Letter to the Editor Regarding “Preemptive Intravenous Nalbuphine for the Treatment of Post-Operative Visceral Pain: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Trial”

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Key Summary Points

This letter was written in response to the recent article by Liu et al “Preemptive Intravenous Nalbuphine for the Treatment of Post-Operative Visceral Pain: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Trial”, in which preemptive intravenous nalbuphine at a dose of 0.2 mg kg⁻¹ was shown to significantly decrease visceral pain and rescue analgesic use in the first 24 h after laparoscopic cholecystectomy.

This letter pointed out severe issues in the method and results of this randomized controlled trial, including unsatisfied report of sample size calculation, uncertain clinical significance of improved postoperative pain control, incomplete comparison of rescue analgesic needs, the lack of assessment on postoperative clinical outcome of patients and others.

This letter questioned the clinical significance of the main findings in this study that preemptive intravenous nalbuphine significantly decreased visceral pain and rescue analgesic use in the postoperative first 24 h.

This letter emphasizes the recommended method in available literature to compare the rescue analgesic use after surgery.

The authors believe that clarification of these issues would improve the transparency of this study and help the interpretation of the main findings.

Re: Liu X, et al. Preemptive Intravenous Nalbuphine for the Treatment of Post-Operative Visceral Pain: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Pain Ther. 2021; 10(2):1155-69.

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TO THE EDITOR,

By a multicenter, double-blind, placebo-controlled, randomized clinical trial including 2094
patients who underwent elective laparoscopic cholecystectomy, Liu et al. [1] showed that preemptive intravenous nalbuphine at a dose of 0.2 mg kg\(^{-1}\) significantly decreased visceral pain and rescue analgesic use in the first 24 h after surgery. A valuable clinical study has been carried out, but there are several issues in the method and results of this study that deserve further clarification and discussion.

First, in statistical analysis, the authors described that sample size calculation of this study was based on their preliminary study on 40 patients. However, the readers were not provided with the main results of their preliminary study, such as mean and standard deviation of primary outcome (postoperative visceral pain score), and difference of primary outcome between groups, though these results are the essential components for a good report of sample size calculation in the randomized controlled trial [2]. Furthermore, a sample size evaluation of 860 per arm in this study was declared to detect a difference of 0.3 points on a 0–10 Visual Analog Scale (VAS) pain score for visceral pain at rest state. In the available literature, however, the recommended minimal clinically important improvement or deterioration of pain control is a change of 1.0 point for the 0–10 VAS pain score [3]. Given the facts that the main results of their preliminary study are not provided and a small predicted between-group difference of postoperative visceral pain score without clinical significance is used, we questioned the validity of sample size calculation in this study.

Second, a VAS score of 3 or less is generally considered as satisfied postoperative pain control [4]. According to the results provided in the Fig. 2 of Liu et al.’s article [1], besides the visceral pain scores with movement at 4 (T3), 8 (T4), and 12 (T5) hours after surgery were slightly more than 3, the means of incisional and visceral pain VAS scores at rest state and with movement in other time points within the postoperative first 24 h were less than 3. Even the means of shoulder pain (referred pain component) VAS scores at all time points in the two groups were less than 0.5. These results indicate that most of the patients have a satisfied postoperative pain control, without obvious discomfort. Furthermore, the between-group differences of postoperative incisional and visceral pain scores were less than 1, which are significantly lower than the recommended minimal clinically important differences of postoperative pain score [3]. Most important, patients’ satisfaction levels with postoperative analgesia were not significantly different between the groups. In this case, it is very difficult for readers to determine whether the improvement of early postoperative analgesia provided by preemptive intravenous nalbuphine should be considered as being clinically important.

Third, sufentanil 5\(\mu\)g was administered as rescue analgesic at the request of the patient and when postoperative pain VAS was 4 or more. Furthermore, the cumulative number of rescue analgesic needs during the postoperative first 24 h was significantly reduced in the nalbuphine group compared with control group. In a clinical trial, however, it is commonly required that total analgesic use for postoperative pain control should be converted into milligram morphine equivalent (MME) for statistical comparison and the recommended minimal clinically important difference of MME is an absolute reduction of 10 mg intravenous morphine in the 24 h [3]. As the authors did not provide the absolute differences of MME between groups, we argue that the clinical significance of postoperative opioid sparing by preemptive intravenous nalbuphine in this study should be interpreted with caution.

Finally, this study showed that preemptive intravenous nalbuphine improved the quality of sleep on the night of surgery and reduced the occurrence of postoperative nausea and vomiting. However, the authors did not assess and compare the quality of postoperative recovery and clinical outcomes of patients, as performed in other studies comparing analgesic efficacy of different techniques after laparoscopic cholecystectomy [5, 6]. In fact, these variables are very important for determining efficacy and clinical availability of an intervention. Especially, the quality of postoperative recovery is very easily measured by the quality of recovery 15 score, which includes 15 questions about
various clinically relevant domains of postoperative recovery, such as sleep quality, pain, general well-being, mood, and nausea and vomiting. The scoring value of each question is 10, with a maximum score of 150 [7]. In available literature, an absolute difference of 8 points in the quality of recovery 15 scores between groups is recommended as the minimal clinically important difference [8]. Because of this design limitation, it is unclear whether improvement of both visceral pain control and sleep quality by preemptive intravenous nalbuphine can be translated into the beneficial clinical outcomes of patients, such as improved quality of early postoperative recovery, reduced times to patient mobilization and start of oral intake, shortened length of ICU or hospital stay, and others.

**Declarations**

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**Authorship** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Author Contributions** All authors carefully read the manuscript by Liu et al., and reviewed their methods and data. Hong Tan suggested comment points and drafted the manuscript. Fu-Shan Xue and Cheng-Wen Li revised the comment points and manuscript. All authors have read and approved the final manuscript.

**Disclosures** Hong Tan, Fu-Shan Xue, and Cheng-Wen Li have nothing to disclose.

**Compliance with Ethics Guidelines** This article is based on a previously conducted study and does not contain any study with human participants or animals performed by any of the authors.

**Data Availability** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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