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BRIEF COMMUNICATION

Transcutaneous supraorbital neurostimulation for the prevention of chronic migraine: a prospective, open-label preliminary trial

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Abstract Since chronic migraine is difficult to treat and often associated with medication overuse, non-invasive neurostimulation approaches are worth investigating. Transcutaneous supraorbital neurostimulation using the Cefaly® device is promising as a non-invasive preventive treatment for episodic migraine, but no data are available for chronic migraine. Our aim was to perform a preliminary evaluation of the efficacy of the Cefaly® device for the prophylaxis of chronic migraine with or without medication overuse. Primary endpoints were 50% reduction in monthly migraine days and 50% reduction in monthly medication use over 4 months. In an open-label study, twenty-three consecutive headache center patients with chronic migraine, diagnosed according to International Headache Society criteria, were recruited prospectively. After informed consent, patients were trained to use Cefaly® and instructed to use it for 20 min daily over 4 months. All patients received active neurostimulation. Thirty-five percent of the patients enrolled in the study achieved the study endpoints. Over half the patients had a greater than 50% reduction in acute medication consumption.

Keywords Chronic migraine · Migraine prophylaxis · Medication overuse · Transcutaneous supraorbital neurostimulation

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Introduction

Chronic migraine (CM) is estimated to affect 2–4% of the population, while the prevalence of CM with medication overuse (MO) is estimated at 0.7–1.7% [1, 2]. Although various acute and prophylactic treatments are effective against episodic migraine, pain remains an unsolved problem in CM patients, who by definition have frequent, disabling headaches that are difficult to treat [3, 4]. Furthermore, because CM patients frequently develop MO, it may be useful to find effective non-pharmaceutical treatment modalities. Invasive neurostimulation procedures (deep brain stimulation, greater occipital nerve stimulation, sphenopalatine ganglion stimulation, vagus nerve stimulation, supraorbital nerve stimulation) have been shown that can be effective in primary headache. However, non-invasive neurostimulation would be preferable to invasive neurostimulation, and several non-invasive methods have been developed over the last decade to prevent headache attacks in patients with migraine without aura. In particular, transcranial magnetic stimulation, repetitive transcranial magnetic stimulation, and transcutaneous supraorbital neurostimulation (TSNS) have proven effective and safe as treatments for episodic migraine without aura [5–8].

TSNS with the Cefaly® device (Cefaly Technology, Liège, Belgium) has been used for preventive treatment in

episodic migraine. The multicentre PREMICE trial conducted by Schoenen and collaborators showed that treatment with the Cefaly supraorbital transcutaneous stimulator was safe and effective as preventive therapy for migraine [9]. However, this treatment has not been used in CM patients. The aim of the present study was to perform a preliminary evaluation of the efficacy and safety of the Cefaly device in CM prophylaxis.

Patients and methods

Twenty-three consecutive patients with a diagnosis of CM with or without MO according to the International Classification of Headache Disorders (ICHD-3) criteria [10] were recruited from among those attending three Italian Headache Centers over the period April to December 2014. Patients were recruited six at a time as only six Cefaly® devices were available for the study. Inclusion criteria were: (a) 18 years old or more (b) CM for at least 1 year, (c) no participation in withdrawal program to stop MO over the previous year, (d) normal neurological examination, (e) normal neuroimaging findings, (f) absence of major neurological, systemic or psychiatric illness, and (g) not pregnant. The absence of major disease and pregnancy was reported by patients at the baseline (T0) visit during which diaries reporting headache days and analgesic consumption over the preceding three months were inspected by the treating neurologist. All patients gave written informed consents to participate. Preexisting preventive and acute treatments for CM were not changed.

All recruited patients were prescribed active treatment with Cefaly® device's Programme 2, designed to prevent migraine. They first received training with the device. Each patient was given a device to take home and use for the duration of the study (4 months). Instructions were to use it for 20 min each day over the 4-month study period. Patients were also asked to continue with their headache diaries, recording days with headache and every time they took acute medication for their headache.

Patients were followed up monthly at the outpatient department of San Carlo Borromeo Hospital, Milan. They brought with them their Cefaly® devices which were checked for correct use (particularly frequency of use) by means of dedicated software. Headache diaries were checked, and patients were questioned about device tolerability.

The primary endpoints were 50% or more reduction in headache days per month, and 50% or more reduction in consumption of acute headache relief medications per month.

The Cefaly® device is provided with a self-adhesive bipolar electrode (30 × 94 mm) which is affixed to the center of forehead and extends bilaterally to the supraorbital nerves. When used for headache prophylaxis, the device generates biphasic rectangular impulses of 250 μs pulse width, 60 Hz frequency, and 16 mA current intensity for a fixed period of 20 min.

Tests of descriptive statistics were used to describe the categorial data.

Results

Eighteen (78.3%) of the 23 patients were female, 14 (60.9%) had MO. Mean age was 43.7 ± 13.6 years; mean duration of headache condition was 26.4 ± 12.8 years, and mean duration of the chronic phase was 10.7 ± 8.7 years. At baseline, patients were experiencing a mean of 20.7 ± 5.7 migraine days per month, and were taking acute headache relief medications a mean of 20.2 ± 12.4 times per month.

All patients were also taking prophylactic medication (tricyclic antidepressants, calcium channel blockers, beta blockers, anti-epilepsy drugs) and had been doing so for at least the previous year.

Four (17.4%) patients dropped out: one a few days after recruitment when another comorbidity (keratoconjunctivitis) occurred. The other three dropped out within one month after enrollment (T1) for inability to tolerate TSNS: one reported headache worsening and two reported development of neck tension.

The remaining 19 patients completed the four-month follow-up. Headache days per month and monthly drug consumption are shown in Tables 1 and 2, respectively. For the 19 patients, the mean overall decrease in migraine days per month was 31.0%, and mean overall decrease in acute medication consumption was 49.6%. Twelve patients reduced acute medication consumption by at least 50%: actual reduction was 65.5% (19.6/month at T0, 6.8/month at T4).

Eight (34.8%) patients achieved both endpoints and were, therefore, considered responders: mean reduction in headache days per month was 57.9% (18.1 at T0, 7.6 at T4, Fig. 1); mean reduction in acute medication consumption was 68.8% (20/month at T0, 6.3/month at T4, Fig. 2). As is evident from Figs. 1 and 2, these improvements in responders were achieved gradually.

Among the 11 patients (47.8% of 23) who completed the study and did not achieve both primary endpoints, migraine days/month reduced by 15.3%, and monthly acute medication reduced by 35.9%. If we consider significant a reduction of at least 50%, neither of these reductions can be considered clinically significant.

Thirteen (68.4%) of the 19 patients who completed the study had medication overuse, including 6 (75%) of the 8

Table 1 Migraine days per month at baseline (T0) and monthly (T1–T4) over the 4-month study period in 23 chronic migraine patients prescribed active supraorbital stimulation with the Cefaly® device

Patients	T0	T1	T2	T3	T4
1	30	30	30	30	30
2	20	20	14	20	15
3	15	14	15	12	12
4	20	9	7	8	21
5	15	12	3	10	16
6	28	16	15	18	7[a]
7	30	30	30	30	30
8	28	22	24	20	18
9	15	15	10	11	13
10	20	14	16	14	9[a]
11	16	8	8	7	8[a]
12	15	14	8	9	7[a]
13	15	14	9	11	7[a]
14	20	7	10	13	10[a]
15	21	20	16	14	19
16	15	5	5	4	5[a]
17	17	10	8	6	8[a]
18	28	29	20	20	18
19	26	24	26	25	18
Tot (mean)	394 (20.7)	313 (16.5)	274 (14.4)	282 (14.8)	271 (14.3)
20	15	n.a.		Drop-out	
21	30	n.a.			
22	20	n.a.			
23	15	n.a.			
Tot (mean)	474 (20.6)				

[a] Decrease ≥50%

responders. These data suggest that MO had no influence on whether or not TSNS was effective.

The monthly tests conducted on the Cefaly® devices using the dedicated software showed that all patients who completed the study used the device (Programme 2 setting) everyday for 20 min. As noted, three patients reported side effects at T1 and withdrew from the study. None of the other patients reported side effects and at any of the monthly follow-ups.

Discussion

Our study, even if there are some limitations, can stimulate several considerations. It is an open-label trial and the number of patients is limited. But to date, there are no available data on supraorbital neurostimulation in chronic migraine. Eight (34.8%) of our recruited patients achieved both endpoints, with a mean reduction in headache days of 57.9% and a mean reduction in medication consumption of 68.8%. Three (13.0%) patients withdrew for inability to tolerate the Cefaly® device. These results are encouraging: they support that Cefaly® is safe and generally well tolerable for CM treatment.

The fact that about 35% of patients achieved benefit over four months is particularly encouraging because headache center CM patients are difficult to treat [11–14], and our patients in particular had long chronic phase illness duration (mean 10.7 years, range 1–44) and most (60.9%) had MO.

If treatments do not produce reliable or significant pain relief, episodic migraine sufferers tend to overuse symptomatic drugs. MO is in fact a major risk factor for the transformation of episodic migraine into CM [15–18]. Thus, it is particularly noteworthy that medication intake reduced by at least 50% in 65% (12 patients about 19 of the group) of the patients who completed our study. Reduced drug consumption may reduce the risk of iatrogenic complications, and may also tend to restore the patient to 'normal' drug user status.

Previous prophylactic treatment had not been changed and this does not seem to modify the response to TSNS.

There is evidence that detoxification improves outcomes and the efficacy of subsequent prophylactic medication in

Table 2 Monthly acute medication consumption at baseline (T0) and over the 4-month study period (T1–T4) in 23 chronic migraine patients prescribed active supraorbital stimulation with the Cefaly® device

Patient	T0	T1	T2	T3	T4
1	60[a]	40	40	40	40
2	20[a]	14	7	11	10[b]
3	15[a]	5	5	6	3[b]
4	30[a]	18	14	5	14[b]
5	10	7	7	8	4[b]
6	20[a]	16	13	13	6[b]
7	5	5	7	6	7
8	8	7	7	6	5
9	20[a]	15	10	11	13
10	20[a]	20	19	17	10[b]
11	10	5	6	4	4[b]
12	22[a]	17	4	4	4[b]
13	28[a]	8	5	6	5[b]
14	25[a]	7	10	13	12[b]
15	21[a]	24	16	14	19
16	5	0	0	0	1[b]
17	30[a]	15	10	6	8[b]
18	12	7	6	8	8
19	22[a]	18	22	21	20
Tot (mean)	383 (20.2)	248 (13.1)	208 (10.9)	199 (10.5)	193 (10.2)
20	20[a]	n.a.		Drop-out	
21	8	n.a.			
22	20[a]	n.a.			
23	12	n.a.			
Tot (mean)	443 (19.3)				

[a] Abuser

[b] Decrease ≥50%

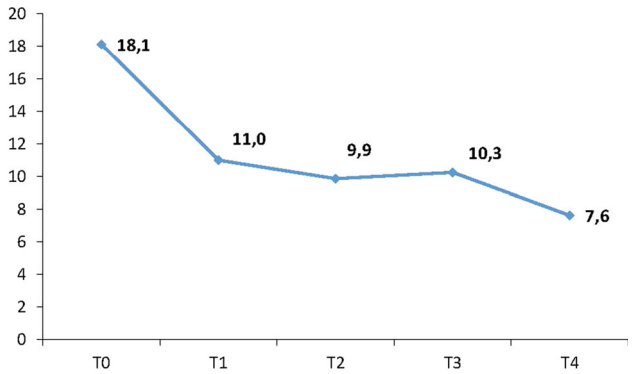

Fig. 1 Mean migraine days per month in responders: 4-month follow-up

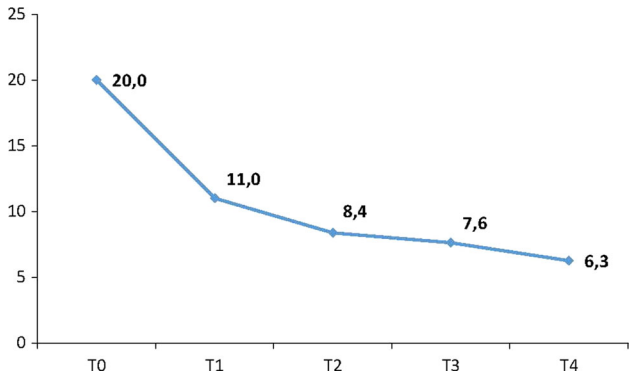

Fig. 2 Mean drugs per month in responders: 4-month follow-up

CM patients with MO [19–21]. Several studies have evaluated the efficacy of pharmaceutical prophylactics in CM. Double-blind placebo-controlled studies on tizanidine [22], gabapentin [23], and sodium valproate [24] showed significant improvements, in all cases without tolerance or safety problems. However, inadequacies in patient selection and study design do not allow firm conclusions about the efficacy of these agents. By contrast, topiramate appears an effective treatment for CM. Double-blind, randomized, placebo-controlled studies conducted for sufficient time show a >50% decrease in attack frequency in 22–77% of treated patients [25–28]. Topiramate with triptans may be able to revert CM with MO to episodic migraine [25]. Results of the PREEMPT double-blind,

randomized, placebo-controlled trials [29–32] indicate that onabotulinumtoxinA is also effective as a prophylactic agent in CM patients with MO.

However, prophylactic pharmaceuticals may be associated with side effects and intolerability, particularly on long-term use. About 15 years ago, central and peripheral neurostimulation techniques started being investigated as treatments for primary headaches, particularly for chronic drug-resistant headache forms [33]. However, while central neurostimulation has not been tested for CM, peripheral neurostimulation has been widely investigated as an alternative to pharmacological prophylaxis for this condition. Options have been proposed that act on occipital, supraorbital, or vagal nerves, the sphenopalatine ganglion peripheral, and that cerebral cortex. Efficacy findings are variable [6, 7, 34–39].

The first double-blind, randomized, sham-controlled trial of TSNS for the prevention of episodic migraine was conducted by Schoenen and colleagues on 67 patients [9]. They assessed the efficacy and safety of the Cefaly® device to stimulate the supraorbital region. They found, for the active stimulation group, that migraine days were reduced by 38.2%, and acute anti-migraine medication intake was reduced by 36.7%. The advantageous effect was achieved fairly early in the study and was maintained during follow-up. The mechanism by which supraorbital stimulation improves the condition of patients with migraine is unclear. It is known that trigeminovascular system is involved in migraine pathophysiology, so it has been suggested that transcutaneous stimulation of the supraorbital region may modulate pain transmission within this system [40, 41]. An alternative suggestion is that stimulation results in modulation of central pain matrix structures. This is supported by a fluorodeoxyglucose-positron emission tomography study on patients with refractory cluster headache. Following percutaneous occipital nerve stimulation, an increase in glucose metabolism was detected in perigenual anterior cingulate gyrus, possibly reflecting an alteration in top-down pain regulation [42].

Conclusions

This was a small, non-controlled study in which all participants received active TSNS with the Cefaly® device. It was in fact a preliminary study designed to indicate whether more rigorous studies are justified. The results are encouraging and suggest that this form of neurostimulation may have efficacy similar to that of established pharmacological prophylactics for CM [43]. It is particularly noteworthy that in over half the patients acute medication consumption was reduced by over 50%, suggesting that TSNS could be useful in reducing MO and medication-associated adverse events in CM patients. These findings justify use of the Cefaly® device in a randomized-controlled trial of real vs. sham neurostimulation in CM patients, including those with MO.

Compliance with ethical standards

Funding This study had no external funding source. Cefaly® devices were made available by the manufacturer (Cefaly Technology, Liège, Belgium) free of charge, for use in the study, Cefaly® Technology had no role in the design or conduct of the study

Conflict of interest The authors certify that there is no actual or potential conflict of interest in relation to this article.

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