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Original Research

Headache Frequency and Pain Severity Following a Nerve Stimulator Implant for Chronic Migraine: A Systematic Review and Meta-Analysis

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Abstract

Migraines affect approximately one billion individuals worldwide. Implanted nerve stimulator devices can provide relief to some individuals who have chronic migraines refractory to other treatments. This study defines the change in headache pain severity and headache frequency following implanted nerve stimulator treatment in chronic migraineurs. A PRISMA-compliant systematic review of six databases was performed to identify all clinical trials treating at least

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10 chronic migraineurs with an implanted nerve stimulator. Inverse variance random effects meta-analyses were performed to define the relative change in headache pain severity and headache frequency as compared to baseline. Nine studies met criteria, including 5 randomized controlled clinical trials and 4 uncontrolled clinical trials, and treated 559 individuals. Among studies that reported gender, 306 females and 154 males were treated. Mean patient ages ranged from 45 to 50 years. All included studies targeted the greater occipital nerve with an implanted nerve stimulator. Implanted nerve stimulator treatment reduced pain severity at 1 month by 36.42% (95%-CI: 28.35-44.49, I^2 = 55%) and 3 months by 50.04% (95%-CI: 39.67-60.42%, I^2 = 26%). Implanted nerve stimulators reduced headache frequency by 49.86% (95%-CI: 31.49-68.23, I^2 = 92%) at 1 to 3 months and 27.43% (95%-CI: 17.68-37.18, I^2 = 63%) at 6 to 97 months. Implanted nerve stimulator devices provide clinically and statistically significant improvements in headache severity and frequency in individuals with chronic migraines.

Keywords
Migraine; headache; neuromodulation; implanted nerve stimulator

1. Introduction

Migraines are estimated to affect 1 billion individuals worldwide [1]. Migraines are defined as a *primary headache* in the 3rd edition of The International Classification of Headache Disorders (ICHD-3), along with tension-type headaches, trigeminal autonomic cephalalgias, cluster headaches and other primary headache disorders [2]. Migraines are defined as lasting for 4 to 72 hours and causing photophobia and phonophobia or nausea or vomiting and also have at least two additional characteristics of unilateral location, pulsating quality, moderate or severe pain intensity, or aggravation by or causing avoidance of routine physical activities like walking [2]. Migraine disorders that persist for over 3 months and entail at least 15 headache days per month, 8 of which meet criteria for a migraine, may be classified as *chronic migraine* rather than *episodic* [2].

Many individuals with migraines do not obtain adequate control with conservative management, lifestyle changes and medications [3]. In recent decades, nerve stimulator treatments have been developed as methods of treating migraines and particularly migraines resistant to conventional therapies [4-27]. Nerve stimulator devices may be utilized transcutaneously as a handheld device or patch that is applied to the skin, via an acupuncture needle that crosses the skin, or as an implanted device.

The purpose of this study was to perform a systematic review of all published clinical trials on implanted nerve stimulator devices and includes a meta-analysis of their efficacy on treating headache frequency and pain severity in individuals with chronic migraines.

2. Methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [28] and is registered on the International Prospective Register of Systematic Reviews (PROSPERO) under the ID: CRD42020199696.

2.1 Search Strategy

Two reviewers (B.L.B. and M.M.I.) performed independent literature searches of the databases Cochrane Library, Ovid MEDLINE, Ovid EMBASE, Web of Science and the clinical trials registries ClinicalTrials.gov (https://www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) (https://www.who.int). Searches were performed from database inception through June 17th, 2020. Free text and Medical Subheading (MeSH) terms searched included "migraine," "headache," "nerve stimulation," "neuralgia," "cephalalgia," "vagal," "trigeminal," "supraorbital," "occipital," combined using the Boolean operators "AND" and "OR" and including similar words and word variations. The full search strategy is included in the **Online Resource**. Bibliographies of included studies were also searched. Disagreement on article inclusion was resolved by discussion with an additional reviewer (A.G.E.). Data extraction was performed using a piloted form excel spreadsheet by two reviewers (B.L.B. and M.M.I.) with an additional reviewer (A.G.E.) checking over 90% of the extracted data. Instances of multiple publications describing the same cohort were handled by conducting meta-analysis with data from only the study with the largest cohort.

2.2 Inclusion and Exclusion Criteria

Studies included were 1) peer-reviewed research articles, 2) prospective studies, 3) in English language, 4) treating patients over age 18 years, 5) treating migraines diagnosed according to ICHD-3 criteria, 6) using a nerve stimulator device and 7) treatment groups containing a minimum of 10 individuals.

Studies excluded were 1) duplicate studies, 2) incomplete trials, 3) treatment groups with fewer than 10 individuals, 4) studies with unclear treatment methods, 5) abstracts, conference proceedings, letters to the editor, editorials, 6) retrospective studies, reviews, meta-analyses, case reports, animal studies, non-peer reviewed "grey" literature.

2.3 Risk of Bias

Risk of bias was assessed for randomized controlled clinical trials (RCTs) at study and outcome levels according to the Cochrane Collaboration Handbook Version 6.1 [29]. The included observational studies all meet high risk-of-bias criteria according to this assessment and did not have a formal assessment of risk-of-bias.

2.4 Outcome Measures

The primary outcomes were headache pain severity and headache frequency. To allow for comparison, headache pain severity data were converted to a 0-10 scale when reported on a 0-100 rating scale. Only headache days per month were included for instances of studies reporting both headache frequency and migraine frequency.

2.5 Statistical Analysis

Statistical analyses were performed using the RStudio meta package (version 4.15-1). When present, intention-to-treat data were used in meta-analyses to minimize the risk-of-bias in the

meta-analyses [30]. Continuous data were presented as mean differences and standard error of the mean (SEM). SEM were calculated from standard deviations, or when neither were provided, were imputed from the average standard deviation of the studies [31]. Heterogeneity between studies was incorporated by calculation of I^2, a measure which indicates the extent of variation attributed to differences between studies rather than sampling error. I^2 values over 75% were considered highly heterogeneous and warranted investigation of contributory study details [32]. Meta-analyses were performed using a random-effects model to account for increased variation between studies [33]. A P value of <0.05 was considered statistically significant. To establish a clinical context for the change in outcomes, a minimum clinically important difference (MCID) for pain severity was set as being a 10% reduction based on other studies suggesting a range for the MCID being between 0.8 and 4 on a 0-10 NRS scale [34], while for headache frequency was set as a 7.5% reduction in these studies based on a 15-headache per month ICHD-3 diagnostic requirement for chronic migraineurs and other studies suggesting 1 day per month is clinically significant [35].

3. Results

The search strategy identified 3822 records. After removal of duplicates, 2868 records were screened by title and abstract, resulting in 240 records eligible for full-text screening. Nine studies met criteria and were included in the systematic review [10, 14-16, 20, 23, 36-38]. The article selection process is described in Figure 1.

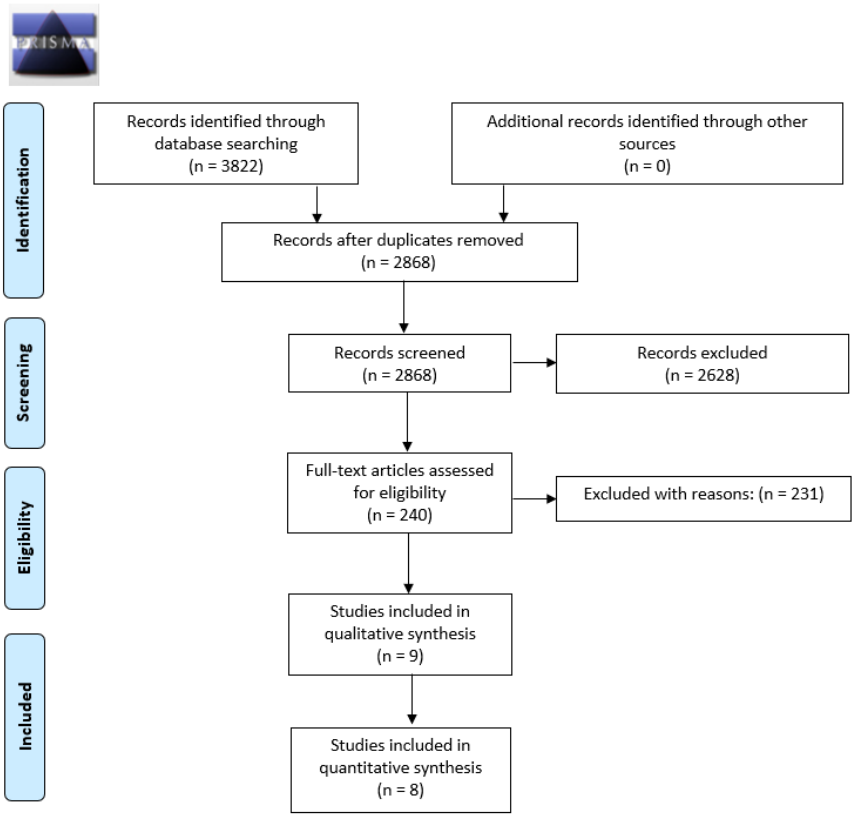

Figure 1 The search strategy identified 3822 records, including 2868 unique records. These records were first screened by title and abstract and then by full text, resulting in the inclusion of 9 studies in the systematic review, of which 8 had comparable data and were included in the meta-analyses.

Studies that met criteria were published between 2012-2017. All included studies targeted the greater occipital nerve with an implanted nerve stimulator. Patient demographics and study details are summarized in the Table 1 but briefly, included were 5 RCTs [10, 20, 23, 37, 38] and 4 uncontrolled clinical trials (UCTs) [15, 16, 36, 38]. Of the 5 RCTs, 4 utilized sham programming [10, 14, 23, 37] and one compared different stimulation settings [20]. Three RCTs [10, 14, 23] included the same cohort but described unique analyses. Three studies preceded the implanted nerve stimulator study by enrolling individuals with a confirmed prior response to either transcutaneous [16], percutaneous [38], or implanted [37] nerve stimulator devices. Five studies were conducted in North America [10, 14, 20, 23, 36] and 4 were in Europe [15, 16, 37, 38]. Treated were 559 patients, including 306 females and 154 males among the studies that reported on patient gender. The mean age of enrolled individuals ranged from 45 to 50 years.

Table 1 Study Details.

Author, Year	Country	Study Design	# Treatment; # Control	Headache Pathology	Stimulation Therapy Type	# Males, # Females	Age: Treated, Control (Mean)
Dodick *et al*., 2015	USA	RCT*	105; 52	Chronic migraine	Implanted	33, 124	45, 45
Kinfe *et al*., 2016	Germany	UCT	12; NA	Chronic migraine or other headaches	Percutaneous trial (10 days) before implant	2, 10	50, NA
Mekhail *et al*., 2017	USA	RCT*	14; 6	Chronic migraine	Implanted	5, 15	NR, NR
Miller *et al.,* 2016	United Kingdom	UCT	53; NA	Chronic migraine and other headaches	Implanted	16, 37	48, NA
Nguyen *et al*., 2016	France	UCT	41; NA	Chronic migraine or other headaches	Transcutaneous trial (1 month) before implant	NR, NR	50, NA
Saper *et al*., 2011	USA	RCT†	33; 17; 17; 8‡	Chronic migraine	Implanted	53, 13	45, 50
Silberstein *et al*., 2012	USA	RCT*	105; 52	Chronic migraine	Implanted	33, 124	45, 45
Serra *et al.* 2012	Italy	RCT	15; 15	Chronic migraine	Implant trial (1 month) before enrollment	Approximately 1:3 ratio for the 34 individuals implanted pre-dropout	46 (combined pre-dropout)
Kiss *et al.* 2012	Canada	UCT†	10	Chronic migraine	Implanted	2, 8	45, NA

USA: United States of America. RCT: randomized controlled trial. UCT: uncontrolled clinical trial. NR: not reported.

*These three studies have an overlap of the enrolled individuals. †These two studies have an overlap of the enrolled individuals. ‡Randomization included 33 individuals to adjustable stimulation, 17 to preset stimulation, 17 to medical management, and 8 were treated with adjustable stimulation in an ancillary group analyzed separately due to not meeting the defined inclusion criteria.

3.1 Risk of Bias

Cochrane collaboration risk-of-bias was calculated for the 5 RCTs and is included in Figure 2. Overall, four studies had high risk-of-bias and one had some concerns for risk of bias.

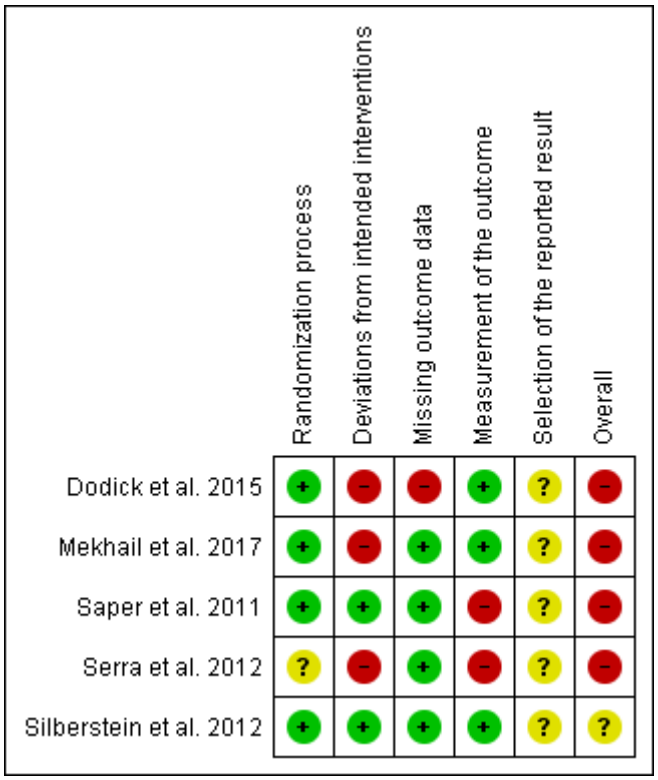

Figure 2 The Cochrane risk of bias tool for randomized controlled trials resulted in 1 study having uncertain risk of bias and 4 studies having high risk of bias.

3.2 Meta-Analyses of Pain Severity

One study was excluded from pain severity meta-analyses due to being an outlier; the study enrolled a mixed cohort of patients with pathologies that included predominately occipital neuralgia as well as cervicogenic headache, chronic migraine and cluster headache [16]. Three RCTs including 4 cohorts had comparable data for a meta-analysis of pain severity at 1 month after initiating an implanted nerve stimulator device treatment. As shown in Figure 3, the pooled mean pain severity at 1 month following implanted nerve stimulator device treatment was reduced by 36.42% (95%-CI: 28.35-44.49, I^2 = 55%) as compared to baseline. Two RCTs assessed pain severity at 3 months after initiating an implanted nerve stimulator device treatment. As shown in Figure 4, the pooled mean pain severity at 3 months following implanted nerve stimulator device treatment was reduced by 50.04% (95%-CI: 39.67-60.42, I^2 = 26%) as compared to baseline.

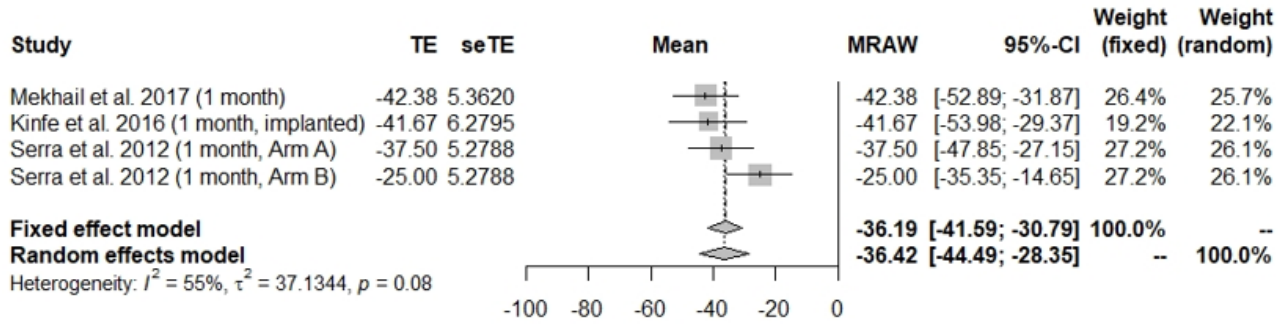

Figure 3 Three studies including 4 cohorts had comparable data for meta-analysis of the percent change in pain severity at 1 month after treatment.

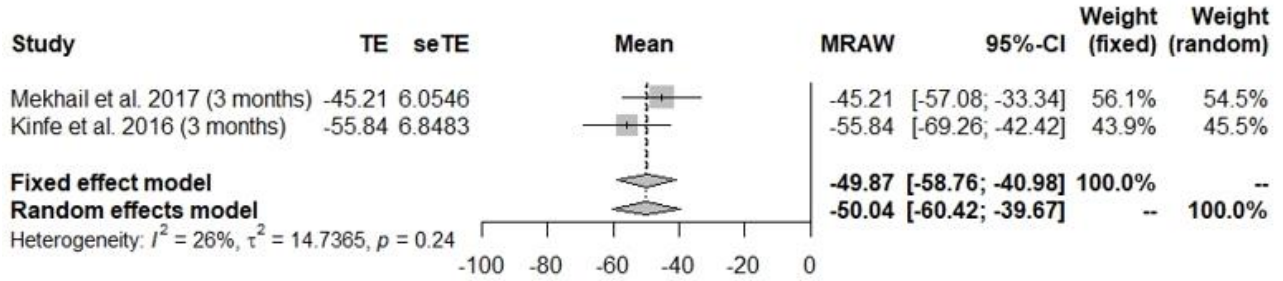

Figure 4 Two studies had comparable data for meta-analysis of the percent change in pain severity at 3 months after treatment.

3.3 Meta-Analyses of Headache Frequency

Eight cohorts from four RCTs and two UCTs had comparable data for a meta-analysis of headache frequency after initiating an implanted nerve stimulator device treatment. Headache frequency at 1 to 3 months was reduced by 49.86% (95%-CI: 31.49-68.23, I^2 = 92%) as compared to baseline, as shown in Figure 5. For the meta-analysis of headache frequency at 6 to 97 months, one study was excluded due to being an outlier and contributing to high heterogeneity [16]. At 6 to 97 months headache frequency was reduced by 27.43% (95%-CI: 17.68-37.18, I^2 = 63%) as compared to baseline, as shown in Figure 6.

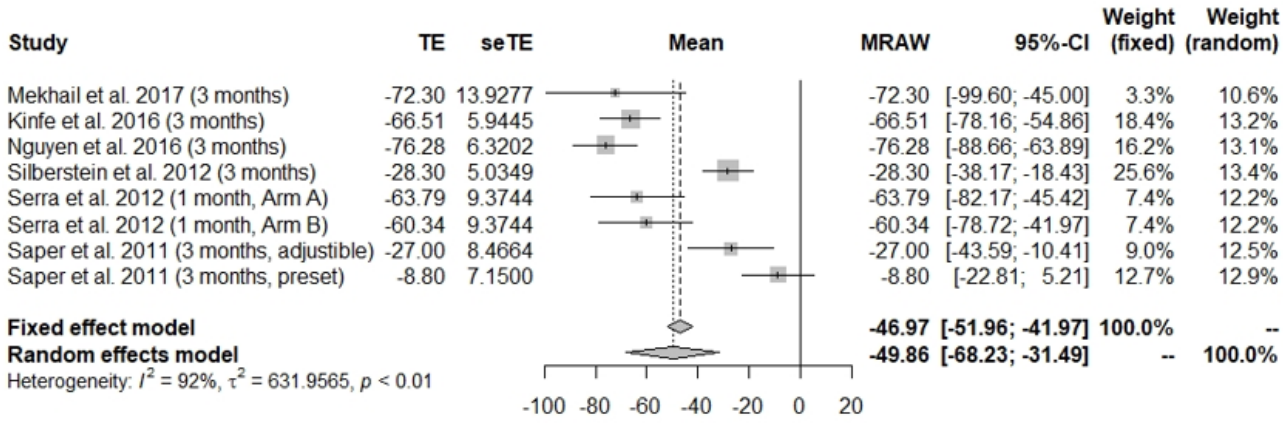

Figure 5 Six studies including 8 cohorts had comparable data for meta-analysis of the percent change in headache days per month at 1 to 3 months after treatment.

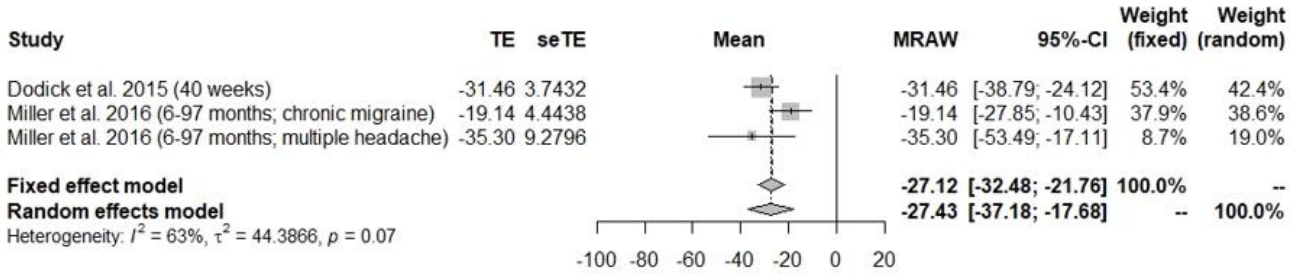

Figure 6 Two studies including 3 cohorts had comparable data for meta-analysis of the percent change in headache days per month at 6 to 97 months after treatment.

4. Discussion

The meta-analyses in this study show that that implanting a nerve stimulator device can be effective at reducing migraine pain severity and headache frequency in migraineurs. The magnitude of improvements exceeded the MCID for headache severity and frequency at all time-points assessed. Headache frequency was reduced by 50% at 1 to 3 months and 27% at 6 to 97 months. The confidence intervals for this decline in efficacy over time were overlapping, suggesting a non-statistically significant difference between the two time points. Alternatively, while adverse effects, such as lead migration may occur and lead to losses of efficacy over time, not all studies saw a decline in efficacy over the assessment of long-term outcomes [16].

Headache severity was reduced by 50% at 3 months as compared to 36% at 1 month and outcomes at longer duration follow-ups were not available for a meta-analysis. The confidence intervals for this difference in headache severity were overlapping, suggesting a non-statistically significant difference between these time points.

4.1 Effects of Migraine Pathology Variations

Each of the 9 included studies targeted the greater occipital nerve with an implanted nerve stimulator to treat chronic migraine. The 2012 UCT with 10 patients by Kiss *et al.* indicated that the pain phenotypes of patients with migraines vary in the proportion of pain at non-occipital areas (i.e. orbital, frontal, temporal) [36]. Although limited by their small sample size, Kiss *et al.* found that patients with greater proportions of their pain being in the occipital scalp were associated with increased likelihood of stimulator use beyond 3 years [36], which suggests that patients with occipital area pain may respond better to occipital nerve stimulation than patients with chronic migraine who do not have occipital area pain [36].

Three studies included patients with additional headache diagnoses to chronic migraine [15, 16, 38]. The 2016 UCT by Miller *et al.* included 18 of 53 patients who had chronic migraine in addition to combinations of chronic cluster headaches, unilateral neuralgiform headaches, or hemicrania continua [15]. The 2016 UCT by Nguyen *et al.* included 35 in their cohort of individuals who had either chronic migraine, cluster headache, cervicogenic headache, or occipital neuralgia [16]. The 2016 UCT by Kinfe *et al.* included 12 individuals with chronic headaches, including 8 with chronic refractory migraine and 1 of each with occipital neuralgia, cervicogenic headache, cluster headache and post-traumatic headache [38]. The treatment effects on headache days per month reported by these 3 studies were among the largest reported, which may warrant additional future research to

investigate populations of individuals who have more than one headache diagnosis. This effect may also be due to each of these 3 studies being UCTs which may confer a bias to their results as others like Evers *et al.* have noted in examining response rates of cluster headache to neurostimulation, which were greater in UCTs than in sham-controlled studies [39].

4.2 Predictive Value of Nerve Blocks

Two of the included studies utilized greater occipital nerve blocks (GONB) prior to implantation [15, 20], and neither study reported on efficacy of the GONB to predict treatment outcomes. In the 2011 UCT by Saper *et al.*, all enrolled individuals had a 50% migraine pain reduction within 24-hours of a GONB, and a separate *non-enrolled Ancillary group* of 5 individuals did not have this pain reduction and were also implanted with a nerve stimulator. The ancillary group also saw improvements following nerve stimulator treatment, but the small sample size prevented any reliable comparison [20]. In the 2016 UCT by Miller *et al*., 53 individuals were enrolled, all of whom had undergone a prior GONB and 23% of whom had successful symptomatic treatment from the block. A subgroup analysis was not performed to differentiate whether these 12 GONB responders had an improved response to the implanted nerve stimulator [15]. A 2015 review by Kinfe *et al.* sought to address the predictive value of GONB, finding that stimulator outcomes may not be predicted sufficiently by GONB [40]. No RCTs have examined the predictive value of GONB before implanted occipital nerve stimulator treatment.

4.3 Nerve Stimulator Use with Other Headache Pathologies and Novel Treatments

Further research may seek to investigate whether nerve stimulators may benefit individuals with other headache pathologies or individuals with incomplete headache resolution following use of the novel treatments such as calcitonin gene-related peptide (CGRP) modulation [41]. Subarachnoid hemorrhage leads to severe headache pain that becomes chronic in up to 25% of survivors and are difficult to treat pain syndrome associated with significant narcotic requirements for pain control [42-44]. Gabapentin, thought to assist with neuropathic pain, seems to reduce pain and opiate requirements in these populations with adjunctive gabapentin, suggesting that nerves may be efficacious targets for treatments [45]. Pterygopalatine fossa blockade was performed by Smith *et al.*, who found that the anesthetic block reduced the pain from a 9.1 to a 2.8 at 8 hours [43]. These additional nerve targets that are associated with headache symptom improvement, such as the pterygopalatine fossa sphenopalatine ganglion or maxillary nerve, may serve as future research targets for implanted nerve stimulators in hopes of providing long-term relief to patients suffering from these difficult to treat headaches.

4.4 Revisions and Adverse Effects

Several adverse effects and revision surgeries were reported in the included studies. The rate of adverse effects varied widely between studies depending on whether minor adverse effects were included such as a suture abscess but ranged from 17% to 70% [14, 20, 23, 36, 37]. Lead migration, which often requires reoperation, was the most common complication in several studies and generally ranged in incidence from 9% to 24% [10, 14, 20, 23, 36, 37]. Kiss *et al.* did not describe lead migration but noted that 40% of their cohort had a loss of the stimulator paresthesia effect

which required reoperation [36]. The 2016 UCT by Kinfe *et al.* described a 0% lead migration in their 12 patients by suturing the electrodes to the muscle fascia [38], and Miller *et al.* also did not have any lead migration at a median follow-up of 42 months in their UCT of 53 patients [15].

Infection was another common complication across studies and was either treated medically or with removal of the stimulator system and generally ranged in incidence from 2% to 14% [10, 15, 16, 20, 23, 37], although Kiss *et al.* reported that 30% of their cohort of 10 individuals had a possible infection and were treated with antibiotics. The 2016 UCT by Kinfe *et al.* did not report any infections in their 12 patients [38], and Mekhail *et al.* also did not report any infections in their 2017 RCT but reported a 5% incidence of an allergic reaction and 5% incidence of a wound site complication [14].

4.5 Investigation of Outliers

Both short-term and long-term headache frequency meta-analyses had high heterogeneity and were investigated for outlier data. The 2016 UCT by Nguyen *et al.* study was an outlier for the long-term outcomes meta-analysis and was excluded [16], resulting in the long-term meta-analysis having acceptable heterogeneity. The headache frequency outcomes of the study of Nguyen *et al.* were superior to the other studies and may be attributed to their study reporting outcomes only on patients who responded to a trial of transcutaneous nerve stimulation, which may cause a selection bias if transcutaneous nerve stimulation predicts a successful response to the implanted nerve stimulator. Their study also enrolled patients with migraines as well as occipital neuralgia or cervicogenic headache diagnoses; these other pathologies may have greater responses to electrical stimulation of the greater occipital nerve [16]. No clear outliers were present in the short-term headache frequency meta-analysis, which had 92% heterogeneity and no studies were excluded. Reasons for the variation in short-term headache frequency outcomes between studies may be attributed to stimulator settings, patient differences, and surgical variability, although the high heterogeneity limits the interpretation of the headache frequency changes.

4.6 Strengths and Limitations

The meta-analyses are strengthened by the inclusion criteria of only prospective studies and that most of the included studies were RCTs. The review is strengthened by a sample size of over 550 patients with an expected female to male gender bias. The mean age of patients enrolled ranged from 45 to 50 years which may limit application of these results to younger or older patients. This study included studies that utilized a variety of devices and device settings in the stimulation of several nerves, which limits the ability to identify which study details led to the variations in outcomes between studies. Several of the included RCTs had high risk-of-bias. Meta-analyses of headache pain severity and long-term headache frequency were possible, although the short-term headache frequency meta-analysis had significant heterogeneity that limits the interpretation of that meta-analysis. Some studies reported migraine days per month whereas other studies reported headache days per month, although these values were similar in studies that reported both headache days and migraine days. Future studies may also benefit from including validated outcome measures assessing headache related disability and the response to treatment of the most bothersome symptom [46]. Lastly, the identification of published studies was strengthened by the PRISMA-compliant methods with a search strategy performed in duplicate, although study selection

may still be affected by a publication bias whereby studies showing an effect are generally more likely to be published.

5. Conclusion

Individuals with chronic migraines may benefit from treatment with implanted nerve stimulator devices. Implanted nerve stimulator devices provided clinically significant improvements in headache severity and frequency. Clinicians may choose to utilize implanted nerve stimulator devices for statistically and clinically significant reductions in migraine frequency and severity that persist without significant declines in efficacy over the study durations. Additional RCTs with low risk-of-bias using validated outcome measures are needed to better establish the changes in headache frequency and severity after implantation of a nerve stimulator.

Author Contributions

All authors read and approved the final manuscript. Study conceptualization and methodology were by Drs. Adam Evans, Salam Al Kassis, Tigran Kesayan and Krista Brooks-Horrar. Literature search and data extraction were performed by Drs. Brady Burns and Maryo Ibrahim, with data checking by Dr. Adam Evans. Data analysis was performed by Drs. Adam Evans and Maryo Ibrahim. Writing was performed by Drs. Adam Evans, Patrick Assi, Jeremy Joseph, Chris Kalmar.

Competing Interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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