Original Article

Noninvasive Neuromodulation of Supraorbital and Occipital Nerves as an Adjunct to Management of Chronic Headache: A Pilot Study

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Abstract

Background: Chronic daily headache (CDH) results in significant distress and a substantial impact on the quality of life. Due to its nature of refractoriness to conservative management, exploring other modalities seems worthwhile. Invasive nerve stimulation, though promising, has seen complication rates in plenty. The goal of the present study was to assess the efficacy of noninvasive neuromodulation of supraorbital and occipital nerves (SON and ON) using hybrid pulsed radiofrequency device (Stimpod NMS460) in patients of CDH. **Methods:** Thirty patients suffering from CDH were enrolled in this randomized double-blind sham-controlled trial and randomly allocated to two groups of 15 patients each. SON and ON stimulations were given using the device Stimpod NMS460 thrice a week for 3 weeks. Follow-up visits were scheduled at 6 and 12 weeks of therapy. Pain relief was measured using numerical rating scale score. The overall change in quality of life (measured by Short Form-12 Health Survey) and associated complications were also noted. **Results:** Successful stimulation (50% or greater decrease in pain intensity) was seen in 66.67% patients; inadequate response in 33.3% in the intervention group. The 50% responder rate in sham control group was 13.3%; remaining 86.6% showed an inadequate response. This response remained sustained up to 12 weeks of follow-up. Similar changes were observed in the quality of life of patients. No adverse effect was documented during the study period. **Conclusion:** Noninvasive neuromodulation may serve as a safer and cost-effective treatment option in CDH refractory to conservative management.

Keywords: Chronic daily headache, neuromodulation, quality of life

Introduction

Chronic daily headache (CDH) as defined by the International Headache Society occurs on 15 or more days in a month for at least 3 months. The term CDH mainly incorporates primary headache disorders, e.g., chronic migraine (CM), chronic tension-type headaches, cluster headaches, paroxysmal hemicranias; secondary causes of CDH such as posttraumatic headaches, temporal arteritis, idiopathic intracranial hypertension, errors of refraction, and chronic sinusitis need to be excluded. Although affecting around 4% of the general population,[1] majority is diagnosed as CM or chronic tension-type headache.[2] It results in significant distress and a substantial impact on the quality of life.[3]

The common medications in use for the treatment of the condition include combination of analgesics with barbiturates and caffeine, antidepressants, anticonvulsants, beta-blockers, etc. Compared to episodic headache disorders, CDH is less likely to respond to acute and preventive treatments.[2] Unfortunately, even with the best preventive medications, <50% response is seen in chronic cases.[4] Due to such nature of refractoriness to conservative management, many a times, exploring other noninvasive modalities to break the pain cycle seems worthwhile. The therapy may also be useful in patients with limitations in drug dosage due to associated adverse effects. Medication use may also be limited due to the patient's clinical condition and the adverse effects associated with the drugs.

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The era of nerve stimulation using electrodes though promising has seen complication rates in plenty, e.g., lead migration, lead allodynia, and infection.[5] Noninvasive modalities may serve as effective alternatives as well as adjuncts to pharmacotherapy in the management of CDH. Devices available for this include Cefaly for supraorbital stimulation,[6] gammaCore for vagus simulation,[7] and SpringTMS for transcranial magnetic stimulation.[8] Of these devices, till date, only transcutaneous supraorbital nerve stimulation (tSNS) with the Cefaly device has trial based evidence for efficacy and safety.[6]

The device used in this study Stimpod NMS460 (Xavant technology, Pretoria, South Africa) applies hybrid pulsed radiofrequency waves to the nerve causing percutaneous peripheral nerve stimulation. The device has received the United States-Food and Drug Administration (US-FDA) approval for use as an adjunct therapy in acute as well as chronic pain conditions.[9]

This study was designed to assess the efficacy of noninvasive stimulation of supraorbital and occipital nerves (SON and ON) in patients of CDH primarily in terms of pain relief. The overall change in quality of life and associated complications was also assessed as secondary objectives.

Methods

Study design and subjects

After due approval from the Institutional Ethics Committee and written and informed consent, 30 patients suffering from CDH, of at least 3 months duration, were included in this pilot study undertaken at the Pain Clinic, Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh, India.

These patients were of age between 25 and 70 years of either sex, American Society of Anesthesiologists I and II, and no previous history of any systemic condition related to neuropathy. Exclusion criteria were pregnancy, active implanted medical devices (pacemaker, spinal cord/peripheral nerve stimulator, cochlear implant), epilepsy, previous trauma to head, neuropathies associated with exogenous toxic agents, metals or drugs, headache due to organic disease.

Randomization

The patients were randomly allocated to two groups of 15 patients each using a random number table; the data were subsequently sealed into envelopes. Oral medications were continued in both groups as per the standard institutional management protocol for chronic headache. Preprocedure interview and postintervention assessment were carried out by clinicians who did not participate in the intervention. Group C served as the sham-control, while in Group S patients, SON and ON stimulation was given. Both the patients and investigators were blinded to the study group assigned. The study duration was of 12 weeks.

Intervention

After explaining the procedure, the patient was made to sit upright in the intervention room. The points of stimulation were marked for the SON and the greater ON using landmark identification [Figure 1]. Stimulation was given with the device Stimpod NMS460 using a current of 5 mA, pulse width of 0.2 ms, and at a frequency of 5 Hz; the duration of stimulation was 5 min at each site. This was repeated three times a week over a period of 3 weeks.

Postprocedure assessment

The extent of pain relief in terms of degree was measured as numerical rating scale (NRS) score of 0–10 (where 0 is no pain and 10 is the worst pain imaginable). The overall change in quality of life was measured by Short Form-12 (SF-12) Health Survey and associated complications were also noted. NRS score was recorded before intervention (baseline), after every 3 cycles of stimulation, i.e., at 1, 2, and 3 weeks from the onset of interventions, and in the follow-up visit at 6 and 12 weeks. SF-12 scores for change in quality of life were noted before intervention and then at 6 and 12 weeks of follow-up period. Associated side effects and complications were also noted.

Data analysis

Normal distribution of the data was tested using Shapiro–Wilk test. Normally distributed parameters were expressed as mean (standard deviation). For normally distributed quantitative parameters, the mean values were compared between study groups using independent sample *t*-test. Time changing quantitative parameters were compared using one-way repeated measures analysis of variance (ANOVA) test.

If statistically significant difference was found in ANOVA, appropriate *post hoc* test (least squares difference/Bonferroni) was used to assess statistical significance of pair-wise comparisons.

Categorical outcomes were compared between study groups using Chi-square test.

A $P < 0.05$ was considered statistically significant. The SPSS 24.0 for Windows (IBM SPSS Inc., Chicago, IL, USA) software was used for statistical analyses.

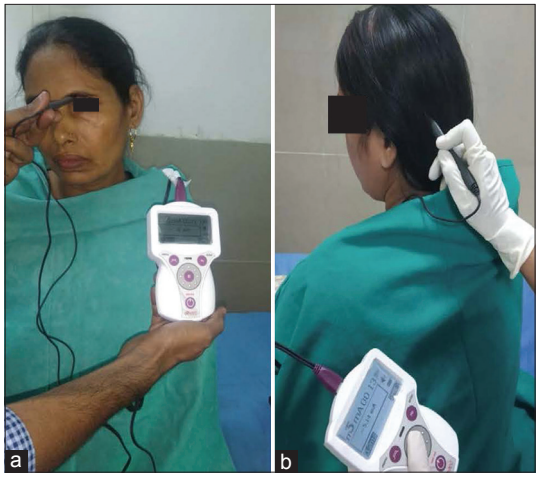

Figure 1: Site of stimulation for (a) supraorbital nerve. (b) Occipital nerve

Results

Subject characteristics

Of the 30 patients included in the study, 15 received SON and ON stimulation and the other 15 comprised the sham treatment group. All patients in both study groups completed the 12 weeks of follow-up. The patients in the two study groups were similar in terms of their demographic profile (age, weight, height, and ratio of males to females), and the minor differences observed were found to be statistically insignificant [Table 1].

Pain relief

Successful stimulation defined as 50% or greater decrease in pain intensity was seen in 66.6% patients; inadequate response was seen in 33.3% in the intervention group; whereas the 50% responder rate in sham control group was 13.3%, the remaining 86.6% showed an inadequate response.

A total of 10 out of 15 patients (66.6%) in the intervention group showed a decline in NRS scores from baseline by 50% or more. This decline was observed only in 2 (13.3%) patients from the control group. The average baseline values in the two study groups were similar with the minor differences being statistically insignificant (NRS = 6.93 and 7.33, $P = 0.1361$).

It can be observed that in the intervention group, there was a statistically significant improvement in NRS scores from baseline after 1 week (3 cycles of stimulation) of intervention ($P < 0.001$) and remained so throughout the study period of 12 weeks. The intergroup difference in NRS scores became significant after 1 week of intervention and this difference was sustained throughout the study period. The changes in NRS scores in the sham-control group during the study period were not found to be statistically significant ($P = 0.21$) [Table 2 and Figure 2].

Quality of life assessment

Change in quality of life as assessed by the SF-12 scores was observed to improve significantly in the intervention Group C as compared to sham-control. The results correlated with the improvement in NRS scores in this study group. An improvement was seen in the physical component summary (PCS SF-12) as well as mental component summary (MCS SF-12) of SF-12 scores. The average baseline values in the two study groups were similar with the minor differences being statistically insignificant (PCS SF-12 = 30.90 and 34.08, $P = 0.0726$; MCS SF-12 = 29.02 and 29.62, $P = 0.81$).

The SF-12 score at 6 and 12 weeks of follow-up in the control group also showed changes from baseline. These observations were, however, not significant statistically (PCS SF-12 baseline = 30.90, 6 weeks = 35.32, 12 weeks = 34.44, $P = 0.12$; MCS SF-12 baseline = 29.02, 6 weeks = 34.84, 12 weeks = 33.89, $P = 0.07$). There was a significant improvement in the quality of life observed at 6 weeks in the intervention group from baseline values as depicted by changes in SF-12 scores. This improvement was sustained up to 12th week of follow-up visit.

It can also be observed that the SF-12 values remained similar at 6 and 12 weeks of follow-up in both study groups [Table 3].

Safety analysis

One patient in each of the groups reported transient paresthesia in the distribution of the stimulated nerves (6.7% in each group). This resolved spontaneously with no need of additional therapy.

One of the patients in the sham-control group reported an increase in pain intensity at the 2nd and 3rd week of intervention (NRS score increased from 7 to 9). It was reported to return to baseline values by 6 weeks and remained the same till the completion of follow-up at 12 weeks.

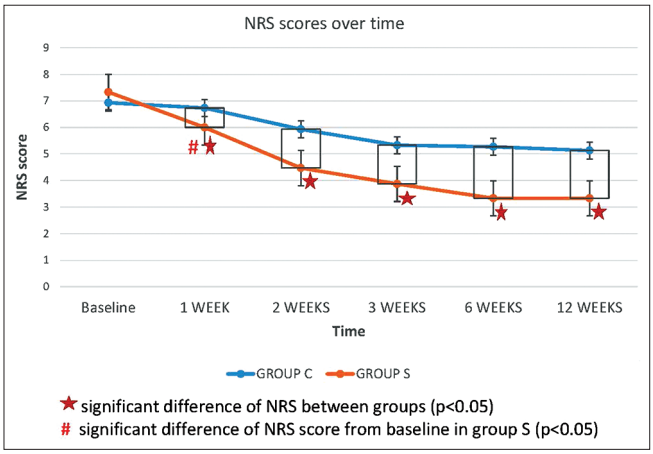

Figure 2: Changes in pain score (numerical rating scale) in the two study groups

Table 1: Demographic profile of patients in the two study groups

Data	Mean±SD		*P*
	Group C	Group S	
Age (years)	41.27±11.23	40.13±10.62	0.779
Height (cm)	159.00±6.19	160.80±7.674	0.485
Weight (kg)	54.13±9.51	60.00±11.48	0.139
Sex (male:female)	6:9	5:10	0.705

SD: Standard deviation

Table 2: Pain scores (Numerical Rating scale) of patients in the two study groups

	Mean±SD		*Pα*
	Group C	Group S	
NRS baseline	6.93±0.79	7.33±0.54	0.1361
NRS 1st week	6.73±0.59	6.00±0.59	0.0063*
NRS 2nd week	5.53±1.25	4.47±1.19	0.0233*
NRS 3rd week	5.33±1.11	3.87±1.19	0.0016*
NRS 6th week	5.27±1.22	3.33±1.54	0.0007*
NRS 12th week	5.13±1.13	3.33±1.50	0.0009*
-	*Pβ*=0.2159	*P¥*=0.0015*	

**P*<0.05 statistically significant. *Pα*: Significance between group C and group S, *Pβ*: Significance of group C from baseline, *P¥*: Significance of group S from baseline, NRS: Numerical Rating scale

Table 3: Quality of life (short form-12) scores in the study groups - before and after the treatment

	Group C	Group S	*Pα*
PCS SF-12			
Baseline	30.90±5.44	34.08±3.74	0.0726
6 weeks follow-up	35.32±9.05	47.43±1.77	0.0001*
12 weeks follow-up	34.44±10.01	50.27±3.76	<0.0001*
-	*Pβ*=0.1162	*P¥*=0.0001*	
MCS-SF 12			
Baseline	29.02±6.61	29.62±6.82	0.8085
6 weeks follow-up	34.84±10.12	51.25±11.43	0.0003*
12 weeks follow-up	33.89±9.22	51.00±10.29	<0.0001*
-	*Pβ*=0.0727	*P¥*=0.0001*	

**P*<0.05 statistically significant. *Pα*: Significance between Group C and Group S, *Pβ*: Significance of Group C from baseline, *P¥*: Significance of Group S from baseline, SF-12: Short form-12, MCS: Mental component summary, PCS: Physical component summary

Discussion

The current study showed beneficial results of noninvasive neuromodulation of SON and ON in patients of CDH with the use of Stimpod NMS460. There was a significant difference in the intervention group from sham-control group in terms of pain relief as well as improvement in the quality of life. No associated complication could be observed.

The most frequently encountered disorder of the nervous system is a headache syndrome.[10] The present study enrolled patients suffering from CDH in general. Although a major fraction of these cases was diagnosed as CM, this study was not limited to CM alone. CM and chronic tension-type headache together constitute most of the cases of CDH.[2] Nevertheless, CDHs experienced holohemispherically may not be limited to above diagnoses only. Producing paresthesia over the parts of the body that hurt has been the traditional approach, which in turn indicates that the correct portion of the nervous system is being stimulated.[11,12] Reed *et al*. also suggested that the central issue in predicting successful neurostimulation is the location of paresthesia in relation to the pain.[11] Dual SON and ON stimulation offers better topographical coverage for all such patients, in accordance with the long established approach of concordant/symphonic paresthesia, as suggested by Hann and Sharan.[5]

The era of noninvasive stimulation is still to see the light of dawn with minimal devices at hand and bare minimal randomized trials to prove efficacy. Nevertheless, the modality may offer more than rays of hope, once established. The efficacy of invasive nerve stimulation for headache disorders has been proved by a number of studies, including ONSTIM study[13] in 2011 for ON stimulation as a part of management of CM. A positive response (a 50% reduction in monthly headache days or a >3-point reduction in pain scores) was seen in 39% of the adjustable stimulation group, 6% in the preset stimulation group, and 0% in the medical group.

Application of SON and ON invasive stimulation has been emerging as a part of management of cephalgia, including management of tension-type and other chronic headache disorders by ON[14-16] and SON[17,18] stimulation. Harnessing this potential of therapy by noninvasive modalities would definitely ablate side effects associated with invasive measures such as lead migration, lead allodynia, and infection.

Currently available noninvasive devices, Cefaly, gammaCore, and SpringTMS, have a defined target; i.e., SON and vagus nerve (electrical stimulation) or the cortex (magnetic stimulation). Stimpod NMS460, a new noninvasive device working on the principle of neuromodulation using hybrid pulsed radiofrequency, is designed such that any superficial nerve may be targeted anywhere along the entire length of the axon, with an eventual effect on the dorsal root ganglion. As a result, it can be used for stimulation of both SON and ON, as utilized in the present study.

The efficacy of noninvasive neurostimulation has been established from the randomized trials of Cefaly device for tSNS. A subsequent US-FDA approval for its use in prevention of episodic migraine has also been obtained.[19] However, its prime limitation is its defined target, supraorbital nerve only. With SNS alone, an appreciable part of the pain-affected area is insufficiently covered.

The device utilized for this study offers the advantage of dual noninvasive neurostimulation for better topographic coverage of the hemicranial headache. Various case reports on the utilization of Stimpod NMS in neuropathic pain of extremities and also for Bell's palsy have been published.[20] Use of the device in patients of headache has not been reported yet. Nevertheless, the device has been approved lately by the US-FDA.[9]

The device may serve as an alternative to pharmacologic treatment, for those resistant or intolerant to medications. It may also be used in combination with pharmacotherapy as was done in this study. The drugs may later be tapered as per the patient's response.

The prime limitation of this trial is that it was a unicentric pilot study on a small sample of patients. Although no adverse effects could be documented in the present study, larger randomized trials to prove its safety and efficacy need to be undertaken. Future studies may also prolong the follow-up period for better assessment of efficacy as well as durability of this treatment modality.

Conclusions

Based on the findings of this study, noninvasive stimulation of supraorbital and ON with Stimpod NMS460 appears as a safe and cost-effective treatment adjunct in patients of CDHs, especially in cases refractory to conservative management.

The ease of portability and the user-friendly nature of such devices may, in addition, help establish this as a management

modality in the therapeutic armamentarium of chronic headache disorders.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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