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RESPONSE TO LETTER

Bradycardia in Ophthalmic Surgery: A Care-Bundle, Not Drug-to-Drug, Comparison [Response to Letter]

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Dear editor

We thank Lin et al[1] for their insightful comments on our article.[2] We appreciate the opportunity to clarify key aspects of our study design and interpretation.

Clarifying the Research Question: Intraoperative NMBA Effects, Not Reversal Regimens

Lin et al raised a valid point regarding the timing of reversal agents. We agree that reversal agents are administered at the end of anesthesia; however, our study was designed to investigate intraoperative bradycardia. As defined in our Methods section (Objectives and Outcomes), the primary outcome was "bradycardia during surgical manipulation" an event occurring while rocuronium or cisatracurium was actively providing neuromuscular blockade, and significantly before the administration of corresponding reversal agents. Therefore, the observed difference in bradycardia rates reflects the pharmacological properties of the NMBAs (vagolytic effect of rocuronium) rather than the reversal agents. Our title—"Comparison of Rocuronium and Cisatracurium"—further emphasizes that our research question focused on intraoperative NMBA effects, not reversal regimens.[2]

Regarding the "Care Bundle" and Multivariate Analysis

We reported higher BIS monitoring utilization in the rocuronium group. The rocuronium group was associated with lower opioid and sevoflurane consumption. We acknowledged these interconnections in our original Discussion,[2] noting outcomes might be influenced by "collective effect of multiple factors." The "care bundle" concept proposed by the critics essentially reiterates our own observations regarding these concurrent anesthetic adjustments. It is also worth clarifying the clinical context of the "self-pay" aspect mentioned by the critics. Our department is deeply committed to anesthesia safety and operates a dedicated pre-anesthesia assessment clinic where we employ shared decision making. It is crucial to emphasize that we do not offer a rigid "combined regimen" or mandatory package. Instead, patients are empowered to make independent, uncoerced choices regarding each individual option (eg, selecting rocuronium-sugammadex and/or BIS monitoring separately) based on their own values. As this is a retrospective study based on real-world data, the observed grouping reflects the natural aggregation of these autonomous patient decisions rather than a pre-assigned "bundle" by the hospital. However, the scientific question remains: which component drives the outcome? Our multivariate analysis is instructive: BIS lost its significance while rocuronium remained highly significant. If BIS were the primary driver, we would expect BIS to retain significance or the NMBA effect to diminish. The opposite occurred. It is important to note that clinically, the primary utility of BIS monitoring is to prevent unnecessarily deep

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anesthesia. While anesthetic depth modulates autonomic reflexes, this influence on the cardiovascular system is indirect. In contrast, rocuronium exerts a direct pharmacological vagolytic effect on cardiac muscarinic receptors. Our multivariate findings align with this biological distinction: the direct pharmacological protection provided by rocuronium outweighed the indirect contribution of monitoring-guided titration. The remarkable consistency between univariate and multivariate estimates demonstrates model stability. Our model appropriately adjusted for BIS as a confounder, revealing rocuronium as the dominant independent predictor.

Regarding Statistical Power and Events Per Variable (EPV)

We acknowledge the valid concerns regarding sample size and the Events Per Variable (EPV) ratio. While the traditional 10 EPV rule is a common guideline, contemporary methodological studies[3,4] suggest that logistic regression models can yield reliable estimates with lower EPV ratios, particularly when associations are strong. Furthermore, our model included granular adjustments for sevoflurane ($mL \cdot h^{-1}$) and opioid consumption (morphine milligram equivalents)—critical physiological determinants that have not been simultaneously adjusted for in previous models. Unlike prior studies that often treated various opioid use as a binary variable (yes/no) or did not account for volatile agent consumption, our model incorporated these as continuous variables. This granular anesthetic adjustment strengthens confidence that observed effects reflect true NMBA pharmacology rather than unmeasured confounding. As already emphasized in our Discussion, we recognize the inherent limitations of this retrospective design and agree that larger prospective trials are needed for confirmation. We sincerely apologize for the typographical error in the manuscript. The correct values are OR 0.08 (95% CI: 0.02–0.29), $p<0.001$, as shown in Table 4. A formal correction has been requested.

Regarding Extubation Time

Standard anesthesia record-keeping worldwide employs 5-minute intervals, creating an inherent ceiling effect that masks pharmacological differences <5 minutes. This limitation reflects a fundamental constraint of retrospective anesthesia research globally, not unique to our institution. More importantly, comparable extubation times attest to high-standard neuromuscular management in both groups, strictly adhering to ESAIC and ASA guidelines.[5,6] The absence of significant differences in extubation time demonstrates that both groups received high-quality neuromuscular management. Significantly prolonged recovery is typically observed only when neostigmine timing is suboptimal or reversal is attempted at inappropriate blockade depths. This finding supports our hypothesis: when both strategies are executed optimally, the intraoperative bradycardia difference persists, suggesting protection stems from rocuronium's intraoperative vagolytic properties during manipulation, not workflow factors.

Conclusion

We thank Lin et al for sharing their perspective.[1] While we acknowledge their interpretation regarding the "care bundle" concept, we wish to emphasize that our study was explicitly designed to compare intraoperative NMBA effects during active neuromuscular blockade, as clearly stated in our title, methods, and primary outcome definition.

Author Contributions

All authors contributed to conception, analysis, and interpretation; participated in drafting and revising; approved the final version; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this communication.

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