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ORIGINAL RESEARCH

Acute Intermittent Hypoxia Did Not Alter Pain Sensitivity or Pain Intensity Ratings for Individuals with Chronic Low Back Pain: A Pilot Study

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Aims and Objective: The purpose of this pilot study was to explore whether AIH produces changes in pain sensitivity or in reports of self-reported pain intensity for individuals with low back pain.

Methods: In a quasi-experimental, cross-over design we compared participants (n = 9) exposed to normal room air and hypoxia using a commercially available gas blender. The treatment period consisted of 5 consecutive days of randomly assigned to AIH or room air. For the participants initially randomized to AIH there was cross-over to receive 5 more consecutive days of room air. Therefore, this design allowed for between group and within subject assessment of AIH effects. Pain sensitivity was assessed with quantitative sensory testing (QST) for posterior superior iliac spine pressure threshold, plantar thermal threshold, and peak pain ratings. Self-reported pain intensity for low back pain was assessed via the Brief Pain Inventory.

Results: There were no between group differences for AIH and room air in pain sensitivity or self-reported pain intensity. In the within subject analyses larger effect sizes favoring AIH were detected for plantar measures of pain sensitivity but not for self-reported pain intensity.

Conclusion: This study, while presenting null findings, describes an initial step in determining whether AIH can be used to increase pain relief. Based on this pilot study we offer guidance for future research including study design, AIH dosage, participant selection, and using AIH in combination with non-pharmacologic treatments.

Keywords: hypoxia, hypoalgesia, low back pain, pain sensitivity

Introduction

In non-human animal models, acute intermittent hypoxia (AIH) has been shown to induce plasticity in motor neurons.[1] The mechanisms of AIH vary and include activation of carotid chemo afferents that stimulate episodic serotonin release,[2] which subsequently strengthens synaptic input and output of motor nuclei.[2–4] The effects of AIH may be most notable in breathing where the persistent increase in phrenic nerve burst amplitude following repeated exposure to AIH has resulted in long-term facilitation.[5] Accordingly, increases in breathing capacity have been demonstrated after exposure to AIH in non-human animal models.[6]

AIH has been safely used in humans for many years, including to improve performance in athletic populations[7–9] and for enhancing neuroplasticity for individuals with neurologic injury.[10] The duration of AIH varies based on the population of interest. For athletes AIH exposure can be for several hours while for individuals with neurologic injury AIH exposure is much shorter. That is, in patients with chronic spinal cord injury 15 cycles of 60–90 s of AIH followed by 60 s of room air increased ankle plantar flexion torque by more than 80%.[11] Furthermore, improvements in 10-meter walk times and 6-minute walk distances were observed following short-term exposure to AIH in patients with chronic spinal cord injury when combined with walking at maximal sustainable exertion.[12]

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Specific to this pilot study, the effect of AIH on sensory nerve function has, to the best of our knowledge, not been reported in humans. This is despite the potential shown for enhancing neuroplasticity in individuals with spinal cord injury.[10,13,14] The rationale for investigating AIH influence on sensory nerves is further driven by chronic pain now being conceptualized as a disorder of the nervous system.[15] Hence, there is merit in investigating treatments for their potential for pain relief that have already shown therapeutic promise in other neurologic patient populations. Accordingly, the exploration of AIH and its impact on sensory processing for those experiencing pain is a logical progression of the work of AIH enhancing excitability of motor neurons.[10] Indeed the potential of AIH has been explored for improving outcomes for cardiac rehabilitation[16] but has not been investigated for improving outcomes for patients with pain conditions to the best of our knowledge. Given the increased interest in non-pharmacologic treatments for pain,[17] the potential for AIH treatment to inhibit the perception of pain could provide important proof of concept for future use of AIH as a therapeutic agent alone or in combination with other pain treatments.

The purpose of this pilot study was to explore whether AIH exposure produces changes in pain sensitivity or patient-reported pain intensity reports. Pain sensitivity was measured with quantitative sensory testing (QST), which has successfully detected short-term pain sensitivity changes in our prior spinal manipulation work.[18–22] Therefore, by using a similar experimental approach we investigated AIH for its efficacy in reducing pain sensitivity or self-reported pain intensity across two different QST modalities. Our hypothesis is that we expect AIH to result in short-term reduction of pain sensitivity which would provide impetus for larger scale investigation of AIH as a pain-relieving modality alone or as a way to increase effects of existing pain-relieving modalities. In contrast we did not have a specific hypothesis regarding the impact of AIH on self-reported pain intensity. These data were collected in an explanatory manner to inform future direction as any favorable changes in pain intensity would strengthen the case for further investigation of AIH.

Materials and Methods

Design and Overview

This pilot study was planned to be a quasi-experimental design including participant cross-over after random assignment to AIH or room air control. The first visit was a screening visit and if eligible and informed consent was obtained, the participant was scheduled for additional study visits. In the first week of the full study, participants completed daily study visits at the Duke Early Phase Clinical Research Unit (DEPRU). Specifically, the intervention phase consisted of 5 consecutive days of receiving either AIH or room air in a blinded manner. Order of air delivery was randomly determined for the first week with cross-over to the opposite condition occurring during the second week. Self-report measures were completed at the first study visit and fifth study visit. QST measures were assessed prior to and following the intervention on the first, third, and fifth study visit. Forty-eight hours after the fifth session participants received a telephone call or text from research staff to collect additional pain intensity ratings and to review any adverse events.

COVID Impact

Recruitment of this study occurred prior to the start of the pandemic. However, recruitment was halted in February 2020 due to restriction of research activities at our institution. When research activities were allowed, this study was given a lower priority and therefore did not continue recruitment in 2020. At that time, a decision was made to halt recruitment for pragmatic reasons (e.g. this was a pilot study, original research staff trained in protocol had turned over, and no funds remained to continue research activities). The main impacts of COVID on this study were (1) lower enrollment than originally planned (i.e. we had planned to recruit up to 15 participants) and (2) not all participants completed the cross-over part of the study. For these reasons we made the a priori decision (i.e. before completing the data analysis) to present data on all the enrolled participants for the first week comparing AIH and room air (i.e. between subject comparisons) and then for the second week we would only include data on those getting AIH followed by room air (i.e. within subject comparisons). Prior to study initiation ethical approval was obtained from the Duke University Institutional Review Board and all participants provided written informed consent prior to study enrollment. In addition this study complies with the Declaration of Helsinki's general principles for conducting ethical research with human participants.

Participants

Study participants with low back pain (LBP) were recruited using a volunteer database, electronic health record query, and study flyers. Potentially eligible study participants were invited via REDCap to attend a screening visit. At the screening visit study staff discussed the study, screened for eligibility, and obtained written informed consent if appropriate. Eligibility screening included negative tests for sickle cell disease and pregnancy. In addition to self-report of health conditions, the electronic health record was used to screen for presence of serious pathology while seeking care at Duke Health (see Exclusion Criteria below). Eligible participants meeting eligibility criteria (see below) and providing written informed consent were enrolled in the study. Participants received compensation for completing research activities.

Inclusion Criteria

- Complain of pain in the lumbar region, between T12 and S1, with a duration of at least 1 month.
- Report at least 2/10 for the "worst" pain intensity rating (i.e. highest rating) in the last 24 hours. This threshold was selected because we were recruiting from a research registry and not individuals currently seeking care for LBP. As such we included a pain intensity threshold to ensure participants were still actively experiencing LBP and also that the pain was at a high enough intensity to be somewhat representative of individuals seeking care.
- Age between 18–65 years.

Exclusion Criteria

- Pain that radiates below the knee.
- Signs and symptoms of lumbar nerve root compression (e.g. sensory loss in dermatomal pattern, myotome weakness, and/or reflex changes).
- Signs and symptoms of cauda equine syndrome (e.g. bowel and bladder changes).
- Confirmed lumbar spinal stenosis.
- Prior surgery to the lumbar spine.
- Other spinal disorders including metastatic disease, visceral disease, or fracture.
- Currently prescribed opioid, TENS, or massage treatment for LBP and unable to terminate the treatment during the study period.
- Known pregnancy in women of child-bearing potential.
- Known sickle cell disorder.
- Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Measures

Characterizing Low Back Pain: Participants completed several questionnaires to characterize their LBP including the Optimal Screening for Prediction of Referral and Outcome Yellow Flag (OSPRO-YF)[23,24] and Review of Symptoms (OSPRO-ROS)[25] Questionnaires. These questionnaires have been validated in our prior investigations of musculoskeletal pain and capture information on pain-related beliefs and coping styles and reporting of symptoms from other body systems respectively.[26] Participants also completed the 10 item Oswestry Disability Questionnaire (ODQ)[27,28] and two items from the NIH Research Task Force (RTF) minimal data set for chronic LBP that allow for categorization of high impact chronic pain.[29] These questionnaires were used to provide descriptive data for the participants and only collected pre-intervention.

Quantitative Sensory Testing: The QST protocols were developed from our prior studies involving thermal and pressure stimuli.[18–22] A standard set of instructions was used so that participants receive the same information prior to QST testing regarding the nature of the testing and the use of the rating scale. All QST measures were collected by a research assistant trained in application and blinded to AIH or room air assignment. Multiple QST trials were administered and the following specific tests were included in the data analysis:

- Pressure pain threshold was assessed in kilograms (kg) at right and left posterior superior iliac spine (PSIS). The 3 trials from the right and left sides were averaged and included in the data analysis as PSIS Pressure Threshold.
- Thermal pain threshold was assessed in degrees Celsius at the right and left plantar surfaces of the foot. The 3 trials from the right and left sides were averaged and included in the data analysis as Plantar Thermal Threshold.
- Participants were exposed to three thermal stimuli at 46, 47, and 48 degrees Celsius for 15 seconds, and asked to rate the intensity of the stimuli on a scale of 0 (no pain) – 100 (worst pain imaginable). The temperature that corresponded with an average pain intensity rating of 50 was then used in a separate test for peak pain intensity. In that test, the thermal stimulus was applied for 30 seconds and pain intensity ratings from 0–100 were collected for 30 seconds. There were two trials and the highest pain intensity rating was selected from each trial with the average used in the analysis as Plantar Peak Pain Rating.

Self-Reported Pain Intensity: Participants completed the Brief Pain Inventory (BPI) for clinical pain intensity ratings of LBP.[28,30] Only BPI items 3, 4, and 6 were administered corresponding with current, best, and worst pain intensity ratings over the past 24 hours and a 0–10 scale was used. These items were summed and the average of the three was used in the data analysis. The BPI was for screening eligibility and then assessed at the first and fifth interventions sessions during study visits; as well as 48 hours after completing the fifth intervention session by phone or text.

Intervention

AIH was delivered via a commercially available gas blender, Reduced Oxygen Breathing Device (ROBD) that was programmed to deliver a specific inspired oxygen fraction (FiO_2) of 8% and thereby attain the subsequent targeted pulse oximeter saturation of 80%. The single AIH sequence comprised 15 cycles with each cycle consisting of 60 s of FiO_2 21% followed by 90 s of FiO_2 8%. The duration of the single AIH was a total of 37.5 minutes, performed each day Monday through Friday. The same approach was used to deliver room air to maintain blinding. The order of the AIH delivery of either air or 8% O_2 was randomly assigned for each participant, and participants remained blinded to the actual protocol received.

Data Analysis

Descriptive statistics were generated using means and standard deviation (sd) for continuous measures and frequencies for categorical measures. For between group (room air vs AIH) comparisons we used repeated measures, general linear models to compare intervention conditions on the three measures of pain sensitivity (PSIS Pressure Threshold, Plantar Thermal Threshold, and Plantar Peak Pain Rating) and the single measure of self-reported pain intensity (BPI). This resulted in four separate models, with each dependent variable being predicted with a factor for intervention and time; the interaction term (intervention x time) was the primary statistical test of interest. Given this was a pilot study with a small sample size and limited statistical power, we used a liberal Type I error criterion of 0.15 in our hypothesis testing of between group differences.

For within subject comparisons we used paired t-tests comparing the pre/post scores when participants received AIH or room air. This resulted in two paired t-tests for each variable of interest, as each participant received both conditions if included in this analysis. This was more of an exploratory analysis so no Type I error rate was set. Instead we present the data with mean differences (sd), effect sizes, and p-value for interpretation of these findings.

Finally, we tested differences in oxygen saturation in between and within subject analyses as a manipulation check of the physiologic effect of AIH. For the between group analysis we used the same repeated measures model as described above, except that the intervention term was the main factor of interest statistically. For the within subject analysis we tested the mean change in oxygen saturation compared with a value of 0 to determine the impact of receiving AIH or room air. A paired *t*-test would not have been informative because it would have compared pre to post differences which would be expected to be 0 when receiving the same intervention.

Results

The participants (n = 9) enrolled in this study were 7 females and 2 males with 5 identifying as White, 2 identifying as Black, 1 identifying as American Indian/Alaska Native, and 1 selecting Other for Race but not providing any additional

information. The mean age of the sample was 48.3 years (sd = 16.8) and 7/9 (77.8%) meeting criteria for having High Impact Chronic LBP using the NIH Task Force definition. The ODI average score was 19.6 (sd = 7.4), OSRPO-YF count (range 0–11) average was 6.4 (sd = 2.5), and the OSPRO-ROS count (range 0–10) average was 2.8 (sd = 1.4).

Between Group Comparison of AIH and Room Air

Overall, there were no intervention x time interactions ($p > 0.15$) detected in the repeated measures models for the measures of pain sensitivity or clinical pain intensity (Table 1). This despite there being physiologic evidence that AIH resulted in a larger change ($p = 0.02$) in oxygen saturation for those receiving AIH compared with those receiving room air (Table 1). Figures 1 and 2 are included as visualizations of the between subject comparisons for measures representing pain sensitivity (PSIS Pressure Threshold) and self-reported pain intensity (Brief Pain Inventory).

Within Subject Comparison of AIH and Room Air

The within subject comparisons are presented in Table 2. Again, there was physiologic evidence that the change in oxygen saturation was different from 0 when receiving AIH, but not when receiving room air (Table 2). When receiving AIH, there were effect sizes larger than 0.30 noted for several of the pain sensitivity measures: PSIS Pressure Threshold, Plantar Thermal Threshold, and Plantar Peak Pain Rating. The direction of these effect sizes indicated decreased sensitivity for the Plantar areas, but increased sensitivity for the PSIS. When receiving room air, there were no effect sizes larger than 0.30 noted for the pain sensitivity measures. Even though the mean differences were very similar, effect

Table 1 Between Group Comparisons of Hypoxia and Room Air

Physiologic Change				
Oxygen Saturation Change	*Day 1*	*Day 3*	*Day 5*	p-value*
Hypoxia	−12.7 (7.9)	−12.3 (4.1)	−15.5 (8.2)	0.02
Room Air	−1.0 (1.4)	−2.0 (1.4)	−1.0 (0.0)	
Quantitative Sensory Testing				
PSIS Pressure Threshold (kg)	*Day 1*	*Day 3*	*Day 5*	p-value*
Hypoxia	4.4 (1.8)	4.4 (1.9)	3.9 (1.2)	0.62
Room Air	4.9 (2.4)	5.8 (2.5)	4.9 (2.7)	
Plantar Thermal Threshold (Celsius)				p-value*
Hypoxia	44.7 (2.4)	44.7 (2.1)	45.7 (3.2)	0.63
Room Air	46.8 (4.5)	47.5 (3.5)	46.5 (4.9)	
Plantar Peak Pain Rating (0–100)				p-value*
Hypoxia	43.0 (14.4)	40.6 (15.0)	37.4 (19.2)	0.17
Room Air	34.5 (7.8)	23.5 (9.1)	22.5 (6.4)	
Self-Reported Pain Intensity Rating				
Brief Pain Inventory (0–10)	*Day 1*	*Day 5*	*Follow Up*	p-value*
Hypoxia	4.0 (1.1)	3.7 (1.9)	3.8 (1.0)	0.53
Room Air	4.2 (0.2)	3.2 (2.6)	2.5 (0.7)	

Note: *Indicates that p-value is for intervention x time interaction.

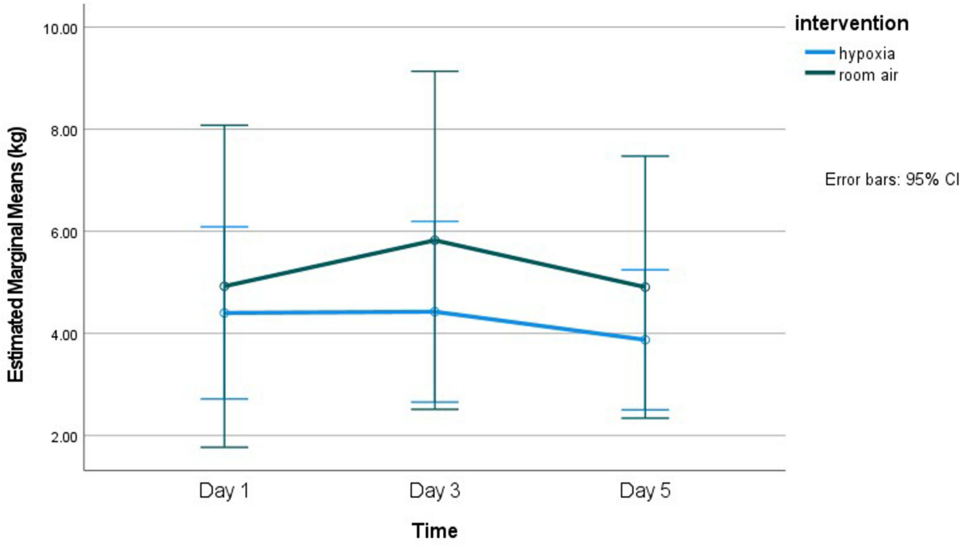

Figure 1 Between group comparison of average pain threshold at posterior superior iliac spines.

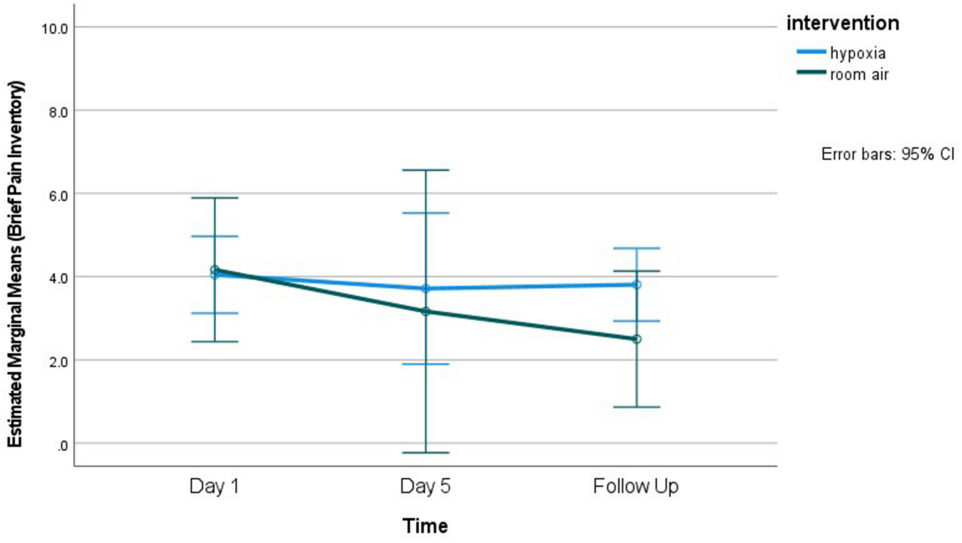

Figure 2 Between group comparison of average pain intensity ratings.

sizes for the self-reported pain intensity rating were larger when receiving room air versus AIH (Table 2, 0.39 and 0.16 respectively). Upon closer inspection this was due to the noticeably smaller variation when receiving room air versus AIH (Table 2, 0.88 and 2.01 respectively).

Discussion

This pilot study investigated whether five consecutive days of an AIH treatment produced changes in pain sensitivity or self-reported pain intensity for individuals with LBP. The motivation for this study was driven by the promising findings of AIH for individuals with spinal cord injury for improving motor function by enhancing potential for neuroplasticity.[4,10,11,14,31–33] In contrast to what has been observed for motor nerve outcomes, we did not find that AIH impacted sensory function when compared with room air. Thus, our primary conclusion is that there may be limited potential for AIH to impact sensory function, thereby reducing pain, at least when represented by measures of pain

Table 2 Within Subject Comparisons Between Receiving Hypoxia and Room Air

	Receiving Hypoxia			Receiving Room Air		
Physiologic Variable	Average (sd)		*p*-value[#]	Average (sd)		*p*-value[#]
Oxygen Saturation Change	16.3 (3.4)		< 0.01	1.9 (2.3)		0.07
Pain Related Variables	Post-Pre Difference	Cohen's D	*p*-value	Post-Pre Difference	Cohen's D	*p*-value
PSIS Pressure Threshold (kg)	−0.53 (1.1)	0.49	0.12	−0.07 (0.73)	0.09	0.41
Plantar Thermal Threshold (Celsius)	0.94 (2.9)	0.32	0.21	0.11 (2.9)	0.04	0.92
Plantar Peak Pain Rating (0–100)	−5.6 (6.8)	0.82	0.07	1.4 (8.1)	0.17	0.36
Brief Pain Inventory (0–10)	−0.33 (2.01)	0.16	0.33	−0.34 (0.88)	0.38	0.17

Notes: [#]For oxygen saturation change a one sample mean test comparing the value with 0 was used instead of a paired *t*-test since there is no expected pre- to post-test difference across sessions when receiving the same intervention.

sensitivity or intensity. Given that this was an initial attempt at investigating AIH as a treatment for pain relief alone, we present some considerations for future research in AIH and pain.

A strength of this study was directly measuring the physiologic effects of AIH by change in oxygen saturation. This option is not possible for many LBP interventions and as expected we consistently observed that change in oxygen saturation was greater for AIH than room air. Despite evidence of a physiologic effect of AIH, there were no changes in pain sensitivity or pain intensity. Indeed, the only evidence of intervention impact was observed in within subject analyses, which indicated larger effect sizes for AIH but not room air. Interestingly AIH effects were in different directions based on the modality and location being tested. At the PSIS, we tested pressure pain threshold and found that AIH was associated with increased pain sensitivity (i.e. lower kg reported to reach pain threshold). At the plantar location we used a thermal stimulus and in contrast AIH was associated with decreased pain sensitivity (i.e. higher temperature for pain threshold and lower pain ratings for peak).

Given that the within subject analyses were exploratory, interpreting these as "AIH effects" is premature. However, these findings provide an indication that larger periods of AIH should be investigated in future research studies, similar to those reported in studies investigating improved performance in athletic populations.[7–9] We based our dosing paradigm on spinal cord injury protocols, but longer AIH exposure times may have been indicated. Future studies using longer AIH exposure times, via higher within session intensity of hypoxia and/or for longer than 5 days of treatment, could address this important issue related to what constitutes adequate dosing for individuals with LBP. In particular if larger effects for pain sensitivity are observed with increased exposure time for AIH, that might indicate better potential as a therapeutic agent.

A major consideration when interpreting these findings is that the COVID pandemic limited the number of participants enrolled. We had planned to enroll up to 20 participants, but restrictions placed on research during the height of the pandemic halted recruitment for at least 6 months. By the time this study received approval to resume activities we had lost momentum due to staff turnover and limited funding. Therefore, a decision was made to analyze the available data. Another aspect of the original plan was to use a cross-over design with 2 consecutive weeks of treatment with a washout period of at least 48 hours between the treatment weeks. This design element was appealing because it followed earlier work in AIH[11] and allowed us to investigate both between group and within subject effects in the same pilot study. However, that design also introduced vulnerability for participants only completing the first week of the study. This vulnerability was becoming evident before the COVID pandemic as several participants only completed the first week. When research activities were stopped other participants had only completed the first week. Therefore, our recommendations moving forward in future studies of AIH would be to recruit a larger sample and prioritize between group designs that limit dropout.

Additional considerations from this pilot study relate to participant selection and testing AIH exposure as a treatment adjunct. For participant selection we did not exclude individuals with chronic LBP and this resulted in 7/9 (77.8%) participants meeting the NIH definition of having high impact pain.[29] This large percentage of those already having

chronic LBP could be another reason for these null findings. Unfortunately, we did not collect information beyond the NIH definition so did not have more granular data on duration of LBP so these participants could not be classified in a different way (e.g. subacute LBP). Therefore, one additional suggestion to consider in future studies would be to update eligibility criteria to exclude those who already have high impact chronic LBP and collect duration of pain in addition to classifying as having high impact LBP or not. Another suggestion would be to consider higher pain intensity thresholds for those receiving AIH. This would allow for a test of AIH effects in a group of individuals that arguably have a higher likelihood of responding positively due to not already having long-standing pain interfering with daily activities and higher pain intensity. For testing AIH as a treatment adjunct we did not incorporate this in our design, following what had been models in spinal cord injury studies where AIH exposure alone was assessed for its impact on upper[33] or lower extremity[11] motor function. Similar to those studies our reason for testing AIH alone was that we wanted to isolate its impact on pain sensitivity and pain intensity, without also factoring in a treatment response. AIH has been further studied in combination with other therapeutic agents, such as caffeine, and its effects on motor function were enhanced.[34] Therefore, we encourage future pain researchers to also consider AIH as a treatment adjunct as this study did not directly address that issue. That is, from our findings we can only report on AIH's direct impact on these pain measures and not whether it has potential to enhance the effects of other nonpharmacologic pain treatments.

Conclusions

This pilot study investigated whether AIH treatment produced changes in pain sensitivity or self-reported pain intensity for individuals with LBP when compared with room air. In contrast to what has been observed for motor nerve outcomes, there was very little evidence of a positive impact on pain sensitivity or self-reported pain intensity. Thus, our primary conclusion is that there may be limited potential for AIH to impact sensory function. Based on these results we offer guidance for future research including study design, AIH dosage, participant selection, and investigating AIH in combination with other non-pharmacologic treatments.

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Disclosure

The authors report no conflicts of interest in this work.

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