CORRESPONDENCE

In reply: Potential statistical issues in a study comparing postoperative hunger in patients anesthetized with propofol or sevoflurane

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Received: 3 March 2020 / Revised: 3 March 2020 / Accepted: 3 March 2020 / Published online: 16 March 2020
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To the Editor,

We thank Drs Zhao and Gao for their relevant comments¹ on our recent study.² First, you propose to use multiple imputation (MI) for the time between the end of anesthesia (EOA) and the recovery of hunger.² Imputation by the median value of the other group (as specified in our protocol) is overly conservatively strengthening the conclusions of a positive clinical trial but weakening the conclusions of our negative trial. That is why a sensitivity analysis is relevant. Since only four (3.4%) data were missing (two per group), as specified in the second sentence of the results section, we used the maximum bias imputation (with the use of rank tests making that possible) with the missing data imputed to values larger than the maximum in one group, and imputed to values smaller than the minimum in the other group. This led to a difference Hodges–Lehman estimator equal to 5 (95% confidence interval [CI], –11 to 21; $P = 0.60$) for propofol vs sevoflurane in one extreme scenario and –6 (95% CI, –23 to 10; $P = 0.46$) in the other. The MI analysis would provide a result that is somewhere between these extreme scenarios. There was 5.9% of missing data

for peptides, imputed by the median value of the other group. We did not conduct sensitivity analyses on them.

Second, you mention the option of repeated measure analysis of variance (ANOVA) to analyze plasma levels of peptides rather than Mann–Whitney tests with a multiple testing procedure. These analyzes (after percentile transformation) had been requested by a reviewer but as they were obscure to the non-statistician, they were eventually removed from the manuscript after editor's feedback. The results of repeated-measures ANOVA (random patient intercept and fixed group effect) after percentile transformation (ranks divided by the number of observations plus one, then multiplied by 100) showed that mean empirical percentiles of plasma levels after anesthesia (mean of measurements at EOA, EOA + one hour, EOA + two hours) were not significantly different for propofol vs sevoflurane (all three P values ≥ 0.49 with Hochberg family-wise error rate correction for three tests) for insulin (–5.7 percentiles in propofol group; 95% CI, –13.6 to 2.2), leptin (–1.7 percentiles; 95% CI, –12 to 8.7), or ghrelin (+3.2 percentiles; 95% CI, –6.8 to 13.3). This analysis was not *a priori* planned in the initial design of the study. We had nevertheless *post hoc* carried it out but did not include it in the final manuscript because of the interpretation difficulties. As one can see, the results are rather similar. The peptides and the time to recovery of hunger data are available in the Electronic Supplementary Material (eTable).

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12630-020-01622-7>) contains supplementary material, which is available to authorized users.

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Conflicts of interest None.

Funding statement None.

Editorial responsibility This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal of Anesthesia*.

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2. Besnier E, Perdrix A, Gillibert A, *et al.* Postoperative hunger after outpatient surgery in patients anesthetized with propofol vs sevoflurane: a randomized-controlled trial. *Can J Anesth* 2020; DOI: <https://doi.org/10.1007/s12630-020-01584-w>.

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