




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

Amany E. Ayad · Ossama H. Salman · Ahmed Mokhtar Fathy Ibrahim ·
Waleed A. M. Al-Taher · Adel M. Mishriky · Joseph V. Pergolizzi ·
Omar Viswanath · Ivan Urits · Martina Rekatsina · John F. Peppin ·
Antonella Paladini · Giustino Varrassi 

Received: July 26, 2021 / Accepted: August 6, 2021 / Published online: August 24, 2021
© The Author(s) 2021

To the Editor,

Thank you for informing us about the letter criticizing our recently published research results [1]. Also, we would like to thank Professor F.S. Xue and colleagues for their kind comments about the publication. Their observations

have prompted us to further clarify some aspects of the protocol we used for the research.

In relation to their *first comment*, we fully agree that the inclusion of a larger sample and only one kind of abdominal surgery probably would have prevented criticism, but they were not scientifically necessary. In fact, we studied the statistical power of our study, as described in the “Methods” section and based on the

A. E. Ayad
Department of Anesthesia ICU and Pain, Cairo
University, Cairo 11566, Egypt

O. H. Salman
Department of Anesthesiology, South Valley
University, Qena 83511, Egypt

A. M. F. Ibrahim
Department of Anesthesiology, Assiut University,
Assiut 71515, Egypt

W. A. M. Al-Taher
Department of Anesthesiology, Ain Shams
University, Cairo 11566, Egypt

A. M. Mishriky
Department of Community Medicine, Suez Canal
University, Ismailia 41511, Egypt

J. V. Pergolizzi
NEMA Research Group, Research and Development,
Naples, FL 34101, USA

O. Viswanath
Department of Anesthesiology, University of
Arizona, Phoenix, AZ 85003, USA

I. Urits
Department of Anesthesia, Critical Care and Pain
Medicine, Beth Israel Deaconess Medical Center,
Harvard Medical School, Boston, MS, USA

M. Rekatsina
Whipps Cross Hospital, Barts Health NHS Trust,
London, UK

J. F. Peppin
College of Osteopathic Medicine, Pikeville
University, c, KT, USA

A. Paladini
Department of MESVA, University of L'Aquila,
67100 L'Aquila, Italy

G. Varrassi (✉)
Paolo Procacci Foundation, 00193 Rome, Italy
e-mail: giuvarr@gmail.com

existing literature, and found it to be sufficient for the protocol used to achieve the main objectives of the study. All studied patients were subjected to major abdominal surgery with the same kind of trauma, resulting in both somatic and visceral nociceptive pain. We purposely excluded patients who underwent gender-related operations (hysterectomy or prostatectomy). Therefore, we believe that our list of surgical interventions led to a homogeneous group of studied patients who were selected based on the included nociceptive stimulus type. Maybe one kind of surgery would have been ideal; however, while preparing the protocol, the feasibility of this was analyzed, and we found that we would have had to double the time needed to collect the required number of patients at each of the participating centers, and it is unlikely that doing so would have significantly improved the statistical power of our results. We also excluded surgeries that lasted less than two or more than four hours because we wanted to include patients with a certain degree of trauma. The duration of surgery commonly reflects the degree of trauma and manipulation. Moreover, all patients were operated on by the same surgeons at the same centers. In our opinion, this prevents any criticism relating to potential differences in the surgical skills of different surgeons. Hence, from our perspective, surgical factors were controlled and scientifically correct.

In relation to the *second comment*, we used nonparametric statistical tests for comparisons. These tests analyze significant differences considering any lack of normal distribution deduced from large standard deviations.

However, for the benefit of the readers, Tables 1 and 2 of this reply list the data already presented in Figs. 2 and 3 of the publication of interest [1], with standard deviations included.

In relation to patient position during the pain evaluation, we agree that pain scores at rest and during movement are different. When presenting a study of the trauma caused by major abdominal surgery, one could argue that it is important to state whether pain was evaluated before or after meals, considering the effect of the gastrocolic reflex. Also, given the possible use of patient-controlled analgesia (PCA) shots when patients feel pain, one could question whether pain was measured before or minutes after a bolus, etc. However, stating all of these data would have led to the presentation of redundant and confounding tables for each item. Hence, we decided to present the average pain score in the last three hours for simplicity and clarity. This was a single score rated by the patient and based on his or her own average. Like any score, it may be criticized, but it is simple and easily understandable.

The *third comment* is also very interesting. Although nalbuphine is an old drug, because of its history it is not well studied, especially in relation to the dose adjustment required due to obesity [2]. It is known to have comparable water solubility to morphine [3], so we assumed that it behaves mostly like morphine (the literature is not completely in agreement about this). It is common practice not to adjust the morphine dose for body weight, as it is the lean body weight, not the total body weight, that is relevant to drug clearance. Hence, the body mass index (BMI) is a better parameter, which is

Table 1 Numerical Pain Rating scores (mean \pm SD)

	Time (h)				
	0	3	6	9	12
A1	6.3 \pm 3.1	4.6 \pm 1.6	3.0 \pm 1.0	2.2 \pm 0.9	1.8 \pm 0.8
A2	7.6 \pm 2.6	4.3 \pm 1.4	2.5 \pm 1.2	1.7 \pm 0.8	1.2 \pm 0.8
B1	6.4 \pm 3.1	4.9 \pm 2.3	3.5 \pm 1.7	2.3 \pm 1.2	1.6 \pm 1.0
B2	8.1 \pm 1.3	5.5 \pm 1.0	3.2 \pm 0.7	2.1 \pm 0.9	1.4 \pm 0.5

Table 2 Total doses of nalbuphine rescue medication (mg) administered throughout the study (mean \pm SD)

	Time (h)			
	3	6	9	12
A1	4.1 \pm 3.5	1.5 \pm 1.2	0.4 \pm 0.8	0.3 \pm 0.7
A2	3.7 \pm 2.1	0.6 \pm 0.6	0.2 \pm 0.4	0.1 \pm 0.4
B1	3.8 \pm 2.5	2.4 \pm 2.1	0.8 \pm 1.0	0.6 \pm 1.3
B2	3.4 \pm 1.4	1.2 \pm 0.8	0.2 \pm 0.5	0.0 \pm 0.0

why it is presented in Ayad et al. [1] in addition to body weight. Also, other researchers found that patients with different body weights who were administered fixed doses of parenteral morphine did not show any differences in analgesic response [4]. Other comprehensive reviews of opioid dose adjustment in obese patients note the dilemma that dose adjustment for weight carries a risk of overdose but the administration of a fixed dose could cause a lack of analgesia [5, 6]. Since we had PCA pumps, we decided to adopt the safest basic dosage, and the analgesic needs of the patients would have been satisfied by the PCA boluses, which are an optimal solution for this purpose [7]. Moreover, lots of medical facilities adopt a policy of not adjusting PCA opioid doses for weight, including our hospitals. Using a research protocol close to our standard protocol increased safety and facilitated the implementation of our study protocol in our hospital settings.

Finally, regarding the *fourth comment*, which related to adverse events (AEs), the AEs associated with nalbuphine are slightly different from those associated with other μ -opioid receptor (MOR) agonists, as nalbuphine is a κ -receptor agonist and a partial MOR antagonist. The AEs registered in the study of Ayad et al. [1] reflect this difference, with more sedation, nausea, and vomiting events but much less respiratory depression and pruritus observed [8]. Although this study was not sufficiently powered to quantitatively assess any single type of AE, there was a significant higher incidence of AEs—mostly sedation, nausea, and vomiting—in females, as reported in Table 3 of Ayad et al. [1],

which is in agreement with the side effects most commonly encountered with nalbuphine use [8]. In our study, this gender difference was clinically noticed for a dose of 2 mg/h and both clinically and statistically noticed for a dose of 1 mg/h. However, we agree with the assertion of our esteemed colleagues that larger randomized controlled studies would be necessary to confirm our conclusion.

We deeply thank our colleagues for allowing us to clarify some aspects of our publication, and would welcome any other criticism.

Sincerely yours.

ACKNOWLEDGEMENTS

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

Medical Writing Assistance. The preparation of this letter was possible thanks to the support of the Paolo Procacci Foundation, who funded the medical writing, provided by Mrs Jo Ann LeQuang, a freelance medical writer.

Authorship. All named authors are equally responsible for the preparation. All of them 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, have reviewed the final text and approved it for the publication.

Disclosures. Amany E. Ayad, Ossama H. Salman, Ahmed Mokhtar Fathy Ibrahim, Waleed A. M. Al-Taher, Adel M. Mishriky, Joseph V. Pergolizzi, Omar Viswanath, Ivan Urits, Martina Rekatsina, John F. Peppin, Antonella Paladini and Giustino Varrassi declare they have no potential conflict of interest.

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 on reasonable request.

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, Al-Taher WAM, Mishriky AM, Pergolizzi JV, Viswanath O, Urits I, Rekatsina M, Peppin JF, Paladini A, Varrassi G. 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. Schmidt WK, Tam SW, Sholtzberger GS, Smith DH, Clark R, Vernier VG. Nalbuphine. *Drug Alcohol Depend.* 1985;14(3–4):339–62. [https://doi.org/10.1016/0376-871\(85\)90068-3](https://doi.org/10.1016/0376-871(85)90068-3).
3. Arnould JF, Pinaud M. Pharmacology of nalbuphine. *Ann Fr Anesth Reanim.* 1992;11(2):221–8. [https://doi.org/10.1016/S0750-7658\(05\)80018-8](https://doi.org/10.1016/S0750-7658(05)80018-8).
4. Patawanla AE, Holmes KL, Erstad BL. Analgesic response to morphine in obese and morbidly obese patients in the emergency department. *Emerg Med J.* 2014;31(2):139–42. <https://doi.org/10.1136/emermed-2012-202168>.
5. Erstad BL. Dosing of medications in morbidly obese patients in the intensive care unit setting. *Intensive Care Med.* 2004;30(1):18–32. <https://doi.org/10.1007/s00134-003-2059-6>.
6. Kramer NM, Gazelka HM, Thompson VH, Batsis JA, Swetz KM. Challenges to safe and effective pain management in patients with super obesity: case report and literature review. *J Pain Symptom Manage.* 2018;55(3):1047–52. <https://doi.org/10.1016/j.jpainsymman.2017.11.005>.
7. Varrassi G, Marinangeli F, Agrò F, Aloe L, De Cillis P, De Nicola A, Giunta F, Ischia S, Ballabio M, Stefanini S. A double-blinded evaluation of propacetamol versus ketorolac in combination with patient-controlled analgesia morphine. *Anesth Analg.* 1999;88(3):611–6. <https://doi.org/10.1097/00132586-200006000-00049>.
8. Zeng Z, Lu J, Shu C, Chen Y, Guo T, Wu Q-p, Yao SI, Yin P. A comparison of nalbuphine with morphine for analgesic effects and safety: meta-analysis of randomized controlled trials. *Sci Rep.* 2015;5:10927. <https://doi.org/10.1038/srep10927>.