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Repetitive transcranial magnetic stimulation in new daily persistent headache patients: a single arm open label study

M.M. Bharath[1], Vimal Kumar Paliwal[1*], Swansu Batra[1], Prabhakar Mishra[2], Naina Mishra[2] and Romil Saini[3]

Abstract

Background New daily persistent headache (NDPH) is a continuous, unremitting headache from onset that yields suboptimal results with traditional medicines. Repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising non-invasive treatment for other headache disorders, such as migraine, and neuromodulation has not been well-studied in NDPH. The objective of the study was to evaluate the efficacy of rTMS in reducing the frequency and severity of headaches, and associated anxiety and depressive symptoms in NDPH patients.

Methods This was an open label prospective, single arm, interventional pilot study conducted between October 2022 and September 2023. All eligible participants received 10 Hz rTMS (600 pulses, 10 trains), delivered to the left prefrontal cortex for three consecutive days. The post-rTMS headache severity was recorded weekly for four weeks and headache free days/functional disability, PHQ-9, and GAD-7 scores at the end of four weeks and compared with pre-rTMS parameters. The primary outcome was defined by ≥ 50% reduction in headache severity on Visual Analogue Scale (VAS) score, decrease in headache days from the baseline and secondary outcome was ≥ 6 point reduction in HIT-6 score at 4 weeks.

Results Fifty NDPH patients (mean [SD] age, 35.06 [13.91] years; 31 females [62%]) participated in this study. Thirty-five patients (70%) reported ≥ 50% improvement in pain severity (p-value < 0.001), with a mean reduction of 10.84 (4.88) headache days per 28 days from a baseline of 28 headache days (p-value < 0.001). Thirty-eight patients (76%) reported a ≥ 6 point's reduction in HIT score at 4 weeks. Maximum improvement in the above parameters was observed in NDPH patients with chronic migraine. Two patients reported intolerance to the sound of the rTMS. The median (IQR) PHQ-9 and GAD-7 scores reduced from 11.5(3.75,20) to 7(2,15) (p-value < 0.001) and 10(3,14) to 5.5(0,9) (p-value < 0.001) respectively.

Conclusion rTMS was well tolerated and effective in reducing pain severity, headache days and headache related disability, depressive and anxiety symptoms.

Trial registration CTRI/2023/05/053247.

Keywords New daily persistent headache, NDPH, Transcranial magnetic stimulation, TMS, Neuromodulation, Headache treatment, Non-invasive treatment, Cortical excitability

*Correspondence:
Vimal Kumar Paliwal
dr_vimalkpaliwal@rediffmail.com; drvimalkpaliwal@gmail.com
[1]Department of Neurology, SGPGIMS, Rae bareli road, Lucknow, UP 226014, India
[2]Department of Biostatistics and Health Informatics, SGPGIMS, Lucknow, India
[3]Department of Psychiatry, Apex Trauma Centre, SGPGIMS, Lucknow, India

Background

New Daily Persistent Headache (NDPH) is a disabling primary headache disorder [1, 2]. NDPH is one of the chronic daily headaches (CDH) that affects 4% of the global population, and it is a major health problem [3, 4]. NDPH accounts for up to 35% of CDH in the pediatric population and 2.5–10.8% in the adult population [5, 6].

International Classification of Headache Disorder-3 defines NDPH as persistent headache with "distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours" for greater than 3 months not better accounted for by another diagnosis [7].

The pathophysiology of NDPH is poorly understood and various hypotheses postulate chronic central nervous system inflammation, cytokine production and persistent glial activation that arise in response to precipitating events [8]. Mood disorders are considerably more prevalent in NDPH in comparison to healthy subjects [9–11].

Clinical description suggests at least two subtypes of NDPH: a self-limited form, which typically goes away within several months to several years without any therapy, and a refractory form which is resistant to treatment and can continue for years [12].

There is currently no known treatment for NDPH. New options must be investigated given the lack of effective therapies. Transcranial magnetic stimulation (TMS) is a noninvasive technique that applies Faraday's law of electromagnetic induction, whereby a rapidly alternating magnetic field can induce an electric current in a nearby conductor. Electric current in the brain is induced parallel to the plane of the coil, which may cause neuronal depolarization and either excitation or inhibition, depending on the type of neuron stimulated [13, 14]. There are various protocols of TMS used for different purposes, including single-pulse (sTMS), paired-pulse TMS, and repetitive (rTMS) stimulation [15]. The dorsolateral prefrontal cortex (DLPFC) has an inhibitory effect on pain perception through negative modulation of the central supra-spinal pain tracts [16]. The cortical thickness of the left rostral middle frontal gyrus has been found to be reduced, especially the prefrontal cortex, in NDPH patients, making it a possible suitable therapeutic target for neuromodulation [17]. A study by Ann Ali Abd Elkader et al. observed that high frequency rTMS was effective in treating patients with primary chronic daily headaches (chronic tension headaches and chronic migraines), with a 94.5% improvement in the headache parameters compared to the control group (P value <0.001) [18]. Misra and colleagues also found that three sessions of high frequency (10 Hz) rTMS delivered to the left frontal cortex every other day, comprising 600 pulses in 10 trains, were beneficial for migraine prophylaxis. About 98% of patients had more than 50% decrease in headache attacks at the end and week after rTMS, and the improvement continued till the fourth week in 80.4% cases [19].

There are no trials employing repetitive transcranial magnetic stimulation device (rTMS) as a treatment for NDPH. We used repetitive transcranial magnetic stimulation device (rTMS) in patients with NDPH with the aim to study its effect on headache severity, disability related to headache and its effect on the depressive symptoms and anxiety associated with NDPH.

Methods

This was a prospective interventional single-arm pilot study done at a tertiary care center located in Northern India. Patients were recruited from October 2022 to September 2023.

We included adults (age >18 years) suffering from new daily persistent headache. Patients with Chronic meningitis, Low CSF pressure headache, High CSF pressure headache, post subarachnoid headache or post-traumatic headache and those with contraindications to magnetic stimulation devices and pregnant women were excluded from the study.

Diagnosis of new daily persistent headache

New daily persistent headache was diagnosed by the Neurologist as defined by International Classification of Headache Disorder 3rd edition (ICHD-3) criteria [7].

Severity of headache and functional disability

All eligible patients were observed for a period of 4 weeks prior to rTMS sessions. Headache severity was assessed using a Visual Analogue Scale (VAS) score. Functional disability due to headache was assessed by the headache impact test (HIT-6) questionnaire. Headache severity, headache free days and functional disability were evaluated at the end of 4 weeks of observation period before the start of rTMS treatment sessions.

Assessment of depression, anxiety, somatic symptom disorder

Depression, anxiety, and somatic symptom disorder were diagnosed based on the DSM-5 criteria. The severity of depression and anxiety were assessed by the Patient Health Questionnaire-9 (PHQ −9) and General anxiety disorder-7 (GAD-7) questionnaires respectively. All the scores were assessed after translation to the language spoken by the participants.

Subgroups

Patients were sub-grouped based on 2 categories:

1) Presence or absence of other primary headache disorders which include episodic migraine, chronic migraine, tension type headache, and chronic tension

type headache. Patient was given a diagnosis of co-morbid primary headache along with NDPH if the primary headache did not show increase in frequency of headache before developing daily headache of NDPH.

2) Presence or absence of a somatic symptom disorder diagnosed by DSM-5 criteria.

rTMS treatment and follow-up

Treatment procedures: repetitive transcranial magnetic stimulation A high-frequency repetitive transcranial magnetic stimulator (MagStim Rapid magnetic stimulator, Magstim Company, Whitland, Wales, UK), connected with a figure-of-eight coil with a diameter of 70 mm was used. The figure-of-eight coil was placed tangentially over the left DLPFC, located 5 cm forward from the hot spot of abductor digiti minimi site on a parasagittal plane, with its handle pointing posteriorly and placed parallel to a mid-sagittal axis of the head. Participants subsequently received active three consecutive days sessions of 10 Hz repetitive transcranial magnetic stimulation (rTMS) comprising 600 pulses in 10 trains with an inter train interval of 45 s, delivered to the left prefrontal cortex. The sessions were given on the first three days of the 28-day study period for all the participants. The patients continued the medications they were taking, and no new medications were added during the trial period.

Headache symptom severity was assessed by the Visual Analogue Scale (VAS) at baseline on the day before the start of rTMS sessions and at 7 days, 2 weeks, and 4 weeks of initiating treatment. Functional disability, depression, and anxiety were assessed before the start of treatment (baseline) and at 4 weeks of rTMS. VAS scores, HIT-6 scores, GAD-7 scores, and PHQ-9 scores were also analyzed among the subgroups and compared.

Primary outcome

The primary outcome of the study was to assess the effect of rTMS on severity of headache and headache free days in patients with NDPH. The change in VAS score of 50% or more post-rTMS treatment was considered significant. Headache free days per month were calculated by the number of days completely free of headache.

Secondary outcome

The secondary outcome was to assess the effect of rTMS on functional disability secondary to headache in NDPH patients. A reduction in HIT-6 scores of ≥6 was considered significant.

The effect of rTMS on co-morbid anxiety and depression was also assessed.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Institute's Ethics Committee on Human Experimentation. The study was registered in the Clinical Trial Registry of India (CTRI/2023/05/053247). A written informed consent was obtained from all eligible patients.

Sample size estimation

No previous data was available regarding the use of transcranial magnetic stimulation in NDPH patients. Considering improvement in 50% of patients with rTMS treatment, a minimum two-sided 95% confidence interval and 15% margin of error in the given incidence yielded an estimate of 43. Considering 10% data loss, a sample size of 50 patients was obtained. The sample size was calculated using the software "Power Analysis and Sample Size, Version-16."

Statistical analysis

Continuous variables were expressed as mean±standard deviations (SD), or as median (interquartile range "IQR"). Categorical variables were expressed as numbers with percentages. To test the difference in proportions between the groups, Fishers exact test was used. Test of difference in means/medians between the two paired groups, Paired samples t test / Wilcoxon signed test was used, respectively. The Cohen d effect size was calculated using mean difference/pooled standard deviation. The effect size ≥ 0.8 for the paired t test is considered a large difference. All the results were evaluated and considered statistically significant on 95% confidence interval, or p value < 0.05. Data was analyzed using the software SPSS-23 (SPSS version-23, IBM, Chicago, USA).

Data availability

The corresponding author is the custodian of the data. Anonymized data not published within this article will be made available upon request from any qualified investigator.

Results

Fifty patients (median age 32 (18–70) years, 31 females) diagnosed with New Daily Persistent Headache received rTMS. Five (10%) patients remembered the exact date of onset, 31 (62%) patients could remember the month and year of onset of headache, and 14 (28%) could not remember the date/month but clearly remembered the circumstances that led to the onset of headache. Comorbid primary headaches were seen in 32 (64%) patients. Somatic symptom disorder (SSD) was present in 21 (42%) patients, depressive symptoms in six (12%) patients, anxiety in five (10%) and 14 (28%) patients had both

Table 1 Baseline characteristics of study participants (*N* = 50)

Variable	Mean ± SD / Number (%)	Median (IR)
Age (Years)	35.06 ± 13.81	32(23,45.25)
Male	19(38)	
Female	31(62)	
Comorbid Headache		
Episodic Migraine headache	19(38)	
Tension type Headache	5(10)	
Chronic Migraine headache	7(14)	
Chronic Tension Type Headache	1(2)	
No associated headache	18(36)	
Duration Of Associated Headache (months)	101.25 ± 34.88	102(75,120)
Comorbid mood disorders		
Anxiety	5(10)	
Depression	6(12)	
Anxiety & Depression	14(28)	
No	25(50)	
Adverse Effects Giddiness and sound intolerance	2(4)	
No	48(96)	
DSM-5 Somatic Symptom Disorder Yes	21(42)	
No	29(58)	
Remember exact onset of headache Remembers the exact date	5(10)	
Remembers the Month	31(62)	
Does not remember	14(28)	

Table 2 Change in VAS score, HIT-6, PHQ-9 and GAD-7 scores from baseline

Variable	Median (IQR)	*P*-value
VAS (0–10)		< 0.001
Baseline	8(8,9)	
Week 1	5.5(3,7)	
Week2	4(2,6)	
Week 4	3(2,5)	
Headache free days		< 0.001
Baseline	0	
Week 4	10.84 ± 4.88	
HIT-6 (36–78)		< 0.001
Baseline	65(63,75.25)	
Week-4	50(48,60)	
PHQ-9 (0–20)		< 0.001
Baseline	11.5(3.75,20)	
Week 4	7(2,15)	
GAD-7 (0–21)		< 0.001
Baseline	10(3,14)	
Week 4	5.5(0,9)	

depression and anxiety. The demographic and clinical profile of the patients is given in Table 1.

Effect of rTMS on pain severity, disability, anxiety, and depressive symptoms

Primary outcome

The improvements in VAS, HIT-6 scores, headache free days, PHQ-9, and GAD-7 scores are given in Table 2. More than 50% improvement in VAS score was achieved by 24 (48%) patients in the first week, 28 (56%) patients in the second week, and 35 (70%) patients in the fourth week after rTMS. The median (IQR) VAS score improved from 8 (8,9) at baseline to 5.5 (3,7), 4 (2,6), and 3 (2,5) after 1, 2 and 4 weeks of rTMS treatment. The mean ± SD headache free days at the end of 4 weeks were 10.84 ± 4.88 days.

Secondary outcome

A reduction in HIT-6 scores of ≥6 was seen in 38 (76%) patients at the end of 4 weeks. The median (IQR) HIT-6 scores were 65 at baseline among the patients, which reduced to 50 (48,60) at the end of 4 weeks (p-value < 0.001). The median (IQR) PHQ-9 score was 11.5 (3.75, 20) and reduced to 7 (2, 15) by 4 weeks (p-value < 0.001). The median (IQR) GAD-7 score was 10 (3,14) and reduced to 5.5 (0,9) by 4 weeks (p-value < 0.001).

Outcome of rTMS in NDPH patients with other comorbid primary headaches

Patients with NDPH and comorbid episodic migraine, tension type headache and chronic migraine showed significant improvement in VAS, HIT-6 scores, GAD-7 scores and PHQ-9 scores. (Tables 3, 4 , 5 and 6). The headache free days were seen in all patients, irrespective of any primary comorbid headache (Table 7). Improvements in pain severity, disability, headache free days, anxiety, and depressive symptoms were seen in subgroup of NDPH patients without any comorbid other primary headache and in NDPH patients irrespective of the presence or absence of somatic symptom disorder.

Safety and tolerability

All the patients accepted rTMS, and none withdrew from the study. No serious side effects of rTMS were noted. Minor adverse effects were noted in two patients [4%] in the form of intolerance to the sound of rTMS (Table 1).

Discussion

In this study, high frequency rTMS of the left dorsolateral prefrontal cortex on 3 consecutive days not only reduced the headache severity and functional disability but also increased headache free days and improved the depression and anxiety scores at 4 weeks of therapy. The pain

Table 3 Change in VAS score in NDPH patients with other comorbid headaches and with/without somatic symptom disorder

Variables	VAS Baseline	VAS after rTMS	WEEK 1	WEEK2	WEEK 4	*P*-Value
Associated Headache						
Episodic Migraine	8(8,9)	6(5,9)	4(3,7)	4(3,6)	3(2,4)	**< 0.001**
Tension Headache	8.5(8,9)	7.5(5,8)	7.5(4,8.5)	5(2,7.5)	4(2,7.5)	**0.048**
Chronic Migraine	9(8,9)	7(3,8)	5(2,7)	4(2,6)	2(2,6)	**0.001**
Chronic Tension Type Headache	8.5(8,9)	7(6,8)	6(6,6)	4.5(3,6)	4(3,5)	0.416
No Associated Headache	8(8,10)	7(5,8)	4.5(3,7)	4(2,6)	3.5(2,5)	**< 0.001**
Somatic Disorder						
YES	9(8,9)	7(5,8)	6(3,8)	4(3,6)	3(2,6)	**< 0.001**
NO	8(8,9)	7(5,8)	4(3,7)	4(2,6)	3(2,4)	**< 0.001**

Data presented in median (interquartile range), compared by Friedman test. P value < 0.05 significant

Table 4 Change in HIT-6 score in NDPH patients with other comorbid headaches and with/without somatic symptom disorder

Variables	HIT-6 Baseline	HIT-6 at week 4	*p*-value
Associated Headache			
Episodic Migraine	65(63,72)	48(48,60)	**< 0.001**
Tension Headache	65(65,75)	50(46,53)	**0.043**
Chronic Migraine	71(65,75)	48(48,63)	**0.027**
Chronic Tension Type Headache	51(51,51)	48(48,48)	0.317
No	65(63,66)	50.5(48,63)	**0.001**
Somatic Disorder			
YES	65(63,75)	50(48,60)	**< 0.001**
NO	65(63,68)	50(48,58)	**< 0.001**

Table 5 Change in GAD-7 score in NDPH patients with other comorbid headaches and with/without somatic symptom disorder

Variables	GAD-7 Baseline	GAD-7 at week 4	*p*-value
Associated Headache			
Episodic Migraine	14(3,15)	7(3,9)	**0.001**
Tension Headache	13.5(8,15)	7.5(3,10.5)	0.066
Chronic Migraine	10(9,12)	7(6,12)	**0.039**
Chronic Tension Type Headache	6(0,12)	3(0,6)	0.317
No Associated Headache	4(0,13)	2(0,4)	**0.005**
Somatic Disorder			
YES	13(12,14)	8(6,12)	**< 0.001**
NO	3(0,12)	3(0,6)	**< 0.001**

Table 6 Change in PHQ-9 score in NDPH patients with other comorbid headaches and with/without somatic symptom disorder

Variables	PHQ-9 Baseline	PHQ-9 at week-4	*P*-value
Associated Headache			
Episodic Migraine	9(3,21)	8(2,15)	**0.003**
Tension Headache	17(10.5,21)	11(6,15.5)	**0.042**
Chronic Migraine	21(20,24)	16(16,18)	**0.018**
Chronic Tension Type Headache	11(6,16)	7(4,10)	0.317
No Associated Headache	6(0,16)	4(0,6)	**0.003**
Somatic Disorder			
YES	20(19,22)	15(12,17)	**< 0.001**
NO	6(0,8)	4(0,4)	**< 0.001**

Table 7 Headache free days post rTMS in patients with NDPH (overall) and those with NDPH and other comorbid headaches

Variable	Mean ± SD	Median (IR)
Headache Free Days Per Month Post RTMS (Overall)	10.84 ± 4.88	10.5(8,14)
Episodic Migraine	10.74 ± 5.02	10(8,13)
Tension Headache	11 ± 5	11(7,15)
Chronic migraine headache	10.57 ± 6.997	12(4,16)
Chronic Tension type headache	18	18(18,18)
No Associated Headache	10.61 ± 3.958	10(8,14)

severity improved every week until 4 weeks. This shows that rTMS may have long-lasting effects that extend beyond the time of treatment sessions, as postulated by Kimbrell et al. (1999).[21] They described a working hypothesis stipulating that high frequency rTMS produces certain molecular mechanisms like long-term potentiation (LTP) and an increase in synaptic efficacy that induces neuroplasticity in the underlying cortex. Therefore, the treatment effects of rTMS outlast the duration of the stimulation [20].

Among subgroups of NDPH patients with comorbid other primary headaches, a beneficial effect of rTMS was observed in headache severity, functional disability, symptoms of anxiety and depression in all except in patients with NDPH and comorbid chronic tension type headache.

We evaluated the effect of rTMS in depressive symptoms and anxiety in our patients with NDPH. A high prevalence of anxiety and depressive symptoms has been reported in NDPH [9–11]. The combination of the treatment refractory nature, associated psychiatry

co-morbidities, and a preceding stressful event suggest that NDPH could be with both psychiatric and neurologic features, where the headache is one manifestation arising out of a vulnerability to central sensitivity and altered interoception [21, 22]. There was a significant reduction in PHQ-9 and GAD-7 scores at the end of 4 weeks of rTMS treatment, with a lasting positive effect on anxiety and depression, and headache disability. Depression as well as chronic pain may share some common neural substrates, such as the DLPFC. Therefore, it has been postulated that rTMS on the left DLPFC for major depression might be useful for chronic pain patients via improved quality of life and pain reducing strategies. These effects could be mediated by descending modulatory (opioidergic) systems, effects on cognitive or affective aspects of the pain experience, or a combination of these mechanisms [23].

Also, somatization and a syndromal SSD have been commonly reported phenomena among patients with NDPH. Our study showed that less than half (42%) of the patients met a criterion of SSD, compared to 85% in another study [22]. Though there is an observable overlap between NDPH and somatization in the literature, a significant treatment response in subgroups of patients with and without SSD has been observed in our study. These findings suggest that a response to rTMS in NDPH patients might be independent of the presence of a baseline co-morbid SSD. However, such non-predictors of treatment response need to be explored further in larger randomized controlled trials.

Transcranial magnetic stimulation (TMS) is a non-invasive and safe way to transiently modify the brain's cortical excitability, through applying brief magnetic pulse(s) over the head [24]. Low frequency rTMS (1 Hz) has been demonstrated to inhibit cortical excitability, whereas high-frequency stimulation (5–20 Hz) may lead to an increase in excitability. The site of stimulation is an important predictor of pain relief. The dorsolateral prefrontal cortex, on stimulation, seems to exert a bilateral control of pain and has a critical antinociceptive role [25]. DLPFC activation may limit or reset decreased frontolimbic dysfunction, which is associated with chronic pain symptoms and results in clinical improvement [26]. A reduction in DLPFC gray matter volume in pediatric patients with chronic painful conditions showed reversal to normal or near normal levels following high-frequency rTMS therapy [23].

rTMS has been shown to improve chronic daily headaches and persistent headaches related to mild traumatic brain injury [27]. rTMS may be beneficial in prophylaxis for such patients with persistent post traumatic headaches refractory to drugs including the CGRP monoclonal antibodies [28]. However, further controlled studies are required to evaluate the effect of rTMS in NDPH and other persistent chronic headaches.

There were certain limitations to our study. We had a small cohort of patients. The RTMS frequency of sessions, total duration of treatment, site of stimulation, and frequency of stimulation were designed as per the protocol used for migraine. We did not assess the patients long-term to determine the mean duration of the response to rTMS in NDPH. Being a single arm study is a clear limitation of the study. However, we did not include a sham stimulation arm owing to the small sample size and issues related to sham stimulation in rTMS.

Conclusion

Repetitive transcranial magnetic stimulation holds promise as a potentially effective and well-tolerated therapeutic intervention for new daily persistent headache patients as a prophylaxis. Improvement in headache symptoms may also improve functional disability, anxiety, depression, and thus the overall quality of life. However, our study requires external validation in a placebo-controlled, large cohort study.

Abbreviations

NDPH	New daily persistent headache
rTMS	Repetitive transcranial magnetic stimulation
DLPFC	Dorsal lateral prefrontal cortex
VAS	Visual Analogue Scale
HIT-6	Headache Impact Test
PHQ-9	Patient Health Questionnaire
GAD-7	General Anxiety Disorder

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Author contributions

BMM Prepared initial draft, major data collection, data analysisVKP Conceptualize the study, prepared initial study methods, prepared the final draftSB Reviewed manuscriptPM Designed Statistical protocol, data analysisNM Data AnalysisRS Reviewed manuscript.

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Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval by 129th Institutional Ethics Committee (IEC code: 2022-170-DM-129) of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareli road, Lucknow – 226014 (India).

Consent for publication

Consent for publication was obtained from the participants.

Competing interests

The authors declare no competing interests.

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