Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial*

Genís Carrasco, PhD, MD; Nacho Baeza, MD; Lluís Cabré, PhD, MD; Eugenia Portillo, RN; Gemma Gimeno, RN; David Manzanedo, RN; Milagros Calizaya, MD

Objectives: To evaluate the clinical effectiveness, safety, and cost of dexmedetomidine for the treatment of agitated delirium refractory to haloperidol in nonintubated critically ill patients.

Design: Nonrandomized, controlled trial.

Setting: Intensive care department of a tertiary care nonprofit hospital.

Patients: All consecutive admissions to a medical-surgical ICU with a diagnosis of agitated delirium.

Interventions: Initial haloperidol titration: all patients received IV bolus doses of haloperidol until agitation was controlled (Richmond Agitation Sedation Scale scoring range, 0 to −2) or reaching the maximum daily dose. Group comparison: patient responders to haloperidol (control group) were compared with nonresponders (dexmedetomidine group).

Measurements and Main Results: A total of 132 nonintubated patients were treated with haloperidol in the initial haloperidol titration phase. Forty-six patients (34.8%; 95% CI, 26.0–43.1%) did not respond to haloperidol, and 86 patients (65.2%; 95% CI, 56.3–73.0%) were responders. During the group comparison phase, dexmedetomidine achieved a higher percentage of time in satisfactory sedation levels than did haloperidol (92.7% [95% CI, 84.5–99.8%] vs 59.3% [95% CI, 48.6–69.3%], respectively; p = 0.0001). Haloperidol was associated with 10 cases (11.6% [95% CI, 6.5–21.2%]) of oversedation and two (2.0% [0.4–8%]) of corrected QT lengthening. Direct cost of dexmedetomidine was 17 times greater than haloperidol, but it achieved a mean savings of $4,370 per patient due to the reduction in length of ICU stay.

Conclusions: In the study conditions, dexmedetomidine shows to be useful as a rescue drug for treating agitation due to delirium in nonintubated patients in whom haloperidol has failed, and it seems to have a better effectiveness, safety, and cost-benefit profile than does haloperidol. (Crit Care Med 2016; 44:1295–1306)

Key Words: cost-benefit analysis; delirium; dexmedetomidine; haloperidol; nonintubated patients; nonrandomized controlled trial; psychomotor agitation

Delirium is a frequent complication in the ICU setting. This is a nonspecific syndrome, which usually consists of a reversible manifestation of acute illness, but it is associated with adverse outcomes (self-extubation, removal of indwelling catheters, and prolonged ventilator dependence), lengthened ICU and hospital stay, and increased healthcare costs (1). In addition, delirium is independently associated with higher 6-month mortality, fewer median days alive and without mechanical ventilation, and a higher occurrence rate of cognitive impairment at hospital discharge (2).

The incidence of delirium is reported to be from 16% (3) to 89% (4), according to the population of critically ill patients studied and diagnostic criteria used. Its definition, as a fluctuating disorder of consciousness, attention, and cognition (5), is useful to interpret the role of different therapeutic interventions.

Haloperidol, a centrally acting dopamine antagonist also used in the treatment of major psychoses, is the drug most commonly used in clinical practice and most recommended by international...
were eligible for the study. Most guidelines recommend atypical antipsychotics (olanzapine, risperidone, quetiapine, and ziprasidone) as alternatives to haloperidol, although available small studies show contradictory results (10–13).

For these reasons, until now, haloperidol was “standard care” in the management of hyperactive or agitated delirium in our ICU.

The ideal treatment for ICU-associated delirious agitation would relieve symptoms without causing excessive sedation, have fewer side effects than haloperidol, have little interaction with other drugs, and be easily titrated (14). Analgesic properties would also be desirable because opioid use would be reduced, also lessening delirium. Dexmedetomidine, a selective α2 agonist with a favorable pharmacologic profile, has all of these properties. Several studies report the successful use of dexmedetomidine in a range of clinical ICU contexts, favorably replacing the usual sedative agents (propofol or midazolam) in mechanically ventilated patients (15, 16) and reporting better outcomes than haloperidol in patients who cannot be extubated due to agitated delirium (14). Unfortunately, its effectiveness and safety in other common and more dangerous clinical ICU settings, such as when haloperidol fails to control agitated delirium in nonintubated patients, remains unknown.

Initially, we hypothesized that dexmedetomidine might be more effective and safer than haloperidol in nonintubated and agitated patients. Unfortunately, in our Hospital Drug Guide, this α2 agonist is approved for treating nonintubated patients only in cases where haloperidol has previously failed. For this reason, the Hospital Committee on Bioethics and Human Research did not authorize our proposal of a controlled, randomized, double-blinded trial comparing haloperidol, dexmedetomidine, and placebo in these patients. Consequently, we had no alternative but to modify the hypothesis that was addressed to demonstrate that dexmedetomidine might be effective and safer as rescue drug when haloperidol fails to control agitated delirium in nonintubated patients. The definitive study design was a nonrandomized controlled trial (quasi-experimental) in which the mandatory condition for the administration of dexmedetomidine would be previous failure of haloperidol.

The definitive aim of this trial was to evaluate the clinical effectiveness, safety, and cost-benefit of dexmedetomidine as rescue agent for the treatment of agitated delirium refractory to haloperidol in nonintubated ICU patients.

MATERIALS AND METHODS

Patients

Subjects admitted consecutively in our 13-bed medical-surgical ICU between December 31, 2013, and December 31, 2014, were eligible for the study.

Risk Factors for Delirium

All patients were initially assessed according to the Prediction of Delirium in ICU Patients scale (PRE-DELIRIC) (17). This tool contains 10 risk factors (age, Acute Physiology and Chronic Health Evaluation II [APACHE II] score, admission group, coma, infection, metabolic acidosis, sedation, morphine use, urea concentration, and urgent admission) that are readily available after intensive care admission and have a high predictive value.

Primary Nonpharmacologic Prevention of Delirium

Patients with high risk of delirium (≥ 50% PRE-DELIRIC score) and/or over the age of 65 years underwent strategies for primary prevention of delirium focused on optimization of risk factors via the following methods: repeated reorientation of the patient by trained volunteers and nurses, provision of cognitively stimulating activities for the patient three times per day, a nonpharmacologic sleep protocol to enhance normalization of sleep/wake cycles, early mobilization activities and range of motion exercises, timely removal of catheters and physical restraints, institution of the use of eyeglasses and magnifying lenses, hearing aids and earwax disimpaction, and early correction of dehydration.

Study Design

The study was a nonrandomized controlled trial (quasi-experimental) and unicenter. Patients were prospectively included as soon as they achieved the predefined criteria.

Inclusion criteria were as follows: 1) age between 18 and 95 years; 2) Richmond Agitation Sedation Scale (RASS) score range of +1 to +4 points (18) (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/B656); 3) acute onset and fluctuating course of mental disturbance characterized by inattention and one of the following: disorganized thinking or altered level of consciousness scale evaluated according to confusion assessment method for the ICU (CAM-ICU) (19); and 4) Intensive Care Delirium Screening Checklist (ICDSC) (3) (Supplemental Table 2, Supplemental Digital Content 1, http://links.lww.com/CCM/B657) score of established delirium (4–8 points).

Exclusion criteria were as follows: 1) intubation, noninvasive ventilation previous to or throughout the study; 2) pregnancy; 3) previous diagnosis of psychopathic disorder or history of substance abuse; 4) administration of antipsychotic medication in the 10 days previous to enrollment; 5) any contraindication to haloperidol or dexmedetomidine (allergy, Parkinson, oropharyngeal dysfunction, arterial hypotension or bradycardia, QTc interval prolongation, and hepatic or renal dysfunction); and 6) neurologic condition that did not allow appropriate neuropsychiatric evaluation (e.g., stupor or coma equivalent to RASS score < −3). In patients requiring physical restraint, an authorization document signed by the ICU doctor and prior permission from the patients’ next of kin, were mandatory.

Initial Haloperidol Titration

All patients received IV haloperidol bolus doses of 2.5–5 mg, with intervals of 10–30 minutes, until control of agitation...
(RASS score, 0 to −2) or until reaching the maximum cumulative daily dose of 30 mg (Fig. 1). According to these results, patients were classified as responders or nonresponders.

**Interval Until Maintain or Achieve RASS Score 0**

Then, each group (responders or nonresponders) received a different treatment (maintenance or rescue) in order to maintain or achieve a safe and comparable level of arousal (RASS score 0 = patient alert and calm).

**Haloperidol Maintenance (Haloperidol Responders)**

In responders, the haloperidol infusion of 0.5–1.0 mg/hr was adjusted as necessary to attain a RASS score of 0. Subsequently, these patients continued treatment with this drug.

**Dexmedetomidine Rescue Infusion (Haloperidol Nonresponders)**

Although receiving a continuing infusion of haloperidol (0.5–1.0 mg/hr), dexmedetomidine was infused without a loading dose at 0.2 μg/kg/hr to attain a RASS score of 0. If necessary to attain a RASS score of 0, the dose of dexmedetomidine was increased progressively to 0.7 μg/kg/min. The time required to attain a RASS score of 0 was recorded. After attaining a RASS score of 0, the haloperidol infusion was gradually tapered and discontinued, with adjustments of the dexmedetomidine infusion if necessary.

**Group Comparison (Haloperidol Responders Versus Nonresponders)**

Only when all patients achieved the same level of arousal (exactly RASS score 0), group comparison (haloperidol infusion vs dexmedetomidine infusion) was started.

The doses of haloperidol in the control and dexmedetomidine in the study group were adjusted to maintain the therapeutic target of drug comparison (RASS scores between 0 and −2). According to the pain control protocol, all patients received IV paracetamol every 8 hours, and when the nurses on care found it necessary, they administered complementary doses of other analgesics (metamizol and/or morphine).

**End of Treatment**

In both groups, treatment was continued throughout the clinically indicated time to maintain stable RASS scores between 0 and −2 and ICDSC between 0 and 1. In cases where drug failure or serious adverse effects were detected, the drug was discontinued and the patient was excluded from the study. In the event of therapeutic failure of either of the two agents, ICU physicians could choose freely, out of study, to prescribe olanzapine, quetiapine, risperidone, propofol, benzodiazepines, or other drugs.

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**Figure 1.** Flow diagram of the study. *RASS = Richmond Agitation Sedation Scale (18). **QTc = heart rate–corrected QT interval.*
Data Collection
ICU admission baseline data collected included demographic characteristics, diagnosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, risk factors for delirium (PRE-DELIRIC scores), use of physical restraint, and sedative medication in the preceding 24 hours. Once the diagnosis of delirium was established, all patients were assessed continuously with the usual physiologic ICU variables (blood pressure, pulse oximetry, continuous ECG, analytic results, requirement and rate of vasopressors, and inotropes), ICDSC scores every 4 hours or less, and RASS scores every 60 minutes or less. Monitoring was prolonged until the patients recovered and met criteria for ICU discharge.

During initial haloperidol titration and group comparison (haloperidol and dexmedetomidine infusions arms), clinical data were recorded by the bedside nurses as representative values for each 1-hour period. Other clinical data collected also included study drug rate; use of other sedatives; requirement for physical restraint; and the presence of arrhythmias, atrioventricular block, or any other adverse event. The QTc interval was assessed every 2 hours. Clinical data were collected until ICU discharge and outcomes sought until hospital discharge.

Endpoints
The primary effectiveness (or efficacy in the daily practice of each drug) endpoint was the quality of sedation defined as the percentage of time that the patient was maintained at the satisfactory level of sedation (RASS score: 0, −1, or −2; ICDSC: < 4) divided by the total sedation time multiplied by a hundred. Secondary effectiveness endpoints were as follows: time needed to perform initial haloperidol titration, time of sedation required during group comparison, time needed to recovery until discharge from the ICU, and the need for supplemental analgesics.

The primary safety endpoint was excessive sedation (oversedation) defined as the induction of undesired pharmacologic coma (RASS score: −3, −4, or −5). Secondary safety endpoints were ICDSC between 0 and 1 previous to discharge, new indication of inotropes or vasopressors due to arterial hypotension (mean arterial pressure < 70 mm Hg) attributable to treatment, increase of 20% or more in inotrope or vasopressor doses indicated before enrollment, sustained supraventricular or ventricular arrhythmias, bradycardia requiring treatment, atrioventricular block requiring therapeutic intervention, extrapyramidal movements, prolongation of QTc interval, and the need to maintain previously established physical restraint.

Cost-Benefit Analysis
For the cost analysis of drugs, 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 agent); and 2) monetary cost of care during and after treatment, or secondary cost (number of hours the patient required special care [respiratory physiotherapy; close monitoring] until his or her level of consciousness and collaboration 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: nursing care hours, medical care hours, upkeeping costs, maintenance, etc.). A computerized system calculates the total cost generated by a patient hourly (20). The total monetary cost of treatment was the result of adding the pharmaceutical cost (primary) and that of care (secondary).

Statistical Analysis
Using quality of sedation as the primary outcome measure, and assuming that the mean ± sd of percent on adequate sedation time was 75 ± 20 hours, we calculated a study of more than 35 patients, in each group, would have a 90% power of detecting a difference in time of adequate sedation in the dexmedetomidine group, with a certainty of 95%. Categorical baseline and outcome data were compared using chi-square tests, whereas continuous data were assessed graphically and compared using Mann-Whitney U tests or Student t tests as required. For group comparisons on severity scores, ICDSC, RASS, and the total daily dose of drug, the repeated-measures analysis of variance with Greenhouse-Geisser correction test was used. Simple main effects were calculated to evaluate differences at each point in time and study patterns of change within each of the two groups. Data are presented with CIs at 95% (95% CI). A p value of less than 0.05 was considered statistically significant. The calculations were performed with Stata version 9.2 (StataCorp, College Station, TX).

Bioethics
The local Committee on Bioethics and Human Research approved the study protocol and the informed consent document. Patients who met the inclusion criteria were, by virtue of their delirium, unable to give informed consent. Consequently, written consent to their inclusion was obtained from their relatives or temporary legal representative.

The study was conducted in accordance with the Declaration of Helsinki and Tokyo for humans and it complies with the standards of Transparent Reporting of Evaluations with Non-randomized Designs (TREND) (21).

RESULTS
During the study, 808 patients were consecutively admitted in our ICU but only 154 patients (32 women and 122 men) developed agitated delirium (19.0%; 95% CI, 16.3–21.7%) and were considered eligible for the study (Fig. 1). We excluded 22 patients (18 for exclusion criteria and four due to negative informed consent). The selected sample for the initial group was 132 patients (26 women and 106 men).

As shown in Table 1, in 86 patients (65.2%; 95% CI, 56.3–73.0%) in the initial group, agitation was controlled during initial haloperidol titration and in the group comparison phase, these patients were assigned to continue with haloperidol (control group). The remaining 46 patients (34.8%; 95% CI, 26.0–43.1%) did not respond to haloperidol despite reaching the maximum cumulative dose authorized by the protocol (30 mg), and in the group comparison phase they were assigned to dexmedetomidine (study group). No differences concerning the period between the ICU admission and diagnosis of
delirium were observed. Patients who did not respond to haloperidol required nearly double the dose of this drug as those who responded.

**Baseline Characteristics**

When comparing the haloperidol group with patients in the dexmedetomidine arm, we observed no statistically significant differences either in demographic characteristics (age and gender) or in most clinical variables (APACHE II, oxygenation index, and presence of respiratory failure). There were also no differences in the diagnoses that motivated ICU admission. Patients in the dexmedetomidine group had slightly worse RASS scores and physical restraint than those assigned to the control group, but this difference was not statistically significant (Table 2).

**Risk Factors for Delirium**

As shown in Table 2, at the time of ICU admission, both groups had higher scores of risk factors for delirium but with a comparable prevalence.

**Incidence of Refractoriness to Haloperidol**

After the initial haloperidol titration, haloperidol failed to control agitated delirium in 46 of 132 patients (rate of haloperidol failure of 34.8% [95% CI, 26.0–43.1%]) who were later allocated to receive dexmedetomidine. If we add to this figure, the 12 patients who were excluded during treatment with this drug due to oversedation or QTc lengthening (Table 3), the overall failure rate reached 43.0% (95% CI, 33.9–51.2%).

**Time to Attain a RASS Score of 0 (Either by Dexmedetomidine Rescue Infusion or by Reducing the Haloperidol Infusion)**

The time to attain a RASS score of 0 was similar in both groups. Addition of the dexmedetomidine rescue infusion promptly controlled the level of sedation in all haloperidol-refractory patients (Fig. 2). After attaining a RASS score of 0 through the rescue dexmedetomidine infusion or by reducing as necessary the infusion of haloperidol, physical restraints were necessary in similar percentages of both groups.

**Effectiveness**

As shown in Table 3, haloperidol failed in 10 patients (eight required temporary noninvasive ventilation and two required intensive physiotherapy) solely due to oversedation, and it caused QTc lengthening in two more who readily responded to isoproterenol. Contrarily, dexmedetomidine was able to control all the agitated patients without respiratory or QTc disturbances.

Regarding time to satisfactory sedation (quality of sedation), which was the primary effectiveness endpoint, Table 4 shows that dexmedetomidine was significantly more effective in achieving 33.4% more time in satisfactory sedation than haloperidol. The same finding was recorded with respect to scores of delirious symptomatology other than agitation. According to ICDSC scoring, dexmedetomidine maintained 32.5% more time in subsyndromal delirium levels (<4) than did haloperidol.

Figure 3 shows greater stability in the sedative effect of dexmedetomidine compared with the fluctuating profile of haloperidol.

As shown in Table 3, the mean sedation time required was slightly higher in the haloperidol group than in patients treated with dexmedetomidine, but the differences were not statistically significant. In all but one case of dexmedetomidine and all but six of haloperidol, physical restraint could be removed. Due to the analgesic effect of dexmedetomidine, patients treated with this drug received one-third the dose of metamizol and six times less morphine than those treated with haloperidol. All patients were discharged from ICU with ICDSC 0 or 1 (Table 4).

**Safety**

In relation to oversedation, which constituted the primary safety endpoint, as pointed out above, 10 of 86 patients treated with haloperidol were oversedated (RASS score: −3, −4, or −5), forcing their exclusion from the study (Table 5). Eight of them also required temporary noninvasive ventilation due to respiratory depression. None of them required intubation. Two patients in the haloperidol group were also excluded due to QTc lengthening, responding to isoproterenol infusion. Five of 46 patients receiving dexmedetomidine and four of 86 patients treated with haloperidol had bradycardia, which was resolved with atropine. Incidence of mean arterial hypotension (MAP < 70 mm Hg) was similar in both groups. In all cases, we restored hemodynamics with fluids or vasopressors. No differences in the new prescriptions or in the increase in requirements of noradrenaline were founded. There were no differences in the rate of transient supraventricular arrhythmias. Atrioventricular block and ventricular arrhythmias were not detected in either group.
Two patients in the haloperidol group died in the ICU: one due to acute postoperative myocardial infarction and the other from hemorrhagic stroke. In none of these patients did death have an apparent relationship with the drug administered. The incidence of in-hospital mortality was also similar between groups. There was no relationship between hospital deaths and sedative agents used in ICU.

Costs
As shown in Table 6, although the stay from admission to discontinuation of sedation was similar in both groups, patients...
treated with haloperidol required seven times longer recovery time than patients in the dexmedetomidine group. This caused twice the length of ICU stay for patients in the haloperidol group, compared with the dexmedetomidine group. Therefore, while drug cost of haloperidol was 17 times lower, longer recovery time of the haloperidol group caused an incremental cost of $4,370 per patient over that originated by dexmedetomidine.

**DISCUSSION**

Dexmedetomidine is a promising agent, which has demonstrated a considerable advantage when compared directly to haloperidol, in facilitating tracheal extubation in agitated patients admitted to the ICU (14). The sedative, analgesic, and anxiolytic effects of dexmedetomidine have been convincingly demonstrated in these patients (22–24). However, to date there were no studies that demonstrated the same effectiveness and safety of this agent to control other common and more dangerous clinical conditions such as agitated delirium in nonintubated patients. These two clinical settings differ significantly from the perspective of patient safety: in patients in the process of tracheal tube removal, the respiratory depression due to sedatives can be controlled at low risk, reconnecting the patient to ventilator, whereas in nonintubated patients, emergency intubation may be required with the consequent high risk for them.

This is, to our knowledge, the first study suggesting that dexmedetomidine is effective, safe, and efficient as rescue agent when haloperidol fails to control agitated delirium in nonintubated ICU patients. However, since our study was nonrandomized due to ethical restrictions, it must be emphasized that other important issues are outside the objectives of our research. The most crucial concern is whether dexmedetomidine could be more effective and safer than haloperidol as first-choice agent in the treatment of agitated delirium in nonintubated patients, hypothesis that, unfortunately, still remain to be demonstrated. For this reason, we believe that further studies with a controlled, randomized, double-blind design are warranted to explore this other important clinical concern.

**Clinical Context**

Our service has a strict protocol for the administration of analgesics and sedatives in nonintubated patients. It includes the evaluation of risk factors at admission, the routine use of tools to confirm diagnosis of delirium (CAM-ICU and ICDSC), and the implementation of nonpharmacologic preventive measures.
measures. All these measures used in daily practice were also included in the study protocol.

Our ICU admits between 800 and 1,000 patients per year, more than half of whom are under postoperative care and, usually, are extubated during the first 3 hours of admission. In daily practice, most of them are screened for risk factors for delirium (PRE-DELIRIC tool). During the study, we observed that the delirious patients were predominantly those who had undergone cardiothoracic or abdominal surgery and had developed agitated delirium after extubation. According to exclusion criteria, no patient had history of drug use, psycho-pathology, or treatment with psychotropic drugs. They were mostly elderly population postoperative patients whose risk factors for delirium were related to anesthesia and surgery. The pathophysiology of this kind of delirium remains obscure although there is agreement that its etiology may be multifactorial and its mechanism could be associated with a cholinergic deficiency or an excess of dopamine (25, 26).

The profile of included patients corresponded to the main case-mix of our service. Analyzing their baseline characteristics, we found that the studied populations were strictly comparable with respect to baseline demographic and clinical variables. An additional analysis including some of the differential factors identified between the two groups, such as different score on the APACHE II scale, or differences in patients with diagnostic criteria for sepsis as covariables, was carried out but no statistically significant differences were found.

We also were not able to identify any risk factors that may have contributed to the failure of haloperidol. The populations studied were strictly comparable with respect to all known factors that could have influenced the refractoriness of this drug. This is other important concern that will require well-designed prospective multicenter studies to clarify the factors influencing the failure of this drug.

**Maximum Haloperidol Daily Doses**

A crucial point of the study is the relatively conservative maximum dose of haloperidol chosen. In the non-ICU setting, most guidelines recommended a starting dose of haloperidol of 0.5–1.0 mg orally or parenterally, with repeated doses every 20–30 minutes until the desired effect is achieved (maximal recommended doses for the elderly should not exceed 12 mg in 24 hr in non-ICU settings) (27). Because of the urgency of the situation in many ICU patients (due to the potential for inadvertent removal of central catheters, endotracheal tubes, urinary catheters), the doses of haloperidol necessary to relieve agitation in the ICU may be higher in comparison to non-ICU settings. Unfortunately, there are little data in the way of formal pharmacologic investigations to guide dosage recommendations in the ICU. Discussion about this problem is still scarce. There are reports about a broad spectrum of IV daily doses from 26 (28) to 1,540 mg (29), which have generated such confusion that, in 2010, the Food and Drug Administration issued a warning about the risks of IV haloperidol in which this authority recommend using it at low doses for the minimum time possible (30). In addition, most international guidelines (7) and the British National Formulary recommend haloperidol doses of 18 mg as a maximum daily intramuscular and 30 mg as a maximum daily in all circumstances. We believe that this recommendation is convincing since, in our daily practice, infusions of this agent at daily dosage higher than 30 mg induce oversedation at a rate near 35%. For all these reasons, the committee that supervised the study decided to establish 30 mg as maximum daily doses of in both boluses and infusion.

**Effectiveness**

In our study, we recorded a rate of haloperidol failure of 34.8%, slightly higher than the 30% reported by Dumont et al.
### TABLE 5. Comparison of Safety During Group Comparison \((n = 132)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine ((n = 46))</th>
<th>Haloperidol ((n = 86))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive sedation (Richmond Agitation Sedation Scale score ([18]): –3, –4, or –5) requiring discontinuation of treatment, (n) ((%; 95% CI))</td>
<td>0</td>
<td>10 (11.6; 6.5–21.2)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Secondaries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with abnormal corrected for heart rate QT interval(^a), (n) ((%; 95% CI))</td>
<td>0</td>
<td>2 (2.3; 0.4–8.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Supraventricular arrhythmia, (n) ((%; 95% CI))</td>
<td>12 (26.0; 14.3–41.4)</td>
<td>24 (27–8; 19.3–34.0)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ventricular arrhythmia, (n) ((%; 95% CI))</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Atrioventricular block, (n) ((%; 95% CI))</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Bradycardia requiring treatment, (n) ((%; 95% CI))</td>
<td>5 (10.8; 4.2–24.3)</td>
<td>4 (4.6; 1.1–12.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Maintained mean arterial hypotension (&lt;70 mm Hg), (n) ((%; 95% CI))</td>
<td>6 (13.0; 5.1–26.3)</td>
<td>18 (20.9; 13.2–31.3)</td>
<td>0.34</td>
</tr>
<tr>
<td>Patients newly requiring norepinephrine(^b) infusion, (n) ((%; 95% CI))</td>
<td>4 (8.6; 2.4–21.5)</td>
<td>11 (12.7; 6.8–22.3)</td>
<td>0.31</td>
</tr>
<tr>
<td>Patients requiring a 20% or more increase in norepinephrine(^b) infusion, (n) ((%; 95% CI))</td>
<td>2 (4.3; 0.7–16.2)</td>
<td>7 (8.1; 3.2–16.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Patients requiring noninvasive ventilation due to oversedation, (n) ((%; 95% CI))</td>
<td>0</td>
<td>8 (9.3; 6.5–21.2)</td>
<td>0.016</td>
</tr>
<tr>
<td>Any other adverse event attributed to the drug, (n) ((%; 95% CI))</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>ICU mortality, (n) ((%; 95% CI))</td>
<td>0</td>
<td>2 (2.3; 0.4–8.1)</td>
<td>0.69</td>
</tr>
<tr>
<td>Hospital mortality, (n) ((%; 95% CI))</td>
<td>4 (8.6; 2.4–21.5)</td>
<td>7 (8.1; 3.2–16.0)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

\(^a\)Excessive prolongation of the corrected for heart rate QT interval on the electrocardiogram, which required discontinuation of the drug.

\(^b\)Norepinephrine was the only inotropic or vasopressor drug used in the study patients.

### TABLE 6. Comparison of Drugs and Care Costs\(^a,b\) \((n = 114)\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine ((n = 42))</th>
<th>Haloperidol ((n = 72))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of recovery care until ICU discharge, mean ± sd ((95% CI)), d</td>
<td>0.41 ± 0.12 ((0.38–0.44))</td>
<td>2.90 ± 0.91 ((2.71–3.09))</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Total ICU stay, mean ± sd ((95% CI)), d</td>
<td>3.1 ± 0.14 ((3.06–3.14))</td>
<td>6.4 ± 0.34 ((6.33–6.47))</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cost of drugs, $, mean ± sd ((95% CI))</td>
<td>86.2 ± 12.6 ((81.7–89.1))</td>
<td>4.9 ± 3.1 ((4.1–5.5))</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Secondary cost of care required between ICU admission and end of sedation, mean ± sd ((95% CI)), $</td>
<td>4,066.3 ± 412.1 ((3,947.2–4,185.3))</td>
<td>3,915.9 ± 399.8 ((3,831.4–4,000.4))</td>
<td>0.66</td>
</tr>
<tr>
<td>Recovery care costs until ICU discharge, mean ± sd ((95% CI)), $</td>
<td>6,836.3 ± 382.1 ((6,725.88–6,946.72))</td>
<td>11,356.2 ± 983.1 ((11,148.4–11,563.9))</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Total costs, mean ± sd ((95% CI)), $</td>
<td>10,902.2 ± 794.2 ((10,673.0–11,132.1))</td>
<td>15,272.2 ± 1,385.9 ((15,063.7–15,480.6))</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

\(^a\)In constant USD at the exchange rate on January 18, 2015.

\(^b\)Time between ICU admission and delirium diagnosis, length of haloperidol test, and length of sedation infusion required were similar in both groups (see also Tables 1, 3, and 4).
(9). However, if we add to this figure the excluded patients in whom haloperidol produced oversedation or other adverse events, the overall failure rate reached 43%, much higher than that observed in the available studies.

Although our patients were predominantly agitated people under postoperative care, our results concerning the effectiveness of dexmedetomidine were similar to those published in other clinical contexts (31). Regarding the comparative effectiveness of both agents, we observed that dexmedetomidine achieved 33.4% more time at satisfactory sedation level and 32.5% more time at satisfactory control of delirious symptoms different from agitation than did haloperidol. These two advantages are statistically significant and give dexmedetomidine a better effectiveness profile. Although, as already mentioned, it is not strictly possible to compare our results in nonintubated patients with other studies in mechanically ventilated patients, other studies suggest the same results. Reade et al (14), in a controlled, randomized trial comparing dexmedetomidine and haloperidol in 20 patients under weaning, also found that dexmedetomidine achieved a higher quality of sedation than haloperidol did (95.5 vs 31.5%). However, this study is hardly comparable to our research. Design of the cited trial was randomized but only included 20 patients (the authors acknowledge that it was a pilot study). They did not have a protocol for sedation or tools to diagnose delirium and therefore they used subjective criteria. Furthermore, the clinical context of patients studied by Reade et al (14) was very different from our study. Their patients received supplemental doses of midazolam and propofol without risk because they could be reconnected safely to the ventilator. Contrarily, in our case, patients did not receive other sedatives because they had a potentially serious risk of intubation in case of respiratory depression. Fortunately, this procedure was not required in any case.

Notwithstanding, we agree with Reade et al (14) in their analysis related to the fact that the observed magnitude of the differences between groups is difficult to attribute to factors other than the different effects of the drugs.

Dexmedetomidine has analgesic properties recognized in several studies that our findings have confirmed by showing that patients treated with this agent needed six times lower dose of morphine than those treated with haloperidol. It is necessary to note that all patients received IV paracetamol on a fixed schedule and metamizol as rescue doses and patients in the dexmedetomidine group also required a two times lower dose of this last agent. This result gives an additional advantage to the α-2 antagonist in avoiding the potential respiratory depressant effect of morphine at high doses.

As Ouimet et al (32) demonstrated, “subsyndromal” delirium (ICDSC score, > 0) could also be associated with poor outcome, therefore we had to ensure that all patients were discharged with ICDSC 0 or 1. Our results showed the absence of “subsyndromal” delirium in all but one patient. In other words, we observed, in all patients, the absence of persistent delirium, defined as remaining delirium previous to ICU discharge. This is an important finding because, often, ICU physicians and nurses are reluctant to discharge patients with delirium from the ICU even when their other critical care issues have resolved due to concerns about patient safety in a ward with a higher patient to nurse ratio (33).

Safety

When analyzing oversedation, which was the primary safety endpoint, we found that dexmedetomidine was also an advantageous drug. No patients treated with this agent showed excessive sedation. In contrast, in the haloperidol group, sedation had to be suspended in 10 patients, and also in all patients in order to establish temporary noninvasive ventilation. It should be noted that in no patient was intubation necessary. All of them were excluded from the study.

Noteworthy was the low incidence of prolongation of QTc interval associated with haloperidol. It was only detected in two patients who were consequently excluded from the study. This result is significantly lower than those reported in other studies (34). The fact that no bolus of haloperidol was used during group comparison and a conservative maximum dose of this agent was established could have helped to reduce its incidence.

The incidence of other adverse effects was low and did not reach statistically significant differences between the two treatment arms. Dexmedetomidine originated more episodes of bradycardia and supraventricular arrhythmias than haloperidol, but these differences did not reach statistical significance. All episodes were recovered with atropine and amiodarone, respectively. Haloperidol was associated with similar usage rates of norepinephrine and dexmedetomidine.

Taken together, the safety profiles observed in secondary endpoints can be considered, in both groups, to be satisfactory. Having not observed serious complications with either drug, we suggest that a larger, randomized, double-blinded trial would be sufficiently safe.

Mortality

Two patients in the haloperidol group died in the ICU, one of acute postoperative myocardial infarction and the other from hemorrhagic stroke. In none of these patients did sedation have an apparent relationship with death. This rate of ICU mortality (2.4%) is similar to our mortality rate adjusted to APACHE II. Chance decided that no patient died in the dexmedetomidine group before ICU discharge.

The same thing happened when we analyzed mortality at hospital discharge. Similar mortality rates were observed in both groups without the possibility of relating this finding to the sedative agent used in ICU.

Costs

We used the hourly cost-calculating system previously described, which allows more accurate billing for the expenses generated by the patient than calculating cost on a daily basis. This may be especially true in patients with a short ICU stay (< 72 hr).

Loirat et al (35) considered the objective of the cost-benefit analysis to be maximization of net benefits (benefit – cost). From this perspective, the benefits of medical activity are classified...
into direct, indirect, and intangible, or of difficult quantification. Although some authors believe that because the high cost of dexmedetomidine (17 times higher than that of haloperidol) precludes the widespread use of this agent for sedation as prohibitively expensive in our current context (22), our cost-benefit analysis shows just the opposite. In our study, dexmedetomidine produced a greater direct benefit due to the decrease in total monetary cost through reduction of ICU stays. Mean savings was $4,370 per patient. Dexmedetomidine also reached higher intangible or difficult-to-quantify benefits resulting in the potential decrease of orotracheal intubation risk.

Strengths and Limitations

This is a previous study, with significant limitations. The principal concern is the lack of randomization and blinding. In consequence, our findings should be evaluated with caution. There are three main methodological limitations that could compromise its external validity. The first limitation is due to the study design itself. Unable to perform a randomized, controlled, double-blinded trial (gold standard) due to ethical constraints, we opted for an alternative nonrandomized intervention design, that is clearly less consistent and subject to greater selection and observation biases. Some authors postulate that nonrandomized controlled studies are preferable to randomized when this design is ethically questionable (36, 37). Without getting into methodological controversies, it is obvious that this alternative method can originate more bias. To minimize this problem, we submitted the design and implementation of the study protocol to the checklist of TREND (21). This implies that nonrandomized design should follow the remaining methodological tools usually employed in randomized trials and the uncertainty induced by the allocation should be explicitly reported (38).

A second limitation is the lack of inclusion of other types of delirium. We must emphasize that only patients with agitated (hyperactive) delirium were studied. However, hypoactive delirium may be eight times more common than delirium associated with agitation (39). These patients were excluded, however, as they did not meet the inclusion criteria. Our results do not allow us to comment on the management of hypoactive delirium.

A third methodological limitation of our study regarding cost analysis might be bias attributable to the delay in discharge due to complications other than oversedation such as gastrointestinal bleeding or nosocomial infections. This only occurred in an insignificant number of patients (one patient treated with haloperidol and one with dexmedetomidine), with the rest of patients being able to transfer to the ward. Obviously, this factor can be produced independently of the treatment used. Also, the two patients who died were not taken into account in the calculations. The 12 patients excluded due to oversedation or QTc lengthening were also not taken into account because they were treated at the discretion of the physician in charge (10 of them received dexmedetomidine when they improved, outside the study). However, if we had taken them into account, the economic results would be even more favorable to dexmedetomidine.

Contrarily, in our opinion, this study has three strengths. The first is that dexmedetomidine was able to control agitated delirium in all haloperidol-refractory patients without intubation or requiring noninvasive ventilation, which attests to the absolute lack of respiratory depression caused by this agent compared with haloperidol.

A second strength is that if dexmedetomidine has a better cost-benefit profile than haloperidol, we believe that its indication should not be avoided solely based upon its pharmaceutical cost.

The third and last strength is that we believe that, considering that we did not observe significant complications with either of the studied agents, a further larger, randomized, double-blinded trial would be sufficiently safe.

CONCLUSIONS

The ideal treatment for ICU-associated delirious agitation would relieve symptoms without causing excessive sedation, have fewer side effects than haloperidol, have little interaction with other drugs, and be easily titrated. Analgesic properties are also desired because a reduction in opioid use could also lessen delirium. In our study, dexmedetomidine appears to possess all of these properties when administered to nonintubated patients, but there is still a long way to go before its widespread use in the ICU can be recommended.

We concluded that, in the study conditions, dexmedetomidine was shown to be useful for treating agitation due to delirium in nonintubated patients in whom haloperidol had failed and had better effectiveness and safety than haloperidol, in addition to a favorable cost-benefit profile. However, due to the nonrandomized, unblinded design and limited sample of our study, a larger, well-designed trial assessing quality of life and follow-up to 90 days is warranted to confirm these preliminary results.

ACKNOWLEDGMENTS

We thank the critical care nurses and consultant critical care physicians of the SCIAS Hospital de Barcelona, who collected much of the data during the study.

REFERENCES
