to more negative potentials while leaving Na^+ current activation intact. This implies that clonidine has an increased affinity for, and a stabilizing effect on, the open and inactivated state of the channel.

Other studies have also evaluated the efficacy of epidural clonidine in spinal surgery. Jellish et al.[7] found that a single epidural bolus dose of 150 μg after laminectomy surgery performed with bupivacaine spinal block significantly reduced postoperative pain scores, although the effect was short lived being most marked in the first 60 min. We have shown that this benefit can be extended by following this initial bolus with a low-dose infusion for up to 36 h.

Bonhomme et al.,[8] studying patients who had undergone lumbar disc surgery under general anesthesia, showed that a single small bolus dose (75 μg) of epidural clonidine plus bupivacaine (10 mL, 0.125%) resulted in PCA usage over 24 h which was not different from controls, suggesting that a single bolus at this low dose is ineffective over this timeframe. However, they also showed that patients receiving the same dose of clonidine plus a small (1 mg) dose of epidural morphine had markedly reduced pain scores and PCA usage, suggesting that clonidine reduces the minimal effective dose of epidural morphine when compared with historical controls.

The reduction in heart rate and arterial blood pressure seen in Group C in our study is statistically significant but quantitively modest; the mean values for Group C were 11%–17% (heart rate) and 8%–12% (arterial blood pressure) lower than Group P. These data are very similar to those reported by Jellish et al.

The fact that little effect on sedation could be demonstrated is in keeping with Hall et al.'s[9] dose-ranging study of systemic clonidine on sedation and cognitive function, for which the lowest dose producing minimal sedation was three times larger than the dose used here.

The marked and significant reduction in postoperative nausea and vomiting (PONV) seen in Group C is notable. Jeffs et al.[2] also reported this incidental finding in their study of the analgesia-enhancing action of clonidine added to morphine PCA devices. To some extent, one might expect the effect on PONV to be due to the that fact that patients who received clonidine also received less morphine. However, the PONV reduction is disproportionately large with respect to the morphine sparing implying that at least some of the effect is directly due to α_2 adrenergic effects in the brainstem and clonidine may deserve further study as an antiemetic in its own right.

CONCLUSION

Epidural clonidine has a satisfactory analgesic effect after spinal surgery and reduces the demand for morphine by approximately 43% over the first 36 h. Epidural clonidine is effective at low doses, probably lower than for IV administration found by others.[1] It produces few side effects of its own, and, by reducing the consumption of morphine, may reduce the side effects of the latter. This technique for postoperative pain control is effective in uncomplicated spinal surgery. Further research is required to determine its efficacy in more complex spinal surgery.

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