



LETTER

# Letter to the Editor regarding “Influences of Gender on Intravenous Nalbuphine Actions After Major Abdominal Surgery: A Multicenter Study”

Fu S. Xue · Cheng W. Li · Liu J. Z. Shao

Received: June 12, 2021 / Accepted: August 6, 2021 / Published online: August 24, 2021  
© The Author(s) 2021

## Key Summary Points

This letter is written in response to the article, “Influences of Gender on Intravenous Nalbuphine Actions After Major Abdominal Surgery: A Multicenter Study,” in which female patients were demonstrated to be statistically more responsive than male patients to the postoperative analgesic effects of intravenous nalbuphine.

The main finding of this study is the well-established clinical fact that kappa opioid nalbuphine can produce gender-dependent analgesia and antianalgesia in patients with postoperative pain.

This letter also points out severe issues in this study that might have confounded interpretation of the results, such as the inclusion of different types of surgeries, the existence of possible factors influencing postoperative pain assessment, expression and comparison of results, power of the sample size, and others.

The authors argue that addressing these issues would improve the transparency of this study.

F. S. Xue (✉) · C. W. Li · L. J. Z. Shao  
Department of Anesthesiology, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong-An Road, Xi-Cheng District, Beijing 100050, People's Republic of China  
e-mail: xuefushan@aliyun.com

To the Editor,

In a randomized double-blind comparative trial including 64 male and 63 female patients undergoing major abdominal surgery, Ayad et al. [1] evaluated the influences of gender on postoperative analgesic efficacy of continuous intravenous nalbuphine with two different dosages. They showed that females were more sensitive than males to the analgesic effects of nalbuphine. In fact, that the kappa opioid nalbuphine can produce gender-dependent analgesia and antianalgesia in patients with postoperative pain is a well-established clinical finding [2]. Furthermore, we noted several issues in this study that would have made the interpretation of their results questionable. We wish to invite the authors to comment.

First, this is a randomized controlled trial with a small sample; each arm only includes 31–32 patients. All patients underwent major abdominal surgery, but at least seven types of operations were performed, including hernia repair, urological, gastric, colorectal, hepatobiliary/pancreatic, small bowel, and splenectomy/omental procedures. Because the severity of postoperative pain is mainly dependent on the type and site of surgery [3], the inclusion of different types of surgeries is undoubtedly an important confounding factor that can affect postoperative pain assessment. To avoid this issue, a better study design would comprise patients undergoing a single type of abdominal surgery as study objects, as performed in previous work [4].

Second, according to their Figs. 2 and 3, female as compared to male patients had lower pain scores at some observed time points. However, we noted that with two different dosages of intravenous nalbuphine, intra-group differences in pain scores were very small at all postoperative observed time points. As the standard deviations of postoperative pain scores were not provided, we cannot exclude the possibility that a great individual difference would have contributed to their findings. Most importantly, it was unclear whether patients were at the same state or position when postoperative pain was assessed. It is generally believed that both activity state and supine position can aggravate pain intensity after major abdominal surgery, especially for patients undergoing upper abdominal surgery [5]. We argue that these unknown factors would have further biased their findings.

Third, in this study, the total nalbuphine consumption (in mg) throughout the study was significantly higher in males compared to females, with mean intra-group dosage differences of 1.88–4.19 mg at two different dosages. However, the mean or median weight was greater in males than in females. We suggest that total nalbuphine consumption dose throughout the study is best calculated according to the body weight of patients and then compared between males and females, as previously reported [6]. We would further like to know whether females still had significantly decreased total nalbuphine dose consumption when expressed per kilogram of body weight.

Finally, in this study, there were no statistical gender differences in adverse events associated with the nalbuphine 2 mg administration. However, the sample size of this study was evaluated based on the possible difference in the mean change in the numeric pain rating score between females and males during the measurement periods. Thus, it may be underpowered to show the differences in the occurrence of most postoperative adverse events associated with nalbuphine administration between male and female patients. To determine the real influences of gender on the occurrence of adverse events associated with nalbuphine administration, we believe that

randomized controlled trials with large samples are still needed.

## ACKNOWLEDGEMENTS

**Funding.** No funding or sponsorship was received for this study or publication of this article.

**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 Ayad et al., and reviewed their methods and data. Fu-Shan Xue suggested comment points and drafted the manuscript. Cheng-Wen Li and Liu-Jia-Zi Shao revised the comment points and the manuscript. All authors have read and approved the final manuscript.

**Disclosures.** Fu-Shan Xue, Cheng-Wen Li and Liu-Jia-Zi Shao declare that they have no conflict of interest.

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

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

**Open Access.** This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or

other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

## REFERENCES

1. Ayad AE, Salman OH, Ibrahim AMF, et al. Influences of gender on intravenous nalbuphine actions after major abdominal surgery: a multicenter study. *Pain Ther*. 2021. <https://doi.org/10.1007/s40122-021-00277-6>.
2. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. The kappa opioid nalbuphine produces gender- and dose-dependent analgesia and antianalgesia in patients with postoperative pain. *Pain*. 1999;83(2):339–45.
3. Gerbershagen HJ, Pogatzki-Zahn E, Aduckathil S, et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology*. 2014;120(5):1237–45.
4. Marcotte JH, Patel KM, Gaughan JP, Dy J, Kwiatt ME, McClane SJ, Desai RG. Oral versus intravenous acetaminophen within an enhanced recovery after surgery protocol in colorectal surgery. *Pain Physician*. 2020;23(1):57–64.
5. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. *Curr Med Res Opin*. 2014;30(1):149–60.
6. Andrieu G, Amrouni H, Robin E, et al. Analgesic efficacy of bilateral superficial cervical plexus block administered before thyroid surgery under general anaesthesia. *Br J Anaesth*. 2007;99(4):561–6.