Migraine prevention with a supraorbital transcutaneous stimulator: A randomized controlled trial
Jean Schoenen, Bart Vandersmissen, Sandrine Jeangette, et al.

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ABSTRACT

Objective: To assess efficacy and safety of trigeminal neurostimulation with a supraorbital transcutaneous stimulator (Cefaly, STX-Med., Herstal, Belgium) in migraine prevention.

Methods: This was a double-blinded, randomized, sham-controlled trial conducted at 5 Belgian tertiary headache clinics. After a 1-month run-in, patients with at least 2 migraine attacks/month were randomized 1:1 to verum or sham stimulation, and applied the stimulator daily for 20 minutes during 3 months. Primary outcome measures were change in monthly migraine days and 50% responder rate.

Results: Sixty-seven patients were randomized and included in the intention-to-treat analysis. Between run-in and third month of treatment, the mean number of migraine days decreased significantly in the verum (6.94 vs 4.88; \( p = 0.023 \)), but not in the sham group (6.54 vs 6.22; \( p = 0.608 \)). The 50% responder rate was significantly greater (\( p = 0.023 \)) in the verum (38.1%) than in the sham group (12.1%). Monthly migraine attacks (\( p = 0.044 \)), monthly headache days (\( p = 0.041 \)), and monthly acute antimigraine drug intake (\( p = 0.007 \)) were also significantly reduced in the verum but not in the sham group. There were no adverse events in either group.

Conclusions: Supraorbital transcutaneous stimulation with the device used in this trial is effective and safe as a preventive therapy for migraine. The therapeutic gain (26%) is within the range of those reported for other preventive drug and nondrug antimigraine treatments.

Classification of evidence: This study provides Class III evidence that treatment with a supraorbital transcutaneous stimulator is effective and safe as a preventive therapy for migraine. Neurology® 2013;80:697–704

GLOSSARY

ICHD = International Classification of Headache Disorders; ONS = occipital nerve stimulation; PREMICE = PREvention of Migraine using the STS Cefaly study; STS = supraorbital transcutaneous stimulator.

The efficacy of preventive antimigraine drugs is limited and the most effective among them can have unpleasant side effects.1 There is thus room for more effective and better tolerable preventive treatments. Peripheral nerve stimulation, an accepted treatment for chronic pain,2,3 is poorly studied in primary headaches. Percutaneous occipital nerve stimulation (ONS) provided relief for chronic migraine in a sham-controlled trial and for chronic cluster headache in prospective open trials.4,5 The combination of percutaneous occipital and supraorbital stimulation was superior to either treatment alone in chronic migraine patients.6 However, percutaneous neurostimulation remains an invasive procedure that may not be acceptable for less disabled patients with episodic migraine. Transcutaneous electrical nerve stimulation is noninvasive and was considered of potential benefit for headache patients as early as 1985.7 Nevertheless, controlled studies have not been performed.

In a pilot study of 10 episodic migraine patients, we found that daily treatment for 3 months with a supraorbital transcutaneous stimulator (STS) (Cefaly, STX-Med., Herstal, Belgium) reduced monthly attack frequency by 1.3 and that 5 out of 9 patients who completed the protocol...
would recommend it to others. Considering these encouraging results, we decided to embark on a multicenter, randomized, sham-controlled trial, the PREvention of Migraine using the STS Cefaly (the PREMICE study).

METHODS  PREMICE was a prospective, multicenter, double-blinded, randomized, and sham-controlled trial of which data were analyzed on an intention-to-treat basis, and per protocol for comparison. The trial was conducted in 5 Belgian tertiary headache clinics run by members of the Belgian Headache Society.

Standard protocol approval and patient consent. The study was approved by the ethics committee of each participating center and written informed consent was obtained from all participants.

Patients. Patients fulfilling the following criteria were included: 18–65 years old, migraine with or without aura (International Classification of Headache Disorders [ICHD]–II code 1.2.1 or 1.1),9 and at least 2 attacks per month. Exclusion criteria were use of a preventive antimigraine treatment in the previous 3 months, failure on ≥3 well-conducted preventive drug treatments, medication overuse headache (ICHD-II 8.2), frequent/chronic tension-type headache (ICHD-II 2.2/2.3), and other severe neurologic or psychiatric disorders.

Neurostimulation. Sham as well as verum neurostimulation were delivered with a 30 mm × 94 mm self-adhesive electrode placed on the forehead and covering the supratrochlear and supraorbital nerves bilaterally (figure 1).

The STS generates biphasic rectangular impulses with an electrical mean equal to zero and the following characteristics:

- pulse width 30 μs for sham and 250 μs for verum, frequency 1 Hz for sham and 60 Hz for verum, maximum intensity 1 mA for sham and 16 mA for verum. The daily sham or verum neurostimulation sessions lasted 20 minutes.

Randomization and blinding. Eligible patients entered a run-in phase of 1 month. After this baseline period, participants still meeting the inclusion criterion of at least 2 migraine attacks per month were randomized into the verum or sham group.

Sham and verum stimulators and electrodes looked alike. Both stimulators buzzed identically during treatment and instructions to patients and user manual were the same. It was thus not possible to distinguish a sham from a verum stimulator without testing both devices in parallel.

Treatment allocation was concealed by the following procedures. Verum and sham stimulators were programmed by the manufacturer STX-Med. They were numbered from 1 to 90 and then randomly distributed in blocks each containing 2 verum and 2 sham stimulators. Each local investigator received initially 3 blocks of 4 stimulators chosen at random by the manufacturer with the instruction to start with the lowest study number. Patients were thus randomized 1:1 to receive a verum or a sham stimulator. To decrease the risk of unblinding due to the difference in sensory perception between verum and sham stimulators, the investigators and their staff members committed themselves to the following: not interrogate patients about sensory perceptions, not enroll patients acquainted with each other, and avoid physical contact between patients during visits. Two investigators (P.G., D.M.), not involved in recruitment, created the database from the paper headache diaries filled in by the patients. The manufacturer concealed the code numbers of stimulators until the trial was completed and the database created.

A built-in electronic system allowed recording usage of the stimulators by each patient for evaluation of compliance at the end of the trial.

Study design. The 30-day baseline was followed by a 90-day treatment period with an intermediate visit after 45 days and a final visit at the end of the trial (figure 2).

Patients filled in diaries recording headache occurrence and its severity on a 4-point scale (0, no pain; 1, mild—not interfering with normal daily activities; 2, moderate—interfering with daily activities; 3, severe pain—prohibiting daily activities), presence of an aura, nausea/vomiting, phonophobia or photophobia, and acute antimigraine drug intake. A migraine day was defined as a day with headache fulfilling ICHD-II criteria for migraine, except for duration if treated. Migraine days not separated by at least one headache-free day were considered to belong to the same migraine attack. A headache of grade 1 severity without associated symptoms and not treated with an acute medication was recorded as “headache,” not migraine.

Outcome measures. Primary outcome measures were 1) change in monthly migraine days between the run-in month and the third month of treatment; and 2) percentage of “responders,” i.e., of subjects having at least 50% reduction of monthly migraine days between run-in and third month of treatment.

Secondary outcome measures were 1) change in monthly migraine days between run-in and the average 3 months of treatment; 2) change in monthly migraine attack frequency; 3) change in monthly frequency of any headache; 4) change in mean headache severity per migraine day; 5) change in monthly acute antimigraine drug use and in associated symptoms per migraine headache between run-in and third month of treatment; and 6) percentage of patients stating at the end of the trial that they are very satisfied, moderately satisfied, or not satisfied with the treatment.
Statistical analysis. In order to keep the trial size within the allocated budget, sample size calculations were based on responder rates. The numbers used were 15% for sham, based on published trials, and 55% for the supraorbital neurostimulation inferred from a 55% patient satisfaction in the pilot study. To detect a significant difference between the 2 treatments (5% significance level) with an 80% power, the minimum size of each treatment group was estimated at 26 patients.

Statistical analysis (R, The R Foundation for Statistical Computing) was carried out on an intention-to-treat basis. Values for patients who dropped out were included according to the last value carried forward method.

RESULTS The PREMICE trial was conducted between September 2009 and September 2011. A total
of 67 patients were randomized; 59 completed the study according to protocol (figure 2). There were no significant demographic differences between verum and sham groups (table 1), but mean age was numerically lower by 4.47 years and disease duration shorter by 3.46 years in the verum group. While all patients had migraine without aura, 20 of them, equally distributed between the 2 groups, also had occasional attacks preceded by visual aura.

Primary outcome measures. Primary outcome measures are detailed in table 2. Both in sham and verum groups migraine days decreased by an average of 20% during the first treatment month. Over the second and third month of the trial, this decrease vanished in sham-treated patients, but amplified in effectively treated patients (figure 3A).

Monthly migraine days decreased significantly (−29.7%) in the verum, but not in the sham group (+4.9%), between run-in and third month of treatment. The difference in migraine day reduction between the 2 groups just failed to reach the level of statistical significance. In the per protocol analysis, the respective changes were −30.3% and +5.3%.

The 50% responder rate was greater in the verum than in the sham group. The results were similar for the per protocol analysis. The therapeutic gain of effective stimulation over sham stimulation was 26.1% in the intent-to-treat and 26.2% in the per protocol analysis.

The percentage of patients with at least 25% improvement in migraine days was also higher in the verum group, both for intention-to-treat and per protocol, with respective 25% responder rates of 31.5% and 32.3% after subtraction of the percentage of responders to the sham device.

The treatment effect was not different between patients having exclusively migraine without aura and those having both migraine types.

Secondary outcome measures. Secondary outcome measures are detailed in table 2. As expected from the time course of treatment effects (figure 3A), the reduction in monthly migraine days between run-in and the average 3 months of treatment was less pronounced, but remained significant in the verum group.

Monthly attack frequency between run-in and month 3 of treatment was reduced by 18.8% in the verum group and by 3.5% in the sham group, a significant difference that is more pronounced in the per protocol analysis.

Between run-in and third treatment month, monthly days with any headache decreased more in the verum (−32.7%) than in the sham group (−4.1%). The difference between groups is significant both in intent-to-treat and per protocol analysis.

There was a slight numerical decrease of mean headache severity per migraine day on the 4-point scale after 3 months of effective treatment which tended to be significant only in the per protocol analysis.

The monthly intake of acute antimigraine drugs decreased in the verum group (−36.6%), but not in the sham group (+0.46%). The difference between groups is significant. In the subgroup of 50% verum responders, the reduction reached 74.55%, which was highly significant (p < 0.005).

There was no change in occurrence of migraine-associated symptoms per migraine day (nausea, vomiting, photophobia, phonophobia).

Percentage of very or moderately satisfied patients was clearly greater in the verum (70.6%) than in the sham group (39.4%). Approximately 1 patient out of 5 was dissatisfied after effective neurostimulation, compared to 1 out of 2 in the sham-stimulated group.

Safety and compliance. No adverse events or side effects occurred during the trial, either in the verum or in the sham group.

The number and duration of applications of the STS by each patient were recorded electronically by the device and read out at the end of the trial. Compliance was moderately satisfactory in both groups.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Intention-to-treat</th>
<th>Per protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verum</td>
<td>Sham</td>
</tr>
<tr>
<td><strong>No.</strong></td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>34.59 ± 11.01</td>
<td>39.06 ± 9.87</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (9)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (91)</td>
<td>30 (91)</td>
</tr>
<tr>
<td>Occasionally migraine with aura</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Exclusively migraine without aura</td>
<td>24</td>
<td>23</td>
</tr>
</tbody>
</table>

*Data are expressed as n (%) or mean ± SD.*
<table>
<thead>
<tr>
<th>Table 2</th>
<th>Primary and secondary outcomes of the trial broken down by analyses and treatment groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td></td>
<td>Verum</td>
</tr>
<tr>
<td>Migraine days (run-in compared to third month of treatment)</td>
<td></td>
</tr>
<tr>
<td>Migraine days run-in month</td>
<td>6.94 ± 3.04</td>
</tr>
<tr>
<td>Migraine days third month</td>
<td>4.88 ± 3.46</td>
</tr>
<tr>
<td>Change from run-in to third month</td>
<td>−2.06</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>−0.54 to −3.58</td>
</tr>
<tr>
<td>p</td>
<td>0.023</td>
</tr>
<tr>
<td>Comparison between groups, p</td>
<td>0.054</td>
</tr>
<tr>
<td>Percentage of responders (±50% reduction in no. of migraine days/month) and of patients with at least moderate improvement (±25% reduction in no. of migraine days/month)</td>
<td></td>
</tr>
<tr>
<td>Responders (±50% reduction)</td>
<td>38.24 (13)</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>21.9–54.5</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.023</td>
</tr>
<tr>
<td>Patients with at least moderate improvement (±25% reduction)</td>
<td>58.8 (20)</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.014</td>
</tr>
<tr>
<td>Migraine days (run-in month compared to average of the 3-month randomized treatment period)</td>
<td></td>
</tr>
<tr>
<td>Migraine days run-in month</td>
<td>6.94 ± 3.04</td>
</tr>
<tr>
<td>Migraine days mean of the 3 months of treatment</td>
<td>5.20 ± 2.99</td>
</tr>
<tr>
<td>Change from run-in to the average of 3 months of treatment, p</td>
<td>0.023</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.366</td>
</tr>
<tr>
<td>Migraine attacks</td>
<td></td>
</tr>
<tr>
<td>Migraine attacks run-in month</td>
<td>4.37 ± 1.87</td>
</tr>
<tr>
<td>Migraine attacks third month</td>
<td>3.55 ± 2.94</td>
</tr>
<tr>
<td>Change from run-in to third month, p</td>
<td>0.058</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.044</td>
</tr>
<tr>
<td>Headache days</td>
<td></td>
</tr>
<tr>
<td>Total headache days run-in month</td>
<td>7.78 ± 4.00</td>
</tr>
<tr>
<td>Total headache days third month</td>
<td>5.27 ± 3.55</td>
</tr>
<tr>
<td>Change from run-in to third month, p</td>
<td>0.011</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.041</td>
</tr>
<tr>
<td>Severity of migraine days</td>
<td></td>
</tr>
<tr>
<td>Migraine severity run-in month</td>
<td>1.96 ± 0.46</td>
</tr>
<tr>
<td>Migraine severity third month</td>
<td>1.80 ± 0.60</td>
</tr>
<tr>
<td>Change from run-in to third month, p</td>
<td>0.131</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.301</td>
</tr>
<tr>
<td>Acute anti-migraine drug intake</td>
<td></td>
</tr>
<tr>
<td>Acute anti-migraine drugs taken in the run-in month</td>
<td>11.45 ± 8.35</td>
</tr>
<tr>
<td>Acute anti-migraine drugs taken in third month</td>
<td>7.25 ± 7.31</td>
</tr>
<tr>
<td>Change from run-in to third month, p</td>
<td>0.0057</td>
</tr>
<tr>
<td>Comparison between the 2 groups, p</td>
<td>0.0072</td>
</tr>
</tbody>
</table>
Instead of 90 stimulation sessions over 3 months, the mean number of sessions was 55.54 (61.7%), i.e., 1,110 minutes, in the verum group, and 49 (54.4%), i.e., 980 minutes, in the sham group. The difference between the 2 groups is not significant.

**DISCUSSION**

The randomized, sham-controlled PREMICE trial provides evidence that daily treatment with an STS has a preventive effect in migraine. We discuss the clinical significance of its results compared to those published with one of the most potent preventive drugs, topiramate,\(^{12}\) and examine possible shortcomings of our trial design.

Both primary outcome measures indicate that effective stimulation with the STS is superior to sham stimulation for the prevention of migraine headaches. The effect size may appear small at first sight. The percentage decrease from baseline ranges from 8% for severity to 37% for acute medication intake (figure 3B). For comparison, the effect size for the 100 mg dose of topiramate is overall superior, according to a pooled analysis of randomized controlled trials,\(^{13}\) and it is well established in large samples of patients. Topiramate decreases migraine days from baseline by 44% and migraine attacks by 48%, while respective changes for the STS are 25% and 19%. The difference between STS and topiramate is less dramatic for the 50% responder rate, an accepted index of treatment effect\(^{14}\): 38.2% in our trial, 45.3% in the pooled analysis of topiramate trials.\(^{15}\) The therapeutic gain for the 50% responder rate is superior with the STS (26.1%) compared to topiramate (23.5%), but this is not the case for other outcome measures.

**Table 2 Continued**

<table>
<thead>
<tr>
<th>Patients' satisfaction after 3 months of treatment</th>
<th>Very satisfied</th>
<th>Moderately satisfied</th>
<th>Not at all satisfied</th>
<th>Not available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verum (34)</td>
<td>29.4 (10)</td>
<td>41.2 (14)</td>
<td>21.2 (7)</td>
<td>8.8 (3)</td>
</tr>
<tr>
<td>Sham (33)</td>
<td>18.2 (6)</td>
<td>21.2 (7)</td>
<td>51.5 (17)</td>
<td>9.1 (3)</td>
</tr>
</tbody>
</table>

*Data are expressed as % (n) or mean ± SD.
measures like reduction in migraine days where the therapeutic gain is 12% in PREMICE but 24.5% in pooled topiramate trials. The responder rate for the STS is within the range of those reported for other anticonvulsants, propranolol, or behavioral therapy.

That the reduction in migraine days after effective STS treatment just failed to reach the level of significance compared to sham stimulation may be due to the fact that the study was powered for responder rates, not for reduction in migraine days. Severity of remaining migraine days was not reduced by the STS, which is a common finding in other preventive drug or neurostimulation trials. The 4-point scale used here may not be sensitive enough to detect a treatment effect on attack severity. Occipital nerve stimulation, for instance, had a beneficial effect in chronic migraine patients when headache intensity was assessed on a visual analogue scale.

Despite methodologic precautions including concealed allocation (see Methods), partial unblinding may have occurred in our trial. It is difficult to blind peripheral neurostimulation trials because the effective electrical stimulation produces intense paraesthesia. We doubt, however, that unblinding markedly influenced our results for the following reasons. The sham response was within the range of that found in other trials with neurostimulation devices. Compared to the ONSTIM trial of occipital nerve stimulation, it was even higher for the 50% responder rate: 6% in ONSTIM, 12.8% in PREMICE. Unblinding could thus have been twice more pronounced in ONSTIM than in PREMICE, if one assumes that it is inversely proportional to the percentage of responders in a sham group. The rather small difference (7.3%) in compliance rates between verum and sham groups also does not favor massive unblinding. If this were the case, one would expect a much lower compliance in the sham group.

Another possible weakness of our trial appeared when data from the different centers were analyzed: patients in the verum group were on average younger than those in the sham group and the duration of their migraine was somewhat shorter. On post hoc statistical analyses we were unable, however, to detect an influence of age or of disease duration on treatment outcome. In the ONSTIM trial, the difference in mean age between the effectively stimulated patients and the smaller “ancillary” group was 9 years. Overall, both patient groups in PREMICE were well in the age range of migraine patients included in other trials.

Beyond statistics, the question whether the results of the PREMICE trial are clinically relevant merits consideration. Besides the therapeutic gain for 50% responders, other outcome measures suggest that STS can be of benefit to migraine patients. It decreases significantly consumption of acute antimigraine drugs, which is a pharmaco-economic advantage. In addition, more than 70% of effectively stimulated patients were satisfied with the treatment.

The patients recruited for PREMICE were not the most disabled migraineurs. Having 4 migraine attacks or 7 migraine days per month, they were similar, however, to those included in topiramate trials and representative of the majority of migraine patients in the general population who are in need of preventive treatment according to international recommendations. Whether STS treatment is effective in patients with more frequent attacks or with chronic migraine remains to be determined.

A major practical advantage of the STS is its excellent tolerance and safety. For comparison, in the pooled topiramate trial analysis, 50% of patients had drug-related side effects and 1 out of 4 patients abandoned the drug because of intolerable adverse effects. Since STS therapy seems to be effective and well tolerated, it can be combined with drug treatments without risking cumulative adverse effects. The benefit of such a combination remains to be determined in an appropriate trial. Despite the excellent tolerance and the user-friendliness of the STS used here that allows patients to continue routine activities, compliance did not exceed 61.7%. In a trial comparing various preventive antimigraine drugs, mean compliance rate was 79.8%. The lower compliance with the STS is likely due to the 20-minute treatment duration that is out of proportion with the time for medication intake. As no dose-response data are available for any neurostimulation method in migraine prevention, the question whether a higher total dose of current applied would produce better results remains open. Meanwhile, compliance should be optimized when the STS is used in clinical practice.

The STS’s mode of action in migraine is not known. In healthy volunteers, high-frequency stimulation with the STS has acutely a sedative effect. Whether this plays a role in chronically treated migraine patients is not known, but it suggests that the stimulation can change CNS activity. Interestingly, in the above-mentioned study, we calculated the total dose of electric current delivered, taking into account intensity and duration of the stimulation. The sedative effect was observed with a dose of 420 μC but not with 8.75 μC, although in both stimulation protocols, action potentials were generated in supratrochlear and supraorbital nerves, as judged from the strong paraesthesia all subjects experienced. Like ONS, STNS might change activity in supraspinal centers belonging to the “pain matrix” or more specifically the “migraine matrix,” hence increasing the “migraine threshold.” Adequate studies are warranted to disentangle the precise mode of action.
AUTHOR CONTRIBUTIONS

J.S. was the principal investigator. B.V., S.J., L.H., and M.V. were local principal investigators at study centers. P.G. produced the database and analyzed the data together with D.M. D.M. edited the trial report and J.S. wrote the manuscript. All investigators were provided with the full data and approved the final report and manuscript.

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DISCLOSURE

J. Schoenen is a consultant for ATI Redwood California, advisory board member for St. Jude Medical USA, Allergan USA, and ATI USA, and received research grants from Medtronic USA and Cyberonics USA. B. Vanderaa and S. Jaegette report no disclosures. L. Herroelen serves on the scientific advisory board for Allergan. M. Vandenheede, P. Gérard, and D. Magis report no disclosures. Go to Neurology.org for full disclosures.

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