Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Original research article

Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using Cefaly® device in prevention of primary headaches

Anna Przeklasa-Muszyńska [a,*], Kinga Skrzypiec [b], Magdalena Kocot-Kępska [a], Jan Dobrogowski [a], Maciej Wiatr [c], Joanna Mika [d]

[a] Department of Pain Research and Treatment, Chair of Anesthesiology and Intensive Therapy, Medical College of Jagiellonian University, Krakow, Poland
[b] Department of Pain Research and Treatment, University Hospital, Krakow, Poland
[c] Chair and Department of Otolaryngology, Medical College of Jagiellonian University, Krakow, Poland
[d] Institute of Pharmacology, Polish Academy of Sciences, Krakow, Department of Pain Pharmacology, Poland

ARTICLE INFO

Article history:
Received 14 September 2016
Accepted 9 January 2017
Available online 20 January 2017

Keywords:
Headaches
Pharmacotherapy
Neurostimulation
Transcutaneous nerve stimulation

ABSTRACT

Headaches are one of the most common pain syndromes experienced by adult patients. International Classification of Headache Disorders identifies about 300 different entities. Primary headaches (migraine, tension-type headache, trigeminal autonomic cephalalgias, other primary headaches) has the common occurrence. Although effective treatment of these disorders is possible, it is inefficient or poorly tolerated in some patients. Neuromodulation methods, being element of multimodal treatment, provide an additional treatment option in pharmacotherapy-refractory patients. Both invasive and non-invasive stimulation methods are used. The non-invasive techniques is transcutaneous nerve stimulation using Cefaly® device. In this study, Cefaly® was used as prevention treatment in patients with pharmacotherapy-refractory headaches. This device is indicated for the prophylactic treatment of episodic primary headaches. A total of 91-patients (30 without and 61 with tSNS) were enrolled in the study, including 60-patients with migraine and 31-patients with other primary headaches. Ten courses of non-invasive peripheral (supraorbitral/supratrochlear) nerves stimulation were delivered to 57-patients; in the remaining 4 patients, the treatment was abandoned due to poor tolerance. Patients were observed for 30 days after stimulation treatment. Compared to the pre-treatment period, the reduction in the intensity of pain was observed in both the migraine group and patients with other types of headaches; this included the number of pain episodes being reduced by half, with simultaneous reduction in average pain intensity and duration of individual pain episodes. The subjective assessment of pain reduction was in the range of 40–47%. Based on our data we recommend tSNS as useful tool in the prophylaxis of primary headaches, including migraine.

* *Corresponding author at*: Department of Pain Research and Treatment, ul. Śniadeckich 10, 31-531 Krakow, Poland.
E-mail address: aprzemusz@wp.pl (A. Przeklasa-Muszyńska).

http://dx.doi.org/10.1016/j.pjnns.2017.01.004

1. Introduction

Headaches are one of the most common pain syndromes today. About 300 types of headaches were described; most of these are rare conditions [1]. The most common are primary headaches (migraine, tension-type headache, trigeminal autonomic cephalalgias, other primary headaches). They may be a serious health problem significantly affecting the daily functioning of patients [2,3]. Numerous randomized, controlled studies were conducted to assess the most efficient and safe pharmacological treatment of headaches [1,2,4]. However, in many cases the treatment (either symptomatic, prophylactic, pharmacological or non-pharmacological) does not meet the patients' expectations due to non-satisfactory efficacy or adverse effects [2–6]. Ongoing research is pursued to develop new treatment methods, both pharmacological and non-pharmacological, to be applied in this group of patients. Neurostimulation has been an established treatment method for many years; recently, numerous articles have been published on the use of neurostimulation techniques in patients suffering from headaches [5,7–10]. Cefaly® transcutaneous nerve stimulation is one of the novel options in peripheral stimulation and is indicated for the prophylactic treatment of episodic migraine in patients 18 years of age or older [12,14]. The method is used in both symptomatic and prophylactic treatment of headaches. As demonstrated by randomized, controlled studies, the method may be particularly efficient in prophylactic treatment of migraine and tension type headaches [8,11,12]. The efficacy of the treatment of migraines by means of peripheral nerve stimulation is currently the subject of extensive research [10–14].

2. Material and methods

2.1. *Study objective*

The objective of our study was to assess the effects of prophylactic, non-invasive neurostimulation of the upper branch of trigeminal nerve, i.e. supratrochlear and supraorbital nerves, using the Cefaly® device on the frequency, intensity, and duration of headache episodes in patients with migraine headaches and patients with other primary headaches (chronic daily and tension type headaches) compared to the patients treated only with pharmacotherapy (control). Every patient in study group was subjected to 10 cycles of stimulation using the prophylactic low-frequency (60 Hz) pulse program available in the device. The duration of active stimulation was 20 min in all patients.

2.2. *Material*

A prospective study was conducted between January 2015 and December 2016 in 91 headache-suffering patients. All the patients enrolled to the study were treated with pharmacotherapy according to valid recommendations of primary headaches therapy. This therapy included prophylactic therapy (the most common: antiepileptic, antidepressant, beta blockers), symptomatic therapy: non-opioid analgesics (the most common: paracetamol, ketoprofen, ibuprofen, acetylosalicylic acid, metamizol). Tryptans were used when was good tolerance to them and were no contraindications to their use. The patients were randomly selected to the 3 control groups (without tSNS) and 3 studied groups (with tSNS), but in both groups pharmacological treatment was continued without any changes during the study depending on individual needs. In the control group (without tSNS treatment) the 30 patients kept their pain diaries where they recorded every episode of headache along with its duration and medications taken during observation period (similar to the tSNS group). The 61 patients was rented tSNS Cefaly® devices (CEFALY-Technology STX-Med in Herstal, Liege, Belgium). Prior to qualification for the tSNS (ca. 30. days) and during the follow-up period, all enrolled patients kept their pain diaries where they recorded every episode of headache along with its duration and medications taken.

Study inclusion criteria for the patients enrolled to the study:

- Age of 18–60 years.
- Migraine headache diagnosed on the basis of International Headache Society diagnostic criteria for migraine with and without aura [1].
- Other primary headaches (tension-type headache, trigeminal autonomic cephalalgias, other primary headaches) according to International Headache Society diagnostic criteria for these disorders [1].
- Patient's consent to participate in the study.
- No contraindications to electrotherapy.
- Patients who had previously undergone other treatment according to valid recommendations.
- No serious general disorders restricting the possibility of treatment.

Study exclusion criteria:

- Incomplete diagnostics of headaches.
- Diagnostic criteria or migraine, tension, or chronic daily headache not met.
- History of arrhythmias, pacemaker implantation, epilepsy or other reasons precluding the use of electrotherapy.
- No previous treatment according to valid recommendations.
- Patient not giving consent for participation at the study and kept pain diaries.

The study was approved by the Local Bioethics Committee. Volunteers qualified for the study were informed of the study objectives as well as the benefits and possible adverse effects of stimulation, and expressed their informed consent to participate in the study. Patients could discontinue their participation at any time. Statistical analysis was provided only for the patients who had unchanged drugs and their doses during whole study. If it was necessary to change pharmacological treatment or notes in the diary raised our doubts the patients were excluded from the study. The statistical analysis was provided blindly when we have collected data from patients. A total of 91 patients (30 without tSNS and 61 with tSNS) were enrolled in the study. The control group (with only pharmacological treatment), which mean the group without tSNS was completed by 30 patients (20 patients with migraine headaches,

including 12 patients suffering from migraine with aura and 8 patients suffering from migraine without aura, and 10 patients with other primary headaches). The tSNS study was completed by 57 patients (36 patients with migraine headaches, including 16 patients suffering from migraine without aura and 20 patients suffering from migraine with aura, and 21 patients with other primary headaches); 4 patients with migraine headaches discontinued the study due to poor toleration of stimulation (inability to tolerate paresthesia, strong discomfort experienced within the stimulated nerves during stimulation, no willingness to continue stimulation).

2.3. Method

Transcutaneous nerve stimulation using the Cefaly® device is a method of non-invasive electrotherapy employing the transcutaneous electrostimulation principle. Appropriate electrodes may be used for stimulation of supraorbital, supratrochlear or occipital nerves. Electric pulses generated by the device selectively stimulate the nerve fibers. The treatment may be delivered using either of 3 available modes: the *treatment mode* used for migraine, tension type headaches and cluster headaches treatment employing high-frequency pulses (100 Hz), the *prophylactic mode* used for preventing headaches between pain episodes, employing low-frequency pulses (60 Hz) and relaxation mode used to deliver relaxation and relief in stress and anxiety. The duration of stimulation session is 20 min in all modes [14]. In our study, the prophylactic mode was used. The device was programmed so that the intensity of pulses increased gradually over the 20-min stimulation period. Escalation of pulses could be stopped at any moment should they become too painful for the patients. Patients could resign from undergoing the treatment session at a particular day or to discontinue their participation in the study. In the study, all patients were subjected to stimulation of the upper branch of the trigeminal nerve: supraorbital and supratrochlear nerves. The study series consisted of 10 stimulation courses. Courses were delivered to individual patients 2 or 3 times a week. Each stimulation session lasted for 20 min. Numerical rating scale (NRS) was used to assess pain before each treatment. The sessions were not administered during headache episodes. Patients were observed for any adverse effects during and after the procedure. Stimulation could be discontinued at any time should there be any need to do so. The efficacy of treatment was assessed 30 days after last stimulation procedure. The assessment included the monthly number of episodes (days with pain), duration of episodes (in hours), and pain intensity in NRS during an episode. The results were compared to the number, duration, and intensity of episodes as assessed before the treatment. Subjective percentage improvement was also assessed by the patients 30 days after stimulation treatment. The results were compared to the appropriate control group.

2.4. Data analysis

The data are presented as mean ± S.E.M. per six groups (three control groups of patients: migraine with aura, $n = 12$; migraine without aura, $n = 8$; other primary headaches, $n = 10$ and three tSNS-stimulated groups of patients: migraine without aura, $n = 16$; migraine with aura, $n = 20$; other primary headaches, $n = 21$). Inter-group differences were statistically evaluated by ANOVA followed by Bonferroni's post hoc test. Significance was defined as $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ before vs. after tSNS and as $\#p < 0.05$, $\#\#p < 0.01$, $\#\#\#p < 0.001$ with vs. without tSNS.

3. Results

3.1. Age and sex analysis of the patients suffering from headaches

Fig. 1 presents the numbers of 91 patients in individual age groups. The number of patients experiencing headaches increases markedly above the age of 30. A strong drop is observed after the age of 60. In general, the incidence of migraine is reduced after the age of 60, particularly in postmenopausal women receiving no estrogen replacement therapy. Ten courses of non-invasive peripheral nerve stimulation (supraorbitral and supratrochlear nerves) were delivered to 57 patients; in the remaining 4 patients, the treatment was abandoned due to poor tolerance.

Importantly, the mean age of patients in individual groups was similar (45 years, Fig. 2A). Also non-significant was the mean duration of the disorder in years, as presented in Fig. 2B. In all patients suffering from migraine, either with or without aura, the duration of the disorder was 19 years while all patients classified into the group of ''other primary headaches'' had suffered for the average period of 8 years.

The analysis of percentage populations of the patients revealed that male patients comprised about 13% of the group complaining of migraines without aura, 5% of the group complaining of migraines with aura, and nearly one half (53%) of the group complaining of other primary headaches (Fig. 3).

3.2. Frequency, duration and numeric rating scale scores in patients with headaches

The study showed that the average monthly number of pain days before the 10 courses of non-invasive peripheral nerves

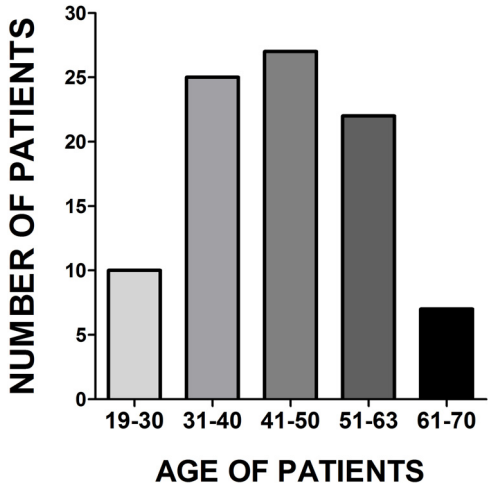

Fig. 1 – The number of 91 patients with headache in individual age groups.

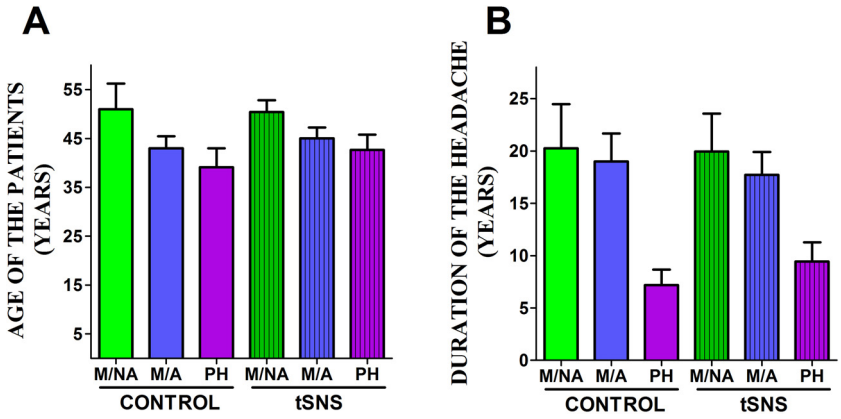

Fig. 2 – (A) Mean age of the patients suffering from individual types of headaches in a group without (control) and with tSNS. (B) Duration of the headache disorder (in years) patients suffering from individual types of headaches. Migraine without aura (M/NA), migraine with aura (M/A) and other primary headaches (PH). Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using Cefaly® device (tSNS).

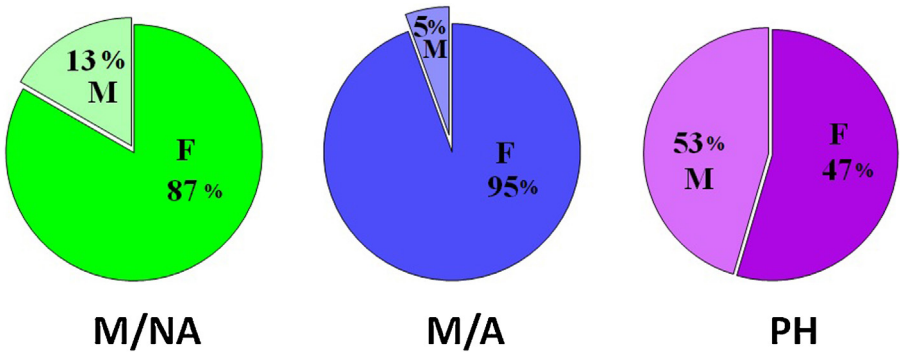

Fig. 3 – Percentage of female (F) and male (M) patients complaining of migraine without aura (M/NA), migraine with aura (M/A) and other primary headaches (PH).

stimulation (supraorbital and supratrochlear) was similar for migraine with and without aura, amounting to about 9 days while being as high as 18 for other primary headaches. Statistically significant reduction in the frequency of the headaches was observed following the treatment in all three pain disorders (Fig. 4). In contrast, in all 3 groups of patients without peripheral nerves stimulation we did not observed such decrease of the frequency of the headaches.

The study showed that the average duration of pain episode before the 10 courses of non-invasive peripheral nerves stimulation (supraorbital and supratrochlear) was similar for migraine with and without aura, amounting to about 23–27 h while being shorter and lasting for 9–13 h. For other primary headaches amounting to about 12 h while being shorter and lasting for 7 h. Statistically significant reduction in the duration of pain was observed following the treatment in all kind of headaches with tSNS (Fig. 5). In all 3 groups of patients without peripheral nerves stimulation we did not observed significant reduction of the duration of pain.

The study revealed that the average NRS intensity of pain as measured before the 10 courses of non-invasive peripheral nerves stimulation (supraorbital and supratrochlear) was similar for migraine with and without aura as well as for other headaches and amounted to about 7.8–8.8. A statistically significant reduction (36–37%) in the intensity of pain during the pain episode was observed after the tSNS treatment in all kind of headaches (Fig. 6). In contrast, in all three groups of patients without peripheral nerves stimulation we did not observed significant decrease of the intensity of pain during the pain episode during observation period.

3.3. *Pain decrease in patients without and with tSNS*

In all 3 groups of patients without peripheral nerves stimulation we observed only slightly 11.5% and 25.6% decrease in pain sensitivity as measured by NRS scale and subjective improvement, respectively. The study revealed that patients with low-intensity of pain (NRS 1–6) experienced lower reduction of pain amounting to about 22% (*data not shown on the graph*). Meanwhile, in patients who experienced stronger pain (NRS 7–10) after the tSNS treatment, the pain reduction as measured by NRS scale was similar and averaged to about 32–34% in migraine with aura, migraine without aura, and other primary headaches (Fig. 7A). Subjective improvement, i.e. the symptom relief 30 days after stimulation as assessed by the patients after the tSNS treatment using the percentage scale

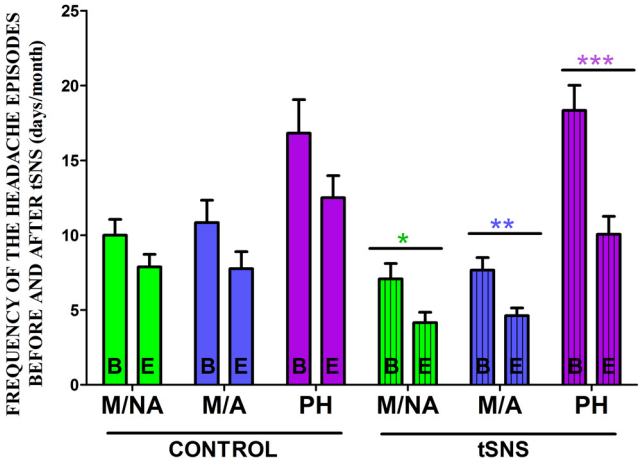

Fig. 4 – The frequency of headache episodes (days/month) in patients with strong pain (NRS 7–10) in individual pain disorders at the beginning (B) and at the end (E) of the examination in a group without (control) and with tSNS. Inter-group differences were statistically evaluated by ANOVA followed by Bonferroni's post hoc test. Significance was defined as $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$ before and at the end of study. Migraine without aura (M/NA), migraine with aura (M/A) and other primary headaches (PH). Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using Cefaly® device (tSNS).

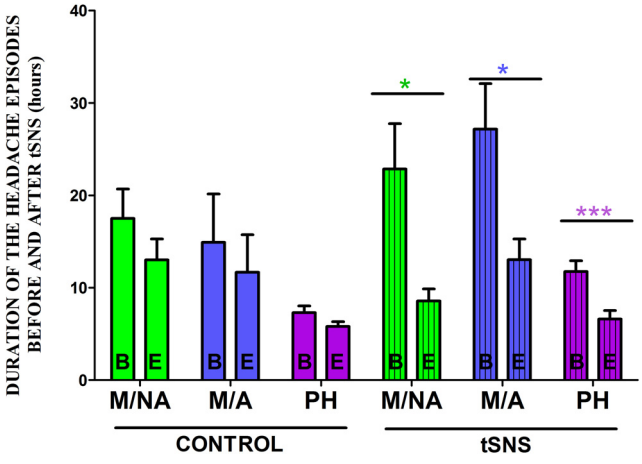

Fig. 5 – The duration of pain episodes (hours) in patients with strong pain (NRS 7–10) in individual pain disorders at the beginning (B) and at the end (E) of the examination in a group without (control) and with tSNS. Inter-group differences were statistically evaluated by ANOVA followed by Bonferroni's post hoc test. Significance was defined as $^{*}p < 0.05$, and $^{***}p < 0.001$ before and at the end of study. Migraine without aura (M/NA), migraine with aura (M/A) and other primary headaches (PH). Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using Cefaly® device (tSNS).

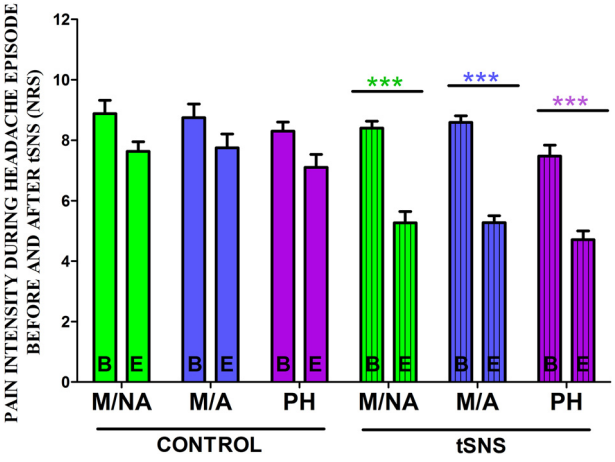

Fig. 6 – Numeric Rating Scale scores in patients with strong pain (NRS 7–10) in individual pain disorders at the beginning (B) and at the end (E) of the examination in a group without (control) and with tSNS. Inter-group differences were statistically evaluated by ANOVA followed by Bonferroni's post hoc test. Significance was defined as $^{***}p < 0.001$ before and at the end of study. Migraine without aura (M/NA), migraine with aura (M/A) and other primary headaches (PH). Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using Cefaly® device (tSNS).

was similar in all the pain disorders and averaged about 40–47% (Fig. 7B).

4. Discussion

Although effective treatment of primary headaches is possible, the proposed pharmacological treatment is inefficient or poorly tolerated in some patients. The available methods for the treatment of migraine headaches are not always satisfactory for patients in terms of symptom relief. It is estimated that chronic headaches experienced every day or nearly every day to a degree reducing individual's abilities may affect about 1.4–2.2% of the overall population. Reduced abilities may result from insufficient efficacy of the treatment or from the adverse effects thereof [5]. The intensity of migraine varied. As many as 25% of patients experience more than 4 severe episodes per month, 48% experience 1–4 severe episodes per month, and 38% experience 1 severe episode per month. Most patients in the study group experienced more than 4 severe pain episodes per month. Symptomatic treatment fails in 1 out of 4 migraine patients and it may cause adverse effects [15,16]. In addition, contraindications to tryptans treatment may exist. About 3% of patients with chronic primary headaches are refractory to prophylactic treatment [13,17,18]. The inefficacy of treatment may significantly affect the quality of life of patients, particularly those with frequent pain episodes. The varied frequency of pain episodes, significant intensity of pain, and unsatisfactory efficacy of the treatment in the study group triggered the search for novel treatment options.

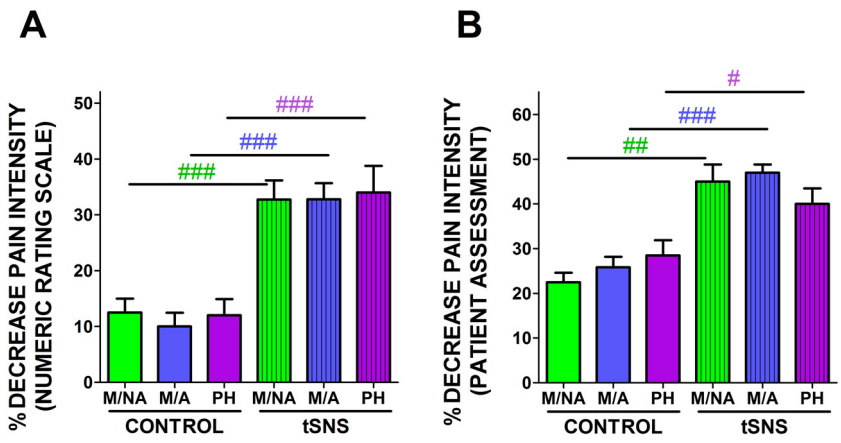

Fig. 7 – Pain decrease in patients with high-intensity pain (NRS 7–10) in a group without (control) and with tSNS. (A) NRS score; (B) subjective % pain decrease as reported by patients. Inter-group differences were statistically evaluated by ANOVA followed by Bonferroni's post hoc test. Significance was defined as #$p < 0.05$, ##$p < 0.01$, ###$p < 0.001$ with vs. without tSNS. Migraine without aura (M/NA), migraine with aura (M/A) and other primary headaches (PH). Non-invasive transcutaneous Supraorbital Neurostimulation (tSNS) using Cefaly® device (tSNS).

Although neuromodulation had been an established treatment method for many years, only recently it has become a subject of particular interest, mostly due to the emergence of new abilities allowing for planned, precise modulation of nociceptive processes. Neuromodulation techniques used in the treatment of headaches may be categorized into invasive methods including peripheral methods such as stimulation of peripheral nerves, and central methods such as motor cortex, spinal cord, deep brain, or sphenopalatine ganglion stimulation. Non-invasive techniques of headache treatment include peripheral methods such as transcutaneous electrostimulation and central methods such as transcranial magnetic stimulation, or transcranial direct current stimulation [8,9,11–13,19].

The main principle of these treatment methods includes modulation of nervous system structures that are directly or indirectly involved in nociception starting from the stimulus generation and ending on its cerebral perception. The methods include direct modulation of brain structures involved in the development of pain episodes (deep hypothalamic stimulation in cluster headaches), modulation of inhibitory antinociceptive systems (stimulation of occipital nerves), modulation of cortical excitability transcranial magnetic stimulation or transcranial direct current stimulation) [7–9].

In case of transcutaneous electrostimulation of nerves, the therapeutic effect is achieved by electrical stimulation of skin within the painful region to interact with the sensory nerves. The method involves the use of currents of varied intensity and frequency. In principle, the mechanism of action is explained by transcutaneous stimulation leading to inhibited nociception by means of interacting with nerve fibers within the area subjected to stimulation treatment. The use of high frequencies of 80–200 pulses per second and low amplitudes results in excitation of thick Aβ fibers (muscle efferent fibers) and segmental analgesia. The use of lower frequencies (conventional TENS) affects thin Aδ fibers as well and leads to suprasegmental analgesia [7,20].

Stimulation of peripheral nerves using implanted electrodes brought about promising outcomes in patients with migraine and cluster headaches [20]. Good therapeutic effect was achieved in about 50% of patients [20]. The electrodes were implanted in the vicinity of supraorbital nerves (migraine headaches) or occipital nerves (cluster headaches) [19–21]. However, due to the need of subcutaneous placement of electrodes, the method is recommended only in patients with particularly strong pain. As shown by our studies, non-invasive methods employing electrodes being placed on the skin, is an alternative approach that may be used in a larger number of patients. Randomized studies demonstrated the efficacy of the stimulation of supraorbital nerves in the prevention of migraine headaches [11–13].

Neuromodulation techniques are an additional option in the currently proposed multimodal model of chronic pain treatment [22]. They may be particularly useful in patients in whom the pharmacological treatment compliant with recommendations was either inefficient or led to unacceptable adverse effects. Neuromodulation techniques may also be used in patients in whom the applicability of pharmacological treatment is reduces due to coexisting diseases. Particularly attractive alternative is proposed by non-invasive techniques that may be used in primary headache patients.

An interesting, non-invasive solution for patients with primary headaches may consist of non-invasive stimulation of peripheral nerves using tSNS with the Cefaly® device. The method is based on the principle of transcutaneous electrostimulation. A self-adhesive stimulation electrode is placed in the frontal region and stimulation affects the upper branches of the trigeminal nerve, i.e. supraorbital and supratrochlear nerves [14]. Three operation modes (treatment mode, prophylactic mode and relaxation mode) may be used for the management or prevention of pain. The treatment mode to be used during pain episodes involves generation of very high-frequency pulses that stimulate the sensory sensitivity of Aβ nerve fibers. Excitation of these fibers blocks the nociceptive information within the central nervous system. The treatment mode is efficient and permits the reduction of pain during the pain episode; however, it may be used only in clinical setting

under supervision of a qualified personnel. Relaxation mode reduces tension and stress which may be helpful in preventing the recurrence of headaches.

As shown by our studies and confirmed by literature reports, prophylactic mode may be safely used at home; in our opinion, this makes this treatment option particularly attractive. The prophylactic mode consists in generation of lower-frequency pulses (60 Hz) that stimulate the Aδ nociceptive fibers. Appropriate frequency of stimulation of these fibers markedly increases endorphin production. Endorphin secretion leads to overall relaxation and good feeling. In addition, endorphins regulate serotoninergic structures within the central nervous system, being impaired in patients suffering from migraine [7,19]. In the prophylactic mode, the device-driven stimulation is delivered outside strong pain episodes. The efficacy of the method was demonstrated in a randomized controlled trial conducted in 5 headache treatment centers in Belgium [11]. The results of this study indicate that stimulation of supraorbital nerves brought about significant improvement in patients receiving active treatment as compared to placebo, consisting in reduced number of days with pain symptoms, and consumption of analgesics being reduced by 75% within the follow-up period of 3 months [11].

In our study, the Cefaly® device was used in patients with migraine headaches presenting both with aura and without aura in whom the symptoms occurred bilaterally, unilaterally, or within the occipital region. A majority of migraine patients was female, which was consistent with observations provided by other authors [1,16,22]; in the remaining types of primary headaches, the percentages of male and female patients were similar, which was also consistent with the literature reports [2,16,22].

In our patients, the average duration of pain episode before the peripheral stimulation was similar for migraine with and without aura, amounting to about 23–27 h, which was in line with literature values [2,16]. Patients with other primary headaches experienced shorter episodes of about 9–13 h. The average pain intensity as measured using NRS was similar and amounted to about 7.8–8.8, which was in line with previous reports in which the pain associated with primary headaches was usually assessed as NRS 7–9 [16,23]. In our study, the prophylactic mode of stimulation was used and the treatment was delivered in pain clinic between the headache episodes. No procedures were performed in patients who experienced strong pain on the day of scheduled stimulation. In our study, all patients were subjected to supraorbital nerve stimulation. The number of stimulation courses delivered as part of the series was 10 regardless of the type of headache disorder. A total of 61 patients were enrolled in the group with tSNS. The study was completed by 57 patients; 4 patients discontinued the treatment due to the discomfort associated with stimulation: they could not tolerate the sensations within the stimulated nerves during the stimulation. This was also reported in previous studies by Magis et al. in 2013, with the intolerance to paresthesia during stimulation comprising the most common adverse effect accounting for 46% of all adverse effects observed in the study [12]. Similar to our observations, patients who could not tolerate paresthesias discontinued their participation in the study [12]. Otherwise, slight skin irritation at electrode application site, persisting for up to 30 min, was observed in 4 patients participating in our study. We could not observe allergic reactions or other adverse effects (sleepiness during the session, headache after a session, vomiting after a session, nausea and vertigo during sessions, migraine feeling during sessions) reported in 2013 by Magis et al. [20].

We observed a significant reduction in the average monthly number of pain episodes (days with pain) in our study group. We were able to demonstrate that in patients with pain of high intensity, i.e. NRS grade 7–10, the average pain relief was in the range of ca. 32–34%. Our study result indicates a measurable reduction in pain as assessed by NRS compared to the baseline conditions. Although the intensity of pain is a measurable parameter which can assessed treatment efficacy, no such assessments were conducted in the remaining studies [12].

The result is considered good as prophylactic pharmacological treatment fails in 1 in 2 patients with most patients experiencing unacceptable adverse effects. Blumenfeld et al. (2013) reported that as little as 28.3% of patients complied with the proposed pharmacological prophylactic treatment. The reasons for treatment discontinuation included lack of efficacy and side effects in an equal proportion. Symptomatic treatment during the pain episodes in ineffective in 1 in 4 patients; in addition, it may lead to adverse effects or be precluded due to certain contraindications [6,18]. Our control group during period of observation similar to the tSNS group confirmed difficulties and lack of full effectiveness of individually matched pharmacotherapy. In light of these data, the proposed non-invasive prophylactic treatment is a very useful method. We have collected our data for a long period of time (24 months), since it was necessary that patients did not change their pharmacological treatment during whole study and diary notes had to be reliable. Moreover, it was impossible to provide the tSNS blindly, because patients have felt stimulation. However, the statistical analysis was provided blindly at the end of the study.

Notably, the proposed method was used with 47 and 40% efficacy, in migraine and other primary headache patients, respectively. The average disease duration of 19 years for migraine patients and 9 for other headache in whom numerous therapeutic options had been previously used. The patient reported treatment satisfaction in the studies conducted in 2013 by Schoenen et al. and Magis et al. was 61.7% and 58.8%, respectively. However, the authors described the patients who has different numbers of tSNS sessions, some of them even more then 20. The results obtain in our studies show that even after 10 tSNS sessions the average percentage pain relief was 40–47% and the patients were satisfied with the proposed treatment.

5. Conclusions

Our study give evidence that following the prophylactic program of supraorbital and supratrochlear nerves stimulation, the average monthly number of pain episodes was reduced by half compared to the pre-treatment period and to the appropriate control groups. In patients who experienced strong pain (NRS 7–10) with only pharmacological treatment the pain reduction as measured by NRS scale was averaged to about 10–12.5%. Meanwhile, in patients with pharmacological

and tSNS treatment, the pain reduction as measured by NRS scale was averaged to about 32.7; 32.8 and 34% in migraine with aura, migraine without aura, and other primary headaches, respectively. We demonstrate for the first time the similar effectiveness of Cefaly in patients with this different types of primary headaches. Subjective improvement assessed by the patients after the tSNS treatment using the percentage scale was averaged about 40–47%, in contrast in the control group was averaged to about 22.5–28.8%. In a similar manner, decrease was observed in the average intensity and duration of pain during the episode compared to the pre-treatment period. Based on our and literature data we recommend tSNS as useful tool in the prophylaxis of different types of primary headaches, including migraine. It is a non-invasive method that is safe for the patients and associated with a low risk of adverse effects and well tolerant.

Conflict of interests

None declared.

Acknowledgment and financial support

Supported by statutory funds of the Department of Pain Research and Treatment, Chair of Anesthesiology and Intensive Therapy, Jagiellonian University Medical College, Krakow, Poland and by statutory funds of the Institute of Pharmacology, Polish Academy of Sciences.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders: 3rd edition (beta version) International Headache Society 2013. Cephalalgia 2013;33(9):629–80.
[2] Buse DC, Manack AN, Fanning KM, Serrano D, Reed ML, Turkel CC, et al. Chronic migraine prevalence, disability, and socio demographic factors: results from the American Migraine Prevalence and Prevention Study. Headache 2012;52(10):1456–70.
[3] Bloudek LM, Stokes M, Buse DC, Wilcox TK, Lipton RB, Goadsby PJ, et al. Cost of healthcare for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS). J Headache Pain 2012;13(5):361–78.
[4] Goadsby PJ, Sprenger T. Current practice and future directions in the prevention and acute management of migraine. Lancet Neurol 2010;9:285–98.
[5] Berg J, Stovner LJ. Cost of migraine and other headaches in Europe. Eur J Neurol 2005;12(Suppl 1):59–62.
[6] Fenstermacher N, Levin M, Ward T. Pharmacological prevention of migraine. BMJ 2011;18. 342:d583.
[7] Jenkins B, Tepper SJ. Neurostimulation for primary headache disorders, part 1: pathophysiology and anatomy, history of neuromodulation in headache treatment, and review of peripheral neuromodulation in primary headaches. Headache 2011;51(8):1254–66.
[8] Jürgens T. Neuromodulation in primary headaches. Pain Clinical Updates International Association for the Study of Pain (IASP) 2012;20(5):1–7.
[9] Rokyta R, Fricová J. Neurostimulation methods in the treatment of chronic pain. Physiol Res 2012;61(Suppl. 2): 23–31.
[10] Clarke BM, Upton AR, Kamath MV, Al Habri T, Castellanos CM. Transcranial magnetic stimulation for migraine: clinical effects. J Headache Pain 2006;7(5):341–6.
[11] Schoenen J, Vandersmissen B, Jeangette S, Herroelen L, Vandenheede M, Gérard P, et al. Migraine prevention with a supraorbital transcutaneous stimulator. A randomized controlled trial. Neurology 2013;80(8):697–704.
[12] Magis D, Sava S, Sasso d'Elia TS, Baschi R, Schoenen J. Safety and patients' satisfaction of transcutaneous Supraorbital NeuroStimulation (tSNS) with the Cefaly® device in headache treatment: a survey of 2,313 headache sufferers in the general population. J Headache Pain 2013;1. 14:95.
[13] Przeklasa-Muszynska A, Skrzypiec K, Kocot-Kępska M, Dobrogowski J. Neuromodulation in headache treatment – clinical use of peripheral nerves stimulation for patients with migraine headache. Ból 2014;15(2):31–8.
[14] Cefaly Supraorbital Transcutaneous Nerve Stimulation Copyright © 2016 Cefaly Technology. http://www.cefalytechnology.com/en/products
[15] Lantéri-Minet M, Duru G, Mudge M, Cottrell S. Quality of life impairment, disability and economic burden associated with chronic daily headache, focusing on chronic migraine with or without medication overuse: a systematic review. Cephalalgia 2011;31(7):837–50.
[16] Lipton RB, Silberstein SD. Episodic and chronic migraine headache: breaking down barriers to optimal treatment and prevention. Headache 2015;55(Suppl. 2):103–22.
[17] Silberstein SD. Preventive migraine treatment. Neurol Clin 2009;27(2):429–43.
[18] Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. Headache 2003;43(1):36–43.
[19] Jenkins B, Tepper SJ. Neurostimulation for primary headache disorders: part 2, review of central neurostimulators for primary headache, overall therapeutic efficacy, safety, cost, patient selection, and future research in headache neuromodulation. Headache 2011;51(9): 1408–18.
[20] Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. Lancet Neurol 2012;11 (8):708–19.
[21] Silberstein SD, Dodick DW, Saper J, Huh B, Slavin KV, Sharan A, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, doubleblinded, controlled study. Cephalalgia 2012;32 (16):1165–79.
[22] Tfelt-Hansen P. Headache. In: Stannard CF, Kalso E, Ballantyne J, editors. Evidence-based chronic pain management, vol. 22. Wiley-Blackwell BMJ/Books; 2010. p. 279–90.
[23] Sharav Y, Katsarova Z, Benoliel R. Migraine and possible facial variants: neurovascular orofacial pain. In: Sharav Y, Benoliel F, editors. Orofacial pain and headache, vol. 9. Elsevier Health Sciences; 2008. p. 319–63.