Late Intraoperative Clonidine Administration Prevents Postanesthetic Shivering After Total Intravenous or Volatile Anesthesia

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Abstract

Postoperative administration of clonidine is an effective treatment for shivering. However, the ability of this drug to stop postanesthetic shivering when administered intraoperatively remains controversial. Furthermore, the relative efficacy of clonidine during isoflurane and propofol anesthesia remains unknown. We therefore evaluated the incidence of postanesthetic shivering in...
patients given clonidine during nitrous oxide/isoflurane or propofol anesthesia. Because clonidine is an analgesic, we also evaluated postoperative pain and analgesic requirements. We studied 60 patients undergoing elective ear or nose surgery. General anesthesia was induced with 2.0 mg/kg propofol, 1.5 micro g/kg fentanyl, and 0.1 mg/kg vecuronium. General anesthesia was maintained with isoflurane and 70% nitrous oxide in one group of patients; in the other, a continuous infusion of propofol (8 mg [centered dot] kg^{-1} [centered dot] h^{-1}) was administered (without nitrous oxide). Five minutes before tracheal extubation, patients in each group were randomly assigned to receive saline, placebo, or 3 micro g/kg clonidine intravenously. Postanesthetic shivering was evaluated by a blind investigator. Postoperative pain was assessed using a visual analog scale. Post-operative shivering was observed in 53% of the patients given isoflurane without clonidine and in 13% of the patients given propofol without clonidine. No patient given clonidine shivered. Clonidine administration significantly reduced postoperative pain. The incidence of postanesthetic shivering was significantly less after propofol anesthesia than after isoflurane/nitrous oxide anesthesia. However, a late intraoperative bolus administration of 3 micro g/kg clonidine prevents postoperative shivering in patients given either type of anesthesia.

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Postanesthetic shivering develops in up to 60% of patients recovering from general anesthesia [1] and approximately 30% of volunteers during epidural anesthesia [2]. Recent studies suggest that the incidence of postanesthetic shivering differs between intravenous and volatile anesthetics; however, randomized studies comparing the incidence of postanesthetic shivering between different anesthetic techniques are rare. Shivering was preceded by central hypothermia and peripheral vasoconstriction after isoflurane anesthesia in healthy volunteers [3] and is often reported in patients recovering from isoflurane/nitrous oxygen anesthesia (20%-100%) [4-6]. Cheong and Low [7] observed that the incidence of postanesthetic shivering in patients recovering from propofol/nitrous oxygen anesthesia was significantly lower than in those given isoflurane/nitrous oxygen anesthesia. However, in that study, different drugs were administered for induction of anesthesia in the respective groups (propofol versus thiopental). Propofol markedly reduces the shivering threshold [8] and is associated with less postoperative shivering than when thiopental is used as an induction drug [9]. The relative incidence of postanesthetic shivering with nitrous oxide/isoflurane and total intravenous anesthesia using propofol remains unknown.

Central adrenergic receptors appear to modulate postanesthetic shivering. Clonidine, a central alpha2-adrenergic agonist, inconsistently decreased postanesthetic shivering when infused during isoflurane, enflurane, halothane, or propofol anesthesia [1]. However, this study failed to identify differences in the incidence of postanesthetic shivering because few patients were given clonidine during isoflurane (n = 3) or propofol (n = 1) anesthesia. Postanesthetic shivering was reduced with clonidine (2 micro g/kg) administration when the drug was infused for 20 minutes near the end of surgery [1,4]. In contrast, Quintin et al. [10] observed no change in the incidence of postanesthetic shivering when clonidine (5 micro g/kg) was infused near the beginning of surgery. These studies suggest that the effect of clonidine on postanesthetic shivering is related to the time, dose, and duration of its administration. They further suggest that clonidine given near the end of surgery, rather than as an infusion during surgery, may be more effective in preventing postanesthetic shivering.

Prevention of postanesthetic shivering and pain in the postoperative period by clonidine may
be limited by clonidine-induced hypotension and bradycardia [11]. However, the postoperative cardiovascular effects of clonidine are controversial. Arterial blood pressure and heart rate did not differ significantly in patients whose postanesthetic shivering was treated with 90 micro g intravenous clonidine or saline [12]. In contrast, administration of 5 micro g/kg clonidine during the first hour of anesthesia significantly decreased heart rate and arterial blood pressure [13]. The hemodynamic effects of a late intraoperative bolus administration of clonidine on patients recovering from intravenous or volatile anesthesia remains unknown. Stimulation of central alpha2-adrenoceptors by intraoperative clonidine administration may also reduce the analgesic requirement during recovery from anesthesia [4]. Our purpose, therefore, was to evaluate the effects of clonidine administration on the incidence of postanesthetic shivering and pain severity in patients recovering from total intravenous or volatile anesthesia.

Methods

This protocol was approved by our local ethics committee. After obtaining written, informed consent, we studied 60 patients (ASA physical status I or II) scheduled for elective ear, nose, or pharyngeal surgery. Patients were excluded when vasoconstrictive drugs were required for the surgery. All patients were orally premedicated with midazolam (0.1 mg/kg) 45 min before induction of anesthesia. A cannula was inserted into a peripheral vein for continuous infusion of lactated Ringer's solution and drug administration. General anesthesia was then induced with propofol (2.0 mg/kg) and fentanyl (1.5 micro g/kg). Vecuronium (0.1 mg/kg) was administered to facilitate orotracheal intubation. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide tension 36-38 mm Hg (Normocap[R], Datex, Helsinki, Finland) using a fresh gas flow of 6 L/min. Patients were covered with warmed sheets during anesthesia but were not actively heated.

After intubation, patients were randomly allocated to maintenance general anesthesia with isoflurane (1.5% +/- 0.4% end-tidal concentration) and 70% nitrous oxide in oxygen (n = 30), or a continuous infusion of propofol (8 mg [centered dot] kg⁻¹ [centered dot] h⁻¹) administered with oxygen/air (FIO₂ = 0.3) (n = 30). When the surgery was finished, anesthesia (isoflurane/nitrous oxide or propofol, respectively) was stopped immediately. Patients in each group were randomly assigned to receive intravenous saline (placebo) or 3 micro g/kg clonidine upon return of laryngeal reflexes (coughing during suctioning of the tracheal airway) and spontaneous breathing (ventilation >or=to50 mL [centered dot] kg⁻¹ [centered dot] min⁻¹). Five minutes later, all patients were extubated and received 2 L oxygen during the first postoperative hour via nasal prongs.

Mean arterial blood pressure (Dinamap[R], Critikon, Tampa, FL), heart rate, rectal body temperature (UM 3[R], Drager, Lubeck, Germany), and oxygen saturation (Pulse Oximeter[R], Nellcor, Hayward, CA) were measured. Postanesthetic shivering was graded by visual inspection, assessed by an anesthesiologist blinded to anesthetic type and clonidine administration, using a 3-point scale (none, moderate, or severe) [3]. Postoperative pain was assessed using a visual analog scale (VAS), where 0 mm indicated no pain and 100 mm indicated maximal pain. A new, unmarked scale was used for each evaluation. Arousal state was assessed by response of the patient to verbal command ("Open your eyes and lift your arms"). Absent or incomplete responses were graded as arousal state = 0, prompt and appropriate responses were graded as awakened (arousal state = 1). Baseline rectal body temperature was measured 5 min prior to induction of anesthesia, as were mean arterial blood pressure, heart rate, oxygen saturation, postanesthetic shivering, and the arousal state. All these variables were measured immediately after extubation and subsequently at 5-min intervals for 60 min. Postoperative pain score was first measured 15 min after extubation and then at 20, 25, 30, and
60 elapsed minutes.

After one-way analysis of variance (ANOVA), Scheffe's F-test was used for post hoc comparison. The incidence of shivering in the four groups was compared using Ott and Free's chi squared test. Data are presented as mean +/- SD; statistical significant difference was assumed at P < 0.05.

**Results**

Data are summarized in Table 1 and Table 2. There were no significant differences in age, gender, weight, height, duration of surgery, or the time to an arousal score of 1 in the four treatment groups. All patients awakened within 20 min of extubation, and arousal scores continued to increase throughout the recovery period. Patients treated with clonidine experienced significantly less postoperative pain 15 min after extubation and required the first analgesic dose later than those given saline regardless of the anesthetic technique. There were no significant differences in core temperature among the groups at baseline or 20 min after extubation. However, core temperature was less than baseline values 20 min after extubation in all groups (Table 1). Oxygen saturation exceeded 95% in all patients at all times.

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane/ saline</th>
<th>Isoflurane/ clonidine</th>
<th>Propofol/ saline</th>
<th>Propofol/ clonidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34 ± 14</td>
<td>48 ± 16</td>
<td>41 ± 15</td>
<td>42 ± 17</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>5/10</td>
<td>9/6</td>
<td>10/5</td>
<td>8/7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 ± 16</td>
<td>73 ± 14</td>
<td>71 ± 9</td>
<td>74 ± 15</td>
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<tr>
<td>Height (cm)</td>
<td>168 ± 11</td>
<td>175 ± 5</td>
<td>173 ± 9</td>
<td>173 ± 9</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>51 ± 27</td>
<td>51 ± 35</td>
<td>56 ± 23</td>
<td>56 ± 28</td>
</tr>
<tr>
<td>Time to arousal state 1 (min)</td>
<td>9.5 ± 2</td>
<td>12.4 ± 1</td>
<td>11.5 ± 1</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Oxygen saturation 15 min after extubation (%)</td>
<td>98.8 ± 1.7</td>
<td>98.1 ± 1.2</td>
<td>99.2 ± 1.7</td>
<td>99.3 ± 1.1</td>
</tr>
<tr>
<td>Baseline core temperature (°C)</td>
<td>36.6 ± 0.4</td>
<td>36.6 ± 0.4</td>
<td>36.5 ± 0.3</td>
<td>36.7 ± 0.3</td>
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<tr>
<td>Temperature 20 min after extubation</td>
<td>35.8 ± 0.8</td>
<td>35.7 ± 0.9</td>
<td>35.6 ± 0.3</td>
<td>35.8 ± 0.7</td>
</tr>
<tr>
<td>Pain 15 min after extubation (mm VAS)</td>
<td>59 ± 11</td>
<td>19 ± 8*</td>
<td>57 ± 12</td>
<td>24 ± 12</td>
</tr>
<tr>
<td>First analgesic required (min)</td>
<td>10 ± 7</td>
<td>28 ± 11*</td>
<td>10 ± 9</td>
<td>29 ± 13*</td>
</tr>
<tr>
<td>Patients shivering (%)</td>
<td>53</td>
<td>0*†</td>
<td>13*</td>
<td>0*</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

* VAS = visual analog scale 0-100 mm.

* P < 0.05 versus isoflurane/saline.

† P < 0.05 versus propofol/saline.

Table 1. Morphometric Characteristics, Anesthetic Variables, Postoperative Pain, and Postanesthetic Shivering

<table>
<thead>
<tr>
<th></th>
<th>MAP HR</th>
<th>MAP HR</th>
<th>MAP HR</th>
<th>MAP HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90 ± 19</td>
<td>79 ± 9</td>
<td>95 ± 11</td>
<td>79 ± 12</td>
</tr>
<tr>
<td>5 min</td>
<td>93 ± 18</td>
<td>77 ± 16</td>
<td>92 ± 15</td>
<td>79 ± 14</td>
</tr>
<tr>
<td>10 min</td>
<td>102 ± 19</td>
<td>82 ± 14†</td>
<td>99 ± 16</td>
<td>80 ± 12†</td>
</tr>
<tr>
<td>15 min</td>
<td>108 ± 17†</td>
<td>91 ± 14†</td>
<td>104 ± 12†</td>
<td>99 ± 11†</td>
</tr>
<tr>
<td>20 min</td>
<td>109 ± 19</td>
<td>89 ± 13</td>
<td>105 ± 13</td>
<td>92 ± 12</td>
</tr>
<tr>
<td>25 min</td>
<td>107 ± 19†</td>
<td>84 ± 12†</td>
<td>102 ± 12†</td>
<td>99 ± 11†</td>
</tr>
<tr>
<td>30 min</td>
<td>109 ± 20</td>
<td>89 ± 12</td>
<td>104 ± 12</td>
<td>100 ± 12</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.

MAP = mean arterial blood pressure (mm Hg); HR = heart rate (bpm).

† P < 0.05 versus baseline.

* P < 0.05 versus isoflurane/clonidine.

† P < 0.05 versus propofol/clonidine.

Table 2. Systemic Hemodynamic Variables Before and After Bolus Administration of Saline or Clonidine

Postoperative shivering was observed in 53% of the patients given isoflurane without clonidine but in only 13% of the patients given propofol without clonidine. In both these groups, shivering occurred 14 +/- 4 min after extubation. No patient given clonidine shivered. There were no clinically important differences in heart rate and mean arterial blood pressure among the groups. When saline was administered, mean arterial blood pressure increased 15 min after
extubation and subsequently remained elevated. After clonidine administration, mean arterial blood pressure remained nearly constant (Table 2).

Discussion

Our results indicate that the incidence of postanesthetic shivering depends on the anesthetic technique. Postanesthetic shivering occurred in 53% of patients given isoflurane but in only 13% given propofol. Clonidine bolus administration (3 micro g/kg), when given five minutes prior to extubation, completely prevented postanesthetic shivering regardless of the anesthetic technique. Additionally, postoperative pain was significantly reduced with clonidine treatment.

These results suggest that the incidence of postanesthetic shivering depends not only on postoperative body core temperature but also on the anesthetic drugs administered. All frequently used volatile anesthetics, such as halothane [14], enflurane [15] and isoflurane [4], are associated with a high incidence of postanesthetic shivering. In contrast, the incidence is less after intravenous anesthesia using continuous infusion of propofol in combination with nitrous oxide [7].

Several studies indicate that clonidine reduces postanesthetic shivering and the associated increases in oxygen consumption and carbon dioxide production [1,16,4]. This drug may prevent postanesthetic shivering in a dose-dependent fashion when administered during surgery [10,4]. However, the optimal timing for the drug administration (maximum antishivering effect and minimum side effects) has not been identified.

In patients undergoing spinal fusion, intravenous clonidine (5 micro g/kg during the first hour and 0.3 micro g [centered dot] kg⁻¹ [centered dot] h⁻¹ thereafter) proved ineffective in preventing shivering [13]. In contrast, the duration of postanesthetic shivering was reduced when clonidine was given as a bolus (75 or 150 micro g) postoperatively [1]. These data are consistent with the present study, in which intraoperative administration of 3 micro g/kg clonidine just before extubation prevented postanesthetic shivering. This suggests that the application mode (bolus application versus long-term infusion) and time of administration determines the antishivering efficacy of clonidine.

Prevention of postanesthetic shivering and pain in the postoperative period may be limited by the principal hemodynamic effects of alpha-agonists hypotension and bradycardia [11]. However, the cardiovascular effects of clonidine in the recovery period from anesthesia remain controversial [13,12,17]. For example, 30 micro g clonidine stopped shivering without altering mean arterial blood pressure or heart rate after extradural block [12] and improved hemodynamic variables during the perioperative period in patients undergoing coronary bypass surgery [17]. There is, however, evidence that general anesthesia may alter or mask the effects of alpha₂-agonists on the cardiovascular system [18]. In our patients, a bolus application of clonidine was not associated with clinically relevant changes in systemic hemodynamic variables. These data suggest that increases of mean arterial blood pressure and heart rate in the recovery period after isoflurane or propofol anesthesia can be prevented by late intraoperative clonidine administration.

Normally, the thermoregulatory system protects body temperature against changes in ambient temperature. The magnitude of the vasoconstriction to shivering range is about 1 degrees C [19]. There is a dose-dependent decrease in the thermoregulatory threshold for shivering during general anesthesia, resulting in core hypothermia in unwarmed patients. During the initial
recovery from general anesthesia, residual anesthetics suppress thermoregulatory responses. Subsequently, however, hypothermia triggers peripheral vasoconstriction and shivering. Postanesthetic shivering is thus largely a thermoregulatory compensation for intraoperative hypothermia [3].

Treatment of visible postanesthetic shivering may be insufficient because even invisible shivering may significantly increases oxygen consumption [20]. Whether postanesthetic shivering is attributed to increased spinal reflexes [21], pain [22], or decreased sympathetic activity [23], clonidine is likely to be effective. Consistent with this theory, small doses of epinephrine (0.02 micro g/kg) or clonidine (0.01 micro g/kg) directly injected into a lateral cerebral ventricle of the brain inhibits postanesthetic shivering in rats [24]. Similarly, shivering is more common before patients fully recover from anesthesia [25]. Clonidine has sedative properties and may reduce postanesthetic shivering by sedation of the patients. However, we did not observe prolonged awakening in clonidine-treated patients (Table 1).

Our data indicate that a late intraoperative bolus administration of clonidine significantly reduce pain and the requirements for postoperative analgesics. This is consistent with clinical studies showing reduced pain after transdermal [26], epidural [27], subarachnoidal [28], or intravenous [29] administration of clonidine. The mechanisms by which afferent pathways are blocked are not completely understood. However, central catecholamine turnover is probably reduced by stimulation of alpha_2-adrenergic receptors. Catecholamines modulate pain at the level of the spinal cord and the brain stem [30]. Thus, decreases in central sympathetic tone may be related to clinically relevant pain relief with clonidine. On the other hand, recent functional and anatomic studies suggest that clonidine analgesia is mediated by cholinergic activation. Intrathecal clonidine or dexmedetomidine directly stimulates acetylcholine release from spinal cord dorsal horn in sheep [31].

In conclusion, the incidence of postanesthetic shivering was significantly reduced when total intravenous anesthesia with propofol (13%) was compared with volatile anesthesia using nitrous oxide/isoflurane (53%). In addition, a late intraoperative bolus administration of 3 micro g/kg clonidine prevented postoperative shivering in patients given either total intravenous or volatile anesthesia without causing clinically important sedation or changes in hemodynamics.

REFERENCES


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