Propofol vs Midazolam in Short-, Medium-, and Long-term Sedation of Critically Ill Patients

A Cost-Benefit Analysis

Genís Carrasco, M.D.; Ricard Molina, M.D.; Josep Costa, M.D.; Josep-Maria Soler, M.D.; and Lluis Cabré, M.D.

The purpose of this study was to evaluate and compare the clinical effects, safety, and economic cost of propofol and midazolam in the sedation of patients undergoing mechanical ventilation in the ICU. Eighty-eight critically ill patients were studied and randomly allocated to receive short-term (less than 24 h), medium-term (24 h to 7 days), and prolonged (more than 7 days) continuous sedation with propofol (n = 46) or midazolam (n = 42). Mean doses required were 2.36 mg/kg/h for propofol and 0.17 mg/kg/h for midazolam. Patients in the group receiving propofol showed a percentage of hours of sedation at the desired level (grade 2, 3, 4, or 5 on the Ramsay scale) of 93 percent, compared with 82 percent (p < 0.05) in the group receiving midazolam. Both agents were considered safe with respect to the induction of adverse reactions during their use in prolonged sedation. Recovery after interrupting sedation was significantly faster in patients treated with propofol than in those sedated with midazolam (p < 0.05). Recovery of total consciousness was predictable according to sedation time in propofol-treated subgroups (r = 0.98, 0.85, and 0.92, respectively), while this correlation was not observed in the midazolam-treated group. In the subgroup with sedation of less than 24 h, propofol provided a cost savings of approximately 2,000 pesetas (pts) per patient, due to shorter stays in the ICU. We conclude that propofol is a sedative agent with the same safety, higher clinical effectiveness, and a better cost-benefit ratio than midazolam in the continuous sedation of critically ill patients.

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GCSC = Glasgow coma score as modified by Cook and Palma;10 pts = pesetas; SAPS = simplified acute physiologic score

The majority of patients admitted to the ICU requires sedation at one time or another during their stay. The need to provide them with mechanical ventilation is one of the most frequent indications for continuous sedation. In these patients, sedation is necessary to suppress cough, provide comfort, prevent respiratory fighting, and facilitate specific procedures such as tracheal aspiration. Although opioids can be very useful in the treatment of pain, they alone cannot be appropriate for prolonged sedation in some patients undergoing mechanical ventilation. This is due to the fact that elimination of opioids and their metabolites may be prolonged in critically ill patients, especially if there is an alteration in renal function. Consequently, it is quite common to supplement analgesia with opioids by adding a sedative agent.

The ideal sedative agent should allow for rapid modifications in the level of sedation by modifying the dosage and should not have depressor effects on the cardiovascular and respiratory systems.8 It would have a short duration of activity without cumulative effects, allowing for rapid recovery of effective spontaneous respiration after the interruption of its administration in patients undergoing mechanical ventilation.3 Etomidate and an alfalphalone-alfadolone acetate combination (Althesin) had most of these characteristics. Unfortunately, the increase in deaths due to adrenal depression attributed to etomidate4 and the high incidence of adverse reactions observed during sedation with the alfaxalone-alfadolone combination5 have precluded their use for continuous sedation.

Midazolam is widely used for this indication and has substituted diazepam because of its shorter half-life and the absence of active metabolites; however, the universal use of midazolam in critical medicine is limited because in some critically ill patients, its elimination can take too long.6,7 Propofol (2,6-diisopropylphenol) is an intravenous anesthetic agent which has been favorably compared with midazolam in the continuous sedation of patients undergoing mechanical ventilation.3 The use of propofol reduces the time needed for recovery of spontaneous respiration.3 One of the disadvantages which can limit the general use of propofol in critical medicine is its high cost.8 So far, no clinical study has been able to demonstrate whether a possible reduction in the length of stay in the ICU patients sedated with propofol would be of benefit in reducing the economic cost of such stays.9 The purpose of this study is to evaluate and compare the safety, clinical effects, and economic cost of propofol and midazolam in the short-,
medium-, and long-term sedation of ICU patients undergoing mechanical ventilation.

**Materials and Methods**

**Patients**

In a prospective study, patients admitted to our general 14-bed ICU were randomized to groups between January and September 1991. Criteria for admission to the study were (1) age above 16 years old, (2) probable need for controlled mechanical ventilation, and (3) severity of illness classified at admission as equal to or higher than 9 points on the simplified acute physiologic score (SAPS).10

Informed consent was obtained either directly from the patient or from his or her relatives. One hundred two patients consecutively admitted to the ICU who complied with these criteria made up the total population allocated to receive propofol or midazolam.

Criteria for exclusion were as follows: (1) known or suspected allergy to propofol or midazolam; (2) known or probable pregnancy; (3) stupor or coma by metabolic or neurologic affection; (4) cranial trauma or neurosurgical operation; (5) use of muscular relaxants (with the exception of succinylcholine for intubation); and (6) gross obesity. Ten patients were excluded because of one or more of these criteria. Four died during the course of the study and were therefore also excluded.

**Sedation**

All patients received analgesia with morphine at doses of 0.2 to 0.5 mg/kg/day (adjusted according to glomerular filtration rate). Propofol was administered in 20-ml vials containing emulsion to a concentration of 10 mg/ml. The initial dose for continuous infusion was 1 to 3 mg/kg/h, with the dosage adjusted to achieve the desired level of sedation. In those cases in which it was considered clinically indicated, an initial bolus of 1 mg/kg was administered. Midazolam was administered in an aqueous solution containing a concentration of 2 mg/ml. The initial dose for infusion was 0.1 to 0.2 mg/kg/h, with the dosage adjusted to achieve the desired level of sedation. In those cases in which it was considered clinically indicated, an initial bolus of 0.1 mg/kg was administered.

The level of sedation was determined on a continuous basis by the nurse caring for the patient. To minimize the subjectivity of the observer, two sedation scales were used: (1) the Ramsay scale of six degrees,11 which is accepted to evaluate the level of sedation in the ICU,12 and (2) the Glasgow coma score as modified by Cook and Palma13 (GCSC), which is based on the best response to evaluate reactivity during postanesthetic recovery. The Ramsay sedation scale consists of the following six points:

1. Anxious and agitated, or restless, or both
2. Cooperative, oriented, and tranquil
3. Responding to commands only
4. Brisk response to light glabellar tap
5. Sluggish response to light glabellar tap
6. No response to light glabellar tap

The Glasgow coma score scale as modified by Cook and Palma13 is as follows:

<table>
<thead>
<tr>
<th>Eyes open</th>
<th>Spontaneously</th>
<th>To speech</th>
<th>To pain</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Response to nursing procedures

<table>
<thead>
<tr>
<th>Obeys commands</th>
<th>Purposeful movement</th>
<th>Nonpurposeful flexion</th>
<th>Nonpurposeful extension</th>
<th>None</th>
<th>Cough</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Spontaneous strong

<table>
<thead>
<tr>
<th>Spontaneous weak</th>
<th>On suction only</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Three levels of sedation were considered: (1) adequate (if sedation level was grade 2, 3, 4, or 5 on the Ramsay scale and if the degree of reactivity was maintained between 8 and 13 points for GCSC), (2) insufficient (if sedation level was grade 1 on the Ramsay scale and if the degree of reactivity was equal to or higher than 14 points for GCSC), and (3) excessive (if sedation level was grade 6 on the Ramsay scale and if the degree of reactivity was between 4 and 7 points for GCSC).

The nursing staff adjusted the doses of both drugs during intravenous infusion by varying the dose by 10 percent increases or decreases in order to maintain the level of sedation within the range previously considered adequate. Total dosages of propofol or midazolam and morphine, the number of dosage modifications, the quality of sedation, and the reactivity level to continuous stimuli were registered in the protocol. Registration of total time in mechanical ventilation (hours) was also recorded. Hourly cardiac frequency, arterial pressure, central venous pressure, and urine production were determined. Fifteen patients had their pulmonary arterial pressures recorded hourly. Continuous arterial O2 saturation was controlled by pulse oximetry, as well as end-tidal CO2 pressures. In six patients, continuous measurements of mixed venous O2 saturation in the pulmonary artery were determined. Gasometric measurements in arterial and venous central blood were performed every 8 h, or more frequently if indicated. All patients underwent daily hematologic and biochemical screening.

Recuperation after sedation was determined every 5 min and included the time from the interruption of sedation up to the appearance of (1) response to simple orders, (2) recuperation of effective spontaneous respiration and start of disconnection of the respirator, (3) exubation, and (4) recuperation at a level of GCSC reactivity above 16 points (total recuperation), at which time the patient no longer required special care and could be discharged to a conventional ward or to the intermediate care unit. Mechanical ventilation was disconnected if the patient (1) maintained arterial O2 pressure of 70 mm Hg or more, with an inspired O2 fraction of 0.4 or less, (2) maintained current volumes of more than 4 ml/kg, (3) showed respiratory frequency of 10 to 25 respirations per minute, and (4) did not have clinical signs of respiratory muscle fatigue or hemodynamic impairment. All patients receiving a mixture of air enriched with O2 through a T tube were disconnected from the respirator.

Patients in both groups were classified into three subgroups based on the length of time they received perfusion with either of the two sedative agents. Consideration was given to (1) short-term sedation (if administered in less than 24 h), (2) medium-term sedation (if used between 24 h and 1 week), and (3) long-term sedation (if infusion lasted for more than 7 days).

**Costs**

For the cost analysis of sedation, consideration was given to (1) primary monetary pharmaceutical costs (the number of milligrams of total dose administered to each patient times the number of perfusion hours, times the price of 1 mg of the sedative agent); and (2) monetary cost of care after sedation, or secondary cost (number of hours in which the patient required special care [respiratory physiotherapy; tracheal aspiration] until his or her level of consciousness allowed transfer to a ward, times the price per hour of stay invoiced to each patient). This last figure was obtained on the basis of the direct costs (pharmaceutical and medical supplies, acquisition cost, etc) plus the indirect or marginal costs (personnel:...
Table 1—Characteristics of Patients

<table>
<thead>
<tr>
<th>Data</th>
<th>Propofol (n = 46)</th>
<th>Midazolam (n = 42)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>71.5±12.6 (45-103)</td>
<td>72.4±12.8 (41-100)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>67.6±6.5 (45-80)</td>
<td>67.7±7.2 (43-81)</td>
<td>NS</td>
</tr>
<tr>
<td>SAPS*</td>
<td>12.5±4.0 (9-21)</td>
<td>13.1±4.0 (9-21)</td>
<td>NS</td>
</tr>
<tr>
<td>GCSC†</td>
<td>10.1±4.2 (4-18)</td>
<td>9.7±4.0 (4-18)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*SAPS, Simplified acute physiologic score before starting sedation.
†GCSC, Glasgow coma score modified by Cook and Palma* before starting sedation.

Results

Group Comparison

Eighty-eight patients were admitted to the study. Forty-six patients (40 men and 6 women) received propofol, and 42 (36 men and 6 women) were sedated with midazolam.

There were no significant differences between groups and subgroups with respect to age, weight, consciousness level before starting sedation (valued by GCSC scoring), and severity of illness at admission (determined by SAPS scoring) (Table 1).

Reasons for Admission: A wide variety of illnesses motivated admission. In the propofol-treated group, 58 percent (27) of the patients were admitted after major surgery, 37 percent (17) due to medical illness, and 5 percent (2) due to multiple trauma. The percentage of admissions due to these causes in the midazolam-treated group were 50 percent (21), 40 percent (17), and 10 percent (4), respectively.

Quality of Sedation: The mean administered doses of propofol and midazolam were 2.3±0.3 mg/kg/h (range, 1 to 4 mg/kg/h) and 0.17±0.03 mg/kg/h (range, 0.05 to 0.3 mg/kg/h), respectively. Requirements for morphine were similar in both groups (1.1±0.7 mg/kg/day in the propofol group and 1.0±0.8 mg/kg/day in the midazolam group). Total monitored hours of sedation were 9,352.

The mean percentage of hours of adequate sedation was 93 percent in the propofol group (range, 1 to 100 percent) and 82 percent in the midazolam group (range, 0 to 100 percent), reaching statistical significance (p<0.05). The percentage of hours of sedation reached in each Ramsay level is shown in Figure 1.

Adverse Effects: Mean cardiac frequency during sedation with propofol was significantly lower than the basal one (p<0.05). Mean basal and postsedation arterial pressures of the propofol group (90.0±3.0 and 89.0±4.4 mm Hg, respectively) were similar to those of patients treated with midazolam (91.3±4.0 and 88.0±4.7 mm Hg, respectively).

Cardiovascular depression limited the dose in only 18 episodes of hypotension, represented by 8 patients in the propofol group and 6 in the midazolam group. There was no need to interrupt sedation, since improving hemodynamic stability occurred with inotropic drugs or with provision of fluids. There were no differences in the rest of the hemodynamic variables or in O2 transport. No allergic reactions were detected if any of the patients studied.

Mortality: Four patients died during the course of the study (two due to multiorgan failure, one due to cardiogenic shock, and one due to adult respiratory distress syndrome). In no case did the investigators relate the cause of death to the type of sedation used.

FIGURE 1. Percentage of hours of sedation reached in each degree of sedation with propofol and midazolam.
Laboratory Studies: Hematologic parameters did not differ significantly from those observed at admission in any of the groups. No significant thrombocytopenia was detected.

Urea and creatinine levels did not show measurable changes compared with those at admission, and the same applies to the rest of the biochemical parameters, except triglyceride levels. Daily lipid determinations were obtained in 22 patients sedated with propofol; in 10 cases, there was an increase in the triglyceride levels to double those before sedation. This finding was observed at day 3 and became normal in all cases after interruption of sedation.

Subgroup with Short-term Sedation

Twenty patients were sedated with propofol and another 20 were sedated with midazolam for a period of less than 24 h. Mean sedation time was similar in both subgroups (Table 2); however, recuperation time up to extubation and the time elapsed until normalization of the alertness level were significantly longer in patients treated with propofol (p<0.05). The time elapsed until extubation correlated statistically with treatment time in patients in the propofol subgroup (r=0.83) (Fig 2), while those in the midazolam subgroup showed no relationship between sedation time and extubation time (r=0.13). There was a correlation between sedation time and total recovery of consciousness in the propofol subgroup (r=0.98) but not in patients sedated with benzodiazepines (r=0.14).

Data related to pharmaceutical sedation costs and to postsedation care cost in both subgroups are shown in Table 2. Propofol had a pharmaceutical cost three times higher than midazolam, but the longer stay of patients sedated with this benzodiazepine caused an expense in postsedation care four times higher than that of the propofol subgroup. The end result was a significantly higher total monetary sedation cost with midazolam.

Subgroup with Medium-term Sedation

Sixteen patients were sedated with propofol and 12 with midazolam for time periods ranging from 24 h up to 7 days. The average duration of sedation was similar in both subgroups (Table 3); however, recovery time until extubation and also the time elapsed until reaching normal alertness level was significantly lower in those patients treated with propofol (p<0.05). The

Table 2—Comparison of Sedation, Extubation, and Total Recovery Times and Costs in Short-term Sedation

<table>
<thead>
<tr>
<th>Data</th>
<th>Mean ± SD</th>
<th></th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propofol</td>
<td>Midazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, h</td>
<td>(n = 20)</td>
<td>(n = 20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation time</td>
<td>11.9±0.5</td>
<td>11.9±2.8</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Time up to extubation</td>
<td>0.3±0</td>
<td>2.5±0.9</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Total recovery time</td>
<td>1.0±0</td>
<td>3.6±0.8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Cost, thousands of pesetas</td>
<td>Pharmacy cost</td>
<td>6.5±2.4</td>
<td>2.1±0.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Postsedation care</td>
<td>2.4±0.6</td>
<td>8.8±2.1</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Total cost</td>
<td>8.9±2.9</td>
<td>10.9±2.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 3—Comparison of Sedation, Extubation, and Total Recovery Times and Costs in Medium-term Sedation

<table>
<thead>
<tr>
<th>Data</th>
<th>Mean ± SD</th>
<th></th>
<th></th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Propofol</td>
<td>Midazolam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, h</td>
<td>(n = 16)</td>
<td>(n = 12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation time</td>
<td>116.4±17.9</td>
<td>113.0±17.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Time up to extubation</td>
<td>0.4±0.1</td>
<td>13.5±4.0</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Total recovery time</td>
<td>1.4±0.5</td>
<td>21.0±5.8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Cost, thousands of pesetas</td>
<td>Pharmacy cost</td>
<td>63.7±17.9</td>
<td>16.6±7.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Postsedation care</td>
<td>3.7±1.2</td>
<td>45.8±15.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Total cost</td>
<td>67.4±18.3</td>
<td>62.4±19.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Figure 2. Correlation between sedation time and interval up to extubation in patients sedated with propofol for less than 24 h.
time elapsed until extubation statistically correlated with perfusion time in patients in the propofol subgroup \( (r = 0.94) \) (Fig 3), while there was no relationship between sedation and extubation times in the midazolam subgroup \( (r = 0.20) \). A correlation between sedation time and total consciousness recovery was found in the propofol subgroup \( (r = 0.88) \) but not in the midazolam subgroup \( (r = 0.16) \).

Data related to pharmaceutical cost of sedation and postsedation care cost in both subgroups are shown in Table 3. The pharmaceutical cost for propofol was nearly 4 times higher than that of midazolam, but the longer stay of patients sedated with midazolam originated a cost about 15 times higher than the cost of postsedation care in the propofol subgroup. Total sedation cost of mean sedation duration with propofol did not differ significantly from that of midazolam.

**Subgroup with Long-term Sedation**

Ten patients were sedated with propofol and ten with midazolam for more than 7 days. The mean sedation time was similar in both subgroups (Table 4); however, recovery time until extubation and the time elapsed to reach normal levels of alertness were significantly lower in those patients treated with propofol. The time elapsed until extubation was statistically correlated in patients in the propofol subgroup \( (r = 0.90) \) (Fig 4), while there was no relationship between sedation and extubation times \( (r = 0.06) \) in the midazolam subgroup. A correlation between sedation time and total consciousness recovery was observed in patients treated with propofol \( (r = 0.92) \), but was not observed in the midazolam subgroup \( (r = 0.14) \).

Data related to the pharmaceutical sedation costs and to the cost of postsedation care in both subgroups are shown in Table 4. The pharmaceutical cost of propofol was 4 times higher than that of midazolam, but the longer stay of patients sedated with midazolam generated a monetary cost, due to longer postsedation care, almost 3 times that of the propofol subgroup. Total long-term sedation cost with propofol was slightly higher, but this difference did not reach statistical significance.

**DISCUSSION**

Elimination of etomidate and the alfalfalone-alfadolone combination (Althesin) has produced difficulties in the search for an ideal sedative agent in intensive care practice. Because of their cumulative side effects, thiopental (thiopentone) and other barbiturates are not advisable for continuous perfusion. Although clomethiazole promised to be useful, its use should be accompanied by a provision of fluids, and recovery delays of up to 48 h have been reported.\(^3\) Ketamine offers the advantage of good analgesic potency but can produce arterial hypertension that is difficult to control.\(^4\)

In the daily practice of intensive care, the trend has been to use a combination of opioids supplemented with bolus of benzodiazepines.\(^5\) Benzodiazepines such as diazepam or lorazepam act rapidly, but the presence of active metabolites can be associated with prolonged recovery.\(^6,7\) Midazolam is a hydrosoluble benzodiazepine with a short elimination half-life and without

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**Table 4—Comparison of Sedation, Extubation, and Total Recovery Times and Costs in Long-term Sedation**

<table>
<thead>
<tr>
<th>Data</th>
<th>Mean ± SD</th>
<th>Propofol ((n = 10))</th>
<th>Midazolam ((n = 10))</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedation time</td>
<td>312.1 ± 103.9</td>
<td>342.3 ± 103.0</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Time up to extubation</td>
<td>0.8 ± 0.3</td>
<td>36.6 ± 6.8</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Total recovery time</td>
<td>1.8 ± 0.7</td>
<td>54.7 ± 12.3</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Cost, thousands of pesetas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacy cost</td>
<td>155.5 ± 89.4</td>
<td>46.7 ± 21.4</td>
<td>&lt;0.05</td>
<td></td>
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<tr>
<td>Postsedation care</td>
<td>45.8 ± 15.3</td>
<td>137.2 ± 31.5</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Total cost</td>
<td>201.3 ± 87.0</td>
<td>184.0 ± 38.5</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
active metabolites. These characteristics have made it very popular for sedation of critically ill patients; however, later published studies did not show differences between diazepam and midazolam in terms of recovery time, and its use in perfusion has been associated with recovery delay. In this context, the new anesthetic agent, propofol, may be useful in the intensive medicine area.

The studied populations were strictly comparable with respect to age, sex distribution, weight, SAPS, GCSC, and causes of admission. In our study, the percentage of adequate sedation hours was significantly higher in the propofol group (93 percent) than in the midazolam group (82 percent). This finding contrasts with other published results. Aitkenhead et al found that the percentage of hours of adequate sedation was similar in both groups (94 percent in patients treated with propofol and 93 percent in those treated with midazolam). Grounds et al, who also considered degrees 2, 3, 4, and 5 of Ramsay to be adequate, found a higher percentage of adequate sedation hours in the propofol group, but maintaining level 3 of Ramsay (optimum level of adequate sedation) for only 44.6 percent of sedation hours with propofol, while our patients reached 70 percent of hours at optimum level. These differences could be explained as due to the different methodology employed. Those authors did not include the evaluation of a reactivity-consciousness scale, which probably influenced to a greater degree our patients’ tendency to maintain at sedation levels nearer the optimum level. Both scales were evaluated by nursing staff to be practical and easily applicable.

Mean dosages of propofol used in our patients (2.36 mg/kg/h) were higher than the required doses in the studies of Grounds et al and Snellen et al (0.79 and 0.9 mg/kg/h, respectively) in patients after cardiac surgery. This finding can be attributable to the pre-sedation with fentanyl received by the patients admitted to those studies. Also, the mean propofol dosages registered in our study were higher than those used by Aitkenhead et al (1.77 mg/kg/h), who studied populations similar to ours in a general ICU. This difference could be due to the fact that in said group, they used morphine doses of near 2 mg/h, which were almost double those needed by our patients (about 1 mg/h). Besides, both results are very difficult to compare because their patients were under sedation less than 24 h, while our series included patients treated for more than 500 h. From the data collected in our study, during prolonged sedation of more than 144 h, one could deduce a tachyphylaxis phenomenon, but due to the small size of the subgroup, no significant conclusions can be made.

Our results confirm the fall in cardiac frequency produced by propofol, but there are no apparent differences between the averages of mean arterial pressure of both groups, before and after treatment. It is of importance to stress the existence of significant cardiovascular depressors in eight patients treated with propofol and six treated with midazolam. This was easily corrected with inotropics or with plasma volume expansion.

We did not observe the adverse effects described in the literature, such as green coloring of urine. Both drugs were considered safe with respect to induction of allergic phenomena. Despite the fact that propofol was administered as a lipidic emulsion and that Lipson et al reported thrombocytopenia in a child treated with this type of infusion, we did not observe this effect; the hematologic and coagulation values were similar to those at admission in all subgroups. The screening of biochemical parameters did not demonstrate worsening in renal function or in any of the studied parameters. Cortisol levels were not determined because there is already sufficient clinical
evidence that propofol does not significantly depress adrenal function evaluated with the cosyntropin (tetraicosactrin) test.\(^3\)

The rise in triglycerides observed in ten patients sedated with propofol for more than 3 days fell to normal values after sedation; this phenomenon had been reported in previous studies;\(^4\) however, Eddleston and Shelly\(^4\) reported a case of hypertriglyceridemia at 72 h after discontinuing the infusion of propofol. In five patients treated with propofol requiring parenteral nutrition during the period of study, lipidic weight was diminished with parenteral nutrition reducing the one provided by propofol. None of these patients presented with hypertriglyceridemia.

In short, both sedative agents were considered safe with respect to the induction of adverse effects during prolonged use.

The mean recovery time until extubation in subgroups with short-, medium-, and long-term sedation with propofol (0.3, 0.4, and 0.8 h, respectively) was inferior to that of midazolam (2.5, 13.5, and 36.6 h, respectively). If mean time up to total recuperation of consciousness and discharge to a normal ward or intermediate care unit is considered, those times in the propofol group were also shorter (1.0, 1.4, and 1.8 h, respectively) compared to those of midazolam (3.6, 21.0, and 54.7 h, respectively). These observations concur with those of other authors. In patients undergoing cardiac surgery who were sedated for less than 18 h, Grounds et al\(^2\) observed a mean recovery time 20 times longer in patients sedated with midazolam than those in the propofol group (202 versus 9.5 min). Similar results were reported by Aitkenhead et al\(^2\) in a study of 101 critically ill patients sedated for less than 24 h, recording a mean time until disconnection of the respirator of 5 min in 21 patients who received propofol and of 148 min in 18 patients treated with midazolam. We agree in establishing that quicker recovery with propofol is a clinical advantage which favors this agent with respect to midazolam in continuous short- and medium-term sedation. This fact can be extended to its use in prolonged sedation of up to 522 h.

The correlation between time of propofol administration and the time required until extubation and total recovery was highly significant in short-, medium-, and long-term uses (\(r=0.83, 0.94,\) and 0.90 for extubation, and \(r=0.98, 0.88,\) and 0.92 for total recovery). On the other hand, in the midazolam group, neither time of extubation nor total recovery could be predicted. Although cumulative effects had been previously observed by Mathews et al\(^2\) in only 1 out of 25 patients, we found those effects in our study in all patients but one sedated with midazolam for longer than 24 h. The reduced recovery variability after propofol use is considered to be an additional clinical advantage.

We used the hourly cost-calculating system described previously, which allows more accurate billing for the expenses generated by the patient than calculating costs on a daily basis. This may be especially true in patients with a short ICU stay.

Loirat et al\(^3\) considered the objective of the cost-benefit analysis to be maximization of net benefits (benefits minus costs). From this perspective, the benefits of the medical activity are classified into direct, indirect and intangible, or of difficult quantification. In short-term sedation, propofol produced a greater direct benefit due to the decrease in the total money cost through reduction of ICU stays. Mean savings were 2,000 pts per patient. In medium- and long-term sedation, propofol reached an even higher indirect benefit, since the additional cost of antagonization was not necessary with propofol.

The antagonization cost with flumazenil of those patients treated with midazolam included in the study was not quantified, but in our ICU, this agent previously generated an expense of nearly 90,000 pts per month. Propofol also reached higher intangible or difficult-to-quantify benefits resulting from the potential decrease of orotracheal intubation risks.

A possible methodologic limitation of our study might be bias attributable to the delay in discharge due to complications such as gastrointestinal bleeding or nosocomial infection. This only occurred in a nonsignificant number of patients (four patients treated with propofol and two with midazolam), with the rest of the patients being able to transfer to the ward or the intermediate care unit (which have a lower cost of stay than the ICU). Obviously, this factor can be produced independently of the treatment used.

In conclusion, we believe that propofol is an agent with the same safety, a higher clinical effectiveness, and a better cost-benefit ratio than midazolam in the continuous sedation of critically ill patients undergoing mechanical ventilation in our environment. It would be advisable to carry out other studies which could validate our results from a cost-benefit and cost-effectiveness perspective in other hospital environments.

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