



# Acupuncture Modalities Differentially Modulate Pain and Joint Damage in a Rat Model of Knee Osteoarthritis [Response To Letter]

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## Dear editor

We express our sincere gratitude to Drs. Wang and Ye for their insightful commentary regarding our article. We welcome this opportunity to engage in a scientific dialogue and agree that their perspectives serve to enhance and elucidate the interpretation of our results. The commentary has underscored significant considerations concerning the heterogeneous character of acupuncture stimuli and the inherent difficulties in achieving standardization of treatment intensity across diverse modalities. We shall address each of their observations sequentially, maintaining a collegial spirit aimed at advancing knowledge within the field. We are appreciative of their constructive critique, which emphasize the critical importance of ongoing refinement and collaborative effort in acupuncture research.

## The Nature of Stimuli

We agree with the commentary that manual acupuncture (MA), electroacupuncture (EA), laser acupuncture (LA), and bee venom acupuncture (BVA) each represent distinct forms of stimuli, with differing mechanisms of action and standardization challenges. EA delivers electrical pulses onto the needle, which can recruit a broader spectrum of neural pathways. Low-frequency EA of 2–10 Hz is well known to induce the release of endogenous opioids like  $\beta$ -endorphin and enkephalin.<sup>1</sup> Our choice of alternating 2/10 Hz frequency at 1 mA intensity for EA was based on a body of preclinical evidence that such parameters produce robust analgesic and anti-inflammatory effects in rodent osteoarthritis models.<sup>2,3</sup> This low-frequency stimulation has been shown to increase central and peripheral endorphin levels and inhibit pro-inflammatory cytokines, thereby alleviating pain and joint inflammation.<sup>1,3</sup> We agree with the commentators that EA's mechanism differs fundamentally from a purely mechanical stimulus, and we acknowledge that this makes direct equivalence with manual needling complex.

LA, as the commentary notes, delivers a photonic stimulus rather than a physical one. Our study employed a low-level 830 nm near-infrared laser at 20 mW power, applied via an optic fiber inserted in the needle “invasive laser acupuncture”. We selected these settings because they fall within established photobiomodulation parameters known to penetrate tissue and modulate biochemical processes in osteoarthritis models.<sup>4–6</sup> Prior studies have demonstrated that laser stimulation at wavelengths in the red-to-infrared range could enhance local microcirculation, promote cartilage metabolism, and reduce pain hypersensitivity in arthritic joints.<sup>4</sup> Thus, although LA is a fundamentally different modality our goal was to deliver a therapeutic dose of light energy consistent with what has proven efficacious in the literature.

BVA introduces another type of stimulus as a biochemical inflammatory challenge. The primary active components of bee venom can cause a brief localized inflammation that, at controlled doses, leads to anti-inflammatory and analgesic effects via activation of the body's own regulatory mechanisms.<sup>7</sup> We agree that standardizing BVA is difficult, as its effects are dose-dependent and can be biphasic. In our protocol we used 0.1 mL of a 1.0 mg/mL bee venom solution per

treatment, which corresponds to a relatively low dose. This decision was guided by earlier preclinical studies in arthritic rats showing that similar doses produce significant anti-arthritic benefits without overt toxicity.<sup>8</sup> We appreciate that Wang and Ye recognized the need to carefully choose such parameters, BVA's efficacy and safety hinge on proper standardization of the venom concentration and volume, and our choices were grounded in the best practices from the literature.

Finally, with respect to MA, we acknowledge the inherent variability in manual stimulation and the difficulty in defining a "standard" dose of needle rotation. In our experiment, we opted for gentle twirling of the needle for 30 seconds per minute over 3 minutes, based on commonly used laboratory acupuncture protocols.<sup>9</sup> This intermittent rotation is intended to provide consistent mechanical stimulation to activate the afferent fibers periodically. Tan et al, for instance, employed a similar approach (1 minute of rotation every 5 minutes) in a rat OA model and demonstrated significant anti-inflammatory and chondroprotective effects with manual acupuncture.<sup>9</sup> We chose GB34 as the uniform acupoint for all modalities, and we kept the treatment schedule consistent across groups. These steps were taken to minimize variability between modalities in terms of timing and location, following the principle of consistency recommended in acupuncture research reporting guidelines. Nonetheless, we agree with the commentary that despite using a uniform schedule and site, the nature of the stimulus differs for each modality in ways that are hard to fully equalize. Our parameter selections for EA, LA, BVA, and MA were each supported by prior studies, as noted above, but we remain cognizant that such choices, while evidence-based, do not guarantee a truly equivalent intensity of stimulation across modalities. We appreciate the commentary's point that each modality's action on the body is unique, and we acknowledge that this is a limitation when attempting direct comparisons. We intended to employ typical effective doses for each therapy, in order to fairly showcase their potential. In this regard, we respectfully defend our parameter choices as reasonable and grounded in the literature, while also recognizing that they represent an initial approximation of equivalence rather than a perfect standardization.

## The Challenge of Achieving Equivalent Stimulation

The authors point out the difficulty of achieving truly equivalent stimulation across such disparate acupuncture modalities. We agree with their proposal to move beyond simple protocol uniformity and toward a more bioeffect-based calibration of dose. In future studies, we agree that it would be ideal to adjust each modality's parameters such that they produce comparable biological and behavioral outcomes, thereby enabling a more meaningful comparison. The idea of using intermediate biomarkers and functional endpoints is an excellent suggestion that we are enthusiastic to incorporate in our subsequent research.

Beyond biochemical markers, we absolutely agree with using behavioral endpoints such as pain thresholds to calibrate stimulus intensity. In our study, we measured the paw withdrawal threshold (PWT) as a common pain outcome, but we did not use it prospectively to equalize treatments. The commentary suggests an excellent refinement to adjust each modality's dose a priori until each produces a 50% improvement in PWT in the OA model. This would ensure that when we compare modalities, we are comparing at an equivalent analgesic impact level. We find this approach very compelling. We also acknowledge the importance of employing appropriate sham controls for each modality, as suggested. In our original study, we included an untreated osteoarthritis group as a control, but we did not include separate sham EA, sham LA, or sham BVA groups, a simplification that we recognize could be improved upon. Going forward, we plan to incorporate modality-specific shams to account for placebo or non-specific effects. Including these controls would address the concern that some of the observed benefits might derive from generic needling or injection effects rather than the specific modality action. As previous studies have shown that such controls are feasible, Tan et al employed a sham manual acupuncture in their rat OA experiment to distinguish the effect of needle manipulation from insertion alone.<sup>9</sup> Likewise, Yuan et al used a sham EA condition to isolate the true effect of electrostimulation.<sup>10</sup> We believe adopting similar methodologies will strengthen the causal conclusions of our future studies. We are fully committed to integrating these more sophisticated control strategies in our next phase of research.

## Conclusion

We sincerely appreciate the commentary by Wang and Ye, which has provided us an opportunity to clarify our rationale and to reflect on important methodological improvements for future studies. Our original work intended to conduct an

exploratory analysis of how different acupuncture modalities might differentially influence pain and joint pathology under similar conditions. Moving forward, as both their commentary and our above responses emphasize, truly meaningful cross-modality comparisons will benefit from a more nuanced approach to standardization. We will carefully consider the suggestions to employ biomarker-guided dosing equivalence, behavioral outcome calibration, and rigorous sham controls. Our shared goal is to better elucidate how each acupuncture modality can be optimally and appropriately utilized for osteoarthritis pain, and through open dialogue and methodological improvements, we move closer to that goal.

## Disclosure

The authors declare that they have no conflicts of interest in this communication.

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