Intrathecal morphine and clonidine for coronary artery bypass grafting

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Background. After cardiac surgery adequate postoperative analgesia is necessary. We assessed analgesia using intrathecal morphine and clonidine.

Methods. In a double-blind randomized study, 45 patients having coronary artery bypass graft surgery were allocated randomly to receive i.v. patient-controlled analgesia (PCA) morphine (bolus, 1 mg; lock-out interval, 7 min) (control group), either alone or combined with intrathecal morphine 4 µg kg⁻¹ or with both intrathecal morphine 4 µg kg⁻¹ and clonidine 1 µg kg⁻¹. Intrathecal injections were performed before the induction of general anaesthesia. Pain was measured after surgery using a visual analogue scale (VAS). We recorded i.v. PCA morphine consumption during the 24 h after operation.

Results. Morphine dosage [median (25th–75th percentiles)] was less in the first 24 h in the patients who were given intrathecal morphine + clonidine [7 (0–37) mg] than in other patients [40.5 (15–61.5) mg in the intrathecal morphine group and 37 (30.5–51) mg in the i.v. morphine group]. VAS scores were lower after intrathecal morphine + clonidine compared with the control group. Time to extubation was less after intrathecal morphine + clonidine compared with the i.v. morphine group [225 (195–330) vs 330 (300–360) min, P<0.05].

Conclusion. Intrathecal morphine and clonidine provide effective analgesia after coronary artery bypass graft surgery and allow earlier extubation.

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After cardiac surgery, pain can be more severe than commonly believed, and up to 60% of patients experience moderate to severe pain. Poor pain control may cause complications such as myocardial ischaemia, and pain may inhibit coughing and deep breathing, leading to atelectasis, with delay in extubation. Better control of extracorporeal circulation and body temperature changes currently allows more rapid extubation after uncomplicated coronary artery bypass grafting (CABG). This requires effective pain control, which can be provided with intrathecal morphine. Chaney and colleagues studied CABG patients given large intrathecal doses of morphine. They found that intrathecal morphine prolonged the need for controlled ventilation.

Intrathecal clonidine not only produces analgesia but can also augment the analgesic effect of morphine. The addition of intrathecal clonidine to morphine allows the dose of morphine to be reduced and reduces the risk of respiratory depression while maintaining good analgesia. Consequently, we assessed the analgesic effect of a combination of intrathecal morphine and clonidine in patients having CABG surgery.

Patients and methods

We recruited 45 patients scheduled for CABG in a prospective double-blind, randomized study, after ethics committee approval and with informed written consent. Patients with chronic cardiac or respiratory failure and those having valve surgery at the same time were excluded. We also excluded patients with a left ventricular ejection fraction of less than 40% and those with significant renal
or neurological impairment. Patients receiving anticoagulants or with a platelet count less than \(100 \times 10^9\) litre\(^{-1}\) were also excluded. On the morning of surgery, patients were allocated randomly to one of three groups with a computer-generated random number table. According to the randomization, patients were given either intrathecal morphine 4 \(\mu\)g kg\(^{-1}\), intrathecal morphine 4 \(\mu\)g kg\(^{-1}\) + clonidine 1 \(\mu\)g kg\(^{-1}\) or no intrathecal injection. Lumbar puncture was done at the L3–4 or L4–5 interspace with an i.m. needle in the control group and with a 27 gauge needle in the two other groups. A dressing was placed over the puncture site in all patients. Morphine was diluted in a 100 \(\mu\)g ml\(^{-1}\) solution with either clonidine 75 \(\mu\)g ml\(^{-1}\) or saline to obtain 4 ml for injection. Anaesthesia was induced with etomidate 0.25 mg kg\(^{-1}\) i.v. and sufentanil 50 \(\mu\)g i.v. for induction, and cisatracurium 0.20 mg kg\(^{-1}\) i.v. was used to facilitate intubation. Anaesthesia was maintained with sufentanil up to 3.5 \(\mu\)g kg\(^{-1}\), propofol 0.1–0.2 mg kg\(^{-1}\) min\(^{-1}\) and isoflurane 0.3–1.2%. Doctors and nurses caring for the patient were masked to treatment group. In the intensive care unit (ICU), patients were extubated when they were awake, oriented and cooperative, with a stable circulation, a temperature >36.5°C, minimal chest drain loss, and after a 30 min trial of spontaneous ventilation from a T piece \((\text{PaCO}_2 <45 \text{ mm Hg}, \text{SaO}_2 >93\%)\). After extubation, patients were given an i.v. patient-controlled analgesia (PCA) pump \((\text{APM}^{[9]}, \text{Abbott, Rungis, France})\) delivering a 1 mg dose of morphine with a 7 min lockout interval. Morphine was diluted to 1 mg ml\(^{-1}\) in a solution also containing droperidol 3 mg in 30 ml. The maximum dose of i.v. PCA morphine was 30 mg in 4 h. All patients also received propacetamol 2 g i.v. every 6 h.

Pain was measured at rest with a visual analogue scale (VAS) graded from 0 (no pain) to 100 (worst pain imaginable) every 30 min for the first 4 h in the ICU, each hour for the next 4 h, then every 2 h to 20 h and finally at 24 h.

We noted any evidence of respiratory depression (respiratory rate <10 bpm), hypertension (systolic arterial blood pressure \(>150 \text{ mm Hg}\)), hypotension (systolic arterial blood pressure \(<75 \text{ mm Hg}\)) and sedation. If necessary, hypertension was treated with a continuous infusion of nicardipine 1–5 mg h\(^{-1}\) i.v. and hypotension with rapid fluid infusion followed by inotropic agents if necessary.

Our aim was to obtain a 50% decrease in i.v. PCA morphine consumption after intrathecal clonidine + morphine compared with the control group. On the basis of experience with i.v. PCA morphine requirements in CABG patients in our hospital, we calculated that a sample size of 15 patients in each group should detect such a difference with a type I error of 0.05 and a type II error of 0.10.

Statistical analysis was with the unpaired Student’s t-test for comparisons of duration of surgery, aortic cross-clamping and extracorporeal circulation. The Mann–Whitney rank sum test was used to analyse morphine consumption, time to start PCA, time to extubation, VAS score, sufentanil consumption and duration of nicardipine treatment. \(P<0.05\) was considered significant. Results are presented as mean (SD) or median (25th–75th percentiles).

### Results

Duration of surgery, extracorporeal circulation and aortic clamping were comparable in the three groups (Table 1). The median dose of i.v. sufentanil during surgery was significantly less in the morphine + clonidine group than in the two other groups (Table 2). The time from admission to the ICU to first use of the PCA was significantly greater in

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**Table 1** Patient characteristics, duration of surgical procedure and postoperative nicardipine infusion, and time to extubation. Data are mean (SD), [range] or median (25th–75th percentiles). Significance of differences between morphine + clonidine group and control group: *\(P<0.05\), **\(P<0.01\)

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<thead>
<tr>
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<th>Morphine + clonidine</th>
<th>Morphine</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Sex (F/M)</td>
<td>1/14</td>
<td>3/11</td>
<td>60.1 [33–78]</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.4 [42–80]</td>
<td>61.0 [47–73]</td>
<td>35.3 (12.4)</td>
</tr>
<tr>
<td>Aortic clamping (min)</td>
<td>49.9 (18.8)</td>
<td>49.4 (19.4)</td>
<td>53.4 (15.5)</td>
</tr>
<tr>
<td>Duration of extracorporeal circulation (min)</td>
<td>76.2 (26.5)</td>
<td>65.2 (27.8)</td>
<td>212.5 (33.3)</td>
</tr>
<tr>
<td>Surgery (min)</td>
<td>264.0 (59.1)*</td>
<td>228.6 (53.2)</td>
<td>330 (300, 360)</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>225 (195, 330)**</td>
<td>292.5 (270, 360)</td>
<td>115 (0, 225)</td>
</tr>
<tr>
<td>Duration of nicardipine administration (min)</td>
<td>25 (2.5, 60)</td>
<td>47 (0, 135)</td>
<td>0.7 (0, 2)</td>
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**Table 2** Median (25th–75th percentiles) opioid consumption and time to first PCA use. *\(P<0.05\), **\(P<0.01\)

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<th>Morphine + clonidine</th>
<th>Morphine</th>
<th>Control</th>
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<tbody>
<tr>
<td>Intraoperative sufentanil ((\mu)g kg(^{-1}))</td>
<td>2.1 (1.8, 2.4)*</td>
<td>2.9 (2.7, 3.3)</td>
<td>3.1(2.7, 3.3)</td>
</tr>
<tr>
<td>Time from ICU admission to PCA use (h)</td>
<td>20 (3.2, 24)**</td>
<td>7.5 (0.6, 24)</td>
<td>0.7 (0, 2)</td>
</tr>
<tr>
<td>Morphine consumption in 24 h (mg)</td>
<td>7 (0, 37)*</td>
<td>40.5 (15, 61.5)</td>
<td>37 (30.5, 51)</td>
</tr>
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the morphine + clonidine group than in the control group (Table 2). Over the first 24 h, PCA morphine consumption was significantly less in the morphine + clonidine group than in the two other groups, but it was similar in the morphine and control groups (Table 3). VAS scores were significantly lower in the morphine + clonidine group than in the control group (Fig. 1). Time to extubation was less in the morphine + clonidine group than in the control group (Table 1). All patients were extubated within 24 h of surgery. The duration of nicardipine administration to control hypertension was comparable in the three groups (Table 1), although there was a trend to a shorter duration in the morphine + clonidine group. No patient required treatment for hypotension. No patient had vomiting or excessive sedation after extubation. All patients were catheterized so urinary retention could not occur as a side-effect.

Discussion
Combining intrathecal clonidine and morphine gives better postoperative analgesia than morphine alone and allows earlier extubation after cardiac surgery.

Previous studies showed that the analgesic effect of intrathecal morphine depends on the time of administration. In CABG patients, giving intrathecal morphine after surgery is ineffective because of the slow onset of action.10 Dosing before surgery is effective provided the morphine dose is greater than 6 μg kg⁻¹.4,6–7 Such doses prolong the duration of controlled ventilation with possible respiratory complications.4,6–7 Some patients had a delayed respiratory depression after tracheal extubation, related to the combined use of intrathecal and i.v. morphine.6–12 On the other hand, smaller doses of morphine, as used in the present study in order to avoid prolonged respiratory depression, did not give adequate analgesia after CABG.

Intrathecal clonidine 1–2 μg kg⁻¹ can provide analgesia after orthopaedic surgery or caesarean section,13–15 although the duration of action and the i.v. morphine sparing were limited. Intrathecal clonidine is thought to act on specific α₂-adrenergic receptors located on the dorsal horn of the spinal cord.16–17 Isobolographic analysis indicates synergism of clonidine with intrathecal morphine.9 After total hip replacement, Grace and colleagues15 found no reduction in pain when clonidine was combined with morphine. However the level of pain was extremely low in the morphine group, making further improvement with clonidine difficult to demonstrate. Conversely, Goyagi and Nishikawa18 found that the duration of analgesia provided by intrathecal morphine 200 μg after abdominal hysterectomy was doubled by oral clonidine 5 μg kg⁻¹ before anaesthesia. In our study, the time to morphine administration was prolonged in the morphine + clonidine group. Although patients in the morphine + clonidine group were extubated earlier, their i.v. morphine requirement was markedly less than in the control group. This result was confirmed by the fact that VAS scores were lower in the morphine + clonidine group.

Clonidine reduces sympathetic activity and arterial blood pressure.19 In addition to its activity in the brainstem, intrathecal clonidine decreases the activity of presynaptic sympathetic neurones at the level of the thoracic spinal cord.20 Thus, clonidine administration may blunt the hypertensive response to pain in ICU patients. Consequently, less nicardipine was needed to control hypertension in patients given clonidine. In addition, in this limited series of patients with normal left ventricular function and an uncomplicated postoperative course, we found no hypotension requiring treatment after clonidine use. In this study, the effects of clonidine on the incidence of myocardial ischaemia were not noted, but others have suggested that clonidine may reduce cardiac ischaemic episodes in patients with known or possible coronary artery disease.21
Extubation was earlier in the morphine + clonidine group. Clonidine can cause sedation, but in our study sedation was never sufficient to prevent extubation. Reduced time to extubation could be explained by less sufentanil used during surgery in the morphine + clonidine group. Indeed, when the intraoperative opioid dose is reduced, the delay to extubation is not prolonged in patients receiving intrathecal morphine 10 μg kg⁻¹. A lower opioid requirement after intrathecal morphine and sufentanil given before surgery has been reported previously, but studies using fixed opioid doses failed to show this.⁴

In conclusion, the combination of intrathecal clonidine and morphine gives effective control of postoperative pain in CABG patients and reduces the duration of controlled ventilation. If patients have no contraindication to intrathecal ventilation, this technique will facilitate fast-track cardiac anaesthesia.

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