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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