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Delirium, Steroids, and Cardiac Surgery

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Delirium is common after cardiac surgery, with an incidence of up to 52%.¹ Because delirium is associated with poor postoperative outcomes, including increased mortality, morbidity, cognitive impairment and functional decline,²⁻⁵ efforts to characterize its pathophysiology and prevent and treat it are critical. Although the pathophysiology of delirium is multifactorial and still not fully understood, inflammation is potentially a key mediator of postoperative delirium.^{6,7} Corticosteroids are potent suppressors of the inflammatory response and therefore may prevent delirium; however, in the setting of critical illness, administration of corticosteroids has been associated with the onset of delirium.⁸ Thus, it is unclear whether administration of corticosteroids in the perioperative period would reduce or increase the incidence of delirium after cardiac surgery.

In this issue, Sauër et al. present the results of a randomized controlled trial evaluating intraoperative high dose dexamethasone for the reduction of delirium after cardiac surgery.⁹ This was a single-center Dutch substudy conducted within a larger multicenter randomized controlled trial evaluating the benefits versus risk of dexamethasone for attenuating cardiac

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surgery-associated inflammation. In the reported substudy, 768 patients undergoing cardiac surgery with cardiopulmonary bypass were randomized to 1mg/kg dexamethasone versus placebo at the time of anesthesia induction, with delirium subsequently assessed over the first 4 postoperative days. The authors found no significant difference between the dexamethasone and placebo groups in either delirium incidence (14.2% vs. 14.9%, respectively, $p=0.79$) or duration (median [interquartile range]; 2[1-3] vs. 2[1-2] days, $p=0.45$). Similarly, there was no difference in administration of haloperidol, benzodiazepines, or opioids, or in the use of restraints, between the 2 groups.

The size and rigor of this randomized trial are compelling. Complete data were available on 737 (96%) patients, and delirium assessments were conducted using well-validated methods, including the Confusion Assessment Method (CAM) and the CAM for the intensive care unit (ICU) (CAM-ICU). However, as the authors acknowledge, delirium episodes occurring after postoperative day 4 were not evaluated, and 7 separate research staff assessed delirium, with no report of interrater reliability statistics. Additionally, some key variables important in evaluating postoperative delirium were not collected in this trial, including baseline cognition and education; however, the effects of such unmeasured confounding are reduced by the large randomized design. Of significant interest, the incidence of delirium was only 14.5%, substantially lower than previously reported (e.g., 34%-52%^{1,10}). Even after accounting for differences in the method of delirium assessment, this unexplained difference is noteworthy and raises questions regarding the generalizability of this trial to other settings.

A key focus of this study is the hypothesis that inflammation is a pathogenic mechanism of delirium. Indeed, systemic inflammation is a prominent component of many conditions associated with delirium, including sepsis and surgery.¹¹ Systemic inflammatory signaling across the blood-brain barrier or through sensory nerves can lead to brain endothelial activation, neuronal apoptosis, and microglial activation, which can lead to neuronal toxicity.⁷ In animal models, a systemic inflammatory response from administration of lipopolysaccharide increases neuroinflammation and impairs cognitive performance.¹² However, given the relative difficulty of obtaining biological samples from the central nervous system in humans, defining the role of neuroinflammation in humans is complicated. Serum levels of proinflammatory cytokines in the periphery, such as soluble tumor necrosis factor receptor-1¹³ and interleukins-6 and 8,¹⁴ have been shown to be elevated in patients with delirium, and cerebrospinal fluid levels of inhibitors of inflammation, such as interleukin 1-receptor antagonist, have been shown to be lower in patients who subsequently develop delirium.¹⁵ Similarly, small autopsy studies examining brain histopathology have demonstrated increased markers of brain injury and inflammation in delirious versus nondelirious patients.¹⁶ Although this randomized trial shows no benefit of its corticosteroid regimen to prevent postcardiac surgery delirium, it is possible that the reduced inflammation might have been counterbalanced by a potential deliriogenic role of corticosteroids.^{8,17} Thus, other antiinflammatory interventions (e.g., statins), may still be worthy of investigation for their potential role in reducing delirium.

This trial also raises a key challenge of how best to assess postoperative delirium in perioperative delirium research. There are multiple tools at the researcher's disposal,

including the CAM¹⁸ and CAM-ICU,¹⁹ as well as the Intensive Care Delirium Screening Checklist,²⁰ Memorial Delirium Assessment Scale,²¹ and Delirium Rating Severity Scale-Revised-1998.²² However, each of these tools differs with regards to the patient population(s) in which it has been validated, its sensitivity and specificity, and the training required. For instance, the CAM-ICU is easy to administer and is both sensitive and specific in mechanically ventilated ICU patients,²³ but the sensitivity of the CAM-ICU markedly decreases in noncritically ill patient populations, such as oncology patients on the ward²⁴ or patients in the postanesthesia care unit.²⁵ Thus, it is incumbent upon the researcher to understand each diagnostic screening tool and select among them appropriately for a specific clinical study. Even within both screening tools and “gold standard” clinical psychiatric diagnosis, there are multiple ways to evaluate key criteria (such as “inattention”), varied protocols to perform the assessments, and variation in training and quality assurance testing in research staff.²⁶ Given this heterogeneity in delirium assessment, there may be variation in estimates of delirium incidence, challenging the comparability of findings across studies and calling for increased standardization in delirium assessment methods used in research.²⁶ Indeed, the larger parent trial in which this substudy was nested²⁷ defined delirium as administration of neuroleptic drugs and reported an opposite result, lower rates of delirium in the dexamethasone arm, thus highlighting the difficulty of comparing results of trials that use different delirium assessments.

Further compounding this problem, there is increasing evidence that specific characteristics of delirium, including patient predisposing factors, hospital-based precipitating factors, and delirium etiology and duration, may be associated with different clinical outcomes. For example, Gottesman et al.² demonstrated that delirium after cardiac surgery was associated with increased long-term mortality in the general cardiac surgery population; however, among the subset of “vulnerable” patients in their study (>65 years old and a history of stroke), delirium was not associated with increased mortality. Thus, patient subgroups or delirium characteristics may provide important prognostic information or identify high-risk populations for targeted interventions.

Where does this discussion leave the field of delirium research? First, it is critical that authors clearly describe how delirium assessments were conducted, not simply the delirium measure that was used. For instance, in using the CAM, key factors include the type of cognitive assessment and how CAM criteria were defined, such as inattention. Similarly, authors need to describe steps taken to ensure the quality of the delirium assessment, including details of staff training and reporting of interrater reliability results. Second, research efforts should report key data, such as predisposing and precipitating risk factors for delirium, and delirium duration and severity. Such data may have important implications for understanding the effect of the intervention on delirium, as well as consequences of the delirium. Finally, continued discussion of how to assess delirium in the research environment is needed. The recent 4th Annual Meeting of the American Delirium Society focused on this exact topic²⁸ and highlighted these challenges for delirium researchers.

Sauër et al. are to be commended for performing a large, rigorous randomized trial of corticosteroids on delirium after cardiac surgery. Their results provide compelling evidence that perioperative use of high dose dexamethasone does not prevent delirium after cardiac

surgery. Further high-quality randomized trials are needed to identify perioperative strategies to reduce postoperative delirium.

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References

1. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, Khuri SF, Lipsits LA, Ramilawi B, Levitsky S, Marcantonio ER. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009; 119(2):229–36. [PubMed: 19118253]
2. Gottesman R, Grega M, Bailey M, Pham L, Zeger S, Baumgartner W, Selnes OA, McKhann G. Delirium after coronary artery bypass graft surgery and late mortality. *Ann Neurol*. 2010; 67(3): 338–44. [PubMed: 20373345]
3. Marcantonio E. Postoperative delirium: acute change with long-term implications. *Anesth Analg*. 2011; 112(5):1202–1211. [PubMed: 21474660]
4. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SD, Jones RN. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012; 367:30–39. [PubMed: 22762316]
5. Rudolph J, Inouye S, Jones R. Delirium: An Independent Predictor of Functional Decline After Cardiac Surgery. *J Am Geriatr Soc*. 2010; 58(4):643–9. [PubMed: 20345866]
6. Inouye S, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014; 383(9920):911–22. [PubMed: 23992774]
7. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010; 119(6):737–54. [PubMed: 20309566]
8. Schreiber MP, Colantuoni E, Bienvenu OJ, Neufeld K, Chen K, Shanholtz C, Mendez-Tellez P, Needham D. Corticosteroids and Transition to Delirium in Patients With Acute Lung Injury. *Crit Care Med*. 2014; 42(6):1480–6. [PubMed: 24589640]
9. Sauër AMC, Slooer AJC, Veldhuijzen DS, van Eijk MMJ, Devlin MW. Intraoperative Dexamethasone and Delirium After Cardiac Surgery: A Randomized Clinical Trial. *Anesth Analg*. 2014 IN THIS ISSUE.
10. Maldonado J, Wysong A. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics*. 2009; 50(3):206–17. [PubMed: 19567759]
11. Gunther ML, Morandi A, Ely EW. Pathophysiology of Delirium in the Intensive Care Unit. *Crit Care Clin*. 2008; 24(1):45–65. [PubMed: 18241778]
12. Sparkman NL, Buchanan JB, Heyen JRR, Chen J, Beverly JL, Johnson RW. Interleukin-6 Facilitates Lipopolysaccharide-Induced Disruption in Working Memory and Expression of Other Proinflammatory Cytokines in Hippocampal Neuronal Cell Layers. *J Neurosci*. 2006; 26(42): 10709–16. [PubMed: 17050710]
13. Girard TD, Ware LB, Bernard GR, Pandharipande PP, Thompson JL, Shintani AK, Jackson JC, Dittus RS, Ely EW. Associations of markers of inflammation and coagulation with delirium during critical illness. *Intensive Care Med*. 2012; 38(12):1965–73. [PubMed: 22903241]
14. de Rooij SE, van Munster BC, Korevaar JC, Levi M. Cytokines and acute phase response in delirium. *J Psychosom Res*. 2007 May; 62(5):521–5. [PubMed: 17467406]
15. Westhoff D, Witlox J, Koenderman L, Kalisvaart KJ, de Jonghe JF, van Stijn MF, Houdijk AP, Hoogland IC, MacLulich AM, van Westerloo DJ, van de Beek D, Eikelenboom P, van Gool WA. Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. *J Neuroinflammation*. 2013; 10:122. [PubMed: 24093540]
16. Munster BC, Aronica E, Zwinderman AH, Eikelenboom P, Cunningham C, de Rooij SE. Neuroinflammation in Delirium: A Postmortem Case-Control Study. *Rejuvenation Res*. 2011; 14(6):615–22. [PubMed: 21978081]

17. Lewis D, Smith R. Steroid-induced Psychiatric Syndromes. *J Affect Disord.* 1983; 5:319–332. [PubMed: 6319464]
18. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990; 113(12):941–8. [PubMed: 2240918]
19. Ely E, Inouye S, Bernard G. Delirium in mechanically ventilated patients. *JAMA.* 2001; 286(21): 2703–10. [PubMed: 11730446]
20. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med.* 2001 May; 27(5):859–64. [PubMed: 11430542]
21. Breitbart WW, Rosenfeld BB, Roth AA, Smith MJM, Cohen KK, Passik SS. The Memorial Delirium Assessment Scale. *J Pain Symptom Manage.* 13(3):128–37. [PubMed: 9114631]
22. Trzepacz P, Mittal D, Torres R. Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci.* 2001; 13(2):229–42. [PubMed: 11449030]
23. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med.* 2001; 29(7):1370–9. [PubMed: 11445689]
24. Neufeld KJ, Hayat MJ, Coughlin JM, Huberman AL, Leistikow NA, Krumm SK, Needham DM. Evaluation of Two Intensive Care Delirium Screening Tools for Non-Critically Ill Hospitalized Patients. *Psychosomatics.* 2011; 52(2):133–40. [PubMed: 21397105]
25. Neufeld KJ, Leoutsakos JS, Sieber FE, Joshi D, Wanamaker BL, Rios-Robles J, Needham DM. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly. *Br J Anaesth.* 2013; 111(4):612–8. [PubMed: 23657522]
26. Neufeld KJ, Nelliott A, Inouye SK, Ely EW, Bienvenu OJ, Lee HB, Needham DM. Delirium Diagnosis Methodology Used in Research: A Survey-Based Study. *Am J Geriatr Psychiatry.* 2014 Mar 15.pii:S1064–7481. [PubMed: 24745562]
27. Dieleman JM, Nierich AP, Rosseel PM, van der Maaten JM, Hofland J, Diephuis JC, Schepp RM, Boer C, Moons KG, van Herwerden LA, Tijssen JG, Numan SC, Kalkman CJ, van Dijk D. Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative high-dose dexamethasone for cardiac surgery: a randomized controlled trial. *JAMA.* 2012 Nov 7; 308(17): 1761–7. [PubMed: 23117776]
28. Arora, R.; MacLulich, A.; Marcantonio, E.; Neufeld, K. Roundtable Discussion: Delirium Measurement. Presented at: 4th Annual Meeting of the American Delirium Society; June 3, 2014; Baltimore, MD.