Comments on "Effect of Continuous Infusion of Intravenous Nefopam on Postoperative Opioid Consumption After Video-assisted Thoracic Surgery: A Double-blind Randomized Controlled Trial"

To the Editor:

In a double-blinded randomized, controlled study with 90 patients undergoing video-assisted thoracic surgery, Yoon et al (1) assessed effects of perioperative nefopam infusion on postoperative opioid consumption and pain control. They showed that perioperative nefopam infusion provided a significant opioid-sparing effect and an improved pain control during coughing at 24 hours postoperatively, without significant between-group differences in postoperative quality of recovery, length of hospital stay and the occurrence of analgesic-related side effects. However, there were several questions in this study that we wished to get further clarifications and authors' reply.

First, 41 patients in the control group were included in the intention to treat analysis for postoperative 24 hours, but only 30 were included in intention to treat analysis for postoperative 48 hours, with a drop-out rate of up to 26.8% which is significantly larger than the allowed range of study design (15%). In contrast, the drop-out rate of patients in the treatment group for intention to treat analysis within 48 hours postoperatively was 9.5% (4/42), which is within the allowed range of study design. We are concerned that significant between-group imbalance in drop-out rate of patients would have biased their findings at 48 hours postoperatively and partly contributed to insufficient power to determine the significant between-group differences in the postoperative outcomes (2).

Second, when intravenous infusion of nefopam was used for postoperative multimodal analgesia, only patients with pain scores of ≥ 7 on a 0-10 point Numeric Rating Scale (NRS) was allowed to administer intravenous fentanyl 50 μg as first-line rescue analgesia. We noted that median NRS rest pain scores at postoperative 24 hours were 3 or more and even median NRS pain scores during coughing at postoperative 24 hours were 5 or more in 2 groups, with large interquartile ranges of 2 to 8. These results indicate that a significant proportion of patients experienced moderate to severe pain after thoracic surgery, especially for movement-evoked pain. This is evidently is not conducive to the postoperative recovery of patients and is unacceptable in the current practice of ERAS, which requires that analgesics should be universally titrated to achieve patient comfort and minimal pain (i.e., a pain score of 3 or less on a 0-10 point NRS) (3). Thus, an important question that this study cannot answer is whether perioperative nefopam infusion can also produce a significant opioid sparing when adequate postoperative pain control with an NRS pain score of 3 or less is required in patients undergoing video-assisted thoracic surgery.

Third, patients receiving perioperative nefopam infusion compared with control patients had a significantly decreased NRS pain score during coughing at 24 hours postoperatively, with a median difference of -1 (95% CI: -2.5 to 0, $P = 0.040$). We would like to remind the readers and authors that the recommended minimal clinically important difference required in a randomized clinical trial assessing postoperative acute pain control is 1.5 reduction of pain score on a 0-10 point NRS (4). Furthermore, the authors did not compare between-group difference in patients' satisfaction with postoperative analgesia. Thus, we argue that improvement of movement pain control by perioperative nefopam infusion at 24 hours postoperatively is statistically significant, but its real clinical value for patients undergoing video-assisted thoracic surgery is debatable.

Finally, in the method, the authors described that patients with postoperative nausea and vomiting were administered intravenous ketorolac 30 mg as an alternative rescue analgesic. In the results, however, the readers were not provided the use of ketorolac for rescue analgesia. If this drug was applied in any patient, we believed that its dosage should be converted into morphine equivalents and added to postoperative opioid consumptions, as performed in other work (5). Based on previously published conversion factors, intravenous fentanyl 100 μg is equivalent to intravenous morphine 10 mg or intravenous ketorolac 30 mg (6). Thus, we consider that this unknown factor would have confounded the findings regarding the between-group comparisons of interval and cumulative postoperative opioid consumptions in the current study.

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