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LETTER

Advancing the Prevention of Postherpetic Neuralgia: Methodological and Clinical Considerations for the TPI Study Protocol [Letter]

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Dear editor

We read with great interest the study protocol by Han et al recently published in the Journal of Pain Research (2026;19:575423), titled "Efficacy of Tender Point Infiltrations (TPI) in Patients with Acute and Subacute Zoster-Associated Pain: Study Protocol for a Randomized, Prospective, Multicenter, Blinded Endpoint, Open-Label Controlled Trial".[1] The authors address a critical clinical challenge: the prevention of postherpetic neuralgia (PHN), a debilitating condition that often remains refractory to conventional pharmacological therapies. By investigating a simple, low-cost, and potentially high-impact intervention—Tender Point Infiltration (TPI) with lidocaine and betamethasone—this multicenter RCT provides a promising framework for early intervention in zoster-associated pain (ZAP). However, from the perspective of clinical pain management and trial methodology, several points merit further discussion to enhance the robustness and interpretability of the forthcoming results.

Defining Postherpetic Neuralgia: The Threshold of Clinical Significance

In this protocol, the primary outcome is defined as the presence of PHN at 12 months, identified as any persistent pain with a Visual Analogue Scale (VAS) score >0.[1] While this "zero-tolerance" approach toward pain is scientifically rigorous, its clinical relevance warrants scrutiny. In many landmark HZ trials, PHN is defined by a more clinically significant threshold, such as VAS ≥3 or the continued need for analgesics, to distinguish between mild sensory disturbances and functionally impairing chronic pain.[2] Using VAS >0 may lead to an overestimation of PHN incidence by including patients with negligible discomfort that does not affect quality of life. We suggest that the authors consider a sensitivity analysis using a higher pain threshold (eg, VAS ≥ 3) to ensure that the observed "preventive effect" of TPI translates into a meaningful reduction in the clinical burden of PHN.

The Placebo Effect and Expectancy Bias in Open-Label Injection Trials

The study adopts an open-label design, comparing standard treatment alone with standard treatment plus TPI. As the authors correctly acknowledge, blinding the TPI procedure is challenging. However, physical interventions involving needles and local anesthesia are known to induce substantial placebo and expectancy effects.[3,4] In an open-label setting, patients in the TPI group might report lower VAS scores and higher satisfaction due to the perceived "intensified" care rather than the pharmacological action of the infiltrates. While the use of blinded endpoint assessment (PROBE design) mitigates detection bias, it cannot fully eliminate the performance bias inherent in the patient's self-reported pain scores. Future studies might benefit from a sham-injection control group (eg, superficial skin pricking or saline injection) to isolate the specific therapeutic effect of TPI from the non-specific effects of the procedure itself.

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Balancing Steroid-Mediated Analgesia with Viral Safety in the Acute Phase

The intervention involves the infiltration of diprospan (betamethasone), a potent corticosteroid. While local steroids are effective in reducing the inflammation and nerve damage that drive PHN, their use during the acute viral replication phase of HZ requires careful monitoring. Although the protocol excludes immunosuppressed patients, even local corticosteroid administration can theoretically modulate the local immune environment. We recommend that the authors systematically record and report the "time to complete crusting" of the HZ rash and the incidence of secondary bacterial infections. Ensuring that TPI does not inadvertently prolong the viral shedding period or delay skin healing is vital for establishing the safety profile of this add-on therapy.

Individualized Pain Management: The Need for Sensory Phenotyping

Zoster-associated pain is highly heterogeneous, involving mechanisms ranging from peripheral sensitization to central disinhibition. The authors aim to explore predictors for the prevention of PHN, which is highly commendable. To further this goal, we suggest incorporating "sensory phenotyping" into the baseline assessment. Patients with prominent mechanical allodynia or "irritable nociceptors" (identifiable via simple bedside Quantitative Sensory Testing) might respond differently to TPI than those with profound sensory loss.[5] Identifying which sensory profile benefits most from TPI would facilitate a transition from a "one-size-fits-all" approach to individualized, precision pain medicine for HZ patients.

Extension Suggestions and Future Perspective

From a public health perspective, the simplicity of TPI makes it an ideal candidate for implementation in primary care and community health centers, where HZ is often first diagnosed. If the results of this trial confirm the efficacy of TPI, it could be integrated into early-intervention guidelines as a "perfect add-on" to standard antiviral therapy. Furthermore, we encourage the authors to include a cost-effectiveness analysis in their final report. Demonstrating that a low-cost injection can reduce the long-term economic burden of PHN (including reduced analgesic consumption and fewer hospital visits) would provide compelling evidence for policymakers to support its widespread clinical adoption.

In conclusion, Han et al have designed a timely and valuable study that could refine our strategy for managing acute and subacute ZAP. Addressing the nuances of PHN definition, potential placebo effects, and patient phenotyping will further enhance the impact of their findings. We look forward to the publication of the trial results and their contribution to the field of pain research.

Abbreviations

HZ, Herpes Zoster; PHN, Postherpetic Neuralgia; PROBE, Prospective Randomized Open Blinded Endpoint; RCT, Randomized Controlled Trial; TPI, Tender Point Infiltration; VAS, Visual Analogue Scale; ZAP, Zoster-Associated Pain.

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Disclosure

The authors declare that they have no competing interests in this communication.

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