Nocturnal Dexmedetomidine in Nonintubated, Critically Ill Patients: Sleep or Sedation?

To the Editor:

In November 2016's issue of Anesthesiology, Wu *et al.*, in their article "Low-dose Dexmedetomidine Improves Sleep Quality Pattern in Elderly Patients after Noncardiac Surgery in the Intensive Care Unit: A Pilot Randomized Controlled Trial,"[1] demonstrated polysomnographic improvement in sleep in patients treated with low-dose (0.1 μg kg^{-1} h^{-1}) prophylactic dexmedetomidine. Although many nonpharmacologic strategies have been proposed to improve sleep quality in the intensive care unit (ICU), nocturnal infusions of the α-2 agonist and sedative dexmedetomidine have been increasingly utilized in nonintubated ICU patients in efforts to reduce the incidence or duration of delirium, which affects 20 to 80% of ICU patients and is associated with prolonged lengths of stay and possibility increased mortality.[2] Because the efficacy of the treatments of delirium have been disappointingly limited, increasing enthusiasm has been placed on preventative techniques, such as ensuring that ICU patients achieve adequate durations of sleep.[3] A pathophysiologic rationale for this therapy comes from observational polysomnographic studies that demonstrated a dramatic reduction in both restorative rapid eye movement (REM) and slow-wave (stages 3 and 4) sleep in ICU patients.[4,5] Dexmedetomidine infusions generate an electroencephalogram pattern that resembles stage 2 non-REM sleep in treated patients, which is the basis of its usage in the ICU to promote sleep.[4,5] However, in these polysomnographic studies, treated subjects also demonstrated severely disrupted overall sleep architecture, with few achieving slow-wave sleep or REM sleep of any significant duration.[4,5] In addition, an animal study demonstrated a complete loss of REM sleep with dexmedetomidine infusions, with treated rats requiring significant posttreatment rebound in both non-REM and REM sleep need.[6] In the study by Wu *et al.*,[1] there was no significant difference in the occurrence of stage 3 non-REM sleep, and REM sleep remained absent in the two groups. Although they demonstrated an improvement in sleep efficiency or the ratio of total sleep time to total monitoring time, this metric does not account for sleep architecture. Importantly, there was also no observed difference in delirium, a predefined secondary outcome. In addition, the authors noted a decreased ICU length of stay but an increased hospital length of stay in dexmedetomidine patients.

Further well-powered studies evaluating patient-oriented outcomes are needed before supporting the routine usage of prophylactic nocturnal dexmedetomidine infusions as a sleep aid, particularly given the two- to threefold increased incidence of bradycardia and hypotension seen in treated patients in this trial and in other studies.[7] In an ICU population, such a high incidence of unfavorable hemodynamic disturbances may outweigh the minimal demonstrated treatment effect.

Because access to dexmedetomidine will continue to increase as the generic formulation becomes widely available, indications beyond just sedation of the mechanically ventilated patient are increasingly explored. Although there are suggestions of potential efficacy, many unanswered questions about the drug remain. First, although it has been consistently demonstrated that nocturnal dexmedetomidine infusion increases duration of a stage 2 non-REM sleep-like electroencephalogram pattern, it is unclear whether this shift in sleep architecture, even if total sleep time is increased, yields a restorative effect. Second, the risks of utilizing dexmedetomidine in nonintubated, critically ill patients, including the possibility of increasing delirium secondary to its sedative effects, have yet to be fully elucidated. Third, and perhaps most importantly, current studies of nocturnal dexmedetomidine infusions have focused primary outcomes on polysomnographic data and have either not evaluated or failed to demonstrate significant clinical benefit. Perhaps enthusiasm for the off-label use of dexmedetomidine as a prophylactic sleep adjunct in nonintubated patients without refractory hyperactive delirium should be tempered until prospective, randomized data are able to adequately define the risks and benefits.

Competing Interests

The authors declare no competing interests.

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Low-dose, Nontitrated Dexmedetomidine Trials: Clarifying Possible Coenrollment

To the Editor:

In the November 2016 issue of Anesthesiology, Wu *et al.*[1] reported the results of their randomized controlled trial of low-dose (0.1 μg kg^{-1} h^{-1}, nontitrated) dexmedetomidine in 76 nonmechanically ventilated noncardiac surgery patients aged 65 yr or older (an off-label use), in which dexmedetomidine was found to improve several polysomnographic and self-reported indices of sleep quality. In August 2016, the same group published in the Lancet the results of an identical drug protocol applied to 700 patients meeting almost identical inclusion/exclusion criteria.[2] This Lancet paper reported a significantly lower incidence of delirium in patients treated with dexmedetomidine compared to the control group, along with several congruent secondary endpoints such as improved subjective sleep quality. One of the two Lancet trial sites, the Peking University First Hospital, was also the location of the Anesthesiology study. Patients in the Anesthesiology study were recruited exclusively during the time that the Lancet study was underway in the same hospital. In their Consolidated Standards of Reporting Trials (CONSORT) patient flow diagrams, neither paper indicates that any patients were excluded because they were enrolled in another trial. It could therefore appear, as published, that the results from some patients have been reported twice, rather than that the two papers report entirely separate experimental series. Duplicate publication without acknowledgment overstates the evidence and could, for example, lead a meta-analysis to the wrong conclusion. Both publications report important (indeed, potentially practice-changing) data from well-conducted trials. It would be helpful for the authors to address this potentially superficially misleading appearance and clarify that patients could not, in fact, be enrolled in both trials, perhaps also indicating how patients were chosen for enrollment in one study in preference to the other.

Competing Interests

Prof. Reade reports receiving a single fee in 2009 to contribute to a Hospira (Melbourne, Australia) clinician advisory board preparing guidelines for the use of dexmedetomidine and a single fee plus travel expenses in 2016 to present the results of the Dexmedetomidine to Lessen ICU Agitation (DahLIA) trial (clinical trial no. NCT01151865) to an educational meeting funded by Pfizer (Melbourne, Australia). Pfizer has provided unrestricted sponsorship for both the DahLIA and Sedation Practice in Intensive Care Evaluation (SPICE) (clinical trial no. NCT01728558) trials, in which Prof. Reade is a chief investigator.

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In Reply:

We agree with Dr. Goucher *et al.* that low-dose dexmedetomidine infusion did not restore the normal sleep architecture because stage 3 non–rapid eye movement sleep and rapid eye movement (REM) sleep remained significantly decreased or absent in our patients.[1] This is also the case when dexmedetomidine was administered for sedation in mechanically ventilated patients.[2,3] It should be noted that the target subjects were patients in the intensive care unit (ICU) after major surgery in our study[1] or receiving mechanical ventilation in another previous study.[3] It is well known that significant sleep disturbances such as fragmented sleep, decreased sleep efficiency, increased stage 1 non-REM sleep, and decreased or absent stage 3 non-REM and REM sleep are often present in those patients. Dexmedetomidine partially improved "sleep architecture" through increasing the percentage of stage 2 non-REM sleep (and decreasing the percentage of stage 1 non-REM sleep), a unique property that has also been demonstrated in other clinical studies previously.[4]

Considering the importance of sleep for ICU recovery and the lack of effective pharmacologic interventions to improve sleep,[5] prophylactic low-dose dexmedetomidine may be a choice, although not the best. Clinical effectiveness was demonstrated in our previous trial in 700 patients admitted to the ICU after noncardiac surgery, in which low-dose dexmedetomidine infusion reduced the incidence of delirium during the first 7 days after surgery (9% compared with 23% with placebo) and also decreased the incidence of nondelirium complications and increased early hospital discharge.[6] We cannot establish a causal relationship between