Original Article

EFFECT OF PERIPHERAL NEUROMODULATION ON HEADACHE IN POST COVID-19 SURVIVORS

Doha G. Awaad[1*], Abdulalim A. Atia[1], Enas Elsayed[2], Tamer S. Elserafy[3], Rania M. Tawfik[1]

[1] Department of physical therapy for neurology and neurosurgery, Faculty of Physical Therapy, Cairo University.
[2] Faculty of Physical Therapy, Galala University.
[3] Faculty of medicine, Zagazig University.
Corresponding author: Doha G. Awaad, Department of physical therapy for neurology and neurosurgery, Faculty of Physical Therapy, Cairo University.

DOI: 10.47750/pnr.2022.13.S07.361

Abstract

Objective: The purpose of present study was to evaluate the impact of peripheral neuromodulation through vagus nerve stimulation on headache in Post COVID-19 survivors. Methods: Thirty Post COVID-19 survivors from both genders (17 females and 13 males) aged from 20 to 40 years who suffered from Post COVID-19 headache were recruited and randomized into two groups of equal number. Subjects in group A (study group) received transcutaneous vagus nerve stimulation as well as the designed physiotherapy program whereas subjects in group B (control group) underwent placebo transcutaneous vagus nerve stimulation on vagus nerve in addition to the same designed physical therapy program. The treatment was carried-out for 5 sessions each week for four weeks. Visual analogue scale (VAS) was used to measure the intensity of headache pain whereas the headache disability index (HDI) was used to measure the disability resulted from headache. Results: The findings showed significant decline in VAS and HDI post treatment in study group (A) and control group (B) in comparison with that pretreatment ($p<0.001$). Between-group analysis showed no significant difference between the two groups pretreatment ($p>0.05$), whereas there was significant decline in VAS and HDI in study group in comparison with that of the control group posttreatment ($p<0.05$). Conclusion: peripheral neuromodulation is more effective in managing headache in post COVID-19 survivors.

Keywords: Peripheral neuromodulation, Headache, COVID-19, Vagus nerve stimulation.

Introduction

The 1st cases of an unknown form of acute pneumonia were reported in Wuhan, China, in December of the year of 2019. The World Health Organization (WHO) announced it as a global pandemic on 11 March 2020 [1] and gave it the name Coronavirus Disease 2019 (COVID-19). Greater than 200 countries as well as territories throughout Asia, Europe, North America, Africa, in addition to South America have been affected by the COVID-19 pandemic [2]. Post-COIVD-19 Neurological Syndrome (PCNS) refers to the ongoing neurological involvement caused by the virus from the time of its initial infection to the protracted recovery process. Both the Wuhan observational study and also other international case reports suggest that COVID-19 can affect the entire neurological system [3].

According to the WHO, the symptoms are not limited to only respiratory manifestations but also, fatigue, dyspnea, and cognitive dysfunction are the most frequent symptoms of this condition. In addition to Anxiety and depression, pain in the muscles and joints, sleep disturbances, problems with your sense of smell or taste, and etc. [4,5].

Mekkawy et al. found, in their cohort study on Egyptian patients, headache to be a very common neurological symptom result from COVID-19 and may also appears as an initial manifestation accompanied by myalgia, dizziness, as well as action tremors [6].

A headache is a type of pain that affects the face and scalp with or without a clear cause and can be occur in various forms [7]. Disabling headaches affect several aspects of a person's life, including their ability to work and interact with others, their health, and their relationships with friends and family [8]. The WHO recognizes that headache sufferers who are under-recognized, under-diagnosed as well as under-treated, that is come back to the patient and financial effect of headache conditions [9,10].

Neuromodulation is a wide field of technologies that are widely described as the manner of inhibition, stimulation, adjustment, regulation as well as therapeutic change of activity using an electrical or chemical implementation, in the central, peripheral, or autonomic nervous system, either invasively or non-invasively [11].

Neuromodulation treatment is most often used to treat pain caused by ischemic pain, visceral pain, neuropathic pain, angina pectoris, peripheral arterial disease, epilepsy, urinary dysfunction, spasticity caused by spinal cord injury (SCI), cerebral palsy (CP), or multiple sclerosis (MS), as well as diabetes mellitus [12].

Neuromodulation, as a new branch of headache treatment, contains invasive surgical methods focused on structures which directly cause headache symptoms and signs and non-invasive methods that focus on the central or peripheral nervous system to modulate pain and other headache-related mechanisms [13,14].

More clearly, focusing on peripheral neuromodulation, as a growing field of study used for the treating of headache disorder aiming at pain reduction through directing structures in the nervous system usually responsible for in headache pathophysiology, including the vagus nerve (VNS) or sphenopalatine ganglion (SPG) aimed at stimulation [15,16].

The vagus nerve (tenth cranial nerve) plays a big role in pain processing and is responsible for transmission of peripheral inflammation signals to the central nervous system [17]. Vagus nerve stimulation gets approval from Food and Drug Administration (FDA) for somatic treatment of different pathologies [18,19]. Recent clinical and experimental studies have demonstrated the effect of vagus nerve stimulation as a therapeutic modality in many diseases including pain syndromes [20,21].

So, the aim of present study was to evaluate the impact of peripheral neuromodulation in the form of vagus nerve stimulation on headache in Post COVID-19 survivors.

Materials and methods

This is a randomized controlled clinical trial (RCT) carried-out to investigate the effect of peripheral neuromodulation in the form of vagus nerve stimulation on headache in Post COVID-19 survivors. The study was carried-out in the outpatient clinic in the Faculty of Medicine, Zagazig University and private clinics in the period from April 2022 to November 2022. The Physical Therapy Research and Ethics Committee at Cairo University gave their approval to this study (P.T.REC/012/003831).

Participants:

Thirty participants (17 females and 13 males) were clinically diagnosed with Post COVID-19 headache (up to 6 months after COVID-19 infection) and referred by the neurologist. Patients with moderate to severe pain according to VAS, and moderate to severe disability according to HDI. They aged from 20 to 40 years. They were initially identified with positive RT-PCR tests for SARS-CoV-2 by means of naso /oropharyngeal swabs or by Rapid antigen test.

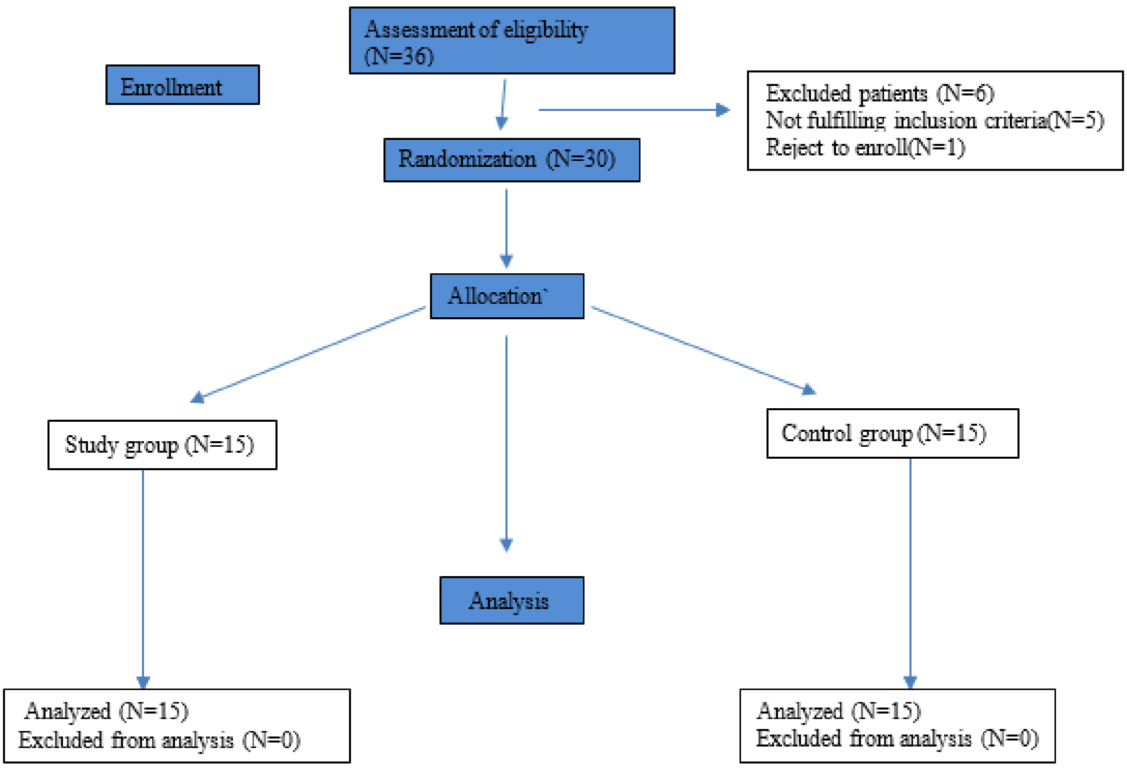
Patients were excluded if they had pre COVID-19 headache, ECG abnormality, orthostatic hypotension with symptoms, history of recurring vasovagal syncope, the patients who were taking NSAIDs were instructed to stop taking them 48 hours prior to the inclusion [22], Skin disease, other conditions such as cardiac arrhythmia, sleep apnea, pregnancy, etc.) [23] and chronic diseases need multiple medications, Primary psychiatric syndrome with or without CNS medication [24].

To ensure an appropriate sample size, a power analysis was done. The sample size was calculated to be 36 patients at a 95 % confidence interval, with an 80.0 % study power. Finally, the study involved 30 participants (6 participants were excluded). Each participant signed an informed consent form before enrolment.

Randomization:

Initial eligibility assessments were performed on 36 Post COVID-19 patients. Five patients failed to fulfill our inclusion criteria, and one patient rejected to participate in the study, the residual 30 patients were randomized into two groups of an equal number using computer generated random. The examiner was blinded to which group the patients belong (CONSORT Flow chart, Figure 1)

Figure 1: Flow chart of the study



Assessment procedures:

Assessment of pain intensity by Visual analogue scale (VAS):

A tool utilized to help one quantify the degree to which one is experiencing sensations and emotions like pain. The pain VAS is a 10-centimeter-long straight line, with zero pain on one end and extreme pain on the other end. A patient marks a point that matches the pain he or she feels [25].

Assessment of disability by Headache Disability Index (HDI):

The Headache Disability Index is composed of 25 questions. It is valid and useful in assessing the impact of headache and its treatment on daily living and quality of life [20]. In HDI, each question has only 3 possible responses:

YES = 4 SOMETIMES = 2 NO = 0

Total score of 10%-28% is considered to indicate mild disability

Total score of 30%-48% is considered to indicate moderate disability

Total score of 50%-68% is considered to indicate severe disability

Total score of 72% or more is considered to indicate complete disability

Treatment procedures

Group A: study group

Patients in this group received tVNS on the left branch of cervical vagus nerve as well as the designed physiotherapy program. For tVNS, the patients received 30 minutes of TENS five sessions per week for 4 weeks (an overall of 20 sessions). The intensity was 2mA with frequency of 25HZ, Adhesive electrodes with size of 2 cm^2 were used with the anode electrode (red one) placed on the left cervical vagus nerve and cathode (black one) placed below the cheek [24]. The left cervical vagus nerve was targeted since this branch has a lesser effect on the sinoatrial node than right one [27]. The designed physiotherapy program consisted of warm-up exercise [28], trigger points release [29,30], stretching exercise [28], craniocervical flexion exercise [31], postural correction and relaxation techniques [28], and muscle energy techniques [32].

Group B: Control group

The control group received placebo tVNS on the left cervical vagus nerve in addition to the same designed physical therapy program.

Statistical Analysis:

Age as well as period of affection were compared between groups using an unpaired t-test. The chi-square test was used to examine the distributions of sexes and headache types distribution among groups. The Shapiro-Wilk test was used to ensure that the data followed a normal distribution. Homogeneity among groups was examined using Levene's test for homogeneity of variances. The VAS and HDI scores of the two groups were compared using an unpaired t-test. The pre- and post-treatment outcomes of each group were compared using a paired t-test. All statistical analyses were performed with a p-value of less than 0.05 considered substantial. The Windows version of SPSS, a statistical program, was used for all analyses (IBM SPSS, Chicago, IL, USA).

Results

- Subject characteristics:

Table (1) revealed the patient's characteristics of the study as well as control groups. There was no significant difference among groups in age, period of affection, sex and headache type ($p > 0.05$).

Table 1. Subject characteristics.

	Study group	Control group	MD	t- value	p-value
	Mean ± SD	Mean ± SD			
Age (years)	30.8 ± 5.99	32.73 ± 6.74	-1.93	-0.83	0.41
Period of affection (weeks)	9.46 ± 4.53	8.33 ± 4.32	1.13	0.7	0.48
Sex, N (%)					
Females	8 (53%)	9 60%)		(χ^2 = 1.36)	0.71
Males	7 (47%)	6 (40%)			
Headache type, N (%)					
Migraine	4 (27%)	3 (20%)			
TTH	5 (33%)	5 (33%)		(χ^2 = 0.22)	0.89
Migraine & TTH	6 (40%)	7 (47%)			

SD, standard deviation; MD, mean difference; p-value, level of significance

Impact of treatment on VAS and HDI:

- Within group comparison:

Post-treatment scores of both VAS and HDI dropped significantly (p> 0.001), compared to their pre-treatment scores. Reductions in VAS and HDI in the experimental group were 62.79 and 45.73 %, while reductions in the control group were 40.59 and 25.08 % respectively. (Table 2).

- Between groups comparison:

The pre-treatment, there was no statistically significant difference between the two groups while the post-treatment, the VAS and HDI scores of study group were significantly lower than those of the control group (p< 0.05). (Table 2).

Table 2. Mean VAS and HDI pre and post treatment of study and control groups:

	Pre-treatment	Post-treatment				
	Mean ± SD	Mean ± SD	MD	% of change	t-value	p value
VAS						
Study group	6.80 ± 1.65	2.53 ± 0.91	4.27	62.79	14.21	0.001
Control group	6.06 ± 1.57	3.6 ± 1.5	2.46	40.59	14.92	0.001
MD	0.74	-1.07				

t- value	1.24	-2.34				
p value	***p = 0.22***	***p = 0.02***				
HDI						
Study group	63.26 ± 11.93	34.33 ± 11.19	28.93	45.73	19.91	0.001
Control group	61.13 ± 12.35	45.8 ± 13.41	15.33	25.08	11.15	0.001
MD	2.13	-11.47				
t- value	0.48	-2.54				
p value	***p = 0.63***	***p = 0.01***				

SD, standard deviation; MD, mean difference; p-value, probability value

Discussion

The study was conducted to evaluate the impact of peripheral neuromodulation in the form of transcutaneous vagus nerve stimulation tVNS on headache in Post COVID-19 survivors; Thirty post COVID-19 survivors from both sexes (17 females and 13 males) were included in this study. Their aged from 20 to 40 years. They were randomized into 2 groups of equal number: group A received tVNS as well as the designed physiotherapy program and group B received placebo tVNS as well as the same designed physiotherapy program.

Data were obtained from both groups regarding VAS and HDI before starting treatment and after 4 weeks of intervention.

According to the data analysis in the current study, the results of (tVNS) group revealed that there was a significant decline in the values of VAS as well as HDI post-treatment in the study group as compared to the control group ($p < 0.05$).

The significant decline in VAS and HDI scores indicated that tVNS might lessen headache pain and disability during therapy sessions by decreasing glutamate and neuronal activity in the spinal trigeminal nucleus as a result of chronic vagus nerve stimulation [34]. Vagus nerve stimulation has been shown to decrease trigeminal basin pain in recent investigations in rats [35]. This may be mediated via the vagus nerve's ascending anti-nociceptive action on the 2nd-order neuron of the spinothalamic as well as spinoreticular tracts, which is essential for the spinal nociceptive transfer to the trigeminal nuclear complex [36,37].

Additionally, the afferent vagal fibers, which are the most (80%), have been found to alleviate pain and reduce inflamation in animal investigations of arthritis, and their afferent fibers may do so independently by activating the brain's pain centers [38,39].

The findings of the study are convenient with the findings of Molero-Chamizo et al. [24] who evaluated the impact of non-invasive vagus nerve stimulation on fibromyalgia symptoms with the primary outcome was pain intensity, the results showed a significant improvement in pain after tVNS sessions.

Similarly, Tavanaiepour & Levy [40] discovered that peripheral neuromodulation was effective in the management of chronic migraine headache by using occipital nerve stimulation with a greater than 50% reduction of pain. Moreover, Timothy et al. (2020) [41] performed a systematic review on peripheral nerve stimulation as a type of peripheral neuromodulation in 14 RCTs for various painful conditions including headache pain with strong evidence supporting the use of peripheral neuromodulation to treat headache pain.

Also, Yuan et al. [21] stated that noninvasive vagus nerve stimulation exhibits a greater safety profile and seems similarly effective to their invasive techniques. This came back to the effect of the vagus nerve in modulating afferent pain signals to the central nervous system, autonomic nervous system and immune function which is altered in COVID-19 patients, thus those patients benefited from this application.

Regarding our results about the headache type, the tension-type headache was found in most patients, these results are convenient with Fernández-Pérez et al. [29] who stated that Post COVID-19 headache usually adopted the criteria of tension-type headache which is defined as a bilateral pain, mainly localized over the temporomandibular or frontal region with pressing feature in addition to with moderate to severe intensity.

Similarly, Hokenek et al. [42] demonstrated that TENS application is a fast-acting, effective, economical therapy and has fewer side effects for the management of acute migraine in the emergency department through using a stimulating TENS device on the supraorbital nerve with VAS as an evaluating scale. Besides, Tassorelli et al. [43] demonstrated the tolerability of vagus nerve stimulation on headache by using low-voltage electric current for 30 minutes up to 60 minutes after the onset of the attack and concluded that efficacy continued up to 120 min which is consistent with the previous studies on oral triptans and NSAIDs.

Also, Molero-Chamizo et al. [24] stated that tVNS should be applied on the left branch of the vagus nerve to avoid the cardiac effect of the vagus nerve by the right cervical branch of the vagus nerve [44], and cardiac arrhythmias [45, 46].

Also, Schoenen et al. & Lipton et al [47,48] reported that the traditional drugs utilized for the treatment of migraine possess a broad spectrum of adverse effects in comparison with TENS devices application, and these adverse effects may make patients to stop the treatment leading to have chronic medical issues or make the treatment ineffective.

Moreover, Llamas et al. & Ford et al. [49,50] stated that TENS treatment not frequently produce such dangerous adverse effects, except for incorrect usage or allergic interactions. Also, tVNS is a well-tolerated and safe technique associated with treatment satisfaction and therapeutic adherence and could achieve pain relief without serious side effects, which in turn reduces patients' reliance on medications [51].

Also, Busch et al. [52] stated that most of the patients reported satisfaction with the treatment with nVNS and their willingness to use its various devices in the future, most of the patients considered nVNS to be safe with some participants reported redness or itching.

Regarding the findings of our study, reduction in pain intensity was as a result of the use of low-intensity electric stimulation, which is not painful and effective in treating pain, using this low intensity of TENS activates A- and B- fibers of the vagus nerve [53], but does not stimulate parasympathetic C fibers of the vagus nerve so it is not painful at all [54,55].

Our data confirmed the optimum frequency used was at 25 HZ which agreed with Straube et al. & Groves et al. [56,57] about the preferred frequency for cervical vagus nerve stimulation between 20-30 HZ which was approved by the food and drug administration (FDA), this low frequency lowers the adverse events related to Carotid sheath direct stimulation, also reduce the permanent injury to the vagus nerve resulted from VNS stimulation at frequency of 50HZ or higher [58].

However, our results contradicted with Goadsby et al. [14] who found that nVNS on the right branch of the vagus nerve may be effective and well-tolerated in the acute treatment of migraine in certain patients, this may be due to short application time with intervals in between.

Also, Laqua et al. [59] results contradicted with our results as they stated that tVNS can provoke both anti- and pro-nociceptive impacts in vulnerable volunteers which may be due to using a broad spectrum of frequencies between (2-100) HZ or due to bilateral stimulation.

Also, Johnson et al. [60] contradicted with our study results about the analgesic effect of TENS and concluded that the application of TENS on the auricular vagus nerve branch in concha did not have any analgesic effect on the pain threshold in the wrist; this may be due to using low frequency, low-intensity current.

Limitations

The possible limitation of our study is the small sample size which is owed to the improvement of the medical situation after the appearance of COVID-19 vaccination which results in difficulties in finding participants in the study. In addition to a lack of following-up to determine the long-term effects of tVNS.

Conclusion

Based on the current data, it is probable to conclude that peripheral neuromodulation (in the form of vagus nerve stimulation) is more effective than traditional therapy in managing the headache pain and disability in Post COVID-19 survivors. Thus, peripheral neuromodulation in the form of tVNS should be included in the rehabilitation program of Post COVID-19 survivors.

Acknowledgments

The authors express their thankfulness to all the study members for their cooperation.

Conflict of interest

The authors stated no conflict of interests.

References

1. Adhanom Ghebreyesus, T. (2020). Addressing mental health needs: an integral part of covid_19 response. World Psychiatry, 19(2), 129-130. doi: 10.1002/wps.20768.

2. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., & Lu, R. (2020). A novel coronavirus from patients with pneumonia in China, 2019. New England journal of medicine .

3. Wijeratne, T., & Crewther, S. (2021). COVID-19 and long-term neurological problems: Challenges ahead with Post COVID-19 Neurological Syndrome .

4. Lopez-Leon, S., Wegman-Ostrosky, T., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (2021). More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Scientific reports, 11(1), 1-12 .

5. Premraj, L., Kannapadi, N. V., Briggs, J., Seal, S. M., Battaglini, D., Fanning, J., Suen, J., Robba, C., Fraser, J., & Cho, S.-M. (2022). Mid and long-term neurological and neuropsychiatric manifestations of Post COVID-19 syndrome: A meta-analysis. Journal of the neurological sciences, 434, 120162 .

6. Mekkawy, D. A., Hamdy, S., Abdel-Naseer, M., Shehata, H. S., Halfawy, A. A., Shalaby, N. M., Shehata, G. A., Ali, A. M., Elmazny, A., Ahmed, S. M., Ismail, J. H., Ibraheim, A., Abdel-Hamid, H. M., Magdy, R., Kabara Ayoub, Y., Taha, A. E., Merghany, N., Soliman, N. M., Elshebawy, H., . . . Wijeratne, T. (2022). Neurological Manifestations in a Cohort of Egyptian Patients with COVID-19: A Prospective, Multicenter, Observational Study. Brain Sciences, 12(1), 74. https://www.mdpi.com/2076-3425/12/1/74

7. Zhou, L., Ashkenazi, A., Smith, J. W., Jen, N., Deer, T. R., & Zhou, C. (2016). Long-term clinical outcome of peripheral nerve stimulation for chronic headache and complication prevention. Anesthesiology and pain medicine, 6(4).

8. Buse, D., Manack, A., Serrano, D., Turkel, C., & Lipton, R. (2010). Sociodemographic and comorbidity profiles of chronic migraine and episodic migraine sufferers. Journal of Neurology, Neurosurgery & Psychiatry, 81(4), 428-432 .

9. World Health Organization. (2011). Atlas of headache disorders and resources in the world 2011.

10. Saylor, D., & Steiner, T. J. (2018). The global burden of headache. Seminars in neurology ,

11. Krames, E. S., Hunter Peckham, P., Rezai, A., & Aboelsaad, F. (2009). Chapter 1 - What Is Neuromodulation? In E. S. Krames, P. H. Peckham, & A. R. Rezai (Eds.), Neuromodulation (pp. 3-8). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-374248-3.00002-1

12. Dyer, A. R., & Aardrup, M. P. (2009). Chapter 3 - Neuromodulation Technologies: Whom Do We Serve? In E. S. Krames, P. H. Peckham, & A. R. Rezai (Eds.), Neuromodulation (pp. 21-27). Academic Press .

13. Akerman, S., Holland, P. R., & Goadsby, P. J. (2011). Diencephalic and brainstem mechanisms in migraine. Nat Rev Neurosci, 12(10), 570-584 .

14. Goadsby, P. J., Lipton, R. B., & Ferrari, M. D. (2002). Migraine--current understanding and treatment. N Engl J Med, 346(4), 257-270. https://doi.org/10.1056/NEJMra010917

15. Divizia, M., Germani, G., Urti, I., Imani, F., Varrassi, G., & Meloncelli, S. (2020). Endoscopic Neuromodulation of Suprascapular Nerve in Chronic Shoulder Pain: A Case Report. Anesth Pain Med, 10(2), e103624 .

16. Puledda, F., & Goadsby, P. J. (2016). Current Approaches to Neuromodulation in Primary Headaches: Focus on Vagal Nerve and Sphenopalatine Ganglion Stimulation. Current pain and headache reports, 20(7), 47-47. https://doi.org/10.1007/s11916-016-0577-5

17. Huston, J. M. (2012). The Vagus Nerve and the Inflammatory Reflex: Wandering on a New Treatment Paradigm for Systemic Inflammation and Sepsis. Surgical Infections, 13(4), 187-193. https://doi.org/10.1089/sur.2012.126

18. Rings, T., von Wrede, R., Bröhl, T., Schach, S., Helmstaedter, C., & Lehnertz, K. (2021). Impact of Transcutaneous Auricular Vagus Nerve Stimulation on Large-Scale Functional Brain Networks: From Local to Global. Front Physiol, 12, 700261. https://doi.org/10.3389/fphys.2021.700261

19. von Wrede, R., Rings, T., Schach, S., Helmstaedter, C., & Lehnertz, K. (2021). Transcutaneous auricular vagus nerve stimulation induces stabilizing modifications in large-scale functional brain networks: towards understanding the effects of taVNS in subjects with epilepsy. Scientific reports, 11(1), 7906 .

20. Lendvai, I. S., Maier, A., Scheele, D., Hurlemann, R., & Kinfe, T. M. (2018). Spotlight on cervical vagus nerve stimulation for the treatment of primary headache disorders: a review. J Pain Res, 11, 1613-1625. https://doi.org/10.2147/jpr.S129202

21. Yuan, H., & Silberstein, S. D. (2016). Vagus Nerve and Vagus Nerve Stimulation, a Comprehensive Review: Part I. Headache, 56(1), 71-78. https://doi.org/10.1111/head.12647

22. Courties, A., Deprouw, C., Maheu, E., Gibert, E., Gottenberg, J.-E., Champey, J., Banneville, B., Chesnel, C., Amarenco, G., Rousseau, A., Berenbaum, F., & Sellam, J. (2022). Effect of Transcutaneous Vagus Nerve Stimulation in Erosive Hand Osteoarthritis: Results from a Pilot Trial. Journal of Clinical Medicine, 11(4), 1087 .

23. Farmer, A. D., Strzelczyk, A., Finisguerra, A., Gourine, A. V., Gharabaghi, A., Hasan, A., Burger, A. M., Jaramillo, A. M., Mertens, A., Majid, A., Verkuil, B., Badran, B. W., Ventura-Bort, C., Gaul, C., Beste, C., Warren, C. M., Quintana, D. S., Hämmerer, D., Freri, E., . . . Koenig, J. (2021). International Consensus Based Review and Recommendations for Minimum Reporting Standards in Research on Transcutaneous Vagus Nerve Stimulation (Version 2020) [Review]. Frontiers in Human Neuroscience, 14. https://doi.org/10.3389/fnhum.2020.568051

24. Molero-Chamizo, A., Nitsche, M. A., Bolz, A., Andújar Barroso, R. T., Alameda Bailén, J. R., García Palomeque, J. C., & Rivera-Urbina, G. N. (2022). Non-Invasive Transcutaneous Vagus Nerve Stimulation for the Treatment of Fibromyalgia Symptoms: A Study Protocol. Brain Sciences, 12(1), 95. https://www.mdpi.com/2076-3425/12/1/95

25. Lundqvist, C., Benth, J., Grande, R., Aaseth, K., & Russell, M. (2009). A vertical VAS is a valid instrument for monitoring headache pain intensity. Cephalalgia, 29(10), 1034-1041. https://doi.org/https://doi.org/10.1111/j.1468-2982.2008.01833.x

26. Jabbari, S., Salahzadeh, Z., Sarbakhsh, P., Rezaei, M., Farhoudi, M., & Ghodrati, M. (2021). Validity and Reliability of Persian Version of Henry Ford Hospital Headache Disability Inventory Questionnaire. Arch Iran Med, 24(10), 752-758. https://doi.org/10.34172/aim.2021.111

27. Hanna, P., Dacey, M. J., Brennan, J., Moss, A., Robbins, S., Achanta, S., Biscola, N. P., Swid, M. A., Rajendran, P. S., Mori, S., Hadaya, J. E., Smith, E. H., Peirce, S. G., Chen, J., Havton, L. A., Cheng, Z., Vadigepalli, R., Schwaber, J., Lux, R. L., Shivkumar, K. (2021). Innervation and Neuronal Control of the Mammalian Sinoatrial Node a Comprehensive Atlas. Circulation Research, 128(9), 1279-1296. https://doi.org/10.1161/circresaha.120.318458

28. Álvarez-Melcón, A. C., Valero-Alcaide, R., Atín-Arratibel, M. A., Melcón-Álvarez, A., & Beneit-Montesinos, J. V. (2018). Effects of physical therapy and relaxation techniques on the parameters of pain in university students with tension-type headache: A randomized controlled clinical trial. *Neurología (English Edition)*, *33*(4), 233-243. https://doi.org/https://doi.org/10.1016/j.nrleng.2016.06.007

29. A. M. Fernández-Pérez, C. Villaverde-Gutiérrez, A. Mora-Sánchez, C. Alonso-Blanco, M. Sterling and C. Fernández-de-las-Peñas. (2012). Journal of Orthopaedic & Sports Physical Therapy 2012 Vol. 42 Issue 7 Pages 634-641.DOI: 10.2519/jospt.2012.4117. https://doi.org/10.2519/jospt.2012.4117

30. Sciotti, V. M., Mittak, V. L., DiMarco, L., Ford, L. M., Plezbert, J., Santipadri, E., Wigglesworth, J., & Ball, K. (2001). Clinical precision of myofascial trigger point location in the trapezius muscle. Pain, 93(3), 259-266 .

31. O'Leary, S., Jull, G., Kim, M., & Vicenzino, B. (2007). Specificity in retraining craniocervical flexor muscle performance. journal of orthopaedic & sports physical therapy, 37(1), 3-9.

32. Chaitow, L., & Crenshaw, K. (2006). *Muscle energy techniques*. Elsevier Health Sciences

33. Stovner L, Hagen K, Jensen R, et al. The Global Burden of Headache: A Documentation of Headache Prevalence and Disability Worldwide. Cephalalgia. 2007;27(3):193-210. doi:10.1111/j.1468-2982.2007. 01288.x

34. Lyubashina, O. A., Sokolov, A. Y., & Panteleev, S. S. (2012). Vagal afferent modulation of spinal trigeminal neuronal responses to dural electrical stimulation in rats. Neuroscience, 222, 29-37. https://doi.org/10.1016/j.neuroscience.2012.07.011

35. Oshinsky, M. L., Murphy, A. L., Hekierski, H., Jr., Cooper, M., & Simon, B. J. (2014). Noninvasive vagus nerve stimulation as treatment for trigeminal allodynia. Pain, 155(5), 1037-1042. https://doi.org/10.1016/j.pain.2014.02.009

36. Bossut, D. F., & Maixner, W. (1996). Effects of cardiac vagal afferent electrostimulation on the responses of trigeminal and trigeminothalamic neurons to noxious orofacial stimulation. Pain, 65(1), 101-109. https://doi.org/10.1016/0304-3959(95)00166-2

37. Nishikawa, Y., Koyama, N., Yoshida, Y., & Yokota, T. (1999). Activation of ascending antinociceptive system by vagal afferent input as revealed in the nucleus ventralis posteromedialis. Brain Res, 833(1), 108-111. https://doi.org/10.1016/s0006-8993(99)01521-8

38. Bassi, G. S., Dias, D. P. M., Franchin, M., Talbot, J., Reis, D. G., Menezes, G. B., Castania, J. A., Garcia-Cairasco, N., Resstel, L. B. M., Salgado, H. C., Cunha, F. Q., Cunha, T. M., Ulloa, L., & Kanashiro, A. (2017). Modulation of experimental arthritis by vagal sensory and central brain stimulation. Brain, Behavior, and Immunity, 64, 330-343 .

39. Randich, A., & Gebhart, G. F. (1992). Vagal afferent modulation of nociception. Brain Research Reviews, 17(2), 77-99. https://doi.org/https://doi.org/10.1016/0165-0173(92)90009-B

40. Tavanaiepour D, Levy RM. (2014). Peripheral neuromodulation for treatment of chronic migraine headache. Neurosurg Clin N Am. 2014 Jan;25(1):11-4 .

41. Timothy R Deer, MD, Michael F Esposito, MD, W Porter McRoberts, MD, Jay S Grider, DO, PhD, MBA, Dawood Sayed, MD, Paul Verrills, MD, Tim J Lamer, MD, Corey W Hunter, MD, Konstantin V Slavin, MD, Jay M Shah, MD, Jonathan M Hagedorn, MD, Tom Simopoulos, MD, David Abejon Gonzalez, MD, PhD, Kasra Amirdelfan, MD, Sameer Jain, MD, Ajax Yang, MD, Rohit Aiyer, MD, Ajay Antony, MD, Nomen Azeem, MD, Robert M Levy, MD, PhD, Nagy Mekhail, MD, PhD. (2020). A Systematic Literature Review of Peripheral Nerve Stimulation Therapies for the Treatment of Pain, Pain Medicine, Volume 21, Issue 8, August 2020, Pages 1590–1603 ,

42. Hokenek, N. M., Erdogan, M. O., Hokenek, U. D., Algin, A., Tekyol, D., & Seyhan, A. U. (2021). Treatment of migraine attacks by transcutaneous electrical nerve stimulation in emergency department: A randomize controlled trial. The American Journal of Emergency Medicine, 39, 80-85 .

43. Tassorelli, C., Grazzi, L., de Tommaso, M., Pierangeli, G., Martelletti, P., Rainero, I., Dorlas, S., Geppetti, P., Ambrosini, A., Sarchielli, P., Liebler, E., & Barbanti, P. (2018). Noninvasive vagus nerve stimulation as acute therapy for migraine. Neurology, 91(4), e364 .

44. Nemeroff, C. B., Mayberg, H. S., Krahl, S. E., McNamara, J., Frazer, A., Henry, T. R., George, M. S., Charney, D. S., & Brannan, S. K. (2006). VNS Therapy in Treatment-Resistant Depression: Clinical Evidence and Putative Neurobiological Mechanisms. Neuropsychopharmacology, 31(7), 1345-1355. https://doi.org/10.1038/sj.npp.1301082

45. Marzec, M., Edwards, J., Sagher, O., Fromes, G., and Malow, B. A. (2003). Effects of vagus nerve stimulation on sleep-related breathing in epilepsy patients. Epilepsia 44, 930–935. doi: 10.1046/j.1528-1157.2003. 56202.x

46. Fahy, B. G. (2010). Intraoperative and perioperative complications with a vagus nerve stimulation device. J. Clin. Anesth. 22, 213–222 .

47. Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, et al. (2013). Migraine prevention with a supraorbital transcutaneous stimulator: a randomized controlled trial. Neurology 2013;80(8):697–704 .

48. Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. (2013). Examination of unmet treatment needs among persons with episodic migraine: results of the American Migraine Prevalence and Prevention (AMPP) study. Headache 2013;53(8):1300–11. https://doi.org/10.1111/head.12154.

49. Llamas M, Santiago D, Navarro R, Sánchez-Pérez J, García-Diez A. (2010). Unusual allergic contact dermatitis produced by a transcutaneous electrical nerve stimulator. Contact Dermatitis 2010;62(3):189–90.

50. Ford KS, Shrader MW, Smith J, Mclean TJ, Dahm DL. (2005). Full-thickness burn formation after the use of electrical stimulation for rehabilitation of unicompartmental knee arthroplasty. J Arthroplasty 2005;20(7):950–3. https://doi.org/10.1016/j.arth.2004.10.018

51. Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G. (2015). Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: an open-label study. J Headache Pain. 2015; 16:61. doi: 10.1186/s10194-015-0542-4. Epub 2015 Jun 30. PMID: 26123825; PMCID: PMC4485661.

52. Busch V., Zeman F., Heckel A., Menne F., Ellrich J., Eichhammer P. (2013). The effect of transcutaneous vagus nerve stimulation on pain perception–an experimental study. Brain Stimul. 6, 202–209 .

53. Mourdoukoutas, A. P., Truong, D. Q., Adair, D. K., Simon, B. J., & Bikson, M. (2018). High-Resolution Multi-Scale Computational Model for Non-Invasive Cervical Vagus Nerve Stimulation. Neuromodulation, 21(3), 261-268. https://doi.org/10.1111/ner.12706

54. Castoro, M. A., Yoo, P. B., Hincapie, J. G., Hamann, J. J., Ruble, S. B., Wolf, P. D., & Grill, W. M. (2011). Excitation properties of the right cervical vagus nerve in adult dogs. Exp Neurol, 227(1), 62-68

55. Yoo, P. B., Lubock, N. B., Hincapie, J. G., Ruble, S. B., Hamann, J. J., & Grill, W. M. (2013). High-resolution measurement of electrically-evoked vagus nerve activity in the anesthetized dog. J Neural Eng, 10(2), 026003 .

56. Straube A., Ellrich J., Eren O., Blum B., Ruscheweyh R. (2015). Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial. J. Headache Pain 16:543 .

57. Groves D. A., Brown V. J. (2005). Vagal nerve stimulation: a review of its applications and potential mechanisms that mediate its clinical effects. Neurosci. Biobehav. Rev. 29, 493–500 .

58. Agnew W. F., McCreery D. B. (1990). Considerations for safety with chronically implanted nerve electrodes. Epilepsia 31, S27–S32 .

59. Laqua, R., Leutzow, B., Wendt, M., and Usichenko, T. (2014). Transcutaneous vagal nerve stimulation may elicit anti- and pro-nociceptive effects under experimentally-induced pain–a crossover placebo-controlled investigation. Auton. Neurosci. Basic Clin. 185, 120–122. doi: 10.1016/j.autneu.2014.07.008

60. Johnson V. K. Hajela C.H. Ashton J.W. (1999). Thompson Clinical Psychopharmacology Unit, Department of Pharmacological Sciences, The Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH U.K. Received 1 1990, Revised 22 January 1991, Accepted 23 January 1991, Available online 24 March 2003.