Transcutaneous electrical stimulation of the vagus nerve as a migraine treatment: systematic review

Estimulação elétrica transcutânea do nervo vago como tratamento da migrânea: revisão sistemática

Tania Gouvêa Thomaz[1], Andrée Carolle Mariane Amany Kouassi[2], Arthur dos Santos Leite Neiva Neves[2], Gisele Fernandes de Sena[2]

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ABSTRACT

BACKGROUND AND OBJECTIVES: Migraine is a type of primary headache that is controlled mainly by drugs to treat the crisis or as prophylaxis. The side effects and high cost of the medication justify the search for non-pharmacological treatment options. There is evidence that electrical stimulation of the vagus nerve (VNS) is capable of modulating structures related to the pathophysiology of migraine. The objective of this review was to investigate the effectiveness of transcutaneous VNS (tVNS) in the acute or prophylactic treatment of migraine with and without aura.

CONTENTS: A search was carried out in the Pubmed database using all descriptors for vagus nerve stimulation and migraine, without time limit and with the filter "randomized clinical trial" (RCT). This search strategy ultimately identified 7 articles that were read in full and subjected to a quality analysis using the Oxford Center for Evidence-Based Medicine tool. Of the 7 RCTs found, 4 were prophylaxis studies and 3 were acute treatment studies.

CONCLUSION: There is some compromise in the internal validity of all studies. Migraine prophylaxis with tVNS did not present relevant benefits that justify its use, especially with a protocol with poor adherence. Acute treatment of migraine with tNVS proved to be effective in some patients and may be a non-pharmacological treatment option. These results justify the carrying out of new RCTs where there are no doubts about their internal validity.

Keywords: Migraine disorders, Review, Vagus nerve stimulation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Migrânea é um tipo de cefaleia primária cujo controle se faz principalmente por fármacos para tratamento da crise ou como profilaxia. Os efeitos adversos e o seu alto custo justificam a busca por opções de tratamento não farmacológicas. Existem evidências de que a estimulação elétrica do nervo vago (VNS) é capaz de modular estruturas relacionadas à fisiopatologia da migrânea. O objetivo deste estudo foi investigar a eficácia da VNS de forma transcutânea (tVNS) no tratamento agudo ou profilático da migrânea com e sem aura.

CONTEÚDO: Foi feita uma busca na base de dados Pubmed utilizando todos os descritores para estimulação do nervo vago e migrânea, sem limite temporal e com o filtro "ensaio clínico randomizado" (ECR). Essa estratégia de busca identificou, no final, sete artigos que foram lidos integralmente e submetidos a uma análise de qualidade através da ferramenta do Centro de Medicina Baseada em Evidências de Oxford. Dos sete ECRs encontrados, 4 eram estudos de profilaxia e 3 de tratamento agudo.

CONCLUSÃO: Existe algum comprometimento da validade interna de todos os estudos. A profilaxia da migrânea com tVNS não apresentou benefícios relevantes que justifiquem seu uso, principalmente com um protocolo de pouca aderência. O tratamento agudo da migrânea com a tNVS se mostrou eficaz em parte dos pacientes e pode ser uma opção não farmacológica de tratamento. Esses resultados justificam a realização de novos ECRs, de modo que não restem dúvidas sobre a sua validade interna.

Descritores: Estimulação do nervo vago, Revisão, Transtornos de enxaqueca.

Tania Gouvêa Thomaz – https://orcid.org/0000-0003-2800-1729;
Andrée Carolle Mariane Amany Kouassi – https://orcid.org/0000-0003-3755-0551;
Arthur dos Santos Leite Neiva Neves – https://orcid.org/0000-0001-7973-5613;
Gisele Fernandes de Sena – https://orcid.org/0000-0002-4074-0164.

1. Fluminense Federal University, Department of Physiology and Pharmacology, Niterói, RJ, Brazil.
2. Fluminense Federal University, Undergraduate Medical Student, Niterói, RJ, Brazil.

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HIGHLIGHTS

- tVNS offers the possibility of a non-pharmacological treatment for migraine with the potential to reduce the adverse effects of current therapeutic approaches.
- This review also summarizes and discusses issues related to the pathophysiology of migraine.
- The critical analysis of each article included in this review exposes the difficulty of interpreting the results presented to the scientific community, especially when the research is carried out in collaboration with the industry that produces the equipment in question.

Associate editor in charge: Camila Squarzoni Dale
https://orcid.org/0000-0002-3421-7799

Correspondence to:
Tania Gouvêa Thomaz
E-mail: tania_thomaz@id.uff.br

INTRODUCTION

Migraine is a type of primary headache that can be episodic or chronic. Symptoms typically last between 4 and 72 hours and can be disabling. The pain is usually unilateral, pulsating, worsens with exertion and is accompanied by symptoms such as nausea and sensitivity to light, sound or smells. Auras occur in around 25% of patients, usually just before the onset of the headache. Diagnosis is essentially clinical[1,2].

Treatment of migraine attacks, with or without aura, is carried out with triptans, dihydroergotamine, antiemetics and various analgesics[3]. Migraine patients usually learn about the situations that can trigger a crisis, which is why preventive measures generally include lifestyle changes. According to the Brazilian Headache Society (Sociedade Brasileira de Cefaleia)[4], patients who experience more than four days of pain in a month should be advised to use a prophylactic drug. Among the drugs indicated for migraine prophylaxis are beta-blockers, anticonvulsants and antidepressants.

Despite the wide range of drugs available for crisis treatment and prophylactic treatment, migraine patients can spend long periods of their lives without effective control of their crises. In addition, many patients would like to control their migraine attacks without the use of prophylactic drugs, many of which have significant adverse effects. These factors justify the search for non-pharmacological therapies for the acute and prophylactic treatment of migraine[5].

The pathophysiology of migraine has evolved from a vascular theory to a sensory processing disorder theory, thus presenting itself as a hereditary neurological disease. The etiology of migraine pain is understood to be the sensitization of the 1st order neurons of the trigeminal ganglion. The cyclical behavior of migraine attacks and the presence of vegetative symptoms suggest the involvement of the hypothalamus in the pathophysiology of migraine. Although this has not been fully clarified, several studies have demonstrated the involvement of the hypothalamus in the pathophysiology of migraine in imaging studies in humans and in electrophysiological recording studies in rodents[6-8].

On the other hand, electrical stimulation of the vagus nerve (VNS) emerged at the end of the 19th century from the observations of the American neurologist James Corning. At that time, seizures were attributed to a disturbance in cerebral blood flow[9]. Corning published several reports that massage and/or compression of the carotid artery in the neck region was able to abort a seizure in some patients. It was Corning himself who linked compression of the carotid artery with stimulation of the vagus nerve and, based on this hypothesis, created the "Corning fork". In addition to mechanical compression, Corning added electrical stimulation to his equipment, thus creating the first transcutaneous vagus nerve stimulation (tVNS) mechanism[10]. The results of Corning's new technique were not encouraging and the technique remained forgotten for approximately half a century.

From 1950 onwards, various animal models of VNS emerged, based on Corning's technique. These models provided evidence of the vagal stimulation action on cortical activity analyzed by the electroencephalogram and, consequently, on epileptic activity.

Human studies began in the 1990s and in 1997 the US Food and Drug Administration (FDA) approved the use of a surgically implanted vagal stimulation device. The indication for use was restricted to refractory epilepsy and chronic depression resistant to treatment.

The rational explanation for using this technique is that stimulation of the afferent fibers of the vagus nerve reaches structures such as the spinal nucleus of the trigeminal nerve and, above all, the solitary nucleus (SN). This, in turn, connects with various structures, including the raphe nuclei, locus ceruleus, amygdala, hypothalamus, thalamus and orbitofrontal cortex[11-13]; thus being able to modulate cortical electrical activity, preventing the excessive synchronization found in seizures of different etiologies.

The approval of the use of the surgically implanted VNS device prompted studies into the use of the technique for indications other than epilepsy and refractory depression, particularly for analgesia. A landmark study[14] was the first to demonstrate that vagus nerve stimulation was capable of suppressing experimentally provoked pain in epileptic patients using the procedure. As the number of epileptic patients using VNS increased, it was observed that some epileptic and migraine patients significantly reduced the frequency and intensity of their migraine attacks[15].

These studies influenced the European Headache Federation's position on neuromodulation in chronic headaches announced in 2013. This position considered that activation of vagal afferents has the potential to inhibit nociceptive transmission from the spinal cord and the trigeminal complex of the brainstem, and could be used as a prophylactic and crisis treatment for migraine. However, the need for randomized clinical trials (RCT) was emphasized, since all the evidence at the time came from studies with surgically implanted VNS in epileptic patients[5].

The difficulty in carrying out RCTs dedicated exclusively to the efficacy of VNS in the treatment of headaches was mainly due to the fact that the procedure was invasive. There was therefore great interest in simplifying the procedure and returning to Corning's original technique with non-invasive VNS.

At the turn of the 20th and 21st centuries, the first contemporary tVNS device appeared, the Nemos® (Cerbomed GmbH; Erlangen, Germany). Using an electrical stimulus with an intensity below the pain threshold, it is possible to stimulate areas of the skin in the vagus nerve region, for example the ear. This type of stimulation has been shown to produce the same pattern of cortical activity produced by invasive VNS in epileptic patients. Almost simultaneously, another tVNS device emerged, which, using the same concept as transcutaneous electrical nerve stimulation (TENS), applies electrical stimulation below the pain threshold, over the vagus nerve pathway through the neck. The gammaCore® (gammaCore; electroCore LLC; Basking Ridge, NJ, USA) is a portable tVNS device that stimulates the carotid vagus nerve[10]. Preliminary non-randomized studies have shown promising results for the use of these devices in the prophylaxis of various types of headache[16-19].

The aim of this study was to investigate the efficacy of tVNS in the acute or prophylactic treatment of migraine with and without aura by critically analyzing the RCTs found in the literature.

CONTENTS

The protocol for this systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and given the code/number CRD 42024510173. This review was designed to answer the following question: is tVNS effective in the acute or prophylactic treatment of migraine with and without aura? This review was formatted as a narrative synthesis and developed according to the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[20].

Research strategy

This review was carried out in March 2024 by consulting the bibliographic database Medical Literature Analysis and Retrieval System Online (Medline/Pubmed). The search strategy included the following descriptors: "((Vagus OR Vagal) *AND* (Nerve Stimul* OR Stimul*)) *OR* Transcutaneous Nerve Stimul* *OR* Transcutaneous Electric Nerve Stimul*) *AND* (Migraine OR Migraine Headache OR Migraine Disorder* OR Disorders, Migraine) *NOT* (occipital OR supraorbital)". The "Randomized clinical trial" filter was used with no time limitation.

Eligibility

The main interest of this research was to identify RCTs that used tVNS for the acute treatment of a migraine attack or for the prophylactic treatment of migraine. There were no restrictions on the study population, which could include men and women of any age. As there are various forms of electrical stimulation for the treatment and prophylaxis of migraine, special care was taken to ensure that the search strategy excluded RCTs that used stimulation of nerves other than the vagus nerve.

Data collection and variables of interest

All the researchers were responsible for selecting the studies and collecting data. A form was drawn up to record the data, taking into account the main characteristics of the study and the questions of interest. Three researchers sought consensus on the inclusion or exclusion of a study. In cases where there was no consensus on the inclusion of a study, the fourth and most experienced researcher (TGT) analyzed the study and made the decision on whether or not to include it. The data extracted included: (i) publication characteristics (authorship, year, country, study classification), and (ii) studies that met the formulated PICO, which was: Population - patients with migraine with or without aura, classified according to the criteria of The International Classification of Headache Disorders; Intervention - transcutaneous electrical stimulation of the vagus nerve; Control - SHAM stimulus or stimulus with a different frequency to the intervention; Outcomes - abolition or reduction of pain in migraine crisis treatment studies, count of the number of days with pain in 1 month for migraine prophylaxis studies.

Quality assessment of included studies

The quality of the studies was assessed by the four researchers using the tool developed by the Oxford Center for Evidence-Based Medicine[21].

Ethical aspects

This work followed the recommendations for research involving human beings and was exempt from evaluation by the research ethics committee because it was a research carried out exclusively with texts retrieved from scientific literature.

RESULTS

The search strategy identified 27 records, with no duplicate articles. Screening by reading titles and abstracts resulted in the exclusion of 20 articles because they were off-topic or did not meet the study design, leaving seven that were read in full (Figure 1).

Despite the consistency of the search terms and filters used, only 7 RCT were found, 4 of them focused on prophylactic treatment and 3 on acute treatment (Table 1).

The seven RCTs were subjected to a quality analysis using the critical analysis tool developed by the Oxford Center for Evidence-Based Medicine[21] (table 2). A detailed analysis of the methodology and results found in the seven RCTs proved to be extremely difficult, as several results were not presented in the original papers but on clinical research registration websites. For each of the RCTs, all the items in the tool were assessed.

Of the four RCTs focused on migraine prophylaxis, all considered the number of headache days/month and achieving a 50% reduction in headache days/month as the main outcomes. When patients achieved a 50% reduction in pain days, they were called "responsive". This last variable, however, was given as a secondary outcome and the results were not always presented. Two studies also evaluated questionnaires completed by patients on the degree of disability and the impact caused by migraine throughout the study and did not always present the results.

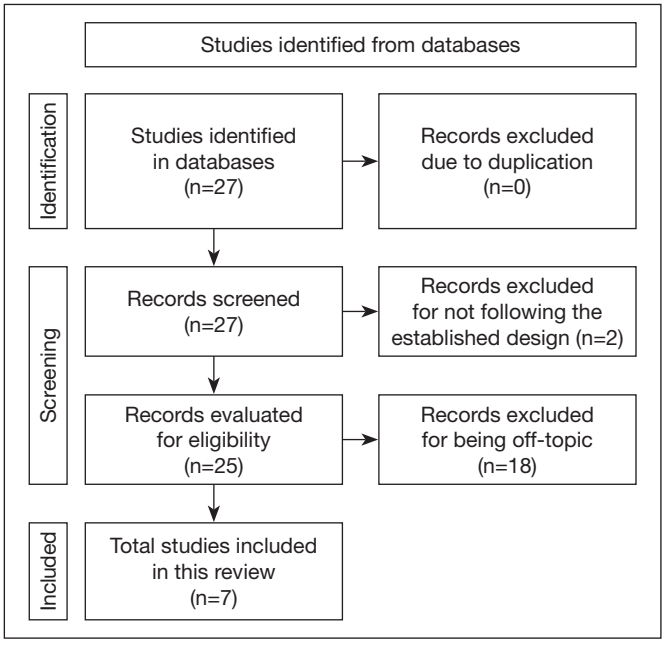

Figure 1. Studies identified on the databases

Table 1. List of randomized clinical studies resulting from the bibliographic survey

Prophylactic treatment					
Authors	Population	Intervention	Control	Outcomes	Results
Straube et al.[22]	40 adults with chronic migraine with and without aura	Ear stimulation 4 hours of daily stimulation at 25 Hz for 12 weeks Nemos®	Ear stimulation 4 hours of daily stimulation at 1 Hz for 12 weeks Nemos®	# reduction in the number of headache days # responsive or not (50% reduction in pain days) # MIDAS # HIT 6	PP and ITT analysis # The control group had a reduction of 7 days of pain in one month, while the intervention group had a reduction of 3.3 days in one month*. # Responsive patients: Control – 29,4 % Intervention – 13,3 % #MIDAS - improved score compared to the beginning of the study in both groups: intervention and control #HIT 6 - improved score compared to the start of the study in both the intervention and control groups
Silberstein et al.[23]	51 adults with chronic migraine with and without aura. 27 patients completed the 8 months of the study	Cervical stimulation 2 sessions of 2 minutes with 5 to 10 minutes rest, 25 Hz, 3x a day, for up to 8 months Gamma Core®	Cervical stimulation 2 sessions of 2 minutes with 5 to 10 minutes rest, SHAM, 3x a day, for up to 8 months Gamma Core®	# reduction in the number of headache days # use of rescue drugs	PP and ITT analysis # After 2 months of use, a reduction of 1.4 days of pain # After 4 months of use, reduction of 2.4 days of pain (open-label) # After 6 months of use, reduction of 2.8 days of pain (open-label) # After 8 months of use, a reduction of 3.6 days of pain. (open-label)* # It did not change throughout the study in both groups
Diener et al.[24]	341 adults with migraine with and without aura (multicenter study)	Cervical stimulation 2 sessions of 2 minutes with 5 to 10 minutes rest, 25 Hz, 3x a day, for up to 9 months. Gamma Core®--Sapphire	Cervical stimulation 2 sessions of 2 minutes with 5 to 10 minutes rest, SHAM, 3x a day Gamma Core®--Sapphire	# reduction in the number of migraine days # responsive or not (50% reduction in pain days)	ITT analysis # After 3 months of use, reduction of 2.26 days of pain. # After 3 months of use, reduction of 2.27 days of pain* (mITT) and reduction of 2.96 days of pain* (mITT) in the subgroup with aura # After 6 or 9 months (open-label), the results remained the same # Responsive patients: 3 months - 28.5% 3 months - 31.9% (mITT) 6 months - no results 9 months - no results
Najib et al.[25]	231 adults with episodic or chronic migraine with or without aura (multicenter study)	Cervical stimulation 2 sessions of 2 minutes with 5 to 10 minutes rest, 25 Hz, 3x a day, for at least 9 weeks Gamma Core®--Sapphire	Cervical stimulation 2 sessions of 2 minutes with 5 to 10 minutes rest, 25 Hz, 3x a day, for at least 9 weeks Gamma Core®--Sapphire	# reduction in the number of headache days # responsive or not (50% reduction in pain days) # MIDAS # HIT 6	ITT analysis # Reduction of 3.12 days of pain between the 9th and 12th week of stimulation. # 44.87% of patients are responsive * (mITT) # did not present the results # did not present the results
Acute treatment					
Tassorelli et al.[26]	248 adults with migraine with and without aura (multicenter study)	Cervical stimulation 25Hz 2 minutes of stimulation on each side (D and E), 20 minutes after the onset of pain, with repetition after 15 minutes if the pain persists Gamma Core®	Cervical stimulation SHAM 2 minutes of stimulation on each side (D and E), 20 minutes after the onset of pain, with repetition after 15 minutes if the pain persists Gamma Core®	First crisis treated # no pain after 30 minutes # no pain after 60 minutes # no pain after 120 minutes # pain relief after 30 minutes # pain relief after 60 minutes # pain relief after 120 minutes All crises treated # responsive or non-responsive (absence of pain after 120 minutes in 50% of treated crises)	ITT analysis First crisis treated # 12.7% of patients * treated with tVNS # 21% of patients * treated with tVNS # 30.4% of patients treated with tVNS # 26.7% of patients treated with tVNS # 35.8% of patients treated with tVNS # 40.8% of patients* treated with tVNS All crises treated # 32.4% of patients are responsive *
Martelletti et al.[27]	248 adults with migraine with and without aura (multicenter study)	Cervical stimulation 25Hz 2 minutes of stimulation on each side (D and E), 20 minutes after the onset of pain, with repetition after 15 minutes if the pain persists Gamma Core®	Cervical stimulation SHAM 2 minutes of stimulation on each side (D and E), 20 minutes after the onset of pain, with repetition after 15 minutes if the pain persists Gamma Core®	All crises treated # no pain after 30 minutes # no pain after 60 minutes # no pain after 120 # pain relief after 30 minutes # pain relief after 60 minutes # pain relief after 120 minutes # decrease in pain scale score after 30 minutes # decrease in pain scale score after 60 minutes # decrease in pain scale score after 120 minutes	ITT analysis # 8.6% of patients treated with tVNS # 16.3% of patients * treated with tVNS # 22.9% of patients * treated with tVNS # 21.4% of patients treated with tVNS # 29.4% of patients * treated with tVNS # 35.2% of patients * treated with tVNS # -0.33 in patients treated with tVNS # -0.42 in patients * treated with tVNS # -0.50 in patients treated with tVNS

Continue...

Table 1. List of randomized clinical studies resulting from the bibliographic survey – continuation

Prophylactic treatment					
Authors	Population	Intervention	Control	Outcomes	Results
Grazzi et al [28]	248 adults with migraine with and without aura (multicenter study)	Cervical stimulation 25Hz 2 minutes of stimulation on each side (D and E), 20 minutes after the onset of pain, with repetition after 15 minutes if the pain persists Gamma Core®	Cervical stimulation SHAM 2 minutes of stimulation on each side (D and E), 20 minutes after the onset of pain, with repetition after 15 minutes if the pain persists Gamma Core®	First crisis treated # >=1 point reduction in pain intensity after 30 minutes # >=1 point reduction in pain intensity after 60 minutes # >=1 point reduction in pain intensity after 120 minutes # Percentage of patients without rescue drugs All crises treated # >=1 point reduction in pain intensity after 30 minutes # >=1 point reduction in pain intensity after 60 minutes # >=1 point reduction in pain intensity after 120 minutes # Percentage of patients without rescue drugs	ITT analysis First crisis treated # 32.2 % of patients* treated with tVNS # 38.8 % of patients * treated with tVNS # 46.8% of patients * treated with tVNS # 59.3 % of patients * treated with tVNS All crises treated # 25.7% of patients treated with tVNS # 33.3 % of patients* treated with tVNS # 39.4% of patients* treated with tVNS # 52.3 % of patients* treated with tVNS

* p<0.5; MIDAS = Migraine Disability Assessment; HIT = Headache Impact Test; PP = Protocol Analysis; ITT = Intention-to-Treat Analysis; mITT = modified Intention--to-Treat Analysis

Table 2. Critical analysis using the Oxford Center for Evidence-Based Medicine tool

	Prophylactic treatment				Acute treatment		
Checklist items/ Articles	Straube et al.[22]	Silberstein et al.[23]	Diener et al.[24]	Najib et al.[25]	Tassorelli et al.[26]	Martelletti et al.[27]	Grazzi et al.[28]
Are the results of the study valid (Internal Validity)?							
1a. Was the distribution of patients to treatment groups random?	Yes	Yes	Yes	Uncertain The allocated population was much larger than the randomized population	Yes	Yes	Yes
1b. Were the groups similar at the start of the trial?	Yes	Yes	Yes	Uncertain If the randomization was not good, it is possible that the groups were not similar	Yes	Yes	Yes
2a. Were the groups treated equally? (Apart from the allocated treatment)	No, after reviewing the stimulation data found, some patients received additional training.	Yes	Yes	Yes	No, in the intervention group, a higher proportion of participants treated their first attack when its intensity was severe and were using preventive drugs	No, in the intervention group, a higher proportion of participants treated their first attack when its intensity was severe and were using preventive drugs	No, in the intervention group, a higher proportion of participants treated their first attack when its intensity was severe and were using preventive drugs
2b. Were all the patients who entered the study counted and analyzed? - And were they analyzed within the groups to which they were randomized to?	Yes	No The text is not clear about the population analyzed by PP or ITT	No The text is not clear about the population analyzed by PP or ITT. The post hoc analysis (mITT) only evaluates patients adhering to the protocol.	No The text is not clear about the population analyzed by PP or ITT. The post hoc analysis (mITT) only evaluates patients adhering to the protocol.	Uncertain, the text does not make it clear which criteria were used for the post hoc analysis (mITT)	Uncertain, the text does not make it clear which criteria were used for the post hoc analysis (mITT)	Uncertain, the text does not make it clear which criteria were used for the post hoc analysis (mITT)
3. Are the outcome measures objective? If not, were patients and clinicians "blinded" to which treatment they were receiving?	Yes	Yes, the outcome measures are objective. It is possible to identify the results of the blinded phase and the open phase.	Yes, the outcome measures are objective, but it doesn't show all the results.	Yes, the outcome measures are objective, but it doesn't show all the results.	Yes, the outcome measures are objective. It is possible to identify the results of the blinded phase and the open phase	Yes, the outcome measures are objective. It is possible to identify the results of the blinded phase and the open phase	Yes, the outcome measures are objective. The analysis was done with results from the blinded phase and the open phase together.

Continue...

Table 2. Critical analysis using the Oxford Center for Evidence-Based Medicine tool – continuation

	Prophylactic treatment				Acute treatment		
Checklist items/ Articles	Straube et al.[22]	Silberstein et al.[23]	Diener et al.[24]	Najib et al.[25]	Tassorelli et al.[26]	Martelletti et al.[27]	Grazzi et al.[28]
Which were the results?							
1a. Relative Risk (RR)	Outcome: 50% reduction in pain days ITT: 0.55 PP: 0.4636363636	Outcome 50% reduction in pain days PP: 6.774193548 note: the article does not provide ITT analysis data	ITT: 1.276	ITT: 1.117647059	ITT: Outcome complete remission of pain 30min: 2.635714286 60min: 1.708333333 120min: 1.419230769	ITT: Outcome complete remission of pain 30min: 1.708333333 60min: 1.863636364 120min: 1.5375	ITT: Outcome >=1 point reduction in pain intensity First crisis treated 30 min: 1.6489133043 60 min: 1,50546875 120 min: 1.658088235 % of pcs* without rescue drugs: 1.250847458 All seizures treated 30 min: 1.310274516 60 min: 1.395442359 120 min: 1.359661786 % of pcs* without rescue drugs: 1.226567169
1b. Absolute Risk Reduction (ARR)	ITT: -0.1022727273 PP: -0.1577540107	PP: 0.09623655914 note: the article does not provide ITT analysis data	ITT: 0.069	ITT: 0.03095975232	ITT: Outcome complete remission of pain 30min: 0.09308943089 60min: 0.08638211382 120min: 0.08861788618	ITT: Outcome complete remission of pain 30min: 0.03455284553 60min: 0.07723577236 120min: 0.07865853659	ITT: Outcome >=1 point reduction in pain intensity First crisis treated 30 min: 0.1213414634 60 min: 0.131504065 120 min: 0.1819105691 % of pcs* without rescue drugs: 0.1203252033 All seizures treated 30 min: 0.06348556374 60 min: 0.100285094 120 min: 0.1077948869 % of pcs* without rescue drugs: 0.1025102178
1c. Relative Risk Reduction (RRR)	ITT: 0.45 PP: 0.5363636364	PP: -5.774193548 note: the article does not provide ITT analysis data	ITT: -0.276	ITT: -0.1176470588	ITT: Outcome complete remission of pain 30min: -1.635714286 60min: -0.7083333333 120min: -0.4192307692	ITT: Outcome complete remission of pain 30min: -0.7083333333 60min: -0.8636363636 120min: -0.5375	ITT: Outcome >=1 point reduction in pain intensity First crisis treated 30 min: -0.6489130435 60 min: -0.50546875 120 min: -0,6580882353 % of pcs* without rescue drugs: -0.2508474576 All seizures treated 30 min: -0.3102745157 60 min: -0.3954423592 120 min: -0.3596617859 % of pcs* without rescue drugs: -0.2265671693
1d. Necessary Number to Treat (NNT)	ITT: -9.777777778 PP: -6.338983051	PP: 10.39106145 note: the article does not provide ITT analysis data	ITT: 14.49275362	ITT: 32.3	ITT: Outcome complete remission of pain 30min: 10.74235808 60min: 11.57647059 120min: 11.28440367	ITT: Outcome complete remission of pain 30min: 28.94117647 60min: 12.94736842 120min: 12.71317829	ITT: Outcome >=1 point reduction in pain intensity First crisis treated 30 min: 8.24120603 60 min: 7,604327666 120 min: 5.497206704 % of pcs* without rescue drugs: 8.310810811 All seizures treated 30 min: 15.75161251 60 min: 9.971571649 120 min: 9.276877867 % of pcs* without rescue drugs: 9.755125113
2. How accurate was the estimate of the treatment effect?	The p-value was presented for each variable and is marked in table 1 when p<.05	The p-value was presented for each variable and is marked in table 1 when p<.05	The p-value was presented for each variable and is marked in table 1 when p<.05	The p-value was presented for each variable and is marked in table 1 when p<.05	The p-value was presented for each variable and is marked in table 1 when p<.05	The p-value was presented for each variable and is marked in table 1 when p<.05	The p-value was presented for each variable and is marked in table 1 when p<.05
Will the results help me to care for my patient (External validity)?							
	Yes	Yes	Yes	Yes	Yes	Yes	Yes

* pcs – patients; PP = Per Protocol; ITT = Intention To Treat; mITT = modified Intention To Treat

In chronological order, the first study[22] investigated patients with chronic migraine, i.e. they had at least 15 headache days per month. The study in question differed from the others not only in the use of the auricular device, but also in the frequency of the stimulus. Another study[22] used a frequency of 25Hz as the "intervention" and 1Hz as the "control". After 12 weeks of daily stimulation for 4 hours, the control group, rather than the intervention group, achieved a greater reduction in the number of headache days per month. Only one third of the patients were considered "responsive" to tVNS.

Despite the result found by the aforementioned study[22], the three other studies aimed at migraine prophylaxis that followed, now using cervical stimulation by the gammaCore™ device, used a frequency of 25Hz as the intervention and a SHAM stimulus of 0.1Hz as the control. The authors of the studies did not offer any arguments for the use of this stimulation protocol.

In a study[23], also on patients with chronic migraine, the reduction in headache days/month after the first 2 months was 1.4 days. Although the reduction in headache days/month after 8 months increased to 3.6 days, it should be borne in mind that patients were only blinded to the treatment for the first 2 months. All other results refer to the open phase of the study. The best result, found after 8 months of stimulation, was the result of the open phase patients who remained in the study, since a large number of patients dropped out.

The third prophylactic study[24] was carried out in 2019 and has a very similar design to the previous one. Unlike the two previous studies, this study included patients with a moderate level of migraine attacks, but still below the diagnosis of chronic migraine. The results were presented in such a way as to separate a "migraine day" from a "headache day", without defining the difference between these 2 episodes.

The results at 3, 6 or 9 months were homogeneous and, despite a slight advantage for tVNS, the reduction in pain days/month was not statistically different between intervention and control. One study[24] carried out a *post hoc* analysis called "modified intention-to-treat analysis" (mITT), which included only patients with more than 67% adherence to stimulation and thus, at 3 months of stimulation, the decrease in headache days in the group receiving tVNS became statistically significant. This treatment effect was greater in the subgroup of patients with migrainous aura.

The fourth and final prophylactic study[25] included patients with chronic and sporadic migraine, but maintained the experimental design of the other RCTs. The intention was to evaluate after 12 weeks with double-blinding, but the study showed results from the ninth week of prophylaxis. There was a reduction of 3.12 days of pain after a minimum of 9 weeks of prophylaxis. For this study, the post hoc analysis (mITT) showed a response rate (50% reduction in pain days) in the intervention group of 44.87%, which is statistically significant.

The three RCTs focused on the acute treatment of migraine actually deal with the same sample of patients. The second and third articles only provide additional results to the first. In the first two studies[26,27], the primary endpoint was complete pain remission between 30 and 120 minutes after tVNS, in the first crisis treated and in all crises treated during the study's blinding period. The secondary endpoints were pain relief also between 30 and 120 minutes after tVNS, a decrease in pain intensity and the percentage of patients who had pain remission in 50% of the crises treated.

The results of these studies[26,27] showed that tVNS is more effective in complete pain remission than SHAM stimulation at 30 and 60 minutes. In terms of pain relief, tVNS is only more effective at 120 minutes. Probably in order to make a correlation with the parameter used for the prophylaxis studies, the number of "responsive" patients was also assessed. In this case, in 50% of the seizures treated within the blinding period, patients were pain-free after 120 minutes of stimulation. For this parameter, tVNS was superior to SHAM stimulation. One study[27] analyzed all the seizures treated. Considering all the seizures treated during the blinding period, tVNS was effective in completely relieving pain at 60 and 120 minutes after stimulation. The same was true for the pain relief parameter at 60 and 120 minutes after stimulation. As for the decrease in the pain scale score, tVNS was effective only 60 minutes after stimulation.

The third study[28] used as its primary endpoint a reduction of at least 1 point on the pain intensity scale in 30, 60 or 120 minutes, in the first crisis treated and in all crises treated. For this analysis, tVNS was effective in reducing pain intensity by at least 1 point at any of the proposed times, both in the first crisis treated and in all crises treated.

DISCUSSION

This systematic review shows the development of methodology over time. The studies start with a modest population and become multicenter studies from which it is possible to carry out post hoc or subgroup analyses. Along the way, and without any argumentation, the studies move from presenting data using two protocols: PP (Per Protocol) and ITT (Intention To Treat) to presenting only ITT and variations of it, which the authors called "modified ITT" (mITT). Even though the authors have defined what a mITT would be, the analysis carried out by the researchers deviates from what is established by epidemiology and good practice in statistical analysis.

The use of tVNS as a prophylaxis for migraine was quite coherent because it was hoped that, in the medium term, tVNS would promote desensitization of the hypothalamus, which is involved in the origin of migraine attacks, and reduce the risk of cortical spreading depression, a phenomenon known mainly in migraine with aura[10]. Prophylaxis studies suggest that the clinical efficacy of tVNS increases according to the length of prophylaxis, which corroborates this hypothesis, since tVNS is modulating the disease[29].

The results of the 4 prophylactic studies showed poor results. The recommended stimulation time practically made adherence to treatment impossible. The presentation of the results and the statistical analysis used were generally unclear and only significant

in the post hoc analyses, in which patients who did not respond to tVNS were excluded from the analysis.

The 3 studies on acute treatment[26-28] were published in the same year (2018) and had the same sample of 248 patients, but were published in two different journals. In addition, in all 3 studies one of the authors is the representative of the manufacturer of the device used, gammaCore™.

As an acute treatment, tVNS was used within 20 minutes of the onset of pain, with repetition after 15 minutes if the pain persisted. The primary endpoint was pain remission within 120 minutes, which agrees with the consensus that effective treatment of migraine attacks eliminates pain within 2 hours of administration, whether of a drug or any other procedure[30].

The results presented for the acute treatment of migraine attacks with tVNS are not insignificant, especially when compared to the efficacy of other pharmacological options, which are more prone to undesirable adverse effects.

Of the 7 RCTs included in this review, 4 were included in a meta-analysis[31], two were prophylactic studies[23,24] and two were studies on acute treatment[26,27]. The meta-analysis[31] analyzed and included studies with migraine and cluster headache patients. This meta-analysis failed to demonstrate the benefit of tVNS in the 50% reduction in pain days/month, a parameter used in prophylactic studies. However, it has been shown that tVNS is effective as an acute treatment of a crisis, whether migraine or cluster headache, in terms of pain resolution within 30 minutes of stimulation, and is also effective in terms of pain relief within 30 and 60 minutes of stimulation.

The quality analysis of the articles showed that, in general, the 7 RCTs were well-designed and seemed to meet the requirements of what is considered a good quality RCT: randomization, double-blinding, control group, adequate statistical analysis (ITT or PP), follow-up time, among others[32-33]. However, in all the RCTs, the information to answer the items on the checklist seems to be hidden, and can only be found with great difficulty.

As already mentioned, the first RCT[22] obtained better results with the stimulation frequency used in the control group (1Hz) and not in the treatment group (25 Hz). Because of this, and for any type of analysis, PP or ITT, the NNT found is negative, which, in principle, would indicate that the treatment has a detrimental effect.

Despite this result, the 6 RCTs that followed the first study, whether with a prophylaxis or acute treatment approach, maintained stimulation in the treatment group at 25 Hz and adopted a sham stimulation of 0.1 Hz as a control. The 0.1 Hz stimulation is so weak that the patients reported feeling nothing and consequently identified themselves as belonging to the control group.

In practically all the prophylactic studies, blinding was precarious and the so-called "open-label" phase, without any blinding, was much longer than the blinded phase.

In the present evaluation, although the concern with adequate study designs and protocols was evident, there was at least one internal validity problem for each study evaluated.

In the results section of the checklist, the difficulty in finding the values corresponding to each parameter (RR, RAR, RRR, NNT) intensified, making it necessary to resort to other publications and clinical research registration websites[34]. In most cases it was not possible to retrieve all the data needed to calculate all the outcomes assessed.

External validity concerns the applicability of the results in the real world. The key question here is whether the patients in the study are representative of the population to which the results are to be applied. Another point to consider is how feasible the procedure or treatment studied is in the real world when compared to a controlled study[35]. In the analysis included in table 2, all the RCTs obtained a positive response on this item. In all the RCTs included in this research, the population studied was representative, although no differences were described between episodic and chronic migraine or between migraine with aura and without aura. The stimulation protocol, both for acute treatment and especially for prophylactic treatment, seems to be unfeasible in the real world, but this hypothesis was not addressed by any of the studies. The fact that many patients dropped out of the studies after the second month may argue in favor of this hypothesis.

On the other hand, external validity can only be properly considered if there is internal validity. If the results of a study are not internally valid, external validity is irrelevant[33].

Although the authors of the last three prophylactic studies included in this review[23-25] interpreted their results optimistically, the meta-analysis[31] which included two of these prophylactic studies[23,24] showed no benefit from the prophylactic use of tVNS. This result, combined with the critical analysis of the studies (table 2), discourages the recommendation of tVNS as a prophylaxis for migraine.

The opinion of experts, co-authors of the studies that investigated tVNS as a prophylactic treatment[36] and included in this review, is nevertheless optimistic and considers tVNS to be a viable option with lower risks of abuse, a phenomenon often seen in relation to pharmacological options.

Regarding the use of tVNS as an acute treatment for migraine, the same meta-analysis[31] concluded that acute treatment with tVNS is effective. However, this result combines the results of migraine patients with those of cluster headache patients and is based on the same sample of patients.

The critical analysis of individual studies has been a way of bringing the statistical results presented in different studies into the real world. It is advisable that, at some point, the results of individual studies contribute to clinical decision-making. One study[37] critically analyzed one of the studies evaluated in this review, the PRESTO[26] study, aimed at the acute treatment of migraine attacks. In a less systematic way than that presented by the Oxford checklist used in this review, this study described the same methodological flaws and emphasized the fact that the study had been funded by electroCore LLC, the manufacturer of the equipment used.

Of the 7 RCTs found, only the oldest[22], from 2015, used the Nemos® device manufactured by the German company Cerbomed GmbH. The study was carried out 2 years after the European Headache Federation's positive stance[5] on neuromodulation in headaches and was funded by the device's manufacturer. In addition to funding the study, two authors received additional

assistance from Cerbomed. All of the other six RCTs used the gammaCore® device, manufactured by the American company ElectroCore and, in all of them, one of the authors of the article is an ElectroCore representative. Cerbomed closed down in 2017, while ElectroCore is still active.

LIMITATIONS

This review searched for articles only in the Pubmed database, whose main search engine is Medline. This online database indexes journals from the United States and 80 other countries. Although Medline is the most widely used search engine in the health field, it is not possible to say that the seven RCTs found here are the only ones in the literature.

CONCLUSION

A critical analysis of the studies included in this review revealed some compromised internal validity in each of the studies, which reduces the strength of the results.

The studies on the prophylaxis of migraine with tVNS have not shown any significant benefits that justify the use of a stimulation protocol that causes poor adherence to treatment. On the other hand, the acute treatment of migraine attacks with tVNS has shown better results and is considered a viable option by specialists.

The results found in the sample of patients who received tVNS as an acute treatment for a migraine attack, combined with the search for a non-pharmacological option for the acute treatment of migraine, justifies new RCTs, so that there is no doubt about their internal validity.

AUTHORS' CONTRIBUTIONS

Tania Gouvêa Thomaz
Data Collection, Conceptualization, Project Management, Investigation, Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Supervision
Andrée Carolle Mariane Amany Kouassi
Data Collection, Methodology, Writing - Review and Editing
Arthur dos Santos Leite Neiva Neves
Data Collection, Methodology, Writing - Review and Editing
Gisele Fernandes de Sena
Data Collection, Methodology, Writing - Review and Editing

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