Journal of Pain Research

Dovepress
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LETTER

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

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Dear editor

We read with great attention the prospective, randomized, double-blind controlled trial by Phothikun et al investigating ultrasound-guided infraorbital nerve block (IONB) with dexmedetomidine-adjuvanted bupivacaine for analgesia in endoscopic transsphenoidal surgery (ETSS).[1] The authors reported significant opioid-sparing effects without hemodynamic compromise, providing valuable insights for neurosurgical multimodal analgesia.

While we acknowledge the clinical relevance of this work, we must highlight a fundamental and critical methodological flaw that may invalidate the trial's core conclusions: the exclusive use of per-protocol (PP) analysis instead of intention-to-treat (ITT) analysis, which directly violates the foundational principle of randomized controlled trials (RCTs).

As clearly presented in the article, 63 patients were randomized, but 16 were excluded post-randomization due to consent withdrawal, surgical procedure changes, or intraoperative navigation use. The final analysis included only 47 patients (74.6% of randomized subjects). The authors chose PP analysis for all primary and secondary outcomes, which is a major limitation in RCT design.[2]

ITT analysis requires that all randomized patients be analyzed in their originally assigned groups, regardless of protocol deviations, dropout, or incomplete follow-up. ITT preserves prognostic balance generated by randomization, minimizes attrition bias, and reflects real-world clinical effectiveness.[3] In contrast, PP analysis only includes patients who fully adhere to the protocol, which can overestimate treatment effects, introduce selection bias, and destroy the baseline comparability achieved by randomization.[4]

In this trial, post-randomization exclusions were not evenly distributed across groups, and baseline operative time showed a significant between-group difference ($P<0.001$). These imbalances strongly suggest that attrition bias may exist. By relying solely on PP analysis, the authors cannot confirm that the reduced fentanyl consumption and prolonged analgesia time truly result from the intervention, rather than from unbalanced baseline characteristics or selective dropout.

This methodological error is not a minor oversight but a critical issue that affects the reliability and interpretability of all reported outcomes. For an RCT aiming to guide clinical practice, ITT analysis is mandatory for primary outcomes, and PP analysis should only be used as a supplementary sensitivity test.[2,3] Without ITT results, the claimed opioid-sparing effect cannot be confidently attributed to the dexmedetomidine-added IONB.

We sincerely appreciate the authors' efforts in exploring regional anesthesia for neurosurgical pain management. However, we strongly recommend that the authors re-analyze all data using ITT principles to validate their conclusions.

https://doi.org/10.2147/JPR.S621107
Received: 30 April 2026
Accepted: 3 May 2026
Published: 6 May 2026

We also encourage future RCTs in this field to strictly adhere to CONSORT guidelines and prioritize ITT analysis to ensure evidence quality.[5]

Acknowledgments

The authors of this article express their gratitude for the support provided by the Talent Development Program of Women and Children's Hospital of Ningbo University.

Funding

This work was supported by the Zhejiang Provincial Medical and Health Plan (2022KY1159, 2025KY1423, 2025KY1417, and 2025HY1019). Key Technology Breakthrough Program of "Ningbo Sci-Tech Innovation Yongjiang 2035" (No.2024Z222). Ningbo Municipal Specialized Training Program for Young Technical Backbone Talents in Health (Yongweifa 2024-102-77). Ningbo High-Level Medical and Health Team Major Tackling Project and the Talent Development Program(2022020405). Ningbo Municipal Key Modern Medical Discipline Development Project (2026-A36).

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this communication.

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https://doi.org/10.2147/JPR.S621107