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Authors
Ji, F
Li, Z
Nguyen, H
et al.

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Fuhai Ji, Zhongmin Li, Hung Nguyen, Nilas Young, Pengcai Shi, Neal Fleming and Hong Liu

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Response to Letters Regarding Article, “Perioperative Dexmedetomidine Improves Outcomes of Cardiac Surgery”

We thank Hyder and colleagues for their careful, insightful reviews and thoughtful comments on our study that demonstrated that perioperative dexmedetomidine use is associated with better outcomes after cardiac surgery.\(^1\) We reported on the impact of a dexmedetomidine infusion started in the operating room after patients were separated from cardiopulmonary bypass. Because this was a retrospective, single-center study, all of the patients in both groups were managed in a similar fashion throughout the perioperative period. Intraoperative anesthesia management was consistent among our cardiac anesthesiologists, with an institutional standard of a volatile anesthetic agent. Similarly, postoperative sedation in the intensive care unit was at the discretion of the intensive care unit care team, but the institutional protocol is infusions of fentanyl or midazolam supplemented by propofol when necessary for patient comfort. This protocol was used for patients who did not receive dexmedetomidine and those who required intubation and sedation for \(>24\) hours. We initiated the dexmedetomidine infusion at the rate of \(0.24\) to \(0.60\) g/kg per hour to minimize the potential for bradycardia or hypotension that might be associated with loading doses or higher infusion rates. Previous studies have demonstrated that, even with loading doses and higher infusion rates, bradycardia and hypotension are not significant complications in this setting.\(^2\) Our dose selection is at the lower end of the recommended range, but we found it to be very effective in this clinical setting and without apparent adverse hemodynamic adverse effects.

Xue and colleagues question how such a low-dose and short-duration dexmedetomidine infusion could possibly be associated with such significant improvement in outcomes. They comment that longer infusion durations might be more efficacious and suggest that our explanations for our results may be overreaching from the basic science observations. Although we too were struck by the results, we do not believe that it was because the patients who received dexmedetomidine were generally healthier. On the contrary, Table 1 in the original article\(^1\) indicates that they actually had more coexisting disease than the patients in the control group. Although longer infusion durations might have further improved outcomes, during the period evaluated by this study, the US Food and Drug Administration had only approved dexmedetomidine for \(<24\)-hour use. A possible explanation for the beneficial impact of early, short-term, lower-dose dexmedetomidine infusions is that the drug disrupts the earlier processes leading to postoperative myocardial infarction by activation of pro-survival kinases after cardiac \(\alpha_1\)-adrenergic receptor stimulation, as seen with studies of dexmedetomidine preconditioning and dexmedetomidine peri-insult administration.\(^3\) Dexmedetomidine inhibits mitochondrial permeability transition pore opening at the beginning of reperfusion and activates mitochondrial ATP-sensitive K\((+)\) channels before ischemia.\(^4\) In addition, it has a direct action on the myocardium to prevent an increase in myocardial norepinephrine levels in the ischemic region via cardiac presynaptic \(\alpha_1\)-adrenoreceptor stimulation. The delayed preconditioning phenomena has also been shown to provide myocardial protection for \(\leq72\) hours.\(^5\) We do not think these hypotheses represent overreaching, but rather use the results of bench research to support clinical findings. No new drugs are used in humans without preclinical bench research. By using different animal models, we are able to explore possible mechanisms of action and use those observations to further guide clinical practice. We also believe that the patient pathophysiological changes are very different during cardiac surgery with cardiopulmonary bypass as compared with noncardiac surgery.

Tripathi and colleagues noted that there was a higher rate of postoperative renal failure and dialysis requirement in patients receiving dexmedetomidine. However, there were significantly more patients with preoperative renal failure and dialysis in the dexmedetomidine group. After excluding those patients with preoperative renal failure, dexmedetomidine is actually associated with improved postoperative renal function, and these data have been submitted for further review and publication.

LaPar and colleagues pointed out that perioperative transfusion has been suggested to worsen the outcomes in cardiac surgery.\(^6\) We did not include blood and blood product transfusions in our propensity matching because there was no evidence that dexmedetomidine adversely affected coagulation. Further exploration of this association or matching for these variables may be warranted.

Hyder and colleagues comment on the odds ratios presented in Figures 2, 3, and 5 of our original article.\(^7\) We understand that there is debate regarding the merits of risk ratios (or relative risk) compared with odds ratios for the analysis and summary of trials and cohort or cross-sectional studies with common outcomes.\(^8\) In our study, the outcome measures (mortality or postoperative complications) are all rare adverse events (\(<10\)%), not common outcomes. Using odds ratio is appropriate compared with relative risk or risk ratio for relatively rare outcomes. In addition to the odds ratios, we also presented the \(95\%\) confidence interval for each point estimate of odds ratios and the \(P\) values for indicating statistical significance to better characterize these results.

As many of the commentators noted, we are fully aware of the limits of retrospective studies. There are many known and unknown variables that could influence our observations. A robust statistical analysis was used to minimize the selection bias. For example, we took into consideration the cardiopulmonary bypass time, aortic cross-clamping time, and intra-aortic balloon pump use in adjusting our results (please see the Methods section on pp. 1577 and 1578 and the legend of Figure 3, p. 1581)\(^9\) Still, we share the commentators’ concerns regarding the interpretation of the results. We agree that association does not prove a causal relationship. We repeatedly stated that perioperative dexmedetomidine use was “associated with” a decrease in postoperative mortality \(\leq1\) year and decreased incidence of postoperative complications and delirium in patients undergoing cardiac surgery. We stated in our conclusion that a prospective, multicenter, randomized study focused on the use of dexmedetomidine in cardiac surgery patients is indicated to confirm these findings.\(^1\) Despite the limitations of this study, we strongly believe that the improved outcomes associated with perioperative dexmedetomidine use suggest that it could potentially be beneficial to patients undergoing open heart surgery.

Disclosures

None.

Fuhai Ji, MD
Department of Anesthesiology and Pain Medicine
University of California Davis Health System
Davis, CA

Zhongmin Li, PhD
Department of Internal Medicine
University of California Davis Health System
Davis, CA

Hung Nguyen, MD
Department of Anesthesiology and Critical Care
University of California San Francisco Health System
San Francisco, CA
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