Nighttime dexmedetomidine for postoperative delirium prevention: a promising step forward

John W. Devlin[a,b,c,*] and Chris G. Hughes[d]

[a]School of Pharmacy, Northeastern University, Boston, MA, USA
[b]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, MA, USA
[c]Harvard Medical School, Boston, MA, USA
[d]Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN, USA

eClinicalMedicine
2023;56: 101812
Published Online xxx
https://doi.org/10.1016/j.eclinm.2022.101812

Postoperative delirium occurs in up to 50% of older adults undergoing cardiac surgery and is associated with substantial patient burden, longer hospital stays and increased postoperative neurocognitive disorder (PND).[1] Non-pharmacologic intraoperative (e.g., personalized blood pressure control, cerebral oxygenation monitoring) and postoperative (e.g., early extubation, mobilization, frequent reorientation) interventions remain the foundation for delirium reduction after cardiac surgery.[1,2]

Investigating pharmacologic interventions to reduce delirium after cardiac surgery has been a major research focus given medications are easy to administer and may modulate delirium mechanistic pathways while non-pharmacologic interventions are challenging to consistently apply.[1,3] However, multiple pharmacologic interventions (e.g., antipsychotics, ketamine, statins, steroids, total intravenous anesthesia) have failed to reduce delirium in rigorous trials and none are currently recommended.[2]

The α2-adrenergic agonist dexmedetomidine has multiple properties conducive to delirium reduction (e.g., anti-inflammatory, analgesic, sleep promotion),[1,3] but whether it reduces delirium after cardiac surgery remains unclear.[1–3] Although older trials found dexmedetomidine during postoperative mechanical ventilation resulted in less delirium,[1,4] newer ICU sedation trials incorporating updated sedation strategies have found delirium and long-term cognition to be similar.[5,6] Moreover, dexmedetomidine started intraoperatively and continued for 24 h is not associated with reduced delirium compared to placebo.[7]

In this issue,[8] Qu et al report the results of a single-center, randomized trial comparing nighttime dosing of dexmedetomidine (1 ug/kg IV over 40 min) vs. placebo to prevent postoperative delirium after elective cardiac surgery in older adults expected to be extubated within 12 h. On postoperative day 1, delirium occurred less frequently with dexmedetomidine [5/175 (2.9%) vs. 16/189 (8.5%); OR 0.32, 95% CI: 0.10–0.83]. However, the proportion of patients with delirium three days after surgery [dexmedetomidine 14/160 (8.8%) vs. 25/177 (14.1%); OR 0.58; 95% CI: 0.28–1.15] was not statistically different. Delirium severity, ventilator duration, length of stay, discharge disposition, and cognitive function and quality of life 30-, 90- and 180-days after surgery were not different between groups. In the dexmedetomidine group, two patients experienced isolated bradycardic events, and 6-h post-infusion vasopressor requirements were significantly greater. Of note, the trial was stopped early due to lower than anticipated day 1 delirium occurrence and the impact of the pandemic on enrollment.

This trial,[8] performed by an experienced research team and that builds on prior nighttime dexmedetomidine delirium prevention research,[9,10] has notable strengths including its blinded design, pragmatic administration strategy, rigorous evaluation of delirium, consideration of baseline and post-discharge cognition, safety assessment, robust accountability of patients, and the use of sensitivity analyses adjusting for prognostic variables for postoperative delirium.

Do the results of this trial warrant the use of dexmedetomidine after cardiac surgery to prevent delirium?[8] The absolute difference in delirium (between groups) of 5.6% on day 1 and only 5.3% by day 3, coupled with a lack of observed difference in relevant hospital and long-term outcomes, raises questions about the clinical relevance of this dosing strategy. Potential dexmedetomidine safety concerns may temper the observed day 1 delirium benefit in the absence of additional clinical benefit. These results are difficult to extrapolate to elective cardiac surgery patients who require >12 h of mechanical ventilation, have different baseline delirium risks, or are managed at centers with less robust postoperative delirium-reduction efforts.

The results of this important trial highlight a number of questions requiring future research. Would the administration of single-dose evening dexmedetomidine on additional postoperative days lead to further

Abbreviations: CI, Confidence Intervals; ICU, Intensive Care Unit; kg, kilograms; OR, Odds Ratio; NCD, Neurocognitive Disorder; ug, micrograms

*Corresponding author. Northeastern University, 360 Huntington Ave, RD216, Boston, MA 02115, USA.
E-mail address: j.devlin@neu.edu (J.W. Devlin).

reductions in postoperative delirium? Should this dosing strategy be investigated in other patient populations, including those on mechanical ventilation or even outside the ICU? A sublingual dexmedetomidine formulation was recently approved in the USA for administration in settings without continuous hemodynamic monitoring. Limited postsurgical physiologic data suggests dexmedetomidine may improve sleep quality; the relationship between preoperative sleep and postoperative delirium, circadian rhythm, and sleep quality requires further research.[11] In addition to sleep, the analgesic, immune-modulating, and increased glymphatic clearance properties of dexmedetomidine that may modulate postoperative delirium effects need further evaluation, including the effect of different administration strategies.[1–3]

While the results of Qu et al represent a promising step forward in highlighting a potential beneficial role for nighttime dexmedetomidine in preventing postsurgical delirium,[8] additional research establishing evidence of delirium reduction and other clinical benefits is required before routine prophylactic dexmedetomidine added to non-pharmacologic perioperative strategies can be advised.

Contributors

J.W.D. and C.G.H. drafted the first manuscript, critically reviewed the manuscript for important intellectual content, and gave final approval of the manuscript.

Declaration of interests

J.W.D. has received research funding from BioExcel Pharma. His contribution to this study are supported, in part, by the National Institute of Aging (R13185760, R33HL23452, and R21/R33 AG05797). C.G.H. has received research funding from the National Institutes of Health (AG061161, AG053582, GM120484, and HL151951), a research grant from Kohler Chemie GMBH, and is a consultant for Sedana Medical.

References

1 Rengel KF, Boncyk CS, DiNizo D, Hughes CG. Perioperative neurocognitive disorders in adults requiring cardiac surgery: screening, prevention and maintenance. *Semin Cardiothorac Vasc Anesth*. 2022 (ahead of press Sept 22).

2 Hughes CG, Boncyk CS, Culley DJ, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus statement on postoperative delirium prevention. *Anesth Analg*. 2020;130(6):1572–1590.

3 Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. *Anesthesiology*. 2018;129(4):829–851.

4 Liu X, Xie G, Zhang K, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: a meta-analysis with trial sequential analysis of randomized controlled trials. *J Crit Care*. 2017;38:190–196.

5 Hughes C, Mailloux P, Devlin JW, et al. Dexmedetomidine vs. propofol for sedation in mechanically ventilated adults with sepsis. *N Engl J Med*. 2021;384(15):1424–1436.

6 Subramaniam B, Shankar P, Shaefi S, et al. Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: the DEXACET randomized clinical trial. *JAMA*. 2019;321(7):686–696.

7 Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet*. 2020;396(10245):177–185.

8 Qu JZ, Mueller A, McKay TB, et al. Nighttime dexmedetomidine for delirium prevention in non-mechanically ventilated patients after cardiac surgery (MINDSS): a single-centrem parallel-arm, randomized, placebo-controlled, superiority trial. *eClinical Medicine*. 2022 (in press).

9 Akeju O, Hobbs LE, Gao L, et al. Dexmedetomidine promotes biomimetic non-rapid eye movement stage 3 sleep in humans: a pilot study. *Clin Neurophysiol*. 2018;129(1):69–78.

10 Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium: a randomized, placebo-controlled trial. *Am J Respir Crit Care Med*. 2018;197(9):1147–1156.

11 Fadayomi AB, Ibala R, Bilotta F, Westover MB, Akeju OA. Systematic review and meta-analysis examining the impact of sleep disturbance on postoperative delirium. *Crit Care Med*. 2018;46(12):e1204–e1212.