Low-dose nocturnal dexmedetomidine prevents ICU delirium: a randomized, placebo-controlled trial

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Running title

Nocturnal dexmedetomidine reduces ICU delirium

At a Glance Commentary

Scientific Knowledge on the Subject: No pharmacologic agent has been shown to prevent or treat delirium in critically ill adults. Among routinely used ICU sedatives, the alpha-2 receptor antagonist dexmedetomidine has least been associated with delirium. Whether this is due to potential delirium-causing effects in other agents (e.g. benzodiazepines, propofol) or delirium reduction with dexmedetomidine itself is unclear. Moreover, dexmedetomidine disrupts the already abnormal sleep patterns described in the critically ill to a lesser extent than these other sedative medications.

What this Study Adds to the Field: To our knowledge, this study, that suggests that the nocturnal administration of low-dose dexmedetomidine significantly reduces delirium without increasing adverse events, is the first to describe an effective pharmacologic delirium prevention intervention in critically ill adults. While sleep quality as measured by a self-reported questionnaire did not improve, important limitations exist with all currently available methods to evaluate sleep in the ICU.

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Abstract

Rationale: Dexmedetomidine is associated with less delirium than benzodiazepines, and better sleep architecture than either benzodiazepines or propofol; its effect on delirium and sleep when administered at night to patients requiring sedation remains unclear.

Objectives: To determine if nocturnal dexmedetomidine prevents delirium and improves sleep in critically ill adults.

Methods: This two-center, double-blind, placebo-controlled trial randomized 100 delirium-free critically ill adults receiving sedatives to receive nocturnal (21:30 to 6:15h) intravenous dexmedetomidine (0.2 mcg/kg/min, titrated by 0.1 mcg/kg/min every 15 minutes until a goal RASS = -1 or maximum rate of 0.7 mcg/kg/min was reached) or placebo until ICU discharge. During study infusions, all sedatives were halved; opioids were unchanged. Delirium was assessed using the Intensive Care Delirium Screening Checklist every 12 hours throughout the ICU admission. Sleep was evaluated each morning by the Leeds Sleep Evaluation Questionnaire (LSEQ).

Measurements and Main Results: Nocturnal dexmedetomidine (versus placebo) was associated with a greater proportion of patients who remained delirium-free during the ICU stay [dexmedetomidine [40 (80%) of 50 patients] vs. placebo [27 (54%) of 50 patients] (RR = 0.44, 95% CI, 0.23 to 0.82, p=0.006). The average LSEQ score was similar [MD 0.02; 95% CI, 0.42 to 1.92] between the 34 dexmedetomidine (average 7 assessments/patient) and 30 placebo (6/patient) group patients able to provide ≥ 1 assessment. Incidence of hypotension, bradycardia or both did not differ significantly between groups.

Conclusions: Nocturnal administration of low-dose dexmedetomidine in critically ill adults reduces the incidence of delirium during the ICU stay; patient-reported sleep quality appears unchanged.

Key words: delirium, sleep, intensive care, dexmedetomidine, randomized controlled trial

The study is registered at clinicaltrials.gov (NCT01791296).

Delirium in critically ill adults independently predicts longer hospital stay, higher costs and mortality, and may alter cognitive recovery (1). No pharmacological preventive intervention administered to critically adults without delirium has been shown to reduce delirium incidence (2). The etiology and pathophysiology of ICU delirium remains poorly understood (3). Most studies describing it use imperfect screening tools that may be confounded by sedation depth (4). However, sedative choice may influence delirium occurrence. Two large randomized controlled trials comparing dexmedetomidine to midazolam (5, 6) and propofol (6) for sedation found dexmedetomidine was associated with a lower delirium prevalence delirium throughout the ICU stay (5) or 48 hours after discontinuing sedation (6). In a trial describing non-cardiac, major surgery patients with low illness severity scores, a dexmedetomidine infusion, administered at a low-dose and for a short period (i.e., up to 24 hours after surgery) reduced delirium incidence (7). Whether dexmedetomidine prevents delirium in medical and surgical ICU adult patients with high illness severity remains unclear (8).

Sleep disruption occurs frequently in the ICU (9, 10). Critically ill patients spend more time in the wakeful stages of sleep [NREM (Non-Rapid Eye Movement) Stage 1 and 2] at the expense of the restorative stages of sleep (slow wave sleep (SWS) and REM sleep), and experience many arousals and awakenings (9, 10). Contributing factors are the ICU environment, pain, illness severity, psychosocial stress, medications, and mechanical ventilation mode. In contrast to dexmedetomidine, sedatives such as propofol and benzodiazepines worsen ICU sleep architecture (11, 12). Very low-dose nocturnal dexmedetomidine infusions in highly selected, non-mechanically ventilated, elderly patients improves sleep quality and efficiency (13).

While non-pharmacological measures aiming to improve sleep hygiene are associated with lower delirium incidence and duration, no pharmacologic sleep intervention has been shown to affect delirium (14, 15). Given that dexmedetomidine does not appear to increase delirium risk nor negatively affect sleep architecture, and in fact may be beneficial to both, we hypothesized nocturnal dexmedetomidine in general medical/surgical critically ill adults would prevent delirium and improve sleep during the ICU admission. Some of the study results of this study have previously been reported in abstract form (16).

Methods

Study Design

This prospective, phase II , randomised, double-blind, placebo-controlled trial was conducted in the 16-bed medical-surgical ICU at the 500-bed Maisonneuve-Rosemont Hospital (MRH), Montreal, Quebec and the 10-bed medical ICU at the 400-bed Tufts Medical Center (TMC) in Boston, Massachusetts. Each institution had well-established pain, sedation and delirium assessment practices. Both centres routinely titrated sedation to light sedation [Richmond Agitation and Sedation Scale (RASS) level of 0 to -1] unless deep sedation was clinically indicated (17). The study was approved by each institutional review board and written informed consent was obtained from each subject (or legally authorized representative) prior to randomization. The trial was registered online before recruitment started (NCT01791296).

Patients

Between February 24, 2013 and January 22, 2016, we enrolled consecutive eligible and consenting adults admitted to the ICU and receiving intermittent or continuous sedatives (i.e., midazolam, lorazepam or propofol), and expected to require 48 or more hours of ICU care. Patients were excluded if they had delirium [Intensive Care Delirium Screening Checklist (ICDSC) score ≥ 4) (18), a history of severe dementia, conditions precluding delirium assessment (e.g., an acute neurologic injury), or dexmedetomidine administration safety concerns [e.g., severe bradycardia (heart rate ≤ 50 beats per minute)]. Exclusion criteria are listed in Table 1.

Randomization

Eligible patients were randomly assigned to receive nocturnal dexmedetomidine (intervention) or dextrose 5% in water (D5W) (control) in a 1:1 ratio. The study drug group assignment sequence was generated by the investigational pharmacist at HMR via a computerized algorithm using permutated blocks of 4. Each institution's investigational drug pharmacist enrolled and allocated patients. All study medication was locally prepared in the pharmacy to ensure that bedside nurses received identical looking 50 mL infusion bags containing either D5W or dexmedetomidine 200 mcg in 50 mL of D5W (4

mcg/mL). Subjects, clinicians, and all study personnel were blinded to study drug assignment throughout the study.

Study Treatments

At 9:30 pm, all current sedatives (i.e. propofol, lorazepam, or midazolam) were halved and dexmedetomidine at 0.2 mcg/kg/hour (or the equivalent mL/hr of the placebo) was initiated (based on the subject's calculated ideal body weight rounded down to the nearest multiple of 5 kg) via a Baxter (Deerfield, IL) smart infusion pump without a bolus. The study drug infusion was halved at 6:00am and discontinued at 6:15am; the nurse subsequently adjusted non-study sedatives as needed.

The targeted sedation goal during the nocturnal study period was a RASS of = -1. The study drug infusion rate was increased by 0.1 mcg/kg/hour every 15 minutes when the RASS score was ≥ 0 up to a maximum rate of 0.7 mcg/kg/hr until the target RASS was achieved. The study drug infusion rate was decreased by 0.1 mcg/kg/hour every 15 minutes when the RASS score was ≤ -2 targeting the RASS goal. During the study period, subjects were initiated at 9:30 pm on the same study infusion rate as the previous mornings. All analgesic and sedative therapy choices were left to the discretion of the bedside clinician. Scheduled medications prescribed solely for the intent of improving sleep (e.g. melatonin, trazodone) were discontinued. The administration of all opioids (i.e., infused or scheduled), oral benzodiazepines, acetaminophen, and nonsteroidal anti-inflammatory drugs were unaltered.

The dexmedetomidine dose relied on the package insert recommendations, favouring doses< 0.7 mcg/kg/hr as most dexmedetomidine safety concerns are dose-related (5). If agitation occurred (i.e., RASS ≥ 2), 'as needed' IV midazolam (1-5 mg IV q1h prn agitation) was administered while the study medication was titrated upwards (by 0.1 mcg/kg/hr every 15 minutes). Existing sedative therapy was only increased above the 50%-reduced dose if the RASS was ≥ 2 after the maximum study medication dose was reached and 'as needed' doses of IV midazolam were administered. Acute pain was treated with 'as needed' fentanyl (25-100 mcg IV q1h prn). Concomitant antipsychotic use was discouraged for sleep induction but permitted at the prescriber's discretion for delirium management (if it occurred). Study medication was administered nightly until either ICU discharge or an adverse effect necessitating study

drug discontinuation occurred.

Mechanical ventilation and patient asynchrony affect sleep architecture; central apneas, worsened sleep efficiency, and sleep fragmentation are less likely with assist-control (AC) or proportional assist ventilation (PAV) modes of ventilation than with pressure support (19, 20). All ventilated subjects were placed on an AC, PAV or pressure control (PC) mode to minimize sleep disruption attributable to mechanical ventilation for the nocturnal (9:30pm-6:30am) duration of the study.

Study Outcomes

The primary study outcome was the proportion of patients who remained free of delirium during their critical illness (i.e., ICU admission). Secondary delirium–related outcomes included ICU days spent without delirium after randomization, Among subjects with delirium, its duration until it first resolved for at least 12 hours was measured. Given the large number of patients transferred from the study ICU directly to another institution at each center, it was not deemed feasible to continue delirium screening after ICU discharge.

Sleep quality was evaluated daily by the Leeds Sleep Evaluation Questionnaire LSEQ score (21). The Leeds Sleep Evaluation Questionnaire (LSEQ) was administered by study personnel to each subject each morning at 9:00am if the RASS was $\geq$ -1 and the patient did not have delirium. If the RASS was never $\geq$ -1 during the day shift then the LSEQ was not completed that day (Supplementary Table 4)(21). Data to calculate a PRE-DELIRIC score was extracted by the investigative team at the time of randomization (22). Other secondary efficacy, post-hoc, outcomes include the proportion of patients who ever developed coma (RASS $\leq$ -4); ICU days spent without coma after randomization, the proportion of nocturnal hours spent at each RASS score; the number of RASS assessments conducted each night, maximal nocturnal pain levels; antipsychotic, corticosteroid, and oral analgesic (including acetaminophen and non-steroidal anti-inflammatory drugs) use; days of mechanical ventilation; ICU and hospital stay duration; and ICU and hospital mortality. Early mobilization was deemed to have occurred when the patient left their bed while mechanically ventilated.

Subjects were monitored at least every 30 minutes for signs of hypotension (SBP ≤ 90 mmHg) and bradycardia (HR ≤ 50 bpm). The ICU team evaluated all potential causes of hypotension (e.g. intravascular volume depletion) and bradycardia (e.g., beta-blocker use). Persistent hypotension and/or bradycardia despite the reversal of other contributing factors that was felt by the investigative team to be attributable to dexmedetomidine use resulted in the study medication being held until the bradycardia and/or hypotension resolved.

A delirium screening protocol had been in place at both centres for more than a decade. All ICU patients without coma (RASS = -4 or -5) were evaluated for delirium by the bedside nurse at least once during each 12-hour shift using the ICDSC (a graded scale with clinical criteria rated at the patient's bedside from 0 to 8); -patients with an ICDSC score ≥ 4 were deemed to have delirium [Supplementary Tables 1 and 2]. Although baseline levels of sedation have not been shown to affect ICDSC reliability, the delirium protocol encouraged delirium assessment when the patient was maximally awake (23). Patients with an ICDSC score of 1 to 3, not meeting criteria for clinical delirium, were labelled as having sub-syndromal delirium (24). Patients with an ICDSC score of 0 were considered cognitively normal. All nursing ICDSC assessments were clinically confirmed by a member of the investigative team using the ICDSC; discordance was resolved through verbal consensus.

Pain was evaluated (daily and nightly) at least every four hours using a 10-point Numeric Rating Scale (NRS) and treated. When the RASS was ≤ -2, pain was assessed using the Behavioural Pain Scale (BPS) (Supplementary Table 3) (25). Sedation level was evaluated with a RASS score at least every four hours during the diurnal period (17). During the nocturnal period, RASS was evaluated every 15 minutes during the period of initial study drug titration (i.e. to reach the RASS goal of -1). After this, RASS was assessed hourly in only those patients where the bedside nurse observed the patient not to be asleep (i.e., eyes open) or agitated. Pain assessments were also not conducted in a patient perceived to be sleeping.

Statistical Analysis

As no controlled study evaluating the efficacy of nocturnal dexmedetomidine for the prevention of delirium in critically ill adults existed at the time the study was designed, and since the incidence of delirium varies widely in published ICU studies (7, 26-28), we were not confident estimating the incidence of delirium based on scale-driven delirium assessments alone that might occur with the study intervention. A convenience sample of 100 patients was thus enrolled. Data was analysed using an intention-to-treat principle. The study statistician was blinded to group assignment until all analyses were completed. Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR); categorical variables as frequencies and proportions. Between-group differences for continuous variables were analysed using the Student's t test when data was normally distributed or the Mann-Whitney *U* test when data was non-parametric, and for dichotomous variables with the chi-square test or the Fisher's exact test. For outcomes reported as a percentage of the time study drug was administered, a percentage was first calculated for each subject; the median (IQR) was then reported for each group.

For the primary outcome, given that time spent in the ICU varied between patients, Cox regression analysis was used to model time to first delirium occurrence between the dexmedetomidine and placebo groups. The proportion (i.e., relative risk) of patients remaining delirium-free during the ICU stay was then compared between the dexmedetomidine and placebo groups. Since only 2 of 9 dexmedetomidine and 1 of 6 placebo patients who died in the ICU did not have delirium prior to their time of death, the completion of a sensitivity analysis to account for the influence of ICU death on patients who remained delirium-free at the time of death was deemed unnecessary. A p value of up to 0.05 was considered significant for all analyses. The data analyses for this paper was generated using SAS software version 9.4 for windows (SAS, Cary, NC).

Results

Enrollment and Baseline Characteristics

Of 374 patients meeting inclusion criteria, 100 without exclusion criteria were enrolled (89 MRH, 11 TMC) (Figure 1). Patients randomized to receive nocturnal dexmedetomidine (n=50) and placebo (n=50) were not significantly different at baseline with the exception that fewer patients in the dexmedetomidine group (as compared to the placebo group) had a RASS score of -2 or -3 [4 (8%) versus 14 (28%), p=0.008] (Table 2). No subject withdrew consent. All randomized patients were included in the analysis. Subjects were primarily medical; severely ill; intubated; frequently admitted with sepsis/acute respiratory distress syndrome (ARDS), pneumonia, non-traumatic major surgery, and/or respiratory failure (not related to ARDS or pneumonia); and enrolled, on average, within 2 days of ICU admission. Based on the baseline PRE-DELIRIC score, patients across both groups had a 52.5% probability for developing delirium during the ICU stay (25).

Main Outcomes

Nocturnal administration of dexmedetomidine was associated with a greater proportion of patients who remained free of delirium during their ICU stay when compared to placebo (p=0.006) (Figure 2). Over the ICU admission, significantly more patients in the dexmedetomidine [40 (80%) of 50 patients] than placebo [27 (54%) of 50 patients] groups remained free of delirium (relative risk = 0.44, 95% CI, 0.23 to 0.82). The dexmedetomidine group spent more median [IQR] days in the ICU free of delirium (8 [4, 11] than the placebo (6 [2, 12] group (p < 0.001). The median [IQR] duration (days) of the first episode of delirium was similar between the dexmedetomidine [2.0 (0.8 to 2.7)] and placebo [2.2 (0.7 to 3.2] groups (p=0.73). For descriptive purposes only, the daily prevalence of delirium over the first ten study days between the dexmedetomidine and placebo groups is presented in Figure 3. The proportion of ICDSC assessments conducted at each RASS score is presented in Supplemental Figure 1.

The LSEQ assessment was successfully completed in a similar proportion of patients [68% (dexmedetomidine) vs 60%; p=0.57] and study days [74.0 % (dexmedetomidine) vs. 70%; p=0.30] between the two groups. The mean difference (MD) in the average a LSEQ score (across all 10 domains; total score = 10) was similar [MD 0.02; 95% CI (0.42 to 1.92). The results for LSEQ assessments by

specific LSEQ domain between the two groups is presented in Supplemental Figure 2. Of note, patients who received dexmedetomidine the prior night felt less tired than patients who received placebo.

Patients in the dexmedetomidine group spent a lower proportion of total study days with coma ($p = 0.009$); total study days spent at a RASS = -2 or -3 was similar between the two groups (Table 3). The dexmedetomidine group spent more median (IQR) days in the ICU free of coma (10 [2, 14] than the placebo (9 [2, 13] group ($p < 0.02$). The proportion of total nocturnal study hours spent at the goal RASS score of -1 was greater in the dexmedetomidine group (55 vs. 24 %, $p < 0.0001$) (Figure 4). On average, patients in the dexmedetomidine group had significantly fewer nocturnal RASS assessments [4.4 ± 3.6 (dexmedetomidine) versus 9.2 ± 7.3 (placebo); $p=0.002$]. During the nocturnal period, pain levels were similar between groups ($p=0.12$). Among patients with pain, dexmedetomidine-treated patients were less likely to have severe pain (40 vs. 66%, $p=0.04$).

The maximum study medication infusion rate (mL/hr) was comparable between the dexmedetomidine (8.0 ± 3.1) and placebo (9.1 ± 2.9) groups ($p=0.20$) (Table 4). Among dexmedetomidine-treated patients, the average maximum infusion rate was 0.51 ± 0.22 mcg/kg/hr. While both the proportion of patients who ever received a propofol or midazolam infusion and their duration of use were similar between the two groups, the dexmedetomidine group was administered a lower average (mcg/kg/min) dose of propofol ($p < 0.001$)). Fewer dexmedetomidine patients ever received a fentanyl infusion (76 vs. 94%, $p=0.02$); neither the duration or use nor the average infusion rate differed between the two groups. Use of a high dose-corticosteroid was greater in the dexmedetomidine group (44 vs. 16%, $p=0.002$); use of antipsychotics and oral analgesics were similar.

Duration of mechanical ventilation, ICU stay, and hospital stay and both ICU and hospital mortality were similar between the two groups (Table 5). A similar number of patients in each group experienced bradycardia, hypotension, or both bradycardia and hypotension in each group (Table 6). No hemodynamic change was serious or persistent enough to warrant removal of a subject from further study drug administration.

Discussion

To our knowledge, this is the first pharmacologic intervention study shown to prevent delirium in critically ill adults. We used a rigorous study design, meticulously titrated the study intervention during the nocturnal period, and evaluated two groups of patients with a similar risk for delirium at baseline (28, 29). Our primary result, that administration of low-dose dexmedetomidine increases the proportion of patients in whom delirium is averted during their ICU stay is unlikely to have been influenced by the level of sedation maintained during the study (5). Low-dose dexmedetomidine was safe. The way in which dexmedetomidine may have influenced sleep quality, and the relationship between sleep quality and delirium incidence remain unclear.

To date, systematic reviews of RCTs have failed to identify a safe and effective pharmacologic strategy to either prevent or treat delirium in critically ill adults (8, 14, 15). The methodological face-value challenges within these studies are numerous. In the studies describing interventions such as haloperidol or simvastatin administration, both delirious and non-delirious patients were enrolled, blurring the differences between prevention and treatment (30, 31). Moreover, some publications combine coma and delirium as a spectrum of 'brain failure', combining iatrogenic and potentially preventable drug-induced excessive sedation with delirium symptoms (32). Studies with antipsychotics have been disappointing, not only for their ineffectiveness, but for their failure to demonstrate any impact on outcomes considered meaningful by patients, such as mortality or discharge destination (33). Finally, no clinical interventional studies evaluating a pharmacologic prevention strategy, ours included, has considered patient perceptions of the often nightmare-like symptoms associated with delirium (e.g., fear, delusions) that have been described in qualitative studies (34).

The interplay between critical illness, delirium, cerebral perfusion, medications and sleep is complex; our understanding of the sleep-delirium relationship in critically ill adults remains at its infancy (9, 10). Our failure to demonstrate a difference in self-reported sleep may reflect the challenges of characterizing highly variable sleep abnormalities in the ICU setting (13-15). Polysomnography (PSG) includes the measurement of electroencephalography, electrooculogram, electromyogram,

electrocardiogram, pulse oximetry, respiratory effort, nasal airflow, and sound and is considered the gold standard method to assess sleep quality in both ICU and non-ICU settings. Although the group of sick, mostly mechanically ventilated patients we studied were very likely to have had highly disrupted sleep patterns (9, 35), a non-PSG sleep assessment method to establish 'normalcy' or a sleep pattern associated with a better prognosis that is non-invasive, reliable, and comfortable does not yet exist (9). The validity of nurse, physician, actigraphy, or other technology surrogate assessment methods is not well-established in sicker, critically ill adults. Prior ICU studies, mostly evaluating the impact of non-pharmacologic intervention(s) in patients less critically ill and more awake than those in our study, while demonstrating a reduction in delirium, have failed to detect improvements in sleep (14, 15, 36).

The lower proportion of patients requiring a fentanyl infusion during the ICU stay in the intervention group may be related to a dexmedetomidine-associated analgesic effect, particularly since fentanyl infusions at the time of randomization were frequent and similar between the two groups. Since only sedative, but not opioid infusions were driven by protocol adjustments and obligatory decrements if the sedation level deepened, opportunities to further lower opiate doses and opiate exposure may have been missed. This potential co-analgesia and opioid-sparing effect is important to study further given increasing concerns about opioid consumption during hospitalization. There may also be an association between opioid use and both delirium (29) and sleep (37).

Optimal sedation appears to have been achieved more readily with dexmedetomidine. In the context where even the strictest light sedation protocol implementation results in a significant proportion of patients being excessively sedated to the point of coma (38), such considerations as the proportion of time in optimal sedation range and mid-to long-term outcomes may further propel clinicians to lower sedatives more aggressively or choose a sedative like dexmedetomidine to maintain arousability. The acquisition cost of administering dexmedetomidine at a low-dose for only 8 hours a day, as it was evaluated in our study, is lower than it would be if administered throughout both day- and night-time periods, and at potentially higher doses. Safety concerns associated with dexmedetomidine were consistent with its pharmacological profile; while it had to be down-titrated or temporarily held in some

instances due to bradycardia and/or hypotension, no patients were removed from the study due to safety issues.

Our study has limitations. The rigorous study criteria led to only 26% of screened patients being enrolled, potentially compromising external validity. Clinical practices that could affect the incidence of delirium reported may have changed over the three years it took to complete the study. Delirium was not evaluated after ICU discharge and its subsequent occurrence may have been missed in patients with shorter ICU stays. However, the ICU stay was similar and relatively long in both groups (median 9 days dexmedetomidine, 10 days placebo). While nurses were blinded to study allocation, they were not blinded to nocturnal heart rate monitoring and may have guessed that patients with lower heart rates were receiving dexmedetomidine. The study may have been too small to detect differences in duration of mechanical ventilation and length of ICU stay. Moreover, ICU stay duration may have been altered by administrative considerations. We did not evaluate whether post-ICU outcomes (e.g., post-hospital disposition) differed between the dexmedetomidine and placebo groups. Neither ICU patients nor their families were included in the selection of outcomes; study endpoints of relevance to patients may have been missed. The use of early mobility, an intervention known to reduce delirium (39), was infrequently used at both centers. The fact the nocturnal midazolam infusion dose (unlike the nocturnal propofol infusion dose) was not lower in the dexmedetomidine group, in the minority of patients receiving it, may be attributable its routine use in patients requiring deeper sedation where the night nurse may not have reduced the midazolam infusion rate by 50% and/or increased the infusion rate quickly back to the pre-nocturnal period rate.

A difference in sleep-related outcomes may have been observed if other methods to evaluate sleep quality such as PSG had been employed. The specific reason for the bedside nurse not evaluating a patient with the LSEQ was not recorded. Patients with obstructive sleep apnea or who were at risk for obstructive sleep were not excluded (40). The fact that close to half the patients were kept on a pressure support mode of mechanical ventilation at night by the ICU team may have affected the sleep quality

observed (41); however, this ventilation feature was similar in both groups. The results of this study cannot be extrapolated to other alpha-2 agonists (e.g. clonidine). The role for nocturnal dexmedetomidine in patients admitted to the ICU with delirium needs to be evaluated.

In conclusion, nocturnal administration of low-dose dexmedetomidine in critically ill adults helps prevent ICU delirium and reduces both days spent with coma and opiate requirements. While patient reported sleep quality appears unchanged, future investigations incorporating PSG may better characterize the relationship between ICU delirium and sleep quality.

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Figure Legends

Figure 1. Patient screening, recruitment, and randomization. ICDSC, Intensive Care Delirium Screening Checklist.

Figure 2. Kaplan-Meier curve for the time to the first occurrence of delirium between dexmedetomidine and placebo groups during the ICU stay for those patients still at risk for developing delirium each day for the first time (log rank p value = 0.006). Patients with persistent coma on any given day were deemed not to have delirium.

Figure 3. Daily prevalence of delirium between dexmedetomidine and placebo groups over the first 10 study days. All patients were free of delirium at baseline. The number of patients evaluated at each time point differs from the Kaplan-Meier analysis as patients were not removed from the risk pool at first delirium onset. This figure is presented for descriptive purposes only; delirium prevalence on individual days was not compared statistically given the concerns associated with multiple testing.

Figure 4. Proportion of time spent at each RASS score during each hour of the nocturnal study period for all patients between dexmedetomidine and placebo groups. Patients in the dexmedetomidine group spent a significantly greater proportion of nights at a RASS = -1 (55 vs. 24%, $p < 0.0001$).