information provided by a risk prediction tool would offer an estimated long-term risk of sepsis for individual patients, potentially allowing for earlier interventions at the first signs of infection in those at highest risk. Second, the sepsis prediction score identified several potentially modifiable risk factors for sepsis hospitalization. Future research may identify modifications that could lead to reduced sepsis incidence. Third, the sepsis risk prediction score could be used to identify a significant number of outpatients at highest risk for sepsis hospitalization for enrollment in future clinical trials or for mechanistic studies of how chronic risk factors alter sepsis risk. For example, observational studies have demonstrated an association of long-term statin use and reduced sepsis mortality, possibly secondary to the immunomodulatory effects of statins (13, 14). The sepsis risk prediction score may identify an ideal population to enroll in a clinical trial of statins for the primary prevention of sepsis. Future research should first focus on validating the sepsis risk prediction tool in independent population cohorts as well as refining the tool with the addition of other clinical risk factors and potentially additional biomarkers or genetic factors. The ultimate goal will be to develop targeted therapies aimed at patients identified by a prediction tool to be at highest risk. In other words, changing from predicting to preventing the future.

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What to Do When Haloperidol Fails to Treat Agitated Delirium: Is Dexmedetomidine the Next Step?*

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In this issue of *Critical Care Medicine*, Carrasco et al (1) present data from a nonrandomized controlled trial evaluating dexmedetomidine as a rescue drug for treating agitated delirium in adult nonintubated ICU patients in whom haloperidol has failed to adequately manage delirium. This single-center study is well powered to evaluate the clinical effectiveness, safety, and cost of dexmedetomidine for nonintubated patients with agitated delirium.

Delirium is a common and morbid diagnosis affecting between 11% and 80% of ICU patients (2). ICU delirium is unpleasant for patients and caregivers and is potentially dangerous because of the risk of self-extubation or removal of vascular catheters; however, delirium is also associated with many long-term adverse outcomes (3). Delirium is associated with a higher frequency of cognitive impairment at hospital discharge, greater 6-month mortality, and increased ICU and hospital length of stays, all of which are associated with increased healthcare costs (3–6).

Early screening and treatment are keys to reducing important adverse outcomes, but clinical guidelines on treatment are conflicting (7, 8). In the United Kingdom, the National

*See also p. 1295.

Key Words: agitated delirium; delirium; dexmedetomidine; haloperidol

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Institute of Health and Clinical Excellence recommends haloperidol or olanzapine for agitated patients (8). However, the 2013 Society of Critical Care Medicine (SCCM) guidelines did not recommend haloperidol because of the lack of evidence to suggest that haloperidol reduces the duration of delirium in adult ICU patients (7).

SCCM guidelines recommend delirium monitoring by using the previously validated and reliable Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) (7). Although no pharmacologic therapy is suggested for delirium prevention, early mobilization is suggested as it may reduce the incidence and duration of illness. Although haloperidol is commonly used in clinical practice for the treatment of agitated delirium, there are few studies to support this practice or guide management for when this fails (3, 4, 9). Carrasco et al (1) shed light on this important question, one that may affect nearly 35% of agitated delirium patients.

The study design incorporates current SCCM guidelines in regard to detecting delirium and implementing prevention strategies. Ultimately, 808 consecutively admitted medical-surgical ICU patients were screened with the Prediction of Delirium in ICU Patients scale for 10 risk factors shown to have a high predictive value for delirium. If a score exceeded 50% or a patient was more than 65 years old, then patients underwent multiple primary prevention strategies (reorientation, use of corrective lenses and hearing aids, cognitively stimulating activities, nonpharmacologic sleep protocol, early mobilization, and timely removal of catheters or restraints). Of 808 patients, 154 developed agitated delirium and 132 ultimately met inclusion criteria (Richmond Agitation Sedation Scale [RASS] score of 1–4, CAM-ICU positive, and ICDSC, 4–8 points).

The authors were constrained by the study institution's prescribing restrictions on dexmedetomidine. Therefore, all patients meeting inclusion criteria were initially treated with IV haloperidol boluses in doses of 2.5–5 mg every 10–30 minutes until a RASS score of 0 to –2 had been achieved or a total daily dose of 30 mg had been given. Carrasco et al (1) noted that this maximum haloperidol dose was chosen because higher doses led to oversedation in nearly 35% of patients. After the initial titration, patients then received a continuous infusion of haloperidol 0.5–1 mg/hr to maintain a RASS score of 0. For patients who failed to respond adequately, a dexmedetomidine infusion was added without a loading dose at 0.2 µg/kg/hr and titrated to a maximum of 0.7 µg/kg/hr to attain a RASS score of 0. Once this goal was reached, the haloperidol infusion was tapered. Furthermore, all patients received IV acetaminophen every 8 hours with additional analgesics as indicated.

Although haloperidol failed to control agitated delirium in 46 of 132 patients (34.8%), addition of dexmedetomidine led to prompt sedation control in all haloperidol-refractory patients. Analysis of the haloperidol and dexmedetomidine groups did not reveal any risk factors or differences in demographic or clinical variables that might have contributed to failure of haloperidol. Oversedation requiring temporary noninvasive ventilation or QTc lengthening was seen in 12 of 86 haloperidol patients, whereas 5 of 46 dexmedetomidine patients (4 of 86 haloperidol patients) developed bradycardia requiring atropine. The incidence of mean arterial pressure less than 70 mm Hg was similar between the groups.

Nearly 93% of dexmedetomidine patients, when compared with 59% of haloperidol patients, achieved satisfactory sedation as noted by a RASS score of 0 to –2. In addition, the dexmedetomidine group had significantly less need for rescue doses of morphine when compared with the haloperidol group (0.09–0.11 vs 0.56–0.64 mg/kg/day, respectively). Finally, the haloperidol group required seven times greater recovery time, which was associated with twice the ICU length of stay and costs of $4,370 more per patient than dexmedetomidine.

This study supports earlier findings and enhances the body of knowledge on the use of both haloperidol and dexmedetomidine in nonventilated ICU patients with agitated delirium. The rigorous screening, prevention, and objective diagnostic criteria for delirium implemented in this study are commendable and set a clinical standard for care although despite these efforts, Carrasco et al (1) still found a nearly 20% incidence of agitated delirium. In addition, although the maximum dose of haloperidol used by Carrasco et al (1) is consistent with guidelines, the optimal dose has not been clearly defined and is often guided by clinical judgment (3, 10, 11).

Finally, as has been noted in other studies, the total cost savings associated with dexmedetomidine can be significant in regard to both short and long-term outcomes (9). Given the role that pain can play in delirium, the use of dexmedetomidine provides an advantage over antipsychotic medications in its ability to provide both sedation and analgesia without respiratory depression. Although there still remain many questions in regard to the use of dexmedetomidine in the treatment of agitated delirium, this study adds to the body of evidence that supports its use in delirium treatment, especially when haloperidol has failed.

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Interventions to Decrease Albumin Utilization: Identifying What Works*

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The processes integral to designing, implementing, and tracking new strategies to change clinical practice are very complex, challenging, and time consuming with no guarantee of success (1–5). Changing practice is especially difficult when the underlying belief systems that guide particular practices may be long standing and deeply rooted in traditions and convictions. Economic factors may also play a role. Emblematic of these issues in the critical care world is the choice of crystalloid or colloid as the ideal intravenous fluid type for resuscitation in shock states (6–10). Needless to say, the crystalloid-colloid debate has been raging for decades with several systematic reviews and meta-analyses examining the varying fluid agendas in terms of outcomes, adverse events, and costs. In recent years, studies have strongly suggested that colloids, as represented by albumin, when compared with crystalloids, may not confer any clinical outcome improvement and certainly are associated with higher costs (6–10).

In this issue of *Critical Care Medicine*, Lyu et al (11) demonstrate that resource utilization can be positively influenced through several types of interventional strategies in a 3-year prospective study designed to encourage decreased use of albumin in the ICU. After 1 year of study (study year 1) to monitor albumin utilization, a 2-year prospective interventional study (study years 2 and 3) was built. In the first interventional year, there was both a financial incentive to reduce albumin use (decrease by 25% from baseline) and regular feedback to the critical care clinicians (physicians and advanced practice providers). In the second interventional year (study year 3), there were hospital-based infrastructure upgrades, including computerized order sets, mandatory justification for order selection, and published institutional albumin utilization guidelines. Of note, there were no financial incentives during the second intervention period. These sequential and multifaceted interventions were studied in 135 ICU beds in eight diverse ICUs (two medical, one coronary care, two cardiothoracic, two neuroscience, and 1 surgical) across two medical centers.

Overall, from the baseline year through the two intervention years, mean albumin utilization per ICU admission (unadjusted) decreased by 37% (from 2.7 to 1.7 orders per admission). This translated to an adjusted 42% relative decrease in the number of albumin orders per ICU admission; a relative reduction of 18% in the probability of a patient receiving albumin; and a 29% reduction in the number of albumin orders per admission among patients receiving at least one albumin order. In addition, between baseline and study end, mortality was unchanged and cost savings were considerable.

However, a fascinating pattern of the nature of the decreasing albumin utilization emerged over the two intervention years. In intervention year 1, the mean number of albumin orders decreased by 23.9%. This was driven by a 25.9% decrease in the number of albumin orders in patients getting at least one albumin order; yet, the probability of a patient receiving any albumin was unchanged from baseline. Thus, the albumin reduction was because of the reduction in the number of albumin orders for those patients who were already receiving albumin. The second intervention year was more successful than the first as the overall albumin utilization decreased by 44.7%. This change was mostly attributable to a 40.1% decrease in the number of patients who had any orders for albumin. This decrease probably reflects a change in clinical decision making and tightened selectivity of patients for whom albumin is appropriate. The further decrease in albumin use in intervention year 2 also suggests that money-based incentives may be less effective than computer-based order sets and guidelines.

This article emphasizes the challenges in determining the efficacy of both sequential and concomitant interventions.

*See also p. 1307.

Key Words: albumin; critical care; crystalloids; incentives; interventions

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

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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

*See also p. 1426.

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All authors contributed to the conception and design of this article. Dr. Carrasco contributed to analysis. All authors contributed to interpretation of results. Drs. Carrasco, Baeza, and Cabré contributed to drafting and final version of the article. Dr. Calizaya contributed to critical revisions of the article. Mrs. Portillo and Gimeno and Mr. Manzanedo contributed to data collection.

This study protocol complies with the standards of Transparent Reporting of Evaluations with Nonrandomized Designs (21). This implies that nonrandomized trials should follow the remaining methodological tools employed in randomized trials and the uncertainty introduced by the allocation mechanism should be explicitly reported and, if possible, quantified.

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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

guidelines (6, 7). However, these recommendations do not determine precisely what should be the drug of choice when haloperidol is contraindicated or fails at high doses. This is a key issue because the rate of adverse effects (extrapyramidal symptoms, neuroleptic malignant syndrome, and prolonged corrected QT [QTc] interval on the electrocardiogram [ECG]) (8) and lack of response to haloperidol is often undervalued in most studies although it can exceed 30% (9). 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 α-2 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 α-2 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

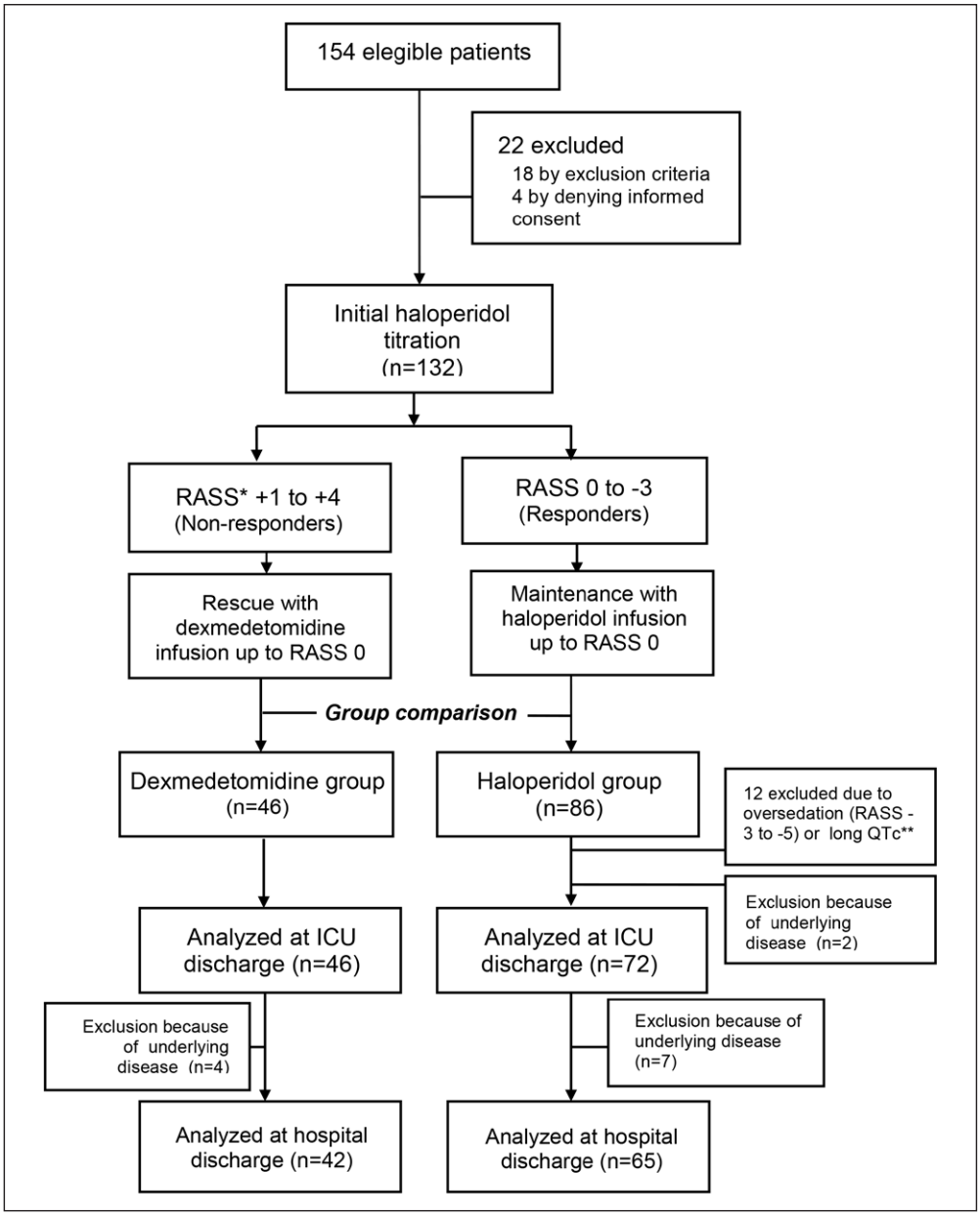

Figure 1. Flow diagram of the study. *RASS = Richmond Agitation Sedation Scale (18). **QTc = heart rate–corrected QT interval.

(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 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.

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

TABLE 1. Characteristics of the Responders and Subsequent Nonresponders at the Time of the Initial Haloperidol Titration ($n = 132$)

Variable	Dexmedetomidine ($n = 46$)	Haloperidol ($n = 86$)	p
Time between ICU admission and initial haloperidol titration, mean ± SD (95% CI), hr	17.2 ± 12.3 (13.6–20.7)	16.9 ± 13.0 (14.1–19.6)	0.89
Duration of initial haloperidol titration, mean ± SD (95% CI), hr	4.1 ± 0.30 (4.0–4.4)	3.9 ± 0.90 (3.7–4.0)	0.16
Total doses of drug during initial haloperidol titration, mean ± SD (95% CI), mg	30.3 ± 10.9 (27.1–33.4)	19.8 ± 8.9 (17.6–21.9)	< 0.001

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 noradrenalin were founded. There were no differences in the rate of transitory supraventricular arrhythmias. Atrioventricular block and ventricular arrhythmias were not detected in either group.

TABLE 2. Demographic and Clinical Characteristics at Diagnosis of Agitated Delirium (*n* = 132)

Variable	Dexmedetomidine (*n* = 46)	Haloperidol (*n* = 86)	*p*
Age, yr, mean ± SD (95% CI)	70.3 ± 12.5 (66.6–73.9)	71.3 ± 11.3 (68.8–73)	0.64
Males, *n* (%; 95% CI)	37 (80; 65–90)	77 (89; 80–94)	0.49
Acute Physiology and Chronic Health Evaluation II score in the 24 hr immediately prior to initial haloperidol titration, mean ± SD (95% CI), points	15.3 ± 6.0 (12.2–14.7)	15.5 ± 7.3 (13.9–17.0)	0.87
Other sedative or antipsychotic use prior to initial haloperidol titration, %	0	0	
Oxygenation index before initial haloperidol titration (Pao_2/Fio_2), mean torr (kPa) ± SD torr (kPa) (95% CI torr [kPa])	276.0 ± 92.0 (36.8 ± 12.2) (249.1–302.3 [33.2 ± 40.3])	289.3 ± 87.1 (38.5 ± 11.6) (182–330 [24.2 ± 43.9])	0.43
Respiratory failure ($Pao_2/Fio_2 < 200$ torr [26.6 kPa]), *n* (%; 95% CI)	5 (11; 4–24)	14 (16; 9–26)	0.44
Richmond Agitation Sedation Scale (18) scores at diagnosis of delirium, mean ± SD (95% CI), points	3.9 ± 1.8 (3.3–4.4)	3.1 ± 1.3 (2.8–3.3)	0.75
Physical restraint prior to initial haloperidol titration, *n* (%; 95% CI)	12 (34.7; 5.4–26.5)	21 (24.4; 12.3–29.6)	0.83
Admission diagnosis			
Sepsis, *n* (%; 95% CI)	5 (11; 4–24)	15 (16; 12–22)	0.08
Cardiothoracic surgery, *n* (%; 95% CI)	11 (24; 13–39)	18 (22; 13–31)	0.97
Abdominal surgery, *n* (%; 95% CI)	19 (41; 27–56)	34 (39; 29–50)	0.57
Others, *n* (%; 95% CI)	11 (24; 13–39)	19 (23; 14–32)	0.97
Delirium assessing			
Prediction of Delirium in ICU Patients scale[a] risk for delirium, mean ± SD (95% CI), points	76.8 ± 12.2 (73.2–80.3)	75.7 ± 13.2 (72.9–78.4)	0.64
Confusion assessment method for the ICU (19) criteria (all four criteria, %)	100	100	
Mean Intensive Care Delirium Screening Checklist (3) scores, *n* (95% CI), points	7.8 ± 3.2 (6.8–8.7)	7.6 ± 2.9 (6.7–8.4)	0.71

[a]High risk of delirium if ≥ 50% Prediction of Delirium in ICU Patients scale score (17).

TABLE 3. Interventions During Study Drugs (*n* = 132)

Variable	Dexmedetomidine (*n* = 46)	Haloperidol (*n* = 86)	*p*
Sedation time, mean ± SD (95% CI), hr	33. 3 ± 11.2 (29.0–35.5)	36.1 ± 14.8 (33.9–40.2)	0.13
Mean doses of drugs during study, mean ± SD (95% CI)	0.47 ± 0.12 (0.43–0.50) μg/kg/hr	1.63 ± 0.11 (1.60–1.65) mg/hr	
Failure of treatment, *n* (%; 95% CI)	0	12[a] (13.9; 1.8–19.7)	0.03

[a]Failure of haloperidol treatment was due to oversedation (*n* = 10) or excessive prolongation of the corrected for heart rate QT interval on the electrocardiogram (*n* = 2).

Mortality

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

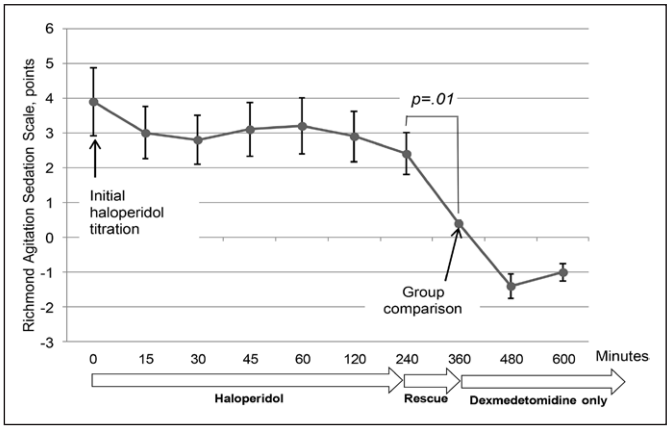

Figure 2. Effect of dexmedetomidine inpatient refractories to haloperidol ($n = 46$). The combined use of dexmedetomidine with haloperidol allowed, in all patients, suspension of this last drug before the end of rescue period. During the group comparison, dexmedetomidine maintained all patients in the desired range of sedation (level of arousal) assessed as Richmond Agitation Sedation Scale score of 0, −1, or −2 to the end of treatment.

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 the 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

TABLE 4. Comparison of Effectiveness During Study Drugs ($n = 132$)

Variable	Dexmedetomidine ($n = 46$)	Haloperidol ($n = 86$)	p
Primary			
Percentage of time under satisfactory sedation (Richmond Agitation Sedation Scale [18], 0–2 points), % (95% CI)	92.7 (84.5–99.8)	59.3 (49.1–78.0)	0.0001
Secondaries			
Percentage of time under satisfactory ICDSC[a] scores (< 4 points), % (95% CI)	52.0 (37.5–66.4)	29.5 (13.0–42.3)	0.005
Removal of physical restraint during treatment, % (95% CI)	97.8 (92.0–100)	93.1 (87.6–98.3)	0.11
Mean doses of additional analgesics: mean ± SD (95% CI), mg/kg/d			
Paracetamol	20.8 ± 5.3 (19.2–22.3)	21.7 ± 7.8 (20.0–23.3)	0.15
Metamizol	28.5 ± 7.1 (26.4–30.5)	80.3 ± 8.3 (78.5–82.0)	< 0.001
Morphine	0.10 ± 0.05 (0.09–0.11)	0.60 ± 0.21 (0.56–0.64)	< 0.0001
ICDSC[a] score 0 or 1 at ICU discharge: % (95% CI)	100	100	

[a]ICDSC = Intensive Care Delirium Screening Checklist (3).

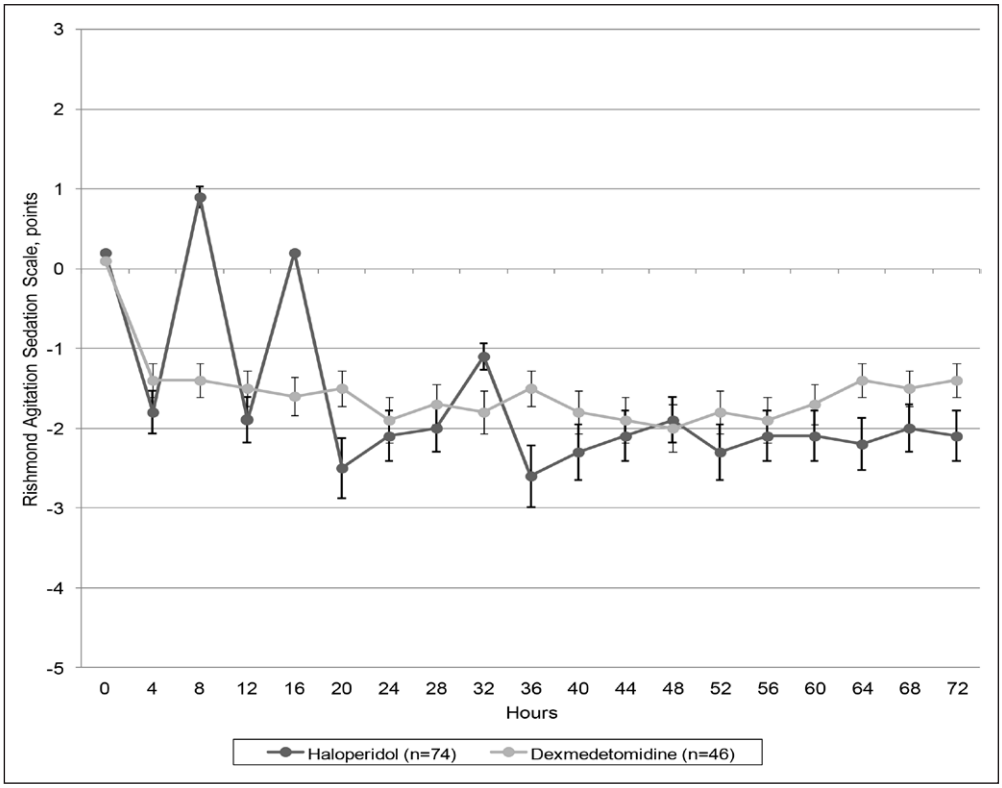

Figure 3. Evolution of sedation level (level of arousal) during the 72 hr of group comparison. Both drugs maintained all patients in the desired range of sedation (level of arousal) assessed as Richmond Agitation Sedation Scale score of 0, −1, or −2 to the end of treatment but dexmedetomidine achieved greater stability in sedative effect compared with the more fluctuating profile of haloperidol.

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, psychopathology, 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)

Variable	Dexmedetomidine (*n* = 46)	Haloperidol (*n* = 86)	*p*
Primary			
Excessive sedation (Richmond Agitation Sedation Scale score [18]: –3, –4, or –5) requiring discontinuation of treatment, *n* (%; 95% CI)	0	10 (11.6; 6.5–21.2)	0.01
Secondaries			
Patients with abnormal corrected for heart rate QT interval[a] (> 0.44 sg), *n* (%; 95% CI)	0	2 (2.3; 0.4–8.1)	0.69
Supraventricular arrhythmia, *n* (%; 95% CI)	12 (26.0; 14.3–41.4)	24 (27–8; 19.3 –34.0)	0.52
Ventricular arrhythmia, *n* (%; 95% CI)	0	0	–
Atrioventricular block, *n* (%; 95% CI)	0	0	–
Bradycardia requiring treatment, *n* (%; 95% CI)	5 (10.8; 4.2–24.3)	4 (4.6; 1.1–12.3)	0.21
Maintained mean arterial hypotension (< 70 mm Hg), *n* (%; 95% CI)	6 (13.0; 5.1–26.3)	18 (20.9; 13.2–31.3)	0.34
Patients newly requiring norepinephrine[b] infusion, *n* (%; 95% CI)	4 (8.6; 2.4–21.5)	11(12.7; 6.8–22.3)	0.31
Patients requiring a 20% or more increase in norepinephrine[b] infusion, *n* (%; 95% CI)	2 (4.3; 0.7–16.2)	7 (8.1; 3.2–16.0)	0.58
Patients requiring noninvasive ventilation due to oversedation, *n* (%; 95% CI)	0	8 (9.3; 6.5–21.2)	0.016
Any other adverse event attributed to the drug, *n* (%; 95% CI)	0	0	–
ICU mortality, *n* (%; 95% CI)	0	2 (2.3; 0.4–8.1)	0.69
Hospital mortality, *n* (%; 95% CI)	4 (8.6; 2.4–21.5)	7 (8.1; 3.2–16.0)	0.09

[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)

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

[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.

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