Review Article

A Review of Deep Brain Stimulation Effect on Cluster Headaches

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Abstract:

Background: Cluster headache affects patients' quality of life significantly. This condition being characterized as a primary headache disorder which affects up 124 in 100,000 individuals during their lifetime while there are current therapeutic modalities for cluster headaches, recent advances showed the beneficial role of Deep Brain Stimulation in treatment of chronic refractory cluster headaches.

Methods: This was a narriative review of literature.

Results: Deep brain stimulation procedure has been used for various neurological condition such as Parkinson's disease, essential tremor and dystonia. This procedure is being done while patients is being awake with the help of stereotactic localizing system. After penetrating the skull, lead extension and pulse generator are implanted with the help of magnetic resonance imaging and programmed using a transdermal implant Deep brain stimulation of hypothalamus and midbrain area could be the possible solution for chronic refractory cluster headache patients to relief and improve their quality of lives. Deep brain stimulation could provide relief for patients suffering from chronic refractory cluster headaches.

Conclusion: By using the targeted neuromodulation of a network around hypothalamic and midbrain neural substrates, Deep brain stimulation is able to generate short- and long-term pain-relief in a large majority of patients. With minimum side effects being reported until now, Deep brain stimulation could be applied in selected cases.

Keywords: Deep Brain Stimulation, Cluster Headaches, Neuromodulation, Headache

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Introduction

The cluster headaches is defined as "unilateral, excruciatingly severe attacks of pain principally in the ocular, frontal and temporal areas recurring in separate bouts with daily or almost daily attacks for weeks to months usually with ipsilateral lacrimation, conjunctival injection, photophobia and nasal stuffiness and/or rhinorrhea" by the International Association for Study of Pain (IASP) (1).

Cluster headaches is being characterized as a primary headache disorder which affects up 124 in 100,000 individuals during their lifetime (2). This condition has been considered to have male predominance, with high female-male ratio with its highest where the age of onset was 20 to 49 years old (3). The phenotype of cluster headaches is similar in both genders however females experience more nausea and vomiting during their attack (4-6). There has been different therapeutics suggested for cluster headaches as sumatriptan subcutaneous, zolmitriptan nasal spray, high flow oxygen and Deep Brain Stimulation (DBS) (7).

DBS is an effective surgical treatment for various neurological and psychiatric disorders (8). The use of DBS in treatment of headaches was started with observing provoked neurovascular headaches when specific brain areas are being stimulated, as Raskin *et al.* described 9% of patients underwent DBS for low back pain developed severe headaches (9). In another study by Veloso *et al.* (10) 23.4% of patients developed chronic headache following DBS in periaqueductal gray, sensory thalamus, and internal capsule.

Pathophysiology of cluster headaches

The etiology and pathophysiology of cluster headaches is yet unknown.

Neuroimaging studies revealed ipsilateral inferior hypothalamic gray matter activation (11), along with structural changes (12) in cluster headaches. The posterior hypothalamic area was hypothesized to be the cluster generator (11).

In addition to neuroimaging studies found the role of hypothalamus in cluster headaches, a study by Leone *et al.* (13) on 32 patients with cluster headaches and 16 in remission phase, 200 μg thyrotropin releasing hormone (TRH) was administered. The study found that thyroid stimulating hormone (TSH) response was significantly lower in patients with cluster headaches during the attack which can show the role of hypothalamus in cluster headaches. A similar pattern was also observed in total, free and carrier protein-bound testosterone levels and luteinizing hormone (LH) peak values after intravenous administration of luteinizing hormone releasing hormone (LHRH) (14). In a study by Barlosse *et al.* (15) on 275 cluster headaches patients, showed that sleep quality is being disturbed during the attacks. As hypothalamus is being involved in sleep regulation, the hypothesis that it is being involved in cluster headaches could become clearer.

Taken together with other clinical findings suggest the central role of hypothalamus in developing cluster headaches.

As there are distinct phases for cluster headaches, Kudrow (16) suggested impaired sympathetic activity and chronobiological aberration leads to dysfunction of autoregulatory chemoreceptor activity.

Neurogenic inflammation also contributes to cluster headache generation as previous studies showed increased vasoactive peptides in patients with cluster headaches (17).

Deep Brain Stimulation

DBS procedure has been used for various neurological condition such as Parkinson's disease, essential tremor and dystonia. This procedure is being done while patients is being awake with the help of stereotactic localizing system. After penetrating the skull, lead extension and pulse generator are implanted with the help of magnetic resonance imaging

and programmed using a transdermal implant (18).

The application of DBS in cluster headaches

The early use of DBS in posterior hypothalamus area was first chosen by Leon *et al.* (19, 20) which resulted decrease in frequency and severity of attack in cluster headache patients. Thereafter, a multicenter case series by Bartsch *et al*. (21) on six patients was done. All patients' undergone DBS surgery and electrodes were implanted in ipsilateral posterior hypothalamus, having mean 17 Hz single unit discharge rate. Four patients had deep relief of pain and frequency of attacks and also improved visual analogue scale during the first six month after surgery. According to their study the stimulation had no side effects and was well tolerated in long-term. In a follow-up study by Leon *et al.* the patients were pain free up to 3 years with no need for add-on pharmacological intervention and only one patients had attacks after 18 months from therapy (22).

A study by Seijo-Fernandez *et al.* (23), 15 drug resistant chronic cluster headaches patients underwent DBS in coordinates 4 mm lateral to the III ventricular wall and 2 mm behind and 5 mm below the intercommissural point. All patients mean attack rate improved from 39 to 2 attacks per week and also decreased pain intensity and cephalgia.

In another randomized placebo-controlled double-blind trial followed by a 1-year open extension by Fontaine *et al.* (24), 11 patients with severe refractory chronic cluster headache and randomized to the DBS and sham surgery. The severity of cluster headaches was assessed by the weekly attacks' frequency (primary outcome), pain intensity, sumatriptan injections, emotional impact (HAD) and quality of life (SF12). No significant change was observed between groups in primary and secondary outcomes in randomization however 6 patients had relief in open phase. Three serios adverse events were recorded including subcutaneous infection, transient loss of conciseness and micronutrition syncope.

A meta-analysis by Nowacki *et al.* (25) on individuals patients data, among 40 patients included into meta-analysis, significant 77% reduction in headache attack rate in the mean follow-up time of 44 months was found. The overall response rate was 75% and had no associations with baseline variables.

The eligibility criteria for DBS of hypothalamus in chronic cluster headache has been recommended by Leone *et al.* (26). Patients must have had recurrent episodes for 24 months or higher, with attacks being strictly unilateral for at least 12 months.

The Ventral Tegmental Area (VTA) has been recently a target for DBS. In a prospective open-label study, 21 patients with chronic cluster headache underwent VTA-DBS. With a median follow-up of 18 months, 60% decrease in headache frequency and 30% in pain severity was recorded. The results of this study suggested VTA-DBS could be safe and effective in chronic refractory cluster headaches.

Overall DBS could provide relief for patients suffering from chronic refractory cluster headaches. By using the targeted neuromodulation of a network around hypothalamic and midbrain neural substrates, DBS is able to generate short- and long-term pain-relief in a large majority of patients. In order to broader the utilization of this treatment modality, understanding the mechanisms of CH pathogenesis and DBS action are being required (27).

Conclusion

Deep brain stimulation of hypothalamus and midbrain area could be the possible solution for chronic refractory cluster headache patients to relief and improve their quality of lives. With minimum side effects being reported until now, DBS could be applied in selected cases.

References

1.Merskey HE. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms. Pain. 1986.

2.Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. Cephalalgia. 2008;28(6):614-8.

3.Ekbom K, Svensson DA, Träff H, Waldenlind E. Age at Onset and Sex Ratio in Cluster Headache: Observations Over Three Decades. Cephalalgia. 2002;22(2):94-100.

4.Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. Neurology. 2002;58(3):354-61.

5.Manzoni GC, Micieli G, Granella F, Martignoni E, Farina S, Nappi G. Cluster headache in women: clinical findings and relationship with reproductive life. Cephalalgia. 1988;8(1):37-44.

6.Rozen TD, Niknam RM, Shechter AL, Young WB, Silberstein SD. Cluster headache in women: clinical characteristics and comparison with cluster headache in men. J Neurol Neurosurg Psychiatry. 2001;70(5):613-7.

7.Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache: The Journal of Head and Face Pain. 2016;56(7):1093-106.

8.Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, Applications, and Mechanisms of Deep Brain Stimulation. JAMA Neurology. 2013;70(2):163-71.

9.Raskin NH, Hosobuchi Y, Lamb S. Headache May Arise From Perturbation of Brain. Headache: The Journal of Head and Face Pain. 1987;27(8):416-20.

10.Veloso F, Kumar K, Toth C. Headache Secondary to Deep Brain Implantation. Headache: The Journal of Head and Face Pain. 1998;38(7):507-15.

11.May A, Bahra A, Büchel C, Frackowiak RSJ, Goadsby PJ. Hypothalamic activation in cluster headache attacks. The Lancet. 1998;352(9124):275-8.

12.May A, Ashburner J, Büchel C, McGonigle DJ, Friston KJ, Frackowiak RSJ, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nature Medicine. 1999;5(7):836-8.

13.Leone M, Patruno G, Vescovi A, Bussone G. Neuroendocrine dysfunction in cluster headache. Cephalalgia. 1990;10(5):235-9.

14.Murialdo G, Fanciullacci M, Nicolodi M, Filippi U, Palma DD, Sicuteri F, et al. Cluster Headache in the Male: Sex Steroid Pattern and Gonadotropic Response to Luteinizing Hormone Releasing Hormone. Cephalalgia. 1989;9(2):91-8.

15.Barloese M, Lund N, Petersen A, Rasmussen M, Jennum P, Jensen R. Sleep and chronobiology in cluster headache. Cephalalgia. 2015;35(11):969-78.

16.Kudrow L. The pathogenesis of cluster headache. Current Opinion in Neurology. 1994;7(3).

17.Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache Neuropeptide changes and effects of acute attacks therapies. Brain. 1994;117(3):427-34.

18.Lyons MK, editor Deep brain stimulation: current and future clinical applications. Mayo Clinic Proceedings; 2011: Elsevier.

19.Leone M, Franzini A, Bussone G. Stereotactic Stimulation of Posterior Hypothalamic Gray Matter in a Patient with Intractable Cluster Headache. New England Journal of Medicine. 2001;345(19):1428-9.

20.Franzini A, Ferroli P, Leone M, Broggi G. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. Neurosurgery. 2003;52(5):1095-101.

21.Bartsch T, Pinsker MO, Rasche D, Kinfe T, Hertel F, Diener HC, et al. Hypothalamic Deep Brain Stimulation for Cluster Headache: Experience From a New Multicase Series. Cephalalgia. 2008;28(3):285-95.
22.Leone M, Franzini A, Broggi G, Bussone G. Hypothalamic deep brain stimulation for intractable chronic cluster headache: a 3-year follow-up. Neurological Sciences. 2003;24(2):s143-s5.
23.Seijo-Fernandez F, Saiz A, Santamarta E, Nader L, Alvarez-Vega MA, Lozano B, et al. Long-Term Results of Deep Brain Stimulation of the Mamillotegmental Fasciculus in Chronic Cluster Headache. Stereotactic and Functional Neurosurgery. 2018;96(4):215-22.
24.Fontaine D, Lazorthes Y, Mertens P, Blond S, Géraud G, Fabre N, et al. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. The Journal of Headache and Pain. 2010;11(1):23-31.
25.Nowacki A, Schober M, Nader L, Saryyeva A, Nguyen T-AK, Green AL, et al. Deep Brain Stimulation for Chronic Cluster Headache: Meta-Analysis of Individual Patient Data. Annals of Neurology. 2020;88(5):956-69.
26.Leone M, May A, Franzini A, Broggi G, Dodick D, Rapoport A, et al. Deep Brain Stimulation for Intractable Chronic Cluster Headache: Proposals for Patient Selection. Cephalalgia. 2004;24(11):934-7.
27.Vyas DB, Ho AL, Dadey DY, Pendharkar AV, Sussman ES, Cowan R, et al. Deep brain stimulation for chronic cluster headache: a review. Neuromodulation: Technology at the Neural Interface. 2019;22(4):388-97.