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RESPONSE TO LETTER

A Critical Methodological Concern: Per-Protocol Analysis Undermines Randomization in Endoscopic Transsphenoidal Surgery Analgesia Trial [Response to Letter]

Natsuda Phothikun[1,*], Pathomporn Pinon[1,*], Ananchanok Saringkarinkul[1,*], Techas Polperm[1,*], Nitchakarn Plubnim[1,*], Amarit Phothikun[2–4,*]

[1]Department of Anesthesiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [2]Department of Biomedical Informatics and Clinical Epidemiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [3]Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [4]Clinical Surgical Research Center, Chiang Mai University, Chiang Mai, Thailand

*These authors contributed equally to this work

Correspondence: Amarit Phothikun, Department of Surgery, Faculty of Medicine, Chiang Mai University, 110 Intravaroros Road, Sri Phum, Mueang, Chiang Mai, 50200, Thailand, Tel +66896333661, Email Armadillos176@gmail.com

Dear editor

We sincerely thank the commentator for the thoughtful and important methodological discussion regarding our randomized controlled trial evaluating dexmedetomidine-adjuvanted infraorbital nerve block during endoscopic transsphenoidal surgery.

We fully acknowledge that intention-to-treat (ITT) analysis is generally considered the preferred analytical approach for superiority randomized controlled trials because it preserves the prognostic balance generated by randomization and minimizes attrition bias. We agree that ITT analysis should ideally be performed whenever feasible and that per-protocol (PP) analysis may potentially overestimate treatment effects.

However, several important considerations should be clarified in the context of our study design. The post-randomization exclusions in our trial were not related to treatment efficacy or outcome assessment but rather resulted from predefined perioperative circumstances that fundamentally altered the operative protocol or prevented completion of the planned intervention. These included withdrawal of consent before intervention administration, changes in surgical procedure, and intraoperative navigation use that modified the surgical approach and perioperative analgesic conditions. Because the primary endpoint was intraoperative fentanyl consumption under a highly standardized anesthetic and surgical protocol, inclusion of these patients in the final efficacy analysis would have introduced substantial clinical heterogeneity and compromised the standardization of the study protocol.

For this reason, we conducted a per-protocol analysis to evaluate the efficacy of the intervention under standardized operative conditions. We acknowledge that this approach carries an inherent risk of attrition bias and limits preservation of the original randomization balance. Therefore, our findings should be interpreted with appropriate caution.

Importantly, the exclusions were determined by perioperative and technical considerations rather than postoperative outcome differences or selective removal based on treatment response. Furthermore, despite the operative time imbalance, the observed direction and magnitude of the analgesic effect remained clinically consistent across the analyzed cohort.

We agree that the absence of a formal ITT analysis represents a methodological limitation of our study and appreciate the opportunity to clarify this issue. Future studies with larger sample sizes and predefined strategies for handling intraoperative protocol deviations should incorporate both ITT and PP analyses in accordance with CONSORT

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recommendations to further strengthen the evidence base regarding regional anesthesia techniques in endoscopic transsphenoidal surgery.

We sincerely appreciate the commentator's constructive observations and believe that this discussion contributes meaningfully to improving methodological quality and transparency in perioperative clinical trials.

Disclosure

The authors report no conflicts of interest in this communication.

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