2023

Does non-invasive vagal nerve stimulation (nVNS) improve migraine headaches in adult patients?

Gavin T. Heard
Philadelphia College of Osteopathic Medicine

Does non-invasive vagal nerve stimulation (nVNS) improve migraine headaches in adult patients?

Gavin T. Heard, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies

Philadelphia College of Osteopathic Medicine

Philadelphia, Pennsylvania

December 16, 2022

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Does non-invasive vagal nerve stimulation (nVNS) improve migraine headaches in adult patients?"

STUDY DESIGN: A systematic review of three randomized controlled trials (RCTs) published between 2011 and 2022.

DATE SOURCES: The studies were found in PubMed and were published in English peer-reviewed journals. The studies were selected based on if they contributed information toward the clinical question.

OUTCOMES MEASURED: Migraine symptom reduction was measured based on patient reported change in migraine pain and frequency from baseline.

RESULTS: The Diener et al. study found that utilizing nVNS 2-3 times a day for 12 months resulted in an average decrease of 2.27 days with migraines in participants in the treatment group and a 1.53 day reduction in the placebo group, there was a statistically significant shown by the p-value of 0.043. The Martelletti et al. study found that utilizing nVNS showed a statistically significant reduction of migraine pain by 25.4% at 60 minutes and 34.8% at 90 minutes compared to the sham group, which reduced 7.7% at 60 minutes and 5.4% at 90 minutes. They also found that utilizing nVNS resolved the migraine in 12.1% of participants at 60 minutes and 18.0% of participants at 90 minutes compared to sham, which resolved 5.6% of migraines in participants at 60 minutes and 10.5% at 90 minutes. The Najib et al.study found that utilizing nVNS resulted in 44.87% of the participants reporting >50% reduction of days with migraine pain, compared to 26.81% of days in the sham group, p-value of 0.0481.

CONCLUSION: Two studies found a significant decrease in days patients reported experiencing migraines while using nVNS. The other study found a significant reduction in migraine pain at 60 and 90 minutes after nVNS and a significant resolution of migraines for patients at 60 and 90 minutes after nVNS. These results indicate that nVNS can serve as a method for reducing and controlling migraine symptoms.

KEY WORDS: non-invasive vagal nerve stimulation, migraine

INTRODUCTION

Migraines are a type of headache disorder caused by hypersensitivity of the central nervous system (CNS). This hypersensitivity typically results in a severe headache triggered or worsened by external factors or stimuli. Patients with migraines often see impairment in their ability to complete their work and personal responsibilities due to being incapacitated by their symptoms. This impairment can quickly cause financial, social, and emotional distress due to missed time at work or missed social engagements. To diagnose a patient with a migraine disorder, they must meet several criteria. This criterion includes having at least five headaches that last 4-72 hours, have symptoms of nausea or vomiting, or photophobia or phonophobia, and have 2 of the following types of pain: unilateral pain, pulsating pain, moderate to severe pain, or pain worse with activity.[1]

Individuals may experience an occasional migraine headache without being diagnosed with a migraine disorder. 75% of people will experience a migraine before they reach age 35.[2] Each year, about 12% of the world's population and about 15% of the U.S. population will experience a migraine.[3]

A specific genetic cause has not been identified in connection to migraine disorders; however, particular loci mutations have been identified to impact systems commonly involved with migraines. These loci mutations affect vascular mechanisms, genetically mediated hypercalcemia, and encoding of casein kinase, which can cause dysfunction with circadian rhythm and sleep phase syndrome.[4] While these mutations may not individually cause migraines, mutations and dysfunctions in these processes can contribute to the disorder. Identifying causative factors of migraines is further complicated because different parts of the central

nervous system can be active at different points of a migraine process. This variability can contribute to difficulty in preventing and treating migraine episodes with targeted treatment.

Current treatments include triptans and ergotamines, which are used explicitly for headaches and migraines. These medications target the vascular system to reduce migraine symptoms related to cerebral swelling. For many patients, these medications can be beneficial, while others are discouraged from using them due to medication interactions or contraindicating disorders. Other treatment options are focused on reducing specific symptoms of migraines. These treatments include analgesics and NSAIDS, which target the pain symptom. Additional therapies include antiemetics, dexamethasone, botox injections, and non-invasive vagal nerve stimulation.

Even with these treatments, individuals who experience chronic migraines are still 1.9 times more likely to file a short-term disability claim than similar individuals who do not experience migraines.[5] These individuals are also more likely to utilize the healthcare system as they are 3 times more likely to be hospitalized, 2.4 times more likely to visit the emergency room, and have 1.8 times more physician office visits than non-migraine patients.[5] These healthcare visits can be expensive for patients, especially if they do not have insurance or have a plan that does not cover the specialists they require. Additionally, patients may need to take time off work, find transportation, or find childcare in order to attend these appointments, all of which may incur additional costs.

In three months, patients with episodic migraines spend an average of $383 trying to find relief from their symptoms.[6] This expense climbs to $1036 in three months for patients with chronic migraines.[6] These expenses demonstrate the need for migraine prevention and treatments that are affordable and effective. One possible option for affordable treatment is non-invasive

vagal nerve stimulation (nVNS) which consists of a handheld device which delivers a mild impulse to the vagus nerve to modulate the pain pathway. This option for treatment that could save migraine sufferers an estimated $500 in treatment costs yearly.[3]

nVNS may be a preventative or abortive resource for patients struggling to manage their migraine symptoms with pharmaceuticals alone. It is currently considered an effective treatment for other types of headache disorders and is first line for cluster headache management.[7] Migraines are complex to treat because of their variable and often numerous causes; thus, patients may get better relief when combining treatment options. While there are many approaches to migraine treatment based on patient presentation and symptoms, nVNS could be beneficial in treating migraines while reducing overall pt treatment costs, risk of drug interactions, and side effects.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does non-invasive vagal nerve stimulation (nVNS) improve migraine headaches in adult patients?"

METHODS

Patients evaluated in these studies are adults aged eighteen to seventy-five who suffer from migraines with or without auras. The measured outcome is the relief of migraine pain and reduction of migraine occurrences from baseline when the nVNS intervention is utilized compared to the sham nVNS intervention.

The trials evaluated are all randomized control trials published in peer-reviewed journals and were chosen based on how well they answered the clinical question and if they addressed patient-oriented outcomes. The articles were located on PubMed by searching for "migraine" and "non-invasive vagus nerve stimulation." The inclusion criteria for article selection included a

published date after 2011, published in English text, and a randomized control style study type. Exclusion criteria for article selection consisted of a published date older than 11 years, effects of nVNS on headaches, and implantable vagus nerve stimulation for migraines. NNT, p-values, change from baseline, and the bang binding index were all statistical analyses used for this data.

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (yr)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Diener HC et al. 2019	RCT	477	18-75	18-75 years old, dx w/ migraines, 5-12 migraine days per month in the last 4 months, at least 2 migraines lasting >2 hrs, first migraine occured before age 50.	Chronic migraine diagnosis, medical condition requiring steroids, aneurysm, intracranial hemorrhage, brain tumors, head trauma, substance abuse, syncope, seizure, spine hardware, pain disorder, abnormal ECG, migraine prevention surgery, uncontrolled hypertension, pregnancy, botox.	134	Non-invasive vagus nerve stimulation 3 times a day vs. sham Non-invasive vagus nerve stimulation 3 times a day
Martellet ti P Et al. 2018	RCT	243	18-75	18-75 years old, diagnosis of migraine with or without aura, first migraine occured before age 50, 3 to 8 migraine attacks per month with < 15 headache days per month during the last 6 months	Aneurysm, intracranial hemorrhage, brain tumors, head trauma, substance abuse, syncope, or seizure, pain disorder, CVD, HTN, pregnancy, botox, nerve blocks in the past 2 months; frequent pain medication use	5	nVNS within 20 minutes of migraine pain onset vs. sham nVNS within 20 minutes of migraine pain onset
Najib U, et al. 2022	RCT	336	18-75	diagnosis of episodic or chronic migraine with or without aura, first migraine occured before age 50, experience 8 to 20 headache days per month and at least 5 of	2 or more migraine therapies, botox or monoclonal antibody drug use within previous six months, hx of medication overuse headache, hx of a	76	nVNS 3 times a day vs. sham nVNS 3 times a day

				the headaches were migraines.	secondary headache disorder		

OUTCOMES MEASURED

Before each study, there was a period where the participant's baseline pain and days with migraines were measured by self-reporting. This self-reporting consisted of the patients marking in an electronic diary if they had a migraine that day. If the study required them to rate the intensity of the pain, they utilized a NRS in the electronic diary to rate the pain. The participants then measured this same data while utilizing nVNS, and researchers compared the results to the baseline period. Two studies examined how many days participants had migraines compared to the baseline period. The other study compared the amount of migraine pain reduction or termination while using nVNS compared to the baseline.

RESULTS

Diener et al. conducted a randomized controlled trial with 477 participants between ages 18 and 75, who were diagnosed with migraines, and experienced 5-12 days a month with a migraine. The criteria for participant inclusion and exclusion are in Table 1. In a 12-week period, the study compared nVNS to sham nVNS in reducing the number of days in which the participant felt migraine pain. This review will not discuss the open-label comparison intervention measured in this study. A computer-generated system, Merge eClinical OS, was used to randomize patient assignments to their testing groups. An unblinded trainer instructed participants about how to use the devices. Blinding effectiveness was assessed after one week into the intervention by asking participants which device they believed they had. The Bang Blinding Index (BBI) evaluated the participants' responses. The BBI concluded that blinding was successful because almost all patients thought they had an nVNS device.[8] 145 participants were lost to follow-up, with losses equal across the study groups. The researchers did not perform a

worst-case analysis on participants lost to follow-up. The study evaluated the change in the number of days the participants experienced migraines from baseline. This data is presented in table 2. Migraine sufferers who utilized the nVNS saw a reduction of 2.26 migraine days in 4 weeks compared to a 1.80 migraine day reduction for those using sham devices.[8] This result was not statistically significant, with a p-value of 0.15. The researchers performed a post hoc analysis and found that >67% adherence to nVNS use resulted in nVNS intervention having a statistically significant benefit over sham intervention. This analysis found that patients using nVNS saw a reduction of 2.27 migraine days, and those with sham devices had a decrease of 1.53 migraine days. The p-value for this analysis was 0.043.[8]

Table 2. Mean Reduction of Migraine Days After 12 Weeks of Intervention

	nVNS	Sham nVNS	P-Value
Reduction in migraine days	2.26	1.80	0.15
Reduction in Migraine days with >67% response rate	2.27	1.53	0.043

Martelletti et al. conducted a randomized controlled trial with 248 participants aged 18 to 75, diagnosed with migraines, and who experienced 3-8 days a month with a migraine. The criteria for participant inclusion and exclusion are in Table 1. In a 4-week period, the study compared nVNS to sham nVNS to alleviate participants' migraine pain. This review will not discuss the open-label portion of the study. Randomization was achieved using a computer-generated system to divide patient assignments into the nVNS and sham groups. An unblinded trainer instructed participants about how to use the devices. After the trainer completed the instruction, they had no further interaction with the participants. Blinding effectiveness was measured after the first treatment and at the end of the trial and was analyzed using the BBI. BBI concluded that blinding was successful. [9] 10 participants were lost to

follow-up. The patient losses were distributed across both study groups equally.[9] There was not a worst-case analysis performed for the participants lost to follow-up. The study examined the amount of pain reduction and pain resolution of participants 30, 60, and 90 minutes from nVNS use at migraine onset. This data is in tables 3 and 4. Migraine sufferers who utilized the nVNS had, on average, a 21.4% decrease in pain at 30 minutes, a 29.4% reduction at 60 minutes, and a 35.2% reduction by 120 minutes from migraine onset. This data can be compared to patients using sham nVNS who, on average, experienced an 16.0% decrease in pain at 30 minutes, a 20.3% reduction at 60 minutes, and a 24.4% reduction by 120 minutes since migraine onset.[9] There was a statistically significant reduction of pain at 60 and 120 minutes with p-values of 0.025 and 0.018 respectively.[9] Following the nVNS treatment, 8.6% of participants were pain-free at 30 minutes, 16.3% at 60 minutes, and 22.9% by 120 minutes from migraine onset. This data can be compared to those using sham nVNS, with 5.5% of participants pain-free at 30 minutes, 8.6% at 60 minutes, and 14.8% by 120 minutes from migraine onset.[9] There was a statistically significant increase in pain-free patients with nVNS use at 60 and 120 minutes with p-values of 0.005 and 0.026 respectively.[9]

Table 3. Mean Pain Reduction 30, 60, and 120 Minutes from Migraine Pain Onset

Intervention	nVNS (Mean 95% CI)	Sham nVNS (Mean 95% CI)	P-Value
30 Minutes	21.4% (16.2-27.8%)	16.0% (11.5-21.7%)	0.149
60 Minutes	29.4% (23.9-35.7%)	20.3% (15.4-26.4%)	0.025
120 Minutes	35.2% (28.9-42.2%)	24.4% (18.8-31.0%)	0.018

Table 4. Participants with Pain Resolution at 30, 60, and 120 Minutes from Migraine Pain Onset

Intervention	nVNS (Mean 95% CI)	Sham nVNS (Mean 95% CI)	P-Value	NNT
30 Minutes	8.6% (5.6-12.9%)	5.5% (3.2-9.3%)	0.133	32
60 Minutes	16.3% (12.1-21.5%)	8.6% (5.6-12.9%)	0.005	13

120 Minutes	22.9% (18.0-28.6%)	14.8% (10.5-20.5%)	0.026	12

Najib et al. conducted a randomized controlled trial with 231 participants aged 18 to 75, diagnosed with migraines, and who experience 8-20 headache days a month with at least five defined as migraines. The criteria for participant inclusion and exclusion are in Table 1. In a 12-week period, the study compared nVNS to sham nVNS in reducing the number of days in which the participant felt migraine pain. A computer-generated system was used to randomize patient assignment to the nVNS and sham groups. The only unblinded member of the study was an unblinded trainer who instructed participants about how to use the devices. Researchers assessed blinding effectiveness in the last week of the intervention by asking participants which device they believed they had. BBI was used to synthesize this data and concluded that blinding was successful. 76 participants were lost to follow-up, with losses equal across the study groups.[10] A worst-case analysis was not performed on participants lost to follow-up. The researchers measured the change in the number of days the participants experienced migraines from baseline. This data is presented in table 5. Migraine sufferers who utilized nVNS saw a reduction of 3.12 migraine days in a four-week period compared to a 2.29 migraine day reduction for those using sham devices. This result was not statistically significant, with a p-value of 0.2329.[10] The researchers further examined this data and found that 44.87% of participants who used nVNS had a ≥50% decrease in days with migraines compared to 26.81% of those in the sham group. The p-value for this comparison is 0.0481.[10] This study has a calculated NNT of 6.

Table 5. Participant Report Reduction in Migraine Days

	nVNS	Sham nVNS	P-Value	NNT
Reduction of migraine days	3.12	2.29	0.2329	

>50% migraine day reduction	44.87%	26.81%	0.0481	5

DISCUSSION

A migraine disorder is a type of headache disorder that can cause patients to experience debilitating pain, which can have detrimental effects on the patient's personal, social, and professional life. The exact cause of migraines is not clear; however, there seem to be numerous factors that can trigger an episode. Due to the multifactorial nature of migraines, there are several treatment modalities on the market, each with its own efficacy rate and associated side effects. This systematic review examined non-invasive vagal nerve stimulation and if utilization helped reduce migraine symptoms in adults. All of the studies reviewed found significant improvement in some aspects of migraine symptoms.

Diener HC et al. initially did not find a statistically significant reduction of migraine days between nVNS and sham treatment, as the difference in the two treatments had a p-value of 0.15. However, after a post hoc analysis and analyzing only the participants who used their device ≥ 67% of the recommended time, the p-value for the two participant groups was 0.043, indicating that there was a significant change. These findings suggest that utilizing nVNS consistently at least twice a day can reduce the number of days a patient will experience migraines. Najib et al. did not find a statistically significant reduction in participant-reported days with migraines, as shown by their p-value of 0.2329. However, they found that a greater number of patients reported a ≥ 50% decrease in migraine days when using the nVNS device than when using the sham device. The comparison for the populations with ≥ 50% relief has a p-value of 0.0481, indicating statistical significance. These findings suggest that nVNS may be useful for the reduction in the amount of migraine days a patient experiences. Martelletti HC et al. found that nVNS use significantly reduced migraine pain 60 and 90 minutes after migraine onset and was

effective at aborting migraines within 60 and 90 minutes of administration; respective p-values are 0.025, 0.018, 0.005, and 0.026. They did not have statistically significant results for reduced migraine pain at 30 minutes, a p-value of 0.149, or for the resolution of migraines at 30 minutes, a p-value of 0.133. These results suggest that nVNS may be beneficial in relieving migraine pain as needed however the patient may not experience relief immediately.

Limitations for this review include the identification and selection process for the studies used. Pubmed was the only database used to locate articles. There may have been additional articles that could have been examined that were not listed on Pubmed and thus were not considered. Additionally, all three of the study participant populations were predominantly caucasian females. This lack of diversity in participant background may impact the accuracy of the findings when applied to populations not involved in the study. In the studies by Martelletti et al. and Najib et al., there were concerns that the sham devices may have inadvertently produced a minimal stimulatory effect on the patient's vagus nerve. The purpose of the sham device is to not have the same effect as the intervention, so there would undoubtedly be limitations of these study's data if the sham devices were giving off any degree of stimulation. Lastly, the Najib et al. study had to terminate early due to the COVID-19 pandemic, which caused the study to lose about 60% of the original participants. This reduction of participants reduced the overall power of the study. The studies of Diener et al. and Najib et al. both struggled with participant compliance likely because they required the participants to administer nVNS treatments three times a day and each day participants had to log if they had migraine symptoms. This inconsistency in treatment administration serves as a limitation because it was found that only consistent use of nVNS results in a significant effect of reducing migraine episodes.

Overall the studies were successful in blinding their participants and providing data that showed a statistically significant improvement in their participants. However the data should be interpreted with the understanding that the sham devices possibly provided minimal therapeutic effect and there was not always consistent use of the nVNS devices from the participants. This data serves as sufficient preliminary data for the understanding of the effects of nVNS in migraine treatment and prevention. Future studies will likely have more reliable information if they ensure the control provides absolutely no vagal nerve stimulation and require patient compliance with the necessary treatment schedule.

CONCLUSION

This systematic review demonstrates that nVNS is an effective management tool in reducing migraine severity and can reduce migraine frequency when used consistently. Future research on this topic should include a greater variety of patient backgrounds to increase the generalizability of the study. Additionally, further research into the ideal interval time between nVNS use for migraine prevention would be beneficial as a longer interval may reduce the amount of needed treatments a day and thus increase compliance.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. doi:10.1177/0333102417738202

2. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB. Cumulative lifetime migraine incidence in women and men. *Cephalalgia*. 2008;28(11):1170-1178. doi:10.1111/j.1468-2982.2008.01666

3. Mwamburi M, Tenaglia AT, Leibler EJ, Staats PS. Cost-effectiveness of noninvasive vagus nerve stimulation for acute treatment of episodic migraine and role in treatment sequence strategies. *Am J Manag Care*. 2018;24(24 Suppl):S527-S533

4. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol*. 2018;17(2):174-182. doi:10.1016/S1474-4422(17)30435-0

5. Bonafede M, Sapra S, Shah N, et al. Direct and indirect healthcare resource utilization and costs among migraine patients in the United States. *Headache*. 2018;58(5):700-714. doi:10.1111/head.13275

6. Stokes M, Becker WJ, Lipton RB, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). *Headache*. 2011;51(7):1058-1077. doi:10.1111/j.1526-4610.2011.01945

7. Ashina M, Katsarava Z, Do TP, et al. Migraine: epidemiology and systems of care. *Lancet*. 2021;397(10283):1485-1495. doi:10.1016/S0140-6736(20)32160-7

8. Diener HC, Goadsby PJ, Ashina M, et al. Non-invasive vagus nerve stimulation (nVNS) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomized, sham- controlled PREMIUM trial. *Cephalalgia*. 2019;39(12):1475-1487. doi:10.1177/0333102419876920

9. Martelletti P, Barbanti P, Grazzi L, et al. Consistent effects of non-invasive vagus nerve stimulation (nVNS) for the acute treatment of migraine: additional findings from the randomized, sham-controlled, double-blind PRESTO trial. *J Headache Pain*. 2018;19(1):101. doi:10.1186/s10194-018-0929-0

10. Najib U, Smith T, Hindiyeh N, et al. Non-invasive vagus nerve stimulation for prevention of migraine: The multicenter, randomized, double-blind, sham-controlled PREMIUM II trial. *Cephalagia*. 2022;42(7):560-569. doi:10.1177/03331024211068813

11. Silberstein SD. Migraine. *Lancet*. 2004;363(9406):381-391. doi:10.1016/S0140-6736(04)15440-8

12. Gilmore B, Michael M. Treatment of acute migraine headache. *Am Fam Physician*. 2011;83(3):271-280