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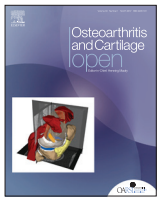

Clinical Trial

Safety and preliminary efficacy of transcutaneous auricular vagus nerve stimulation on chronic knee pain: A pilot trial

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ABSTRACT

Objective: Transcutaneous auricular vagus nerve stimulation (**tVNS**) may be an innovative treatment for symptoms of knee osteoarthritis (OA) due to possible shared pathological mechanisms between diminished parasympathetic function, central pain mechanisms, and knee pain. Thus, we sought to test the safety and preliminary efficacy of tVNS in people with knee OA.

Design: A pilot trial in which participants received a 60-min tVNS was conducted. At baseline, immediately after, and 15 min after tVNS, we assessed knee pain, pressure pain threshold (**PPT**), temporal summation (**TS**), conditioned pain modulation (**CPM**), and high-frequency power of heart rate variability (**HF**). We examined the extent to which these outcome measures changed after tVNS using linear mixed models.

Results: 30 participants with knee OA were included, and all completed the intervention without any major side effects. Compared to baseline, knee pain was reduced by 1.27 (95 % CI, −1.74, −0.80) immediately after and by 1.87 (−2.33, −1.40) 15 min after tVNS; CPM improved by 0.11 (0.04, 0.19) and 0.07 (−0.01, 0.15); and HF improved by 213.29 (−0.38, 426.96) and 234.17 (20.49, 447.84). PPT and TS were not changed after tVNS.

Conclusions: Our preliminary data demonstrated that tVNS may be a safe pain-relieving treatment for people with knee OA. Our findings suggest that improvement of knee pain might be derived from improvement of parasympathetic function and central pain mechanisms as no local therapy was applied. A large study is needed to confirm that tVNS is a novel intervention to ameliorate knee pain in people with knee OA.

Clinical Trial: ClinicalTrials.gov (NCT05625178).

1. Introduction

Osteoarthritis (OA) is the most common joint disease, affecting 654 million adults worldwide, and contributes substantially to global disability [1]. The knee is the most commonly affected site of OA, and pain is the primary symptom, yet treatment approaches are only modestly effective, and often have side effects or contraindications [2]. More treatment options are urgently needed. The pain experience in knee OA has been recognized to be multifactorial [3–5], and central pain mechanisms, such as central sensitization and inefficient descending pain inhibition, are major contributors to pain in knee OA [5]. However, current pain management strategies do not fully address this issue. Importantly, although non-pharmacological treatments are recommended for symptoms of knee OA [3,6,7]. There are no established treatments specifically targeting central pain mechanisms to date.

One potential means of impacting central pain mechanisms and thereby ameliorating knee pain is through modulation of parasympathetic function [4,8,9]. Attenuated parasympathetic function has been reported in some chronic pain conditions, including knee OA [4,10–12]. Diminished parasympathetic function leads to suppression of analgesic molecules (e.g., norepinephrine, serotonin, endogenous opioids) in the midbrain, which play essential roles in descending pain

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inhibition, and thereby causes enhanced pain perception as a major central pain mechanism [4,13,14]. Further, vagus nerve activity, the main component of the parasympathetic nervous system, has a major role in systemic anti-inflammatory effects [4,8], and systemic inflammation has been associated with central pain mechanisms [15,16]. Thus, diminished parasympathetic function contributes to both systemic inflammation and central pain mechanisms. Thus, it is reasonable that addressing the vagus nerve may improve central pain mechanisms and, thus, knee pain through modulating parasympathetic function.

Transcutaneous auricular vagus nerve stimulation (tVNS) is a safe and non-invasive intervention that entails stimulation of the auricular (i.e., the ear) branch of the vagus nerve and has effects on improving parasympathetic function as reliably and validly assessed with heart rate variability [4,9,17,18]. tVNS has been shown to improve clinical symptoms in various conditions [9,19]. For example, tVNS is an FDA-approved treatment for depression and epilepsy and can produce clinically meaningful treatment effects [20,21]. Further, tVNS has been expanding its use to other conditions, such as traumatic brain injury, Alzheimer's disease and migraine, to ameliorate symptoms [19,21]. Notably, tVNS has also been safely demonstrated to reduce pain severity and pain sensitivity as assessed with quantitative sensory testing (QST) in the hand [22], back [23], face [24], and the gastrocnemius muscle [25] among people with hand OA, chronic back pain, episodic migraine, and chronic pelvic pain, respectively. However, tVNS has not yet been used in knee OA and the efficacy of tVNS on central pain mechanisms and pain in knee OA is unstudied to date. Therefore, we sought to test the safety and preliminary efficacy of tVNS on knee pain, central pain mechanisms and parasympathetic function in people with knee OA. We hypothesized that a tVNS intervention would be safe for people with knee OA and demonstrate improvements in knee pain, central pain mechanisms, and parasympathetic function.

2. Materials

2.1. Study participants

Participants included people with knee OA, using the National Institute for Health and Care Excellence's clinical diagnostic criteria, which does not require radiographic knee OA severity [3,26–28]. The clinical diagnostic criteria include: age $\geq$45, activity-related knee pain, and either no morning joint-related stiffness or stiffness that lasts $\leq$30 min. The other inclusion criteria included the average knee pain $\geq$4/10 on a 0–10 numeric rating scale in the last seven days, the presence of knee pain during walking, and understanding English. Those with the following conditions were excluded from the study: 1) current skin disease of the ear interfering with the application of the auricular electrode for stimulation, 2) recurrent vagal syncope or history of vagotomy, 3) use of other electrically active medical devices (e.g., pacemaker), 4) auditory canal not adapted to the application of the ear electrode, 5) known history of cardiac rhythm disturbances, atrioventricular block >1st degree, conduction disturbances, 6) peripheral neuropathy or other sensation loss on the body sites for pain measurements (i.e., the wrist, knee, the forearm), 7) chronic use of opioids, 8) pregnant women, 9) serious and uncontrolled concomitant disease, including cardiovascular, nervous system, pulmonary, renal, hepatic, endocrine, gastrointestinal or epileptic disease, and 10) any intervention procedures for knee pain in the last 3 months. Further, we required participants not to take analgesics and beta-blockers 24 h prior to the study visit, as they may potentially affect pain sensitivity and HRV [23].

2.2. Study design

This was a pilot clinical trial with a single study visit at which participants received a 60-min tVNS intervention, allowing for assessment of safety and preliminary efficacy for tVNS in people with knee OA. The study protocol was approved by The University of Texas at El Paso Internal Review Board and was registered on ClinicalTrials.gov (NCT05625178). We screened participants via emails, text messages, and phone calls and scheduled them for the study visit once eligibility was confirmed. All participants visited the University of Texas at El Paso for the study and provided informed consent. At the study visit, all participants completed demographic questionnaires, outcome measures (i.e., heart rate variability: HRV, quantitative sensory testing: QST, and knee pain) and the 60-min tVNS intervention. The outcome measures were assessed immediately before (baseline), immediately after, and 15 min after the tVNS intervention (Fig. 1). We repeated the post-tVNS assessments twice to increase the precision to evaluate the immediate efficacy of tVNS in knee OA.

2.3. tVNS protocol

tVNS was performed by applying an auricular electrode placed at the cymba concha of the ear, which is exclusively innervated by the auricular branch of the vagus nerve [9,19,22,25]. Once the electrode was fitted to the cymba concha, the participant was seated or took a comfortable position. Once in position, we initiated tVNS for 60 min with a 'strong but comfortable' intensity (up to 15 mA) with 25 Hz, pulse width 250 uS, and 30 s on/off cycle [9,25]. We used a commonly used tVNS device (tVNS® R, GmbH, Germany) and followed the recommended stimulus parameters to ensure safety and target engagement of the vagus nerve [9,25].

2.4. Outcomes

2.4.1. Knee pain

Knee pain was assessed on a 0–10 numeric rating pain scale during a 20-m walk [29] to evaluate the extent to which the pain rating changed immediately and/or 15-min after the tVNS intervention. We also assessed the minimal clinically important improvement defined as $\geq$ 1.5/10 to reflect the participants' perception of their pain after the intervention [30].

2.4.2. Quantitative sensory testing (QST)

Central pain mechanisms were assessed with the following QST measures:

1) **Pressure Pain Threshold (PPT).** We assessed PPT at the right distal radioulnar joint (wrist) using a pressure algometer (Wagner FDIX25) as a measurement of central sensitization [31,32]. The algometer was applied at a constant rate of 0.5 kg/s [31,32]. PPT was defined as the point at which the participant verbally indicated that the pressure first changed to slight pain. The PPT at the wrist was calculated by averaging 3 trials for analysis. PPT at a remote body site is thought to assess central pain sensitivity, with a lower PPT value indicating greater sensitivity [31,32].
2) **Mechanical Temporal Summation (TS).** TS is a sensitive and valid measure of central sensitization [31,32]. We assessed TS using a standard set of weighted probes (MRC Systems, Germany). Participants rated the pain experienced by each weighted probe being touched on the skin of the wrist until a pain rating of $\geq$4/10 was achieved; otherwise, the highest weighted probe was used [32,33]. The selected probe was then applied at a frequency of 1 Hz for 10 s. Participants provided a pain rating before and after the train of 10 stimulations. A post-stimulation pain greater than the initial pain (i.e., post-stimulus pain rating – pre-stimulus pain rating >0) was considered to be reflective of facilitated TS (i.e., central sensitization) [32,33].
3) **Conditioned Pain Modulation (CPM).** CPM evaluates the efficiency of the descending pain inhibitory pathways [34]. We used PPT at the wrist (mean of 3 trials) as the test stimulus, before and after forearm ischemia using a blood pressure cuff as the conditioning stimulus [32,33]. Specifically, we inflated a blood pressure cuff to 10 mm Hg above systolic on the upper arm contralateral to the wrist and had the

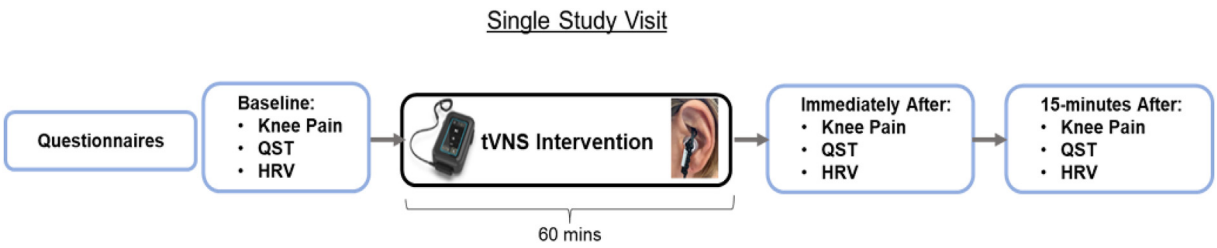

Fig. 1. Overall Study Flow.
Abbreviations: QST, quantitative sensory testing; HRV, heart rate variability; tVNS, transcutaneous vagus nerve stimulation.

participant perform hand exercises until pain in the forearm reached ≥4/10, or 2 min had passed. At that point, PPT was reassessed at the wrist (mean of 3 trials) immediately after deflating the cuff [32,33]. CPM was computed as the ratio of the post-conditioning stimulus PPT to the pre-conditioning stimulus PPT (i.e., PPT2/PPT1), with a ratio ≤1 indicating inefficient CPM [35,36].

The same-day test-retest reliability for the wrist PPT, TS, and CPM in our QST protocols were intraclass coefficients of 0.89, 0.75, and 0.76, respectively, suggesting good reliability.

2.4.3. Parasympathetic function

Parasympathetic function was assessed with the high frequency (HF) power of HRV data. We used high-frequency band (0.15–0.40 Hz) to calculate milliseconds squared divided by cycles per second as HF power (ms^2 or ms^2/Hz) [10,11,37]. HF power, which generally ranges from 80 to 4000 ms^2 and assesses parasympathetic function, is most recommended for short-term recordings (e.g., 5 min of HRV monitoring) and has been correlated with other domains of HRV that also assess parasympathetic function [9,37,38]. We used a Bluetooth heart rate monitor (Polar H10, Bethpage, NY) paired with a smartphone application (Elite HRV™, Ashville, NC) to obtain HRV data [39–41]. Participants were supine for 5 min with the heart rate monitor while research personnel monitored the heart rate data [39–41]. At the end of the 5 min, the smartphone application provided the HRV data. Elite HRV application has a built-in proprietary algorithm to correct ectopic beats and other artifacts [42] and HRV data obtained from these devices have excellent agreements (ICC ≥0.95) with the gold standard HRV measure (i.e., electrocardiogram) and other common HRV software (e.g., Kubios) [39,40]. The same-day test-retest reliability for HF power in our QST protocols was an intraclass coefficients of 0.83, suggesting good reliability.

2.5. Feasibility, acceptability, and safety

We assessed the intervention completion rate as the number of participants who successfully completed the 60-min tVNS intervention divided by the total sample size. To demonstrate the feasibility of the 60-min tVNS intervention in people with knee OA, >80 % of participants needed to complete the full intervention [43,44]. Further, we asked participants about whether they would return if there were more tVNS sessions. We also closely monitored any intervention-related side effects during the study visit and recorded them accordingly. tVNS has been used as a treatment for other medical conditions with few adverse events reported [9,19], so we adopted a safety target of fewer than 5 % of knee OA subjects reporting side effects.

2.6. Sample size justification

Based on the Napadow et al., 2012 study of tVNS for chronic pelvic pain [25], we expected a pain improvement of ≥2/10 on the 0–10 numeric rating scale after the tVNS intervention. Using the SD of 11.6 from the Napadow et al. study, an enrollment of 25 participants was computed to provide a 95%CI of width 1.0 around the estimate, for example, extending from 1.5 to 2.5 if the pain improvement estimate is 2. We increased the target sample size from 25 to 30 in case some participants do not complete the entire study visit. This sample size of 30 participants should provide adequate precision to determine whether the effectiveness of tVNS should be tested in a subsequent large-scale clinical trial.

2.7. Statistical analysis

Descriptive statistics were computed to characterize the participants and summarize the feasibility, acceptability, and safety of the tVNS intervention. For the main analyses, we examined the extent to which the outcome measures (knee pain, QST measures, and HF) changed immediately and 15 min after the tVNS intervention using separate linear mixed models with each participant as a random effect, adjusting for age, sex, and body mass index. The statistical significance level was set at a 2-sided α level of 0.05 for all analyses. All analyses were conducted using R version 3.6.3.

3. Results

We screened 105 people and included 30 participants with knee OA between December 2022 and June 2023 (Fig. 2).

The mean age of the participants was 55 years, the mean body mass index was 33, and the majority were female (67 %) and people of Hispanic background (83 %) (Table 1). The baseline mean knee pain during the 20-m walk was 3.1 on a 0–10 pain scale. The mean PPT, TS, and CPM values were 3.73 kgf/cm^2,1.2, and 0.97, respectively. The mean HF value was 331 ms^2.

3.1. Feasibility, acceptability, and safety of a 60-min tVNS intervention for people with knee OA

All 30 participants fully completed the 60-min tVNS intervention without any breaks during the intervention. 28 out of 30 (93 %) participants had no side effects or adverse events and completed the intervention without difficulty. One experienced momentary slight nausea while another participant experienced momentary dizziness. Both participants presented with these symptoms right after the 60-min tVNS intervention, but those symptoms were relieved after a few minutes. These side effects from tVNS have been commonly reported and are considered to be minimal side effects in other conditions [9,19]. Additionally, 28 out of 30 (93 %) participants expressed the willingness to return if there were more tVNS sessions.

3.2. Efficacy of tVNS for people with knee OA

Changes in the outcome measures after the tVNS intervention are presented in Fig. 3.

3.2.1. Knee pain

11 out of 30 participants (37 %) exceeded the minimal clinically important improvement after tVNS. Compared to baseline, knee pain was

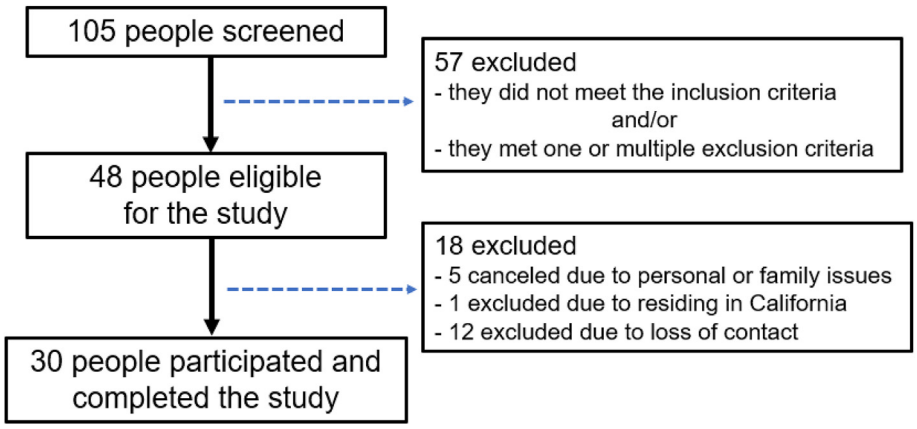

Fig. 2. CONSORT diagram.

reduced by 1.27 (95 % CI: −1.74, −0.80, $p < 0.001$) immediately after and by 1.87 (95 % CI: −2.33, −1.40, $p < 0.001$) 15 min after the tVNS intervention (Fig. 3A). Furthermore, 11 out of 30 participants (37 %) exceeded the minimal clinically important improvement.

3.2.2. *Quantitative sensory testing*

PPT and TS were not changed after the tVNS intervention (Fig. 3B and C): changes in PPT immediately and 15 min after the tVNS intervention were −0.16 (95 % CI: −0.47, 0.15, $p = 0.32$) and −0.06 (95 % CI: −0.38, 0.25, $p = 0.68$), and changes in TS immediately after and 15 min after the tVNS intervention were −0.25 (95 % CI: −0.70, 0.20, $p = 0.28$) and −0.29 (95 % CI: −0.73, 0.16, $p = 0.22$). In contrast, CPM was improved by 0.11 (95 % CI: 0.04, 0.19, $p = 0.01$) and 0.07 (95 % CI: −0.01, 0.15, $p = 0.07$), respectively, though it was of borderline statistical significance 15-min after the intervention (Fig. 3D).

3.2.3. *Parasympathetic function*

HF power increased by 213.29 (−0.38, 426.96, $p = 0.06$) and 234.17 (95 % CI: 20.49, 447.84, $p = 0.04$) immediately after and 15 min after the intervention, respectively, though it was of borderline statistical significance immediately after the intervention (Fig. 3E).

4. Discussion

This is the first study to evaluate the safety and efficacy of tVNS for people with knee OA. Our data demonstrated the safety, feasibility, and acceptability of a tVNS intervention as a pain-relieving treatment for people with knee OA. In addition, we found improvements in knee pain, descending pain inhibition, and parasympathetic function while measures of central sensitization were not changed. Our preliminary findings provide important insights into developing novel non-pharmacological treatments in a large clinical trial targeting parasympathetic function and central pain mechanisms to ameliorate pain in people with knee OA.

Table 1
Baseline participant characteristics.

Baseline Participant Characteristics	N = 30
Age (years), mean (SD)	55.0 (7.8)
Women, n (%)	20 (66.66 %)
Body mass index (kg/m^2), mean (SD)	33.1 (6.2)
Ethnicity, Hispanic, n (%)	25 (83.3 %)
Knee pain with a 20-m walk, 0–10 pain scales, mean (SD)	3.1 (2.1)
PPT, kgf/cm^2, mean (SD)	3.73 (1.53)
TS, continuous, mean (SD)	1.2 (1.4)
CPM, continuous, mean (SD)	0.97 (0.22)
HF, milliseconds squared (ms^2), mean (SD)	330.9 (519.3)

PPT: pressure pain thresholds, lower values reflect greater central pain sensitivity, TS: temporal summation, computed as post-stimulation 0–10 pain rating subtracted from pre-stimulation 0–10 pain rating, post-stimulus pain rating – pre-stimulus pain rating >0 indicates the presence of temporal summation; CPM: conditioned pain modulation computed as a ratio of post-conditioning stimulation PPT (PPT2) to pre-conditioning stimulation PPT (PPT1), a ratio ≤1 indicates inefficient CPM; HF: High frequency power, higher values indicate greater parasympathetic activity.

All of our participants completed the full 60-min tVNS protocol without any major side effects and >one-third exceeded the minimally clinically important threshold for knee pain improvement [30,45]. This suggests that improvement of their symptoms might be derived from improvement of parasympathetic function and/or central pain mechanisms because no local intervention to the knee was applied. This finding is aligned with prior studies in hand OA [22], chronic pelvic pain [25] and chronic low back pain [23], where tVNS improved pain at a body site that was also distal to the tVNS application site.

We also found that parasympathetic function as assessed with HF power increased after tVNS. HF power of heart rate variability has reliably and validly assessed what may be the target engagement of tVNS (i.e., the efferent vagus nerve) for many disorders [4,46], and our results suggest that tVNS adequately engaged the cardiovagal pathway and altered parasympathetic function in our sample with knee OA. This finding is aligned with prior findings on changes in parasympathetic function after tVNS [47,48]. These studies reported an increase in HF power of approximately 100 ms^2 to 500 ms^2 following the intervention, while the improvement in our sample of individuals with knee OA also falls within this range. Improvement of parasympathetic function potentially has various biological effects, including anti-inflammatory effects and enhancing the release or activity of endogenous analgesic molecules (e.g., norepinephrine, serotonin, endogenous opioids) in the descending pain modulatory pathways in the central nervous system [4]. Since systemic inflammation and diminished analgesic molecules contribute to central pain mechanisms [13,14], our tVNS intervention might improve knee pain and central pain mechanisms by adjusting parasympathetic function. In support of this, our data demonstrated the efficacy of the tVNS in improving the efficiency of descending pain inhibition as assessed with CPM, potentially indicating an increase in the release or activity of those analgesic molecules after the tVNS. These findings are consistent with prior data on exercise-induced hypoalgesia, where pain-relieving effects from exercise (i.e., a non-pharmacological treatment for pain) are associated with improvement of anti-inflammatory mechanisms and/or activation of the descending pain modulatory pathways involved in CPM [49,50].

In contrast, PPT and TS did not improve after the tVNS intervention. This preliminary finding may indicate that tVNS might not have effects on central sensitization, i.e., alterations in ascending pain pathways, but rather effects may be primarily through descending pain modulatory pathways. To our knowledge, only two prior studies have examined PPT

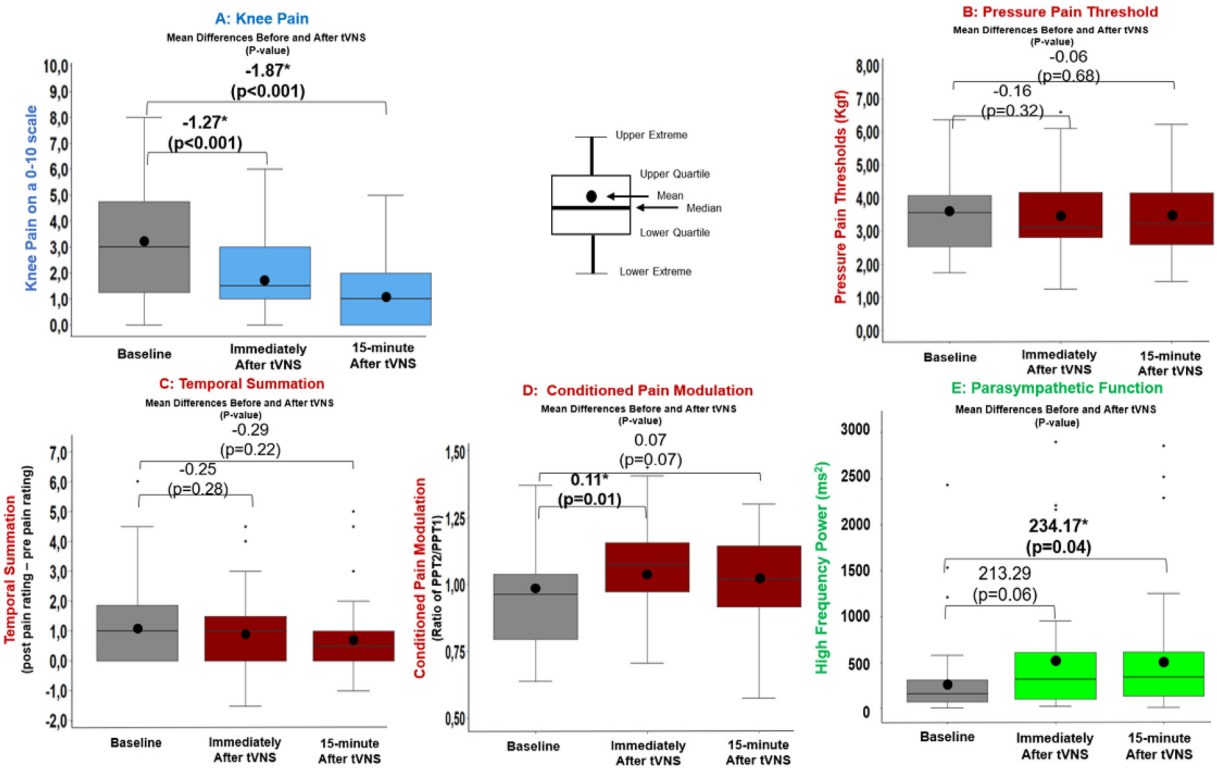

Fig. 3. Changes in Outcomes post-tVNS Intervention.
Knee pain: A higher score represents greater knee pain; improvement when the mean change is "-", negative; Pressure Pain Threshold: A lower value indicates greater central pain sensitivity; improvement when the mean change is "+", positive; Temporal Summation (post pain rating – baseline rating): a higher value indicates greater central pain sensitivity; improvement when the mean change is "-", negative; Conditioned Pain Modulation (post-PPT/pre-PPT): A lower value indicates more inefficient conditioned pain modulation; improvement when the mean change is "+", positive; High Frequency Power: A higher value represents greater parasympathetic function; improvement when the mean change is "+", positive.

and/or TS after tVNS interventions in chronic pain conditions and have conflicting results [23,25]. These studies used a tVNS intervention with small sample sizes, similar to our study. Thus, current understanding of tVNS efficacy on central sensitization is likely inconclusive due to low precision and/or a single tVNS session, which warrants future studies with larger samples and multiple sessions to confirm our results.

We have several limitations to acknowledge. First, we did not have a control group and therefore the efficacy of tVNS might be due to placebo or other non-specific effects. Secondly, a single tVNS intervention may not be clinically applicable or only have limited temporal effects on chronic pain. Third, because of the nature of the pilot study, our findings might be confounded. For example, negative affect has been reported as an effect modifier to tVNS interventions [25]. Fourth, we did not control for HRV-affecting substances (e.g., nicotine, caffeine) and the assessment time, which might influence HRV. However, our pilot study assessed the change in HRV pre- and post-tVNS on the same day within the same individuals, assessed within a 1-h period. Thus the use of these substances, as well as circadian effects, are broadly controlled for within subjects; as such, variations in substance consumption and assessment time within the sample are unlikely to have confounded our results. Fifth, our HRV HF data may not fully account for ectopic beats and other artifacts due to the use of a proprietary algorithm. We also acknowledge that lying down or sitting quietly for 60 min may, in itself, increase HRV HF power. A future trial with a control group is needed to address these limitations. Sixth, we did not perform mediation analyses due to the exploratory nature to determine whether the improvement of knee pain was mediated by the improvement of parasympathetic function and/or central pain mechanisms after tVNS. Finally, most of our sample was people with Hispanic background and thus our findings may not be applicable to other demographic groups. However, despite these limitations, our novel preliminary data have shown promising signals of the safety, feasibility, acceptability, and efficacy of tVNS for symptoms of knee OA and support the promise of a larger study with multiple tVNS sessions, the addition of a control group, and controlling of potential confounders in diverse samples to develop tVNS as an effective and safe pain-relieving treatment for people with knee OA.

In conclusion, we have demonstrated the safety, feasibility, and acceptability of a 60-min tVNS as a pain-relieving treatment for people with knee OA. We found that the tVNS intervention improved knee pain, central pain inhibition, and parasympathetic function, suggesting that improvement of knee pain might be derived from improvement of parasympathetic function and/or central pain mechanisms as no local therapy was applied. Our pilot study has provided important preliminary insights into developing novel non-pharmacological interventions with innovative targets to ameliorate knee pain in people with knee OA. Larger clinical trials are needed to evaluate the effects of tVNS compared with a control group with more robust methodologies.

Credit author statement

Kosaku Aoyagi: conceptualization, methodology, validation, formal analysis, resources, writing original draft, writing review & editing, visualization, supervision, funding acquisition; **Elias Rivas:** investigation, data curation, writing – review & editing, project administration; **Roxanna Shababi:** investigation, data curation, writing – review & editing, project administration; **Robert Edwards:** conceptualization, methodology, validation, writing review & editing; **Michael LaValley:** methodology, validation, formal analysis, writing – review & editing: **Julia Lechuga:** conceptualization, methodology, validation, writing review & editing; **Vitaly Napadow:** conceptualization, validation, writing – review & editing; **Tuhina Neogi;** conceptualization, methodology, formal analysis, validation, supervision, writing review & editing.

Role of the funding sources

KA was funded by the College of Health Sciences award at The University of Texas at El Paso. The funding sources had no role in study design, data collection and analysis, data interpretation, or the decision to submit the manuscript for publication.

Declaration of competing interest

Vitaly Napadow is a paid consultant for Cala Health, a bioelectronic medicine company developing wearable neuromodulation therapies. Dr. Napadow's interests were reviewed and are managed by Spaulding Rehabilitation Hospital and Mass General Brigham in accordance with their conflict of interest policies. All other authors have no known conflicts of interest associated with this publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2024.100545.

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