I.v. clonidine: does it work as a hypotensive agent with inhalation anaesthesia?

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In a double-blind, randomized, placebo-controlled study, 41 patients received clonidine 3 µg kg⁻¹ or placebo at induction of isoflurane and nitrous oxide in oxygen anaesthesia. Metoprolol was also given to achieve a systolic arterial pressure of 80 mm Hg. Requirements for metoprolol were significantly less in the clonidine group (P<0.00035), with no significant difference in mean arterial pressures over time. It would appear that clonidine is an i.v. hypotensive agent worthy of consideration, but data during the recovery period are required to comment further on the safety of this technique.

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Clonidine has been available for decades but is licensed only for i.v. use in hypertensive crises. It has been used as premedication to facilitate induced hypotension,1 to reduce the requirements for both i.v.2 and volatile anaesthetics,3 to reduce the pressor response to intubation4 and to induce hypotension when used with total i.v. anaesthesia.5 There have been no studies to date of its use as an i.v. hypotensive agent with inhalation general anaesthesia.

The aim of this double-blind, randomized, placebo-controlled study was to compare the hypotensive effects of clonidine with placebo when used as part of a balanced hypotensive anaesthetic technique in middle ear and nose surgery.

Methods and results

A power calculation was performed6 setting the minimum relevant difference in mean arterial pressure (MAP) to be detected at 20 mm Hg (pilot study data). In view of the repeated comparisons, a critical P value of 0.015 was taken, and it was planned to randomize equal numbers of subjects to both groups in order to optimize the power of the study. For a power of 80%, this resulted in 19 patients being required in each group.

An Exemption from Licence was obtained and the study was approved by the Hospital Ethics Committee. Patients (ASA I or II) aged 18–65 yr undergoing middle ear or nasal surgery expected to last more than 45 min were eligible. Written informed consent was obtained and 46 patients were allocated randomly to a treatment (clonidine) or control group. All received temazepam 20 mg, 90 min before operation. An infusion of 1 litre of Hartmann’s solution was commenced and anaesthesia was induced with fentanyl 1 µg kg⁻¹, propofol 2.5 mg kg⁻¹ and atracurium 0.5 mg kg⁻¹. The airway was maintained with a reinforced laryngeal mask, and anaesthesia continued with 1% end-tidal isoflurane and 70% nitrous oxide in oxygen. The following monitoring was used: non-invasive arterial pressure, electrocardiogram, pulse oximetry, isoflurane, oxygen and carbon dioxide analysis (Datex A/S3), and intermittent neuromuscular function. In view of the nature of the surgery, it was felt inappropriate to use intra-arterial monitoring.

Independently, clonidine 3 µg kg⁻¹ in 0.9% saline or 0.9% saline was drawn into a 20-ml syringe marked ‘test’ according to the allocation; this was given i.v. over 20 min. I.v. bolus doses of metoprolol in 0.5-mg aliquots (5 min between injections) were given if required to achieve a systolic arterial pressure of 80 mm Hg, with MAP greater than 60 mm Hg. If MAP decreased to less than 50 mm Hg, ephedrine 1 mg in incremental doses was given and the patient was removed from the study.
**Statistical analysis**

Age, weight and metoprolol dose were analysed using the Mann–Whitney U test because of the lack of normality of the data. Sex prevalence was analysed by a chi-square test for frequencies. The incidence of metoprolol administration was compared using Fisher’s exact test. Unique sums of squares were used to investigate between-subject and within-subject effects. MAP changes with time were investigated using Bonferroni’s correction to allow for the number of comparisons. Analysis of the data was performed using the Statistical Package for the Social Sciences for Windows (version 6.1).

Five patients whose operations lasted less than 45 min were excluded. There were no significant differences in patient data (Table 1). MAP did not decrease to less than 50 mm Hg in any patient.

The total amount of metoprolol used (for those requiring it) was calculated on a milligram per kilogram body weight basis. Mean values were 0.064 (sd 0.033) mg kg⁻¹ in the clonidine group and 0.070 (0.044) mg kg⁻¹ in the control group (ns). However, the incidence of metoprolol administration was significantly less in the clonidine group ($P<0.00035$). The majority of patients in the clonidine group did not require metoprolol (Table 1).

There were no significant differences in MAP in the two groups before and during anaesthesia. There was a significant reduction in MAP in both groups over the period of study ($P<0.012$), with initial values and values at 45 min of 83.5 (sd 12.2) and 60.26 (9.4) mm Hg in the clonidine group and 78.6 (14.0) and 64.2 (7.9) mm Hg in the control group.

Data were incomplete in the recovery period, although there were no reported differences between the time spent in the recovery ward in patients in the clonidine and control groups. There were no adverse incidents related to anaesthesia before discharge.

**Comment**

Significantly fewer patients in the clonidine group required metoprolol to produce moderate hypotension than in the control group. Arterial pressures were not significantly different between the two groups, with both showing a significant reduction over time. However, the use of clonidine as a sole hypotensive agent warrants further study: in some patients an insufficient hypotensive effect was seen at the dose used. Data during the recovery period are required to comment further on the safety of this technique.

### Table 1 Patient data (mean (range) or number) and incidence of metoprolol administration

<table>
<thead>
<tr>
<th></th>
<th>Clonidine (n=19)</th>
<th>Control (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>32.5 (18–60)</td>
<td>33.9 (18–60)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>8/11</td>
<td>13/9</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>70.1 (52–102)</td>
<td>73.8 (52–102)</td>
</tr>
<tr>
<td>Metoprolol not required (n)</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Metoprolol required (n)</td>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>

Hypotensive techniques are used widely in anaesthetic practice in cases where major blood loss may occur or to aid a ‘bloodless surgical field’. They are adjuncts to smooth anaesthesia, careful patient positioning and meticulous surgery. The ideal hypotensive agent is specific, titratable, reversible, with no pharmacologically relevant interactions, and a short duration of action. It also should not precipitate deterioration in any other disease process. No drug currently available meets these criteria leaving a choice based on individual patient requirements and clinical preference. Clonidine is not contraindicated in the increasingly large group of patients with some form of reversible airways disease, in whom β-adrenergic antagonists (often used for inducing hypotension) should not be used. Giving clonidine after induction by the i.v. route causes a more immediate effect than oral administration and is under the direct clinical supervision of an anaesthetist, able to respond to any adverse effects.

In summary, we believe that clonidine is an hypotensive agent worthy of further consideration for use i.v. at induction in middle ear and nose surgery.

**References**