NEUROSTIMULATION FOR REFRACTORY PRIMARY CHRONIC HEADACHE DISORDERS: A REVIEW

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ABSTRACT

Headache is the commonest symptom seen in both primary and secondary care. Vast majority are primary i.e. for which no underlying cause has been detected. Tension Headaches, Migraine and Cluster Headaches are the most common primary headache disorders in the population. Although most of the primary headache disorders can be satisfactorily treated with both acute and preventive medications, those that are refractory to conventional treatment pose a great challenge to the headache physician. Moreover some patients are not able to use traditional treatment due to intolerance and co-morbidities. Neurostimulation is a treatment modality that has been used in other neurological disorders such as movement disorders, multiple sclerosis and chronic neuropathic pain and there has been emerging evidence to its usefulness in primary headache disorders. These range from being invasive treatments like deep brain stimulation to minimally invasive one like occipital nerve stimulators. Non-invasive neurostimulation is gradually emerging as a potential non-pharmaceutical option in managing primary headache disorders. The article reviews the evidence of Neurostimulation in primary headache disorders with a view to ascertain its efficacy and safety.

KEY WORDS: Neurostimulation, Occipital nerve stimulator, peripheral nerve stimulator, Deep brain stimulation, transcranial magnetic stimulation, refractory headaches

INTRODUCTION

Primary headache disorders affect almost half of population; although primary chronic headaches occur only in around 3%. However, these forms of headache prove to be quite challenging for our conventional therapeutic modalities, due to high prevalence of acute analgesics misuse, the relatively-unimpressive response rate to available pharmacological agents which reaches 50% in the best cases as well as the adverse events profile [1]. Neurostimulation is a novel therapeutic approach, which has been tried in different neurological conditions, namely movement disorders [2], chronic pain[3], and epilepsy[4]. In this article, we review the evidence for neurostimulation in different primary headache disorders, using diverse modalities of delivery that range from invasive ones like deep brain stimulation, less invasive techniques such as occipital nerve stimulation and sphenopalatine stimulation, to the non invasive modalities such as transcranial direct current stimulation, transcranial magnetic stimulation and the vagal nerve stimulation.

INVASIVE NEUROSTIMULATION

Deep brain stimulation (DBS) for Trigeminal autonomic cephalalgias (TACs):
Hypothalamic deep brain stimulation has been used as potential therapeutic target for chronic cluster headache due to evident hypothalamic hyperactivity during cluster attack [5]. A significant responder rate (pain free or 50% responder rate) has been noted in about 64% across all the cases done worldwide using open-label bases[6-19]. A randomised, double-blind, placebo-controlled trial, using active and sham stimulation, has failed to produce comparable results, likely due to the short blinding phase, as significant responder rate of 60% has been noted during the subsequent open-label phase [16]. It is worth mentioning that majority of patients experienced re-emergence of cluster attacks once their stimulator has stopped working which emphasise the role of stimulation as a form of symptomatic therapy. The positive results of DBS in treating chronic cluster headache has encouraged researchers to explore its potentials for other types of TACs with positive results in 3 cases of Short lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) where patients attained significant reduction in their attacks' frequency after at least one year of stimulation[20-22]. Another positive result has been achieved with one case of chronic paroxysmal hemicranias[23].

DBS is not a risk-free procedure, various adverse events have been reported including fatal intracerebral haemorrhage (3%), intraoperative panic attacks induced by autonomic disturbance[19], intraoperative TIA with hemiplegia lasting 5 minutes[6], ocular movement disturbances[18-19], tremor [17], and sneezing[24]. A positive effect of DBS has been an improved quality of sleep likely to be related to reduction of the nocturnal attacks frequency [6].

PERIPHERAL NERVE STIMULATION

The pain modulation following an electrical stimulation not only has direct effects on stimulated nerve but also a secondary effect on the central nervous system. The Melzack-Wall gate control theory states that, 'there is an inverse relationship between activity in small diameter nociceptive afferents and large diameter nerve fibers'. Large diameter nerve fibre stimulation results in reduction of the small diameter fiber nociceptive input and elevation of pain thresholds which in turn results in pain relief [25]. Hence in the Occipital nerve stimulation (ONS), electrical stimulation of C2, C3 nerve branches are expected to reduce the small diameter nociceptive fibers activity causing pain relief. According to gate control theory, this interaction occurs in the dorsal horn of spinal cord, but some studies suggest that neurostimulation alters the conduction velocity and the amplitude of both the A-alpha and beta and the A-delta waves with the more slowly-conducting A-delta component showing the greatest changes. This direct alteration of peripheral nerve activity distal to the first synapse in the spinal cord might contribute to the mechanism of pain relief [26].

Peripheral nerve stimulation also has secondary central nervous system effects. Some of the animal and human studies have shown that the trigeminocervical pathway is multidirectional, therefore activation of one part of the system results in activation of other parts. Both mechanical and electrical stimulation of the superior sagittal sinus results in activation of the neurons that extend from trigeminal nucleus to C1,C2 dorsal horns2[7, 28]. The greater occipital nerve stimulation has also been shown to increase the metabolic activity of the dorsal horn at C1,C2 and trigeminal nucleus caudalis [29]. Positron emission tomography (PET) studies of chronic migraineurs treated with bilateral ONS showed central nervous system effects including alteration of the thalamic activation that resulted in pain relief [30].

Occipital nerve stimulation (ONS)

There are three nerves that innervate occipital region, namely the greater occipital nerve, lesser occipital and least occipital nerve. The greater occipital nerve is a branch of the C2 spinal root. The lesser occipital nerve is composed of branches of the C2, C3 spinal roots. The medial branch of the posterior division of the C3 root gives off a branch called the least occipital nerve. ONS is used for many intractable headache syndromes such as occipital neuralgia, migraine, cluster headache and some of less common conditions like SUNCT and hemicranias continua (HC). There is anatomical and functional correlation between trigeminal and cervical afferents called the trigeminocervical complex from the trigeminal caudal nucleus to at least the C2 segment [31], hence ONS can modulate pain in the areas not only in the occipital nerve distribution but also in the trigeminal nerve distribution.

IMPLANTATION TECHNIQUES

ONS treatment was introduced by Weiner and Reed. There are various implantation techniques described[32]. Implantation procedure can be done under local or general anaesthesia. ONS is typically done with equipment that is normally used for spinal cord stimulation (SCS).

Medication overuse headache should be ruled out prior to offering ONS. Often positive but transient response to occipital nerve blockade has been used prior to offering ONS trial although evidence suggests that this may not be a good predictor[33]. Many centres are using 5-7 day percutaneous stimulator trial to test the efficacy and tolerability before permanent implantation. The predictive values of both methods are questionable [34]. Permanent implantation can be undertaken with midline or retromastoid approach and is usually done in two steps. The first step is conducted under local anaesthesia to test the stimulation and optimal placement of electrodes followed by insertion of the remaining ONS under general anaesthesia. It can be successfully implanted under general anaesthesia as a single procedure with the same desired outcome [35].

There is a wide variation in the stimulation settings used, with the amplitude ranging from 0.1 to 10 V, the frequency ranging from 3 to 130 Hz and pulse width ranging from 90 to 450 ms[36]. Further studies are needed to establish impact of specific parameters on outcome. Alternatively, there are miniaturized devices called 'Bion' which can be implanted over the occipital nerves [37]. Recently Trentman and colleagues described the implantation technique and the stimulation parameters of the bion microstimulator in nine patients with medically intractable primary headache disorders [38]. Their results showed that the bion may provide effective occipital stimulation without requiring anchoring or tunnelling of exten-

sions to remote power sources. Other advantage is reduced risk of lead migration. However it needs frequent recharging and may get encapsulated requiring increased energy to stimulate occipital nerve. The efficacy and safety need to be established with further studies.

EFFICACY AND SAFETY OF ONS

ONS has been studied in primary headache syndromes although it is also used in secondary headaches such as cervicogenic headache, post traumatic headache and occipital neuralgia. Popeney and Aloused C1 through C3 peripheral nerve stimulation to treat 25 Patients who met the International Headache Society (IHS) criteria for episodic migraine refractory to pharmacological treatments. Mean duration of headache was 10 years (range 1-30 years). All patients completed a successful5-7 day trialof outpatient stimulation with an externalised quadripolar electrode system before a permanent implant. The mean stimulation parameters were 55 Hz frequency, 3.2 V voltage, 400 μs. 60% patients used the stimulator intermittently and 40% used it continuously. Patients were followed up for 18 months (range 8-36 months). 88% reported at least 50% reduction in headache frequency or severity after ONS was implanted. The average 3 month headache frequency reduced from 76 days pre ONS to 38 days post ONS. The Visual rating scale (VRS 0-10) reduced from an average 9.38 to 5.72. The average migraine disability assessment score reduced from grade IV (severe) to grade I (mild). Medication usage reduced to less than 15 doses per month for residual symptoms. Complications included traumatic lead migration in 6, spontaneous migration in 3 and infection in 1 patient [39].

Oh and colleagues studied ONS in 10 patients with transformed migraine refractory to preventive and physical treatments. The mean duration of headache was 12 years (range 2-25 years). 9 patients had shown complete but transient pain relief with greater occipital nerve block and 1 patient had partial (80%) relief. 7 patients had previous success with dural percutaneous cylindrical electrodes that migrated. All 10 patients were then implanted with dual paddle style electrodes. At one month 9 out of 10 patients reported more than 90% pain relief while 1 reported 75-90% improvement. At 6 months, 7 patients reported more than 90% relief, 2 had 75-90% and 1 was lost to follow up. All the patients were happy to undergo the operation again. Complications included infections in 2 patients which led to removal in 1 patient with replacement 2 months later [40].

Schwedt and colleagues studied ONS in 8 patients with IHS defined chronic migraine refractory to pharmacological therapy. Each patient had pain involving the C2 distribution with or without pain in the other regions of the head. All patients had undergone a 5-7 day percutaneous stimulator trial prior to permanent placement. 3 had unilateral stimulator and 5 had bilateral stimulation with percutaneous cylindrical leads. Patients were able to change the stimulator parameters and also medication changes during their follow up period. At mean 18 months follow up, 3 month headache frequency reduced from 90 to 60 days while the VRS reduced from 6.8 to 4.5. Patients also reported significant reduction in disability and depression after the ONS operation. Complications include 3 patients requiring revision for lead migration and 1 required IPG revision. Neck stiffness and incision site pain was also reported [41].

ONS for the treatment of intractable chronic Migraine (ONSTIM) was a multicentre, randomised, single blind, controlled study by Saper et al 42. The study recruited 66 patients who met the revised International Classification of Headache Disorders (ICHD-II) criteria and those who had successful response to occipital nerve blocks. The average duration of migraine was 22 years (1-51 years) and chronic migraine for an average of 10 years prior to the study enrolment (range 1-30 years). Patients were randomised in a ratio of 2:1:1 to adjustable stimulation, preset stimulation and medical treatment. The responder rate was defined as 50% reduction in headache days/month or at least 3 point drop (on VRS 0-10) in pain intensity at 3 months. The responder rate was 39% in the adjustable stimulation group compared with 6% in the preset group and none in the medical treatment group. Complication of lead migration occurred in 12 of 51 patients (24%). It was concluded that Occipital nerve blocks are not predictive of ONS response. There were limitations to this study as blinding was not possible with ONS trials and paraesthesia resulting from stimulation and the feasibility to change the stimulator parameters gave some placebo effect in adjustable stimulator group. However, the results overall suggest that ONS might represent a therapeutic option for some patients with chronic migraine. Further studies are needed to assess therapeutic response and complications 42. Weiner and Reed reported the benefit of ONS in a series of patients with intractable occipital neuralgia but detailed phenotyping in some of these patients through functional imaging revealed that they had chronic migraine [43, 44].

ONS IN CLUSTER HEADACHE

Magis et al in their study of 8 patients with medically

intractable cluster headache showed that treatment with ONS was beneficial. Weekly headache frequency reduced from 13.4 pre to 2.8 post ONS. Attack intensity reduced from 2.62 to 1.47 post ONS (scale of 4, 1 being mildest to 4 being worst pain). Majority of the patients who responded to ONS were able to reduce their preventative medication but only one was able to stop them completely. Lead displacement and electrode migration were reported in one patient each [45]. Burns et al in their study of 14 patients with medically intractable cluster headache using bilateral ONS showed variable results but yet demonstrating that it is fairly beneficial in 10 out of 14 patients. There was approximately 20-30% to 90% improvement in headache reported in this study. Lead migration was reported in 29% of patients, other complications were muscle recruitment, neck stiffness, skin discomfort, superficial infection, painful paraesthesias [46, 47].

Schwedt et al reported ONS use in 3 patients with chronic cluster headache. It was a small series and the efficacy of ONS was low. Headache frequency did not change and as a matter of fact one patient reported an increase in frequency. Headache severity in two patients had reduced from VRS 8 to 5 and 8 to 3.5 respectively. Lead migration was the main adverse event [48].

Although the above published open label studies show some benefit from ONS in chronic cluster headache, there were a few drawbacks in study design, patient selection, and outcome measurement. Hence, Leone et al made recommendations on the criteria for neurostimulation in primary headaches. These include daily or almost daily headache frequency for 2 years, all the medical therapy to be tried for sufficient period of time unless contraindicated, post implant follow up should be at least a year, psychological assessment should be done prior to implantation surgery, patients to maintain prospective headache diary to document frequency, severity, duration of headache episodes and any painkillers consumed, quality of life measurements, self assessment of pain [49].

ONS IN HEMICRANIA CONTINUA (HC)

There are few small series suggesting some benefit in hemicrania continua. Schwedt el al 37 described a patient with HC who had discontinued indomethacin due to intolerance and had unilateral bion device implanted. There was significant improvement to pain free state at baseline with superimposed severe headaches five times in 3 months.Same group of colleagues treated two patients with a diagnosis of HC who had developed intolerance to indomethacin with ONS, one unilateral and one bilateral respectively. At follow up, 3 month headache frequency had dropped from 90 days to 10 and 12 days respectively. Pain severity had reduced from VRS 7.5 to 3-7. Both patients had lead migration and one had infection [37].

Burns et al studied 6 patients with HC using bion device. It showed improvement in pain ranging from 30% to 80-95%. One patient had worsening of pain by 20%. Adverse effects were mild and associated with transient overstimulation. Authors later reported that the one patient who got worse had chronic migraine after going through the medical notes and treatment response review [48].

ONS in Short lasting Unilateral Neuralgiform headache with Conjunctival injection and Tearing (SUNCT) and Short lasting Unilateral Neuralgiform headache Attacks with cranial autonomic features (SUNA) There is limited evidence to suggest the usefulness in treating SUNCT and SUNA.

Matharu and Colleagues did a study of 7 patients with medically intractable SUNCT and one patient with SUNA treated with bilateral ONS showing some benefit. No major side effects were reported [50].

NON-INVASIVE NEUROSTIMULATION

TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS)

tDCS is a non-invasive modality that uses a weak direct current in order to change the resting neuronal potential, it utilises two types of stimulation, either cathodal (inhibitory) or anodal (excitatory) stimulations which can modulate the function of the stimulated part of the brain to achieve a desired effect. The effect of tDCS is thought to be restricted to the cerebral cortical potentials, studies have shown that anodal tDCS did not change the nociception-specific blink reflex which usually reflects brainstem electrophysiological changes [51]. Animal models of cortical spreading depression (CSD) (a key mechanism in migraine with aura) showed that this process could be modulated using the above mentioned technique [52].

The above mentioned findings have paved way to study the effect of cathodal tDCS application on the primary visual cortex, over 6 weeks, in 26 patients with migraine with aura and compare it to sham stimulation. Interestingly, the improvements of the study parameters were not statistically significant except for migraine intensity [53]. Anodal tDCS of primary motor cortex has been used in different pain syndromes with considerable success; similar result were found in 13 subjects with chronic migraine, however it took about 3 months for pain intensity and period to improve [54]. The largest study using tDCS during the migraine attack in 62 patients showed a reduction in pain intensity that is comparable to sham stimulation [55].

TRANSCRANIAL MAGNETIC STIMULATION (TMS)

TMS has been an investigative tool in clinical neurophysiology for the last two decades; however its potential utilisation in treating migraine could revolutionise the way we approach migraine treatment in the future. TMS utilises a rapidly changing magnetic field (delivered by a single or multiple pulses) to induce hyperpolarisation or depolarisation in the cerebral cortex, this is best applied to migraineur with aura due to CSD which is an intense depolarization of neuronal and glial membranes[57]. CSD indicates underlying brain hyperexcitability particularly the occipital cortex excitability that has been demonstrated in migraine with aura[56, 58,59]. CSD in animal studies has shown to result in neurogenic inflammation and activation of nociceptive trigeminal afferents [60]. The animal studies with transcranial magnetic stimulation has shown to inhibit CSD and hence potentially terminate the aura and reduce the duration or severity of migraine in those with migraine aura [61]. Commercially available devices have a microprocessor-controlled power source that is connected to an insulated wire coil. The stored energy is rapidly discharged through the wire coil in response to a trigger. This results in high current pulse passing through the coil creating a transient magnetic pulse lasting less than 1 millisecond. When coil is placed against the head, the transient magnetic field passes through the scalp and skull, inducing an electrical current in the underlying cortex. The peak magnetic field strength of a conventional device is 1.5-2 Telsa comparable to fields from clinical magnetic resonance imaging (MRI) scanners. The US Food and Drug Administration characterize TMS by frequency. Low frequency TMS refers to a stimulus delivered less than 1 pulse per second and this is not considered to be a serious risk to health and safety. High frequency TMS refers to a stimulus that is delivered at 1 pulse per second or more and this is considered as a potential risk. Effect of single pulse stimulation has been evaluated in migraine using migrainous pain response and pain recurrence in 24 hours, In 42 patients (migraineurs with and without aura) using two single pulses of high and low intensities; migraine intensity has improved with both intensities and up to one third of patients did not experience migraine recurrence in 24 hours [62]. The above results led to study the outcome of the same technique on 164 migraineurs with aura using a sham-controlled design; pain freedom at 2 hours was significantly better in the TMS arm; the headache recurrence rate at 1 and 2 days after treatment were better in the TMS arm, however the use of acute analgesics and consistency of response was comparable between groups[63]. Cortical responses from repetitive TMS (rTMS) have been sustained for a longer periods than those produced by single pulse stimulation which found the theory bases for usage of rTMS in chronic pain syndromes such as fibromyalgia and chronic migraine. Dorsolateral prefrontal cortex is believed to affect migrainous pain pathogenesis negatively, which makes a target for rTMS studies. Results of rTMS on chronic migraine are inconsistent, with a sham-controlled study involving a total of 11 patients showed a sustained reduction in attacks frequency, headache index, and acute analgesics use for 2 months [64]. However this positive outcome could not be attained in another sham-controlled trial in 13 patients [65, 66].

NON CLINICAL SAFETY DATA OF TMS ON BRAIN AND NERVES

An animal studies have shown that there is little or no neural injury, [67] no delirious effect on the central nervous system,[68] and no short or long term deficits in higher cerebral function or any other adverse events were reported.[69]

CLINICAL SAFETY DATA OF TMS

There are no short or long term sequelae reported with the use of TMS in normal individuals or those with neurological disorders although few adverse events are described. Discomfort of scalp which is mild to moderate in severity has been reported and it respond to analgesics [70]. Minor adverse effects like dizziness, drowsiness, fatigue, increased nausea, itchy or tingly sensation, increased headache and neck pain have been reported. These adverse events are mild and short lasting. No serious adverse events have been reported [63, 71-74]. One of the tolerability study where subjective response to TMS treatment was evaluated in children. They were asked to complete a questionnaire to rank order their TMS experience with few ordinary life encounters. The children felt TMS was less enjoyable than watching television but more enjoyable than a long car ride [75]. Doses up to 12,960 pulses per day were safe and tolerable in healthy men and showed no effect on sleep [76]. Overall, sTMS or rTMS is regarded as safe and tolerable treatment both in normal and those with neurological disorders provided there are no exclusion criteria such as presence of metal anywhere in the head excluding the mouth, skull defects, intracardiac lines, and cardiac pacemakers [77].

POTENTIAL SAFETY CONCERNS WITH TMS

RISK OF SEIZURE

There is a hypothetical risk of inducing an epileptic

seizure. It can selectively activate the epileptic focus or foci in patients with medically intractable complex partial seizures [78]. Schrader et al reported that crude risk of TMS associated seizure in patients with epilepsy ranged from 0.0%-2.8% for sTMS and 0.0%-3.6% for rTMS. The nature of reported seizures in all cases was similar to each patient's typical seizure. There were no long term sequelae[79]. Those with subcortical lesions did not have seizures 80. Concurrent use of medications that lower the seizure threshold such as tricyclic antidepressants or neuroleptics, has been thought to be a potential risk factor to induce seizure 80. Patients with stroke may have a risk of seizure after the use of TMS [81].

RISKS TO THE ATTACHED OR IMPLANTED ELECTRONIC EQUIPMENT

The risks of sTMS to implanted or attached electronic devices have been studied both empirically and theoretically by Cadwell. In most cases, the effects of the magnetic field on metal objects are minimal. However, TMS is contraindicated in those with cardiac pacemakers and other implanted metallic objects with electrically conductive properties as it can dislodge the objects or induce electrical currents.[82] Study of TMS use in patients with spinal cord stimulator pulse generators implanted in the lower abdomen has been proven safe, both when the device is on and off [83].

Patients with Deep Brain Stimulator (DBS) who received TMS treatment, no damaging stimuli to the brain or damage to the DBS was observed but it was noted that inadvertent administration of TMS directly over the implanted DBS could result in malfunction [84]. In those with Vagus nerve stimulator (VNS) the study has shown that sTMS use does not result in nerve stimulation or damage and the function of pulse generator was unaffected[85].

TMS USE IN PREGNANCY

The evidence of safety of TMS use in pregnant women is limited. There are 2 case reports in which depression was treated in pregnancy with repetitive transcranial magnetic stimulation and there were no adverse effects reported in both mothers and their babies [86, 87]. The Committee on the Possible Effects of Electromagnetic Fields on Biologic Systems, a committee of the National Research Council, reviewed exposure to electric and magnetic fields concluded that extremely low frequency electric or magnetic fields exposure do not affect the reproduction and development in animals especially mammals [88]. It was also concluded that epidemiologic evidence of an association between magnetic fields and pregnancy outcome is not supported 89. The frequency of the sTMS device meets the definition of very low frequency (ie, <100,000 Hz) [55, 59]. Further research studies are necessary to fully assess the safety data in pregnancy. Further clinical data does not show any significant effect of TMS on brain tissue, blood pressure, pulse rate, hypothalamic limbic structures hence no effect on cortisol or prolactin levels, no transient or permanent effect on hearing [91].

FRONTIERS OF NEUROSTIMULATION

Stimulation of the sphenopalatine ganglion, through its important connections to the hypothalamus and the trigeminovascular complex, was found to be effective in aborting around 50% of cluster and migraine attacks in two initial studies [92, 93] with further studies being conducted to verify initial findings. The stimulator is implanted in the pterygopalatine fossa which gets activated by a hand-held controller by putting it on the cheek where the stimulator is located. Following the emergence of TMS, many novel non invasive modalities of neurostimulation are being considered e.g., Cefaly which utilises the supraorbital nerve stimulation for stopping migraine attacks. Another device, GammaCore is currently going through a randomised double-blind controlled trial in Europe on patients with cluster headache both during attack and as preventive treatment. GammaCore works through stimulation of vagus nerve to exert its effect on acute attacks. It utilises the findings from previous retrospective studies in patients with epilepsy who achieved a significant improvement in headaches after having a vagal nerve stimulator implanted for refractory epilepsy [94, 94].

CONCLUSION

The future of primary headache disorders looks promising. The invasive nature and the high cost of DBS and ONS makes it a very last choice for intractable primary headache disorders, the arrival of non-invasive treatment may well change the way we treat headaches. sTMS is currently undergoing appraisal through the National Institute of Clinical Excellence to evaluate its cost effectiveness in treating migraine under the National Health Service and the outcomes are awaited with interest. We are aware of the post-marketing data being collected for sTMS in the UK and the results will indicate its effectiveness and safety in the real life setting. If successful this will open doors for more devices of similar nature, albeit smaller and cheaper to overtake pharmaceutical options.

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