



A Response to: 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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Dear Editor,

We are very glad that Dr. Tan and his colleagues have noticed our work [1] and raised several important issues regarding sample size calculation. Since the sample size calculation for repeated measurement requires the specifications of the assumed variance and correlation pattern between repeated measurements [2]. In our preliminary study of 40 patients, the overall means of pain score at eight time points within 24 h postoperatively were 1.7 and 1.4 in two groups. Therefore, the calculation was performed with the standard deviation assumed as 2, and the correlation between observations on the same subject assumed as 0.7 with the compound symmetry covariance structure using PASS software according the tests for two means

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in a repeated measures design. Based on our results, the difference of 0.3 point has already shown the identified clinical effects.

The overall postoperative analgesic effect of nalbuphine in patients undergoing laparoscopic cholecystectomy was not overstated. Based on the results, we prudently described the conclusion as nalbuphine administration at a dose of $0.2 \text{ mg} \cdot \text{kg}^{-1}$ was safe, and efficiently reduced both early visceral pain and supplemental analgesic use in patients underwent laparoscopic cholecystectomy. It also achieved a better visceral pain relief for patients with symptomatic gallbladder disease longer than 6 months. However, there was no treatment effect in nalbuphine group for the incisional pain at either rest or movement, and shoulder pain compared with control group. Therefore, preemptive intravenous nalbuphine should be differentiated according to the patient's conditions. It may be a good choice for patients with a long term gallbladder disease who is more vulnerable to visceral pain.

Milligram morphine equivalent (MME) is not necessary for postoperative sufentanil consumption [3], although many studies reported the total analgesic with conversion into MME for a variety of different postoperative analgesics [4]. In our study, sufentanil was used as the only rescue analgesic, which could directly indicate the effect of pain control. Regarding to the opioid sparing effect, this was not the purpose of our study since nalbuphine itself is an agonist–antagonist opioid [5].

The main purpose of our special article was to investigate the efficacy and safety of preemptive nalbuphine on the visceral pain for patients after cholecystectomy. The amelioration of visceral pain at first 8 h after surgery in Fig. 2 appeared sufficient to support the main aim of this report. Several studies related to post-operative visceral pain have been limited methodologically and underpowered, without ultimately addressing factors and mechanisms responsible for the visceral pain in laparoscopic cholecystectomy [6].

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Disclosures. Xiaofen Liu, Jun Hu and Ye Zhang have nothing to disclose.

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

Data Availability. All the extra data presented are available from the corresponding author on reasonable request.

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