Wireless Subcutaneous Trigeminal Nerve Field Stimulation for Refractory Trigeminal Pain: A Single Center Experience

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ABSTRACT

Introduction: Subcutaneous trigeminal nerve field stimulation (sTNFS) is a neuromodulatory treatment for neuropathic trigeminal pain with the ability to reduce the intensity and frequency of pain attacks. However, hardware issues including lead migration, skin erosion, infection, so-called pocket pain at the site of the implanted neurostimulator are reported. Implantable wireless neurostimulation technology promises not only an even less invasive sTNFS treatment and thinner and more flexible electrodes better suited for facial implants, but also provides further advantages such as lack of an implantable neurostimulator and 3T magnetic resonance imaging compatibility.

Material and Methods: All patients who had received trial stimulation with a partially implantable sTNFS system were analyzed for ICHD-3 (3rd edition of the International Classification of Headache Disorders) diagnosis, success of trial stimulation, pre- and postoperative pain intensity, frequency of attacks, complications, and side-effects of sTNFS.

Results: All patients (N = 3) responded to sTNFS (≥50% pain reduction) during the trial period. According to ICHD-3, N = 2 of the patients were classified with trigeminal neuralgia (TN) with concomitant persistent facial pain and N = 1 patient with multiple sclerosis associated TN. The time of the test period was 44 ± 31.24 days (mean ± SD). The average daily duration of stimulation per patient amounted 2.5 ± 2.2 hours (range 1–5). The pain intensity (defined on a visual analog scale) was reduced by 80% ± 17% (mean ± SD). Reduction or cessation in pain medication was observed in all patients. No surgical complications occurred in the long-term follow-up period of 18.84 ± 6 (mean ± SD) months.

Conclusion: The partially implantable sTNFS device seems to be safe, effective, and reliable. Compared to conventional devices, the equipment is not limited to the length of trial stimulation. Furthermore, the daily stimulation duration was much shorter compared to previous reports.

Keywords: Neuropathic trigeminal pain, peripheral nerve stimulation, refractory pain, subcutaneous nerve stimulation, wireless stimulation

Conflict of Interest: The authors reported no conflict of interest.

INTRODUCTION

Trigeminal neuropathic pain, which is referred to as trigeminal neuralgia (TN) by The International Classification of Headache Disorders (3rd edition), is characterized as “recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli” (1). The terms neuralgia and neuropathic pain are therefore used as equivalent in the following study. Patients describe the pain as shooting or stabbing triggered by innocuous stimuli like talking, face washing, chewing, or brushing teeth on the face or in the oral cavity, thus seriously affecting their daily activities (2). Trigeminal neuropathic pain most frequently involves the distribution of the second or third division of the trigeminal nerve. The medical treatment is challenging in cases when available drugs are not effective anymore or associated with unacceptable side effects. In this case, neurosurgical interventions may be considered, of which decompressive, ablative and neuromodulatory techniques are

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available. Microvascular decompression (MVD) of the trigeminal nerve may be considered as the gold-standard in cases in which a neurovascular conflict is suspected (3). Despite the lack of prospective randomized controlled trials, meta-analyses have shown that MVD is the most effective surgical intervention in classic TN with a 61–80% pain relief five years after MVD (4,5). In contrast, patients suffering from TN with concomitant persistent facial pain (formerly called “atypical TN”) have a significantly lower rate of pain relief (51%) after MVD (6). In elderly patients who cannot be treated with MVD due to contraindications for general anesthesia or lack of neurovascular conflict, percutaneous ablative treatment options such as radiofrequency thermocoagulation of the trigeminal ganglion might be considered. However, these techniques bear the risk of possible permanent side-effects such as hypo- or anesthesia of face and cornea with consecutive risk of corneal ulcers (2,7).

Neuromodulatory therapies, such as epidural spinal cord stimulation (SCS), dorsal root ganglion stimulation, or subcutaneous peripheral nerve field stimulation (sPNFS), are established treatment options for chronic neuropathic and refractory trunk and extremity pain syndromes. In contrast, there is a lack of certified neuromodulatory therapies for refractory trigeminal pain. Deep brain stimulation, stimulation of the primary motor cortex or direct electrical stimulation of the trigeminal ganglion, could achieve long-term pain reduction of 30–50%. But these therapies are complex, invasive, and consequently carry a potential risk for more severe side-effects (8–11). sPNFS is already renowned as a minimally invasive technique for refractory localized pain such as chronic lower back pain. Its use for trigeminal pain as subcutaneous trigeminal nerve field stimulation (sTNFS) has been explored by several study groups. Recently, studies with small cohorts have shown that sTNFS does not only reduce the intensity of pain but also the frequency of painful attacks (2,12). However, these studies also mention drawbacks of the available implants such as: large diameter leads and lead anchors to secure the electrodes as well as lack of magnetic resonance imaging (MRI) compatibility. In addition, so-called “pocket pain” which can occur after implantation of an internal pulse generator (IPG) can present a challenge for neuromodulation therapies (13). To avoid local wound infections and minimize the risk of infections of the implants, the length of the test trial in conventional sTNFS is limited to 7–14 days (14). Furthermore, trial leads are sometimes removed and replaced with new permanent leads, which can make positioning them at the exact same position challenging.

A recently introduced wireless stimulation technology for implantable neuromodulation therapies (Stimwave LLC, Pompano Beach, FL, USA) incorporates a 3T MRI-compatible electrode with an integrated microchip and a receiver which can be activated via transcutaneous energy transfer using a paddle antenna and an extracorporeal neurostimulator. This type of stimulation technology is currently available for SCS, peripheral nerve stimulation, and dorsal ganglion stimulation therapy. The length of the trial phase can be extended up to several weeks (15). Since no IPG is required, perioperative complications, such as wound infections after IPG-replacements, pocket pain, and discomfort, might be reduced (15,16).

Here, we present our experience with the partially implantable sTNFS systems and focus our report on pain reduction, duration of stimulation, complications, possible benefits, and limitations compared to the traditional devices.

MATERIAL AND METHODS

Study Design
This trial was a single-arm, open-label and monocentric prospective feasibility study.

Patient Classification
Classification for our patients was made based on the International Classification of Headache Disorders, 3rd edition (ICHD-3) (17).

Surgical Procedure
In all patients, the leads of wireless sTNFS devices were implanted under local anesthesia. Single-shot antibiotics were administered intravenously and immediately prior to surgery. The electrodes were implanted subcutaneously through a Tuohy needle (2). After insertion of the electrodes, a tonic stimulation was performed intraoperatively to check for paresthesia coverage of the painful area. The anchors are integrated at the proximal end of the electrode and do not have to be attached separately and are accordingly less space-occupying. The implanted electrodes were shortened at the distal end behind the receiver and the distal ends were positioned subcutaneously behind the ear. Thus, tunneling and externalization the electrodes were not needed. Figures 1 and 2 illustrate the wearing of the neurostimulator and the position of the electrodes in wireless sTNFS.

Follow-Up
After surgery, patients were instructed in the use of the patient handheld programmer. The initial test period was 28 days and was prolonged depending on pain reduction. During this period, patients were stimulated with multiple stimulation modi including paresthesia-free stimulation and were questioned by a trained pain nurse about their pain intensity, the length of stimulation each day, and their experience with the partially implantable device. Pain evaluations based on a visual analog scale (VAS) and changes in pain medication after implantation are evaluated for all patients. Information was gathered according to the research proposals approved by the Institutional Review Board at the Medical Faculty Heidelberg.

Data Collection
Data of the pain evaluation, quantity of pain attacks, and the handling and usability of the partially implantable device were collected prospectively. The patients were all diagnosed and treated by neurological specialists according to the guidelines.

Data Analysis
Descriptive statistical analysis was performed with IBM® SPSS® Statistics (released 2020; IBM SPSS Statistics for Mac, Version 27.0, IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics
From 2018 to 2020, \(N = 3\) patients suffering from refractory trigeminal pain associated with considerable neuropathic pain were deemed eligible for sTNFS. All wireless Stimwave® (Stimwave LLC) Freedom-4A leads with the corresponding microreceiver were implanted in the fashion described above. The mean patients’
age was 60 ± 16.8 years (range 47–79) (18). N = 2 patients were female. According to ICHD-3, two patients fulfilled the criteria for an idiopathic TN with concomitant continuous pain (13.1.1.3.2). None of the two patients showed significant abnormalities in cranial MRI. The third patient met the criteria for a TN attributed to multiple sclerosis (13.1.1.2.1). All patients received extensive...
medical treatment with insufficient benefit and high levels of side-effects (Table 2). In $N = 2$ patients, two subcutaneous electrodes were implanted alongside the supraorbital nerve (V1) and the infraorbital nerve (V2). The third patient received implantation of two subcutaneous electrodes along the infraorbital nerve (V2) and mandibular nerve (V3). None of the patients had a relevant neurovascular conflict in high-resolution MRI scans. Therefore, none of the three patients met the requirements for MVD or percutaneous radiofrequency thermocoagulation (involvement of V1) (3). Nerve blocks and behavioral therapy were also implemented in our cohort before neuromodulatory therapy. Patients were given a choice between the fully implantable and the partially implantable sTNFS systems. All patients opted for the partially implantable solution. The demographical data with patient characteristics is listed in Tables 1 and 2.

### Test Trial

Traditional sTNFS test trials aim to determine the potential responders (most commonly defined as reduction in pain rating by 50% or more), which will be eligible for the permanent therapy and IPG implantation. In our department, the maximum duration of such test trials is 14 days to avoid wound infections of the externalized leads. Due to the lack of externalized leads, the partially implantable sTNFS system features fully closed wound without skin penetrations, which in turn enables an extended testing period compared to conventional systems. Average length of the trial was 44 ± 31.24 days (mean ± SD). In the first four weeks of the test trial, $N = 2/3$ patients reported a reduction in pain of less than 50%. Slight pressure pain in the area of the implanted subcutaneous electrodes was reported which resolved during the later follow-up.

### Complications and Handling Issues

No surgical complications occurred with the implantation of the sTNFS device during a mean follow-up of 559 ± 117.8 days (±SD). No device complications occurred in this cohort. None of the three patients experienced any problems with handling, wearing, or charging the neurostimulator during the follow-up.

### DISCUSSION

Overall, the minimally invasive implantation of the partially implanted sTNFS system was feasible and no surgical complications were noticed in this patient cohort. In our collective, TN was...
attributed to multiple sclerosis and idiopathic TN with concomitant continuous pain. It is well-known that these patient populations do not benefit well from MVD therapy (6). These patients were either not included in trials or if they were included, they did have the lower response rates (2,12). Accordingly, there is a treatment deficit in this patient population. In contrast, we could identify two patients suffering from idiopathic TN with concomitant continuous pain as responders after a prolonged test trial. This can illustrate the effectiveness of a prolonged test trial due to closed wound conditions. The delayed response seems to be due to increased pressure sensitivity of the skin in the facial region after tissue repair.

In addition, the test trial period without externalized electrodes and complex wound bandage seems to be more acceptable and comfortable.

In conventional sTNFS therapies, patients were continuously stimulated. Surprisingly, we could show a pain reduction with stimulation 2–3 times a day for one hour, respectively. This is reported in sTNFS for the first time. Small-scale studies have shown similar results with transcutaneous nerve stimulation although the duration of therapy was not specified (19,20).

The implantation of the IPG can lead to the already mentioned pocket pain. In a cohort of N = 554 patients with IPG, pocket pain was reported in 63% (13). By implanting partially implantable sTNFS systems without IPG can avoid these possible complications. Studies showed that 85% of infections in SCS therapy were mainly caused by infections at the site of the IPG (15,16). If this also plays a particular role in sTNFS, infection rate may be reduced by avoiding IPG in sTNFS. The lack of handling issues in a patient population aged 60 and older may indicate that age is not necessarily a contraindication for wireless sTNFS that requires more therapy awareness compared to a fully implantable system.

Main limitations of our study were low number of patients and the small spectrum of etiologies of TN. Data from a larger patient collective with several chronic trigeminal pain syndromes might enable better assessment of the effectiveness of wireless sTNFS. Prospective follow-up studies with larger patient cohorts are necessary to investigate our findings. Because of the rare incidence of the disease and strict indications, these aspects would be best addressed with a multicenter trial.

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Authorship Statement

Drs. Hajiabadi and Ahmadi designed and conducted the study. Dr. Hajiabadi was responsible for patient recruitment, data collection, and data analysis. Dr. Hajiabadi prepared the manuscript draft with important intellectual input from Drs. Ahmadi and Jakobs. All the authors had complete access to the study data. All the authors approved the final manuscript.

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COMMENTS

Peripheral nerve stimulation treatment of craniofacial pain syndromes including trigeminal neuropathy is in its infancy, however, advances in device design and waveforms will help implanters gain needed experience in techniques and outcomes to recommend this treatment option for intractable facial pain conditions.

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This is an interesting feasibility study demonstrating a clinical effect of subcutaneous (field-) stimulation for trigeminal pain in a small number of patients over a reasonable time span of 1 1/2 years. The authors clearly demonstrate the advantages of a wireless system as compared to the fully implanted systems connected to an implantable pulse generator (IPG). Another advantage is the possibility to treat pain in the supraorbital area, which is usually not suitable for lesional procedures. The term testing or trial period however must be redefined, because the required components are all implanted at the first step. Due to the limited number of patients the question remains open whether this treatment is rather an option for permanent neuropathic pain as compared to mainly attack-like pain associated with a minor permanent pain component.

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This is an innovative procedure of the trigeminal pain treatment. Even the method seems to be very new and needs some improvement of the extracorporeal stimulation form. This therapy is a very good option for patients, who avoid the IPG.

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