C2 Area Neurostimulation: A Surgical Treatment for Fibromyalgia

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A B S T R A C T

Background. Fibromyalgia (FM), a disorder characterized by diffuse pain, fatigue, and a variety of other symptoms, is thought to derive from dysfunction of the central nervous system. Neuromodulation is a technique to treat pain from a variety of causes, including disorders of the central nervous system (CNS). Occipital nerve stimulation is a neuromodulation technique currently under study to treat various migraine headache disorders. This study examines a technique of neurostimulation that appears to affect the pain and symptoms of FM.

Objective. To evaluate the effect of a new technique of peripheral neurostimulation of the C2 scalp area on pain, fatigue, depression, and quality of life in FM patients.

Methods. In total, 12 patients (nine females and three males; mean age 48 years) who met criteria for FM, and with comorbid headache disorder, were trialed and implanted with this C2 area stimulation technique. Outcome was prospectively studied with standard evaluation tools at baseline, 3 and 6 months post implant.

Results. Visual Analog Scale (VAS) pain levels for FM-related pain decreased significantly at 6 months, and pain-drawing total area and number of areas colored in also decreased dramatically. Chronic fatigue and depression as assessed by the Beck Depression Inventory and Fatigue Impact Scale were markedly improved. Overall quality of life as assessed by the Health Survey Short Form 36 (SF-36) was markedly improved. There were no infectious or technical complications.

Conclusion. C2 area scalp stimulation may diminish pain and related symptoms in patients with FM.

Key Words. Stimulation; Neuromodulation; Fibromyalgia; Pain; Headache

Introduction

Fibromyalgia (FM) is a disorder characterized by widespread chronic musculoskeletal pain, fatigue, and other symptoms including co morbid headache disorders and depression [1,2]. American College of Rheumatology criteria indicate that widespread pain be present for at least 3 months in the axial skeleton and all four body quadrants. Pain must be present to 4 kg pressure digital palpation in at least 11 of 18 paired tender points including the occiput—suboccipitalis insertion, intertransverse spaces of C5-7, upper border of the trapezius, supraspinatus muscle, second conostochondral junction, lateral epicondyle, upper outer quadrant of buttocks, greater trochanter, medial knee fat pads, etc. [2].

Multiple pathophysiological theories have been investigated. Although earlier studies have suggested disorders of muscle, more current literature, based on biopsies [3,4] magnetic resonance spectroscopy [5] and electromyogram studies [6] suggest that FM patients have normal muscle structure and physiology. Although FM patients more frequently meet criteria for affective and anxiety disorders than do rheumatoid arthritis patients or healthy controls, there is evidence that these psychological features in FM represent common correlates of chronic pain syndromes [7,8].
There is evidence that hypothalamic pituitary axis and neurendocrine abnormalities may exist in patients with FM and this is an area of intense investigation [9,10].

There is mounting evidence of abnormal function of the central nervous system among patients with FM. Analysis of both mechanical and heat hyperalgesia in FM patients has suggested a supraspinal central nervous system (CNS) etiology for both [11]. Studies of FM patients utilizing functional brain imaging techniques have demonstrated that FM is characterized by cortical and subcortical augmentation of pain processing [12,13]. Functional magnetic resonance imaging (fMRI) studies have also demonstrated that both the sensory–discriminative and motivational affective components of FM-related pain can be altered by serotonin reuptake inhibitors [12], and that nonselective serotonin plus norepinephrine modulators improve symptoms better than selective serotonin reuptake antagonists [14], suggesting that the autonomic system might be involved in the pathophysiology of FM. Supporting data for the autonomic nervous system dysfunction in FM come from heart rate variability studies: FM is characterized by increased sympathetic and decreased parasympathetic tones [15–17].

Recently, it has been shown that electrical stimulation of the occipital nerves with subcutaneously placed electrodes affects such “centralized” pain syndromes as primary migraine and transformed migraine headache disorders [18,19]. Functional brain imaging of patients treated with this technique shows an effect on regional cerebral blood flow in the dorsal pons, anterior cingulate cortex, cuneus, and left pulvinar [20]. The surgical technique of occipital stimulation implant involves placement of subcutaneous electrodes at the C1 level, roughly even with the tips of the mastoid processes. A wide range of stimulation parameters have been described for the treatment of headaches with this technique [18,19].

We have modified the prior described technique of occipital nerve stimulation for headaches in regard to lead position and optimal stimulation parameters and incidentally discovered it affects not only headache in FM patients, but also bodily pain and affective symptoms related to FM. We present here 12 patients with FM who were treated for comorbid chronic daily headache with peripheral stimulation in the C2 region of the scalp. We prospectively studied headache severity, quality of life, and symptoms related to FM, in particular, diffuse pain, fatigue, and depression. There are no other reports of peripheral nerve stimulation for treatment of diffuse pain, whether or not related to FM. Therefore, this uncontrolled case series may be of interest.

Methods

Twelve patients (nine women and three men; mean age 48 years; range 22–61 years) who met clinical criteria for FM, and suffered comorbid chronic daily headache, with or without migraine, were evaluated for C2 area stimulation to control symptoms of headache. Records were reviewed to ascertain whether the patient had an magnetic resonance imaging (MRI) of the brain within the past 5 years. If not, an MRI of the brain was obtained to rule out intracranial pathology as a cause of the patients headaches. A screening psychological interview was obtained to determine any contraindications for a trial stimulation, and potential future implant.

Baseline information was obtained prior to the C2 area stimulation trial regarding the severity of headache associated pain, severity of diffuse pain related to FM, and associated features of FM such as fatigue, depression, and decreased quality of life. All patients had a successful trial stimulation meaning at least a 50% reduction of headache intensity. These patients were subsequently implanted with a permanent stimulation system.

The study is conducted in accordance to ethical approval obtained by the University Hospital Antwerp Belgium and the Copernicus Institutional Review Board, USA.

Surgical Procedures

Trial Stimulation Lead Placement
Quatrode leads (ANS Medical, Plano, TX) with 4 mm spacing between contacts were used for the trial stimulation period. These were placed bilaterally in the occipital scalp with a percutaneous technique. A 14 gauge Touhy needle was used to place the leads subcutaneously. Initial puncture was made about 2 cm above the inion, and the needle tunneled subcutaneously in the scalp about 4.5 cm such that the tunnel was just above an imaginary line drawn between the top of the ears (Figure 1). The leads were then placed subcutaneously and anchored with sutures. All trials were performed with local anesthesia with sedation in the operating room. Fluoroscopy was not used.
Trial Stimulation Parameters
The contacts were made + – + – on both sides. The pulse width was placed at 50 microseconds for all patients, and the frequency to start the trial was 6 Hz. The minimum stimulation amplitude was set at 5 milliamps and the max at 25.5 milliamps. The patients were instructed to increase the amplitude to the maximum they could tolerate, and to increase as tolerated throughout the day. At night, they were instructed either to turn the unit off to sleep, or to turn it down to a minimum 5 milliamps. If the patient did not have pain relief at the 6 Hz setting after 3 days, they were trials of 12 Hz, 18 Hz, 24 Hz, and 30 Hz, each for about 3 days. The leads were removed in the office after the trial stimulation period which typically lasted 1 to 3 weeks.

Permanent Implant Procedure
All permanent implants were performed under general anesthesia without the use of fluoroscopy. The occipital scalp was shaved of hair. A midline incision in the scalp was made above the inion. A Quatrode lead (ANS Medical) with 4 mm spacing was placed subcutaneously from the midline incision to both the right and left sides aimed at a point about 2 cm above the top of the ear. The lead was tunneled approximately 4.5 cm laterally from the midline incision. The leads were anchored directly to the deep fascia of the scalp with nonabsorbable sutures. The leads were then tunneled in a loop like fashion toward the paracervical area, then back to midline at about C7/T1 vertebral level, and then to the internal pulse generator (IPG) (Genesis, ANS Medical) placed in the buttock area (Figure 2).

Permanent Implant Stimulation Parameters
All patients were placed on a pulse width of 50 microseconds (lowest setting of the IPG). Frequencies were set depending on the preferred frequency during the trial, usually 6 Hz but also 12 Hz, 18 Hz, 24 Hz, and 30 Hz. These frequencies could be changed during the course of therapy to one of the five frequencies listed above if the patient began to lose effectiveness on a previous setting. Amplitude parameters were the same as the trial (5–25.5 milliamps) and the patients instructed to turn the amplitude up to the maximum tolerated during the day and either off or down to no more than 6 milliamps at night. Stimulation was kept on continuously except for some patients who preferred to turn the unit off at night.
Outcome Data
The following data were acquired from each patient prior to their stimulation trial (baseline), at 3 months and 6 months after implant.

Pain Levels
Pain was assessed by separate Visual Analog Scale (VAS) scores for headache pain, and pain elsewhere in the body (diffuse pain). The VAS is a 100-mL line anchored or both ends by the descriptors “No Pain” and “Very Severe Pain.” The patient marks on the line the point they feel represents their perception of pain. A second measure of pain in general was the bodily pain score on the Health Survey Short Form 36 (SF-36).

Diffuse pain was also assessed by pain drawings. The pain drawing allows the patient to visually map out their points of pain on a representative diagram showing both the anterior and posterior views of the human body. The patients are asked to draw in the diagram the area(s) affected. Pain drawings were scored by both the number of painful sites (drawings divided into areas of head, neck, upper extremities, thorax, abdomen, low back, pelvic, genital, lower extremities), and total area. Area was scored by placing a grid over the drawings and counting the number of squares containing any shading. There were a total of 400 possible squares on the grid, and the area was reported as the raw number of squares.

Fatigue
The Fatigue Impact Scale (FIS) is a validated self-report instrument designed to rate the extent to which fatigue affects perceived function over the preceding 1-week time interval [21]. The FIS includes three subscales to assess the impact of fatigue on cognitive functioning (10 items), physical functioning (10 items), and psychosocial functioning (20 items). Each item is rated on a scale of 0 (no problem) to 4 (extreme problem) with a maximum score of 160.

Mood
Mood was assessed with the Beck Depression Inventory-II (BDI-II).

The BDI-II is a 21-question multiple choice self-report inventory that is one of the most widely used instruments for measuring the severity of depression. Validation of the BDI-II has been studied against the Hamilton Psychiatric Rating Scale for depression and the Hamilton Rating Scale for Anxiety [22]. Each item is a list of four statements arranged in increasing severity (0–3) about a particular symptom of depression. Maximum score is 63 with 20–28 considered moderately depressed and above 29 severely depressed.

Quality of Life
The SF-36 is a measure of generic health status in the general population and has been tested and validated extensively [23]. The SF-36 is designed for self-administration. From the 36 items, eight health profiles are derived from summarized scores. All dimensions are independent of each other.

Results
Results showed significant improvement 3 and 6 months after intervention for all obtained data. Preliminary analyses with Kolmogorov-Smirnov’s tests accepted the hypothesis of normality of distribution for all data (P > 0.2). For pre-/post-intervention comparative analyses, paired t-tests were used (α = 0.05).

Pain Levels
VAS scores for headache improved significantly after 3 months, t(11) = 10.754, P < 0.0001, and 6 months, t(11) = 11.898, P < 0.0001, as compared with baseline as well as VASFM scores (3 months, t(11) = 7.427, P < 0.0001; 6 months: t(11) = 9.702, P < 0.0001). Bodily pain scores on SF-36 were significantly improved 3 months post implant, t(11) = 3.901, P < 0.001, and 6 months post implant, t(11) = 3.838, P < 0.05, as compared with baseline. In addition, post-implant scores of the pain drawings were significantly improved at 3 months, t(11) = 6.004, P < 0.0001, and at 6 months, t(11) = 6.843, P < 0.0001, as compared with baseline for the area and for the number of painful sites (3 months: t(11) = 4.195, P < 0.0005; 6 months: t(11) = 3.941, P < 0.001). These scores clearly indicate an improvement in the patient's perceived pain from FM (diffuse pain) (Figure 3).

Fatigue
The total scores on the FIS improved significantly 3 months, t(11) = 6.185, P < 0.0001, and 6 months, t(11) = 6.525, P < 0.0001, post-intervention as compared with pre-intervention.

Mood
Beck Depression Inventory scores improved significantly 3 months, t(11) = 5.131, P < 0.0001, and 6 months post intervention, t(11) = 5.757, P < 0.0001, as compared with baseline scores.
On a subjective level, all patients appeared very happy with the therapy, and reported more vigor in their everyday lives.

**Quality of Life**
All scales on the SF-36 showed a significant improvement at 3 months (Table 1).

**Discussion**
There are numerous pharmacological regimens for FM. As the pain in this condition is most likely central in origin, drugs acting predominantly on peripheral receptors such as nonsteroidal anti-inflammatory drugs might be less effective than centrally acting drugs such as tricyclic and other classes of antidepressants and antiseizure drugs [24]. At present, the best options for medication treatments include certain antidepressants, in particular tricyclics, and a wide variety of anticonvulsants [24]. Many of these drugs act on the serotonin-norepinephrine system. The use of opioids in FM is controversial and has generally been found to have some efficacy in neuropathic pain conditions.

The use of C2 stimulation as described here is a novel therapeutic approach. The magnitude and duration of improvement may represent a direct physiological response to the stimulation; however, placebo effect needs to be explicitly ruled out in subsequent studies. Headache and diffuse pain improvement was about equal indicating a general effect on pain, rather than a regional pain relief of headache only. Furthermore, the results obtained on FM-related pain and symptoms were not expected, as the study was primarily performed to evaluate headache improvement.

The improvements in our patients spanned not only the sensory-discriminative components of
FM-related pain, but also the motivational-affective components such as fatigue, depression, and quality of life measures suggesting that serotonin modulation might be involved in the clinical results [12]. This is worthwhile of further investigation.

As mentioned before, much evidence points to FM being, at least in part, a disorder of central pain processing. Signs, symptoms, and lab results in this disorder suggest dysfunction of the brain in multiple spheres, including supraspinal pain regulation and hypothalamic pituitary regulation [11]. There have been observations suggesting a high rate of FM among patients with whiplash and Chiari I malformation suggesting that certain traumas or disorders of the upper cord or brain may predispose patients to this condition [25,26]. Furthermore, clinical evidence suggests that FM in these patients might actually be due to cervical myelopathy [27], and more specifically of the upper cervical sensory pathways [26].

The mechanism(s) responsible for the observed effect of C2 stimulation on FM-related diffuse pain are still unknown. The technique constitutes a retrograde, high amplitude, low pulse width, low frequency stimulation of terminal axons of the C2 roots. This type of stimulation may exert influence on the lateral spinothalamic pathways, as the largest population of the cells of origin of the spinothalamic pathways (35%) are found at the level of C2-C3 (in the old world monkey) [28]. Interrupting the C1-C2 spinothalamic tract of the myelum is a well-known neurosurgical technique, causing contralateral loss of pain sensation below the level of the lesion [29,30]. Evidence using spinal cord and thalamic stimulation has been presented that C1-C2 spinal neurons (in the primate) mediate an inhibitory effect of visceromotor input on spinothalamic neurons [31]. This suggests not only lesioning, but also electrical stimulation might exert a suppressing effect on the spinothalamic input below the level of the electrical input. We therefore hypothesize the generalized pain suppressive effect of the C2 stimulation herein described mediates its effect via modulation of the lateral spinothalamic cell bodies and nerve fibers of C2.

The procedure described here differs significantly from “occipital nerve stimulation” for migraine headache and occipital neuralgia [18,19]. The latter procedure places the stimulating electrodes in the subcutaneous tissue at the C1 level of the spine, using the intermastoid line as a landmark (Figure 4). In our experience, this position is effective for headache treatment, but appears to have no significant effect on pain elsewhere in the body. The procedure which is the subject of this article places the electrodes well up in the scalp, above the occipital protuberance and in a position which is slightly above an imaginary line drawn from the top of the pinna (of the ears) (Figure 2). In addition, the stimulation parameters to affect pain in regions of the body other than the head in FM patients involve using narrow pulse widths, higher amplitudes, and lower frequencies than that previously described for “occipital stimulation.”

While recognizing the limitations of this small, uncontrolled study, the relief of pain, fatigue, and depression experienced by our patients was quite

Figure 4 Lead placement occipital nerve stimulation vs C2 area scalp stimulation.
dramatic. More study is required to confirm the results and unravel the pathophysiological mechanisms underlying these beneficial clinical results of this small sample of patients. The first author is currently the Primary investigator (PI) on a Food and Drug Administration (FDA)-approved investigational device exemption to study the effect of this implant technique on patients with multi-focal/diffuse pain.

**Conclusion**

Subcutaneous C2 area stimulation may represent a novel approach to treat FM-related symptoms, treating both pain and affective components. Further studies are needed to validate its effect and understand the pathophysiological mechanism involved.

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**References**


