Neuromodulation versus standard care for migraine prophylaxis

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BACKGROUND

Migraine is the second cause of disability in the world, according to the Global Burden of Disease study 2019, and approximately 1 in 7 people globally suffers from this disease. Migraine is characterized by recurrent episodes of moderate to high-intensity headache. There are two main aspects of migraine therapy: migraine attack management and prophylactic therapy. The latter is aimed at reducing the number of days with migraine and making the headache less intense. Preventive medications are effective and currently widely used, but they have side effects and prescription limitations (especially in pregnant and elderly patients). Therefore, neuromodulation techniques remain a relevant option for migraine prophylaxis.

RESEARCH QUESTIONS

PICO question: should neuromodulation be used in patients with migraine for prophylactic therapy?

Through a Delphi procedure, we agreed on a set of 6 outcomes for our search, 3 of which were rated critical (days without migraine, intensity of migraine and acute drugs intake) and 3 important (side effects, functional disability and patients' satisfaction). Guideline development was carried through according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

IDENTIFICATION OF STUDIES

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements, based on the PubMed/MEDLINE and Cochrane Central databases of studies published before April 2021. We also searched grey literature and accessed relevant databases looking for full economic evaluations, although we were able to find only one suitable study regarding our topic.

Using the following unfiltered key-words string in PubMed, we retrieved 94 unique results in PubMed, and other 27 results in Cochrane Central with an adapted string: *(migraine OR headache) AND (neuromodulation OR TMS OR transcranial magnetic stimulation OR tDCS OR transcranial direct current stimulation OR tPEMF OR transcranial pulsed electromagnetic field OR TENS OR transcutaneous electrical nerve stimulation OR vagus nerve stimulation OR REN OR remote electrical neuromodulation OR occipital nerve stimulation) AND (prophylaxis OR prevention).*

After exclusion of titles and abstracts not relevant to our topic, we proceeded to retrieve and read the full text of the 9 remaining papers, which included 7 RCTs, one meta-analysis and one economic evaluation, which finally lead to the inclusion of 4 RCTs in our guideline. We also screened the references of the included articles to identify additional eligible studies, but we could not include any other publication.

DATA EXTRACTION AND QUALITY APPRAISAL

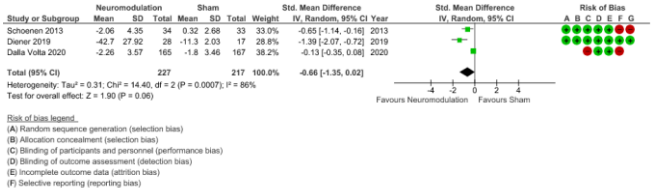
We performed data extraction for each of the included trials according to our outcomes. We performed a meta-analysis about days without migraine for three studies using RevMan 5; standard deviations were calculated from confidence intervals using the Cochrane RevMan Calculator tool. Since the included studies measured the same outcomes differently, the standardized mean difference was used as a summary statics. Given the heterogeneous nature of the studies, estimates were pooled using a random-effect meta-analysis. The three studies considered for the meta-analysis included 227 patients receiving different neuromodulation techniques and 217 patients receiving sham stimulation. For the other outcomes, the data did not allow a meta-analysis, so we performed a narrative review of the results to judge the available evidence and included it in the Summary of Findings table on GradePro. The quality of all included trials was assessed with Cochrane methods. The overall risk of bias was judged low.

IMPLEMENTATION STRATEGIES

- Print or write educational materials, including patient versions, and disseminate them electronically or on paper among healthcare staff, patients and other stakeholders, including national societies, patient organizations, task forces and policymakers
- Use social media to disseminate knowledge about evidence-based guidelines and achieve awareness among professionals and patients
- Publish the evidence-based guidelines and present them at conferences
- Promote meetings and workshops to improve compliance with the current clinical guidelines
- Information dissemination by neuromodulation technology companies to promote their products
- Audition of healthcare workers behavioral with feedback of results

EVIDENCE PROFILE (GRADEPro)

There is probably a **small benefit of neuromodulation on migraine days** (SMD 0.66 lower [1.35 lower to 0.02 higher]); although the result of the meta-analysis included the line of no effect, two of the three included studies showed a statistically significant difference favoring neuromodulation. **The level of certainty of the available evidence was moderate.** Regarding migraine attack **intensity** two studies report a **positive effect** of neuromodulation, while one study reports no difference between intervention and control. The three studies assess pain intensity in different, non-comparable ways, and **the level of certainty of evidence is low** (downgraded twice due to inconsistency).Three studies show a significant **reduction in acute medication intake**, while one study fails to demonstrate a significant difference; **the level of certainty regarding this outcome is low** (downgraded twice due to inconsistency). Two studies report **no side effects**, while one study reports one episode of transient drowsiness, and a difference in discomfort on the Face's Pain Scale of 3.10 vs 0.14 (p=0.0001); there was however no withdrawal from the study. Another study reports rash, pain, erythema, discomfort, dizziness; there was no serious adverse event. **The level of certainty is high.** Only one study explored **functional disability**, reporting a **reduction** of 2 (3.24 to 1.24) vs 1.19 (3.25 to 2.06) on a 0-4 scale (p=0001). **The level of certainty is high.** One study reported that 70.6% vs 39.4% of **patients were very or moderate satisfied**. Another study reported that 77.5% vs 73.5% of patients were at least a little satisfied. Finally, another study reported that satisfaction favored rTMS (74% vs 28% of patients expressed satisfaction, p=0.0001). **The level of certainty is high.** Taken together, the **balance of effects probably favored neuromodulation** (small desirable effects vs trivial undesirable effects), with **overall moderate certainty of evidence**. Although we couldn't identify any relevant study addressing patients' values, migraine prevention is likely to be valued positively by the vast majority of people, given its significant burden both at the individual patient and healthcare levels. We had no evidence on resources required, since we could not identify any relevant study on the costs of neuromodulation for migraine prevention. Costs are likely to be country-specific, and different in different healthcare systems. No inference on cost-effectiveness could be made. We reasoned that in healthcare systems in which neuromodulation is offered at low, affordable prices in a widespread number of centers, equity would probably not be affected. In healthcare systems in which neuromodulation is paid for completely by the patient, or when it's available only in few selected centers which are not easy to reach by a significant proportion of the population, equity would be probably reduced. Given the results of the included studies, the intervention is probably acceptable to the key stakeholders, while feasibility is likely to depend on country and healthcare systems characteristics.



RECOMMENDATIONS

We suggest to offer neuromodulation (with either tDCS, rTMS, VNS or tONS) as a short-term migraine prophylaxis choice, alone or in addition to best medical prophylaxis, in healthcare settings in which this intervention is economically cost-effective and in which it doesn't reduce equity, and according to patients' values and preferences.

Type of recommendation: conditional recommendation for the intervention

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