


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

Xiangjun Zhou<sup>1</sup>, Rong Han<sup>2</sup>, Zhigang Zhao<sup>2</sup>, Fang Luo <sup>1</sup>

<sup>1</sup>Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, People's Republic of China; <sup>2</sup>Department of Pharmacy, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, People's Republic of China

Correspondence: Fang Luo, Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, 100070, People's Republic of China, Tel +86 010 59976664, Email 13611326978@163.com

## Dear editor

We would like to thank you for the opportunity to respond to the comments raised in the Letter to the Editor about the publication “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”. We would also like to thank the authors for their interest in our paper and for taking the time to express their views, here are our responses to each of the suggestions they raised.

## Defining Postherpetic Neuralgia: The Threshold of Clinical Significance

As the authors noted, there are two main approaches in the literature for defining postherpetic neuralgia (PHN). Several published studies use a very sensitive PHN definition (any presence of pain at week 12 after rash onset) to evaluate interventions.<sup>1</sup> In a large natural-history study, Petersen et al acknowledged that using “presence of pain” tends to overestimate the number of patients negatively impacted by ongoing pain.<sup>2</sup> We acknowledge that in many clinical trials and guidelines, PHN is often defined using a more conservative threshold (for example, VAS  $\geq 3$  or continued need for analgesics) to capture clinically significant pain. In designing our randomized trial, we chose the more sensitive definition—persistent pain with a score of higher than 0 on the VAS for the reason of TPI is a minimally invasive, low-cost intervention with a potentially large effect on zoster-associated pain (ZAP), using a sensitive definition increases our ability to detect differences between groups and ensures that even slight persistent discomfort is captured. The PROCESS randomized controlled trial likewise defined PHN as “any pain intensity score other than 0 mm” on a visual-analog scale (VAS) at 12 weeks, with secondary outcomes based on the number of participants with VAS  $\geq 3$ .<sup>3</sup> We acknowledge your concern about overestimating PHN incidence. Should TPI prove effective, we will add a sensitivity analysis using VAS  $\geq 3$  as the threshold to determine whether our findings hold when only moderate to worse pain is considered. We will also examine analgesic consumption and quality-of-life scores to contextualize pain severity.

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

We agree that the absence of a sham injection or placebo group is a limitation. For ethical reasons, we felt it inappropriate for herpes zoster (HZ) participants receiving a painful and invasive placebo procedure merely for blinding purposes. Consequently, this study uses an open-label, blinded-endpoint design rather than a double-blind, placebo-controlled design. Recognizing this constraint, we will interpret our findings with great caution. We also note this limitation in our discussion and encourage future studies to explore feasible, ethically acceptable methods for better blinding and controlling for expectation effects.



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

We understand the concern that corticosteroid injection during the acute phase of herpes zoster could theoretically affect local immunity and delay lesion healing. For this reason, our protocol excludes patients using immunosuppressants and those with severe systemic diseases such as hematological malignancies, cancers, or autoimmune disorders. Current literature indicates that intralesional injection of corticosteroids (triamcinolone acetonide, hydrocortisone, dexamethasone, and methylprednisolone) in for oral lichen patients provide a higher local dose while producing minimal systemic absorption.<sup>4</sup> In our trial, we will use a very low dose of betamethasone. We appreciate the suggestion to record crusting time and secondary infection. We will include these safety outcomes in our monitoring and will report them in detail.

## Individualized Pain Management: The Need for Sensory Phenotyping

We appreciate the suggestion to include a simple quantitative sensory test at baseline to explore how different pain phenotypes in HZ patients might respond to TPI. Our study is designed to collect a range of baseline characteristics such as pain intensity, affected dermatomes and disease duration. Because participating centers vary in resources and methodology, we have not adopted a uniform sensory phenotyping evaluation protocol. However, we will use the available data to explore potential predictors in our analyses and lay the groundwork for future sensory phenotype assessment. We have also noted your recommendation as a valuable consideration for designing subsequent studies and developing individualized treatment strategies.

## Extension Suggestions and Future Perspective

We appreciate the comment that TPI is simple, easily implemented, and potentially a promising supplementary early-intervention approach, as well as the suggestion to include a cost-effectiveness analysis. We will record reductions in patients' use of oral medications to provide a foundation for subsequent health-economic analyses.

We would like to thank the authors once again for their attention and constructive suggestions regarding our study. We will carefully consider their recommendations to continuously refine our study protocol and reporting. We look forward to the results of the clinical trial, which we hope will provide higher-quality evidence for the management of ZAP.

## Disclosure

The authors report no conflicts of interest in this communication.

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