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LETTER

Beyond Opioid Comparison: Interpreting Oliceridine in Contemporary Thoracic Recovery Pathways [Letter]

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Dear editor

We read with interest the randomized double-blind trial by Hu et al comparing perioperative oliceridine with sufentanil in patients undergoing thoracoscopic lobectomy.[1] The study addresses a clinically relevant question. An opioid that can preserve analgesia while reducing opioid-related adverse effects would be of clear interest in thoracic surgery. The authors report lower rates of postoperative nausea and vomiting and respiratory depression with oliceridine, despite similar analgesic outcomes. These findings are encouraging, but several aspects of the study design and interpretation deserve closer attention.

A first issue is the choice of comparator. In current thoracic enhanced recovery practice, analgesia is increasingly built around multimodal and opioid-sparing strategies, often including regional techniques such as thoracic paravertebral block or erector spinae plane block.[2] Against that background, showing benefit over a sufentanil-based anesthetic and intravenous analgesia regimen does not necessarily establish an advantage over contemporary thoracic perioperative care. A more informative design would have compared oliceridine-based management with a modern multimodal pathway, or examined whether oliceridine adds value when used within such a pathway rather than simply replacing one systemic opioid with another.

The reduction in respiratory depression should also be interpreted with caution. In this study, respiratory depression was defined by oxygen saturation below 90% or respiratory rate below 8 breaths per minute, with continuous pulse oximetry and intermittent ward assessment. That approach may miss a meaningful proportion of postoperative respiratory events. Pulse oximetry is an imperfect marker of hypoventilation, especially when supplemental oxygen is used, and intermittent bedside observation can easily overlook transient episodes of opioid-induced respiratory depression. Continuous capnography and oximetry have been shown to detect more events than routine clinical monitoring alone.[3] For that reason, the apparent respiratory safety advantage of oliceridine may be more difficult to quantify with confidence than the authors suggest.

Another concern is the handling of post-randomization exclusions. Although 177 patients were randomized, only 166 were included in the final analysis. When patients are excluded after randomization, the balance created by random allocation can be weakened, particularly in a trial of this size. Unless a clearly prespecified intention-to-treat analysis is presented, the possibility of attrition bias remains.[4,5] Reporting both intention-to-treat and per-protocol results, together with sensitivity analyses for missing data, would make the findings more robust.

The study population also appears narrower than the group in whom oliceridine's putative benefits may be most relevant. Patients with body mass index above 28 kg/m^2 and those with moderate-to-severe sleep apnea were excluded. Yet these are precisely the types of patients in whom concern about opioid-related respiratory complications is often greatest. As a result, the external validity of the study is somewhat limited. Prior analyses of oliceridine have specifically explored outcomes in older or higher-BMI patients,[6] and future thoracic trials would be more clinically useful if they deliberately included such higher-risk groups.

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A final point is the absence of consideration of pharmacokinetic variability. Oliceridine is metabolized mainly via CYP3A4 and CYP2D6, and reduced CYP2D6 activity may increase systemic exposure.[7] In a relatively small study, unmeasured interindividual differences in drug metabolism could influence both efficacy and adverse effects, including sedation, respiratory depression, and quality of recovery. Some acknowledgment of this source of variability, or ideally incorporation of pharmacokinetic or genotype-informed analyses in future work, would help clarify whether the reported advantages reflect the drug's intrinsic pharmacology, differences in exposure, or both.

These points should not detract from the value of the study. The trial offers useful early data suggesting that perioperative oliceridine may have a role in thoracic surgery. At the same time, broader adoption will require confirmation in larger multicenter studies, conducted in more representative patient populations and benchmarked against current multimodal thoracic analgesic pathways.

Disclosure

The authors report no conflicts of interest in this communication.

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