Non-inferiority or non-reproducibility? A call for rigor in pain outcome trials

We read with great interest the recent article by Fujino *et al*[1] evaluating the noninferiority of popliteal plexus block compared with Infiltration between the Popliteal Artery and Capsule of the Knee for posterior knee pain management after total knee arthroplasty (TKA). While the study offers intriguing insights, we would like to raise several statistical and methodological concerns that may influence the interpretation and reproducibility of its findings.

First, the authors used a one-sided α of 5%, corresponding to a 90% CI for their noninferiority analysis. While technically acceptable, the standard recommendation for noninferiority trials is a one-sided α of 2.5% (ie, a two-sided 95% CI) to ensure greater statistical rigor and minimize the risk of false-positive findings. Using a more permissive 90% CI increases the likelihood of incorrectly concluding noninferiority when it is not truly established. In this case, recalculating an approximate 95% CI from the reported data yields a range of −7.3% to +17.1%, which still supports the noninferiority conclusion. However, this result should be interpreted with caution. Although the conclusion may not differ a posteriori, these findings should be validated in larger, adequately powered trials to ensure robustness and generalizability. Importantly, under the authors' planning assumptions (Δ=17%, expected event rate=11%, power=80%), adopting the more conservative one-sided α=2.5% would increase the required sample to approximately 81 patients per group (≈180 total including anticipated dropout), rather than the 45 per group enrolled. Furthermore, the methodological details used to compute the CIs—for example, whether a Huber-Sandwich (robust) variance estimator was applied—should be clearly reported to enable reproducibility and accurate external interpretation.

Second, the observed incidence of moderate-to-severe pain was lower than anticipated (6.7% vs the expected 11%), which may have underpowered the study to detect subtle but clinically relevant differences. This underscores the value of sensitivity analyses to test the robustness of the noninferiority conclusion under varying assumptions about effect size and event rates.

Third, while multiple secondary outcomes were analyzed, no adjustments for multiplicity were applied, increasing the risk of type I error. Moreover, postoperative pain is inherently longitudinal and autocorrelated; analyzing point estimates at fixed time points without modeling within-subject correlation can bias inference. Repeated-measures or mixed-effects models (or generalized estimating equations) are better suited to characterize pain trajectories over time.

Fourth, generalizability is limited by the anesthetic regimen. All patients received general anesthesia with substantial perioperative/postoperative opioid use. Spinal anesthesia—recognized for its opioid-sparing benefits—is widely used in contemporary TKA pathways and associated with favorable outcomes.[2] The lack of neuraxial techniques and reliance on higher opioid doses may, therefore, restrict external validity, particularly in centers prioritizing opioid-sparing care.

In conclusion, while the study addresses an important clinical question, its methodological limitations—particularly in statistical design, outcome analysis, and generalizability—warrant caution in interpretation. We advocate for sensitivity analyses, adherence to standard noninferiority criteria, and statistical models appropriate for longitudinal outcomes. Aligning future trials with current anesthetic practice will enhance clinical relevance and reproducibility. We nevertheless sincerely congratulate the authors on their well-constructed research hypothesis and the valuable evidence they have presented, which contributes meaningfully to the ongoing discussion in perioperative pain management after TKA.

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2 Heckmann ND, De A, Porter KR, *et al*. Spinal Versus General Anesthesia in Total Knee Arthroplasty: Are There Differences in Complication and Readmission Rates? *J Arthroplasty* 2023;38:673–9.