1.2 kHz High-Frequency Stimulation as a Rescue Therapy in Patients With Chronic Pain Refractory to Conventional Spinal Cord Stimulation

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ABSTRACT

Objectives: We aimed to investigate the efficacy of new subperception stimulation paradigms including 1.2 kHz-high-frequency stimulation (HFS) and advanced-HFS field-shaping algorithm (dorsal horn HFS [DHHFS]) in refractory cases which initially benefited from conventional spinal cord stimulation (SCS) and lost the effect throughout time.

Materials and Methods: In the context of a rescue-therapy, patients underwent externalization of the implanted SCS-leads and were tested with multiple combinations of new SCS paradigms. Pain intensity was analyzed using the numeric rating scale (NRS), and data were collected preoperatively and at multiple postoperative follow-ups.

Results: Thirty-seven patients underwent externalization of the leads. Mean preoperative NRS-score was 8.1/10 points (SD ± 0.9) for the ON-stimulation period. Patients received a combination of either tonic, burst and 1.2 kHz-HFS, or burst and 1.2 kHz-HFS, DHHFS, or 1.2 kHz-HFS and DHHFS, or 1.2 kHz-HFS alone. The mean postoperative NRS-score after the testing-phase was 3.8/10 points (SD ± 2.5), showing a 48.0% mean reduction (p < 0.001). In total, 29 patients reported a significant reduction above 50% in NRS-scores and therefore were reimplanted with new generators that could deliver the new paradigms. Eight patients underwent full SCS-system explantation. The patients who continued with the new paradigms (n = 29) reported mean NRS-scores of 3.5/10 points (SD ± 1.7) 12 months postoperatively, still showing a significant reduction of 43.3% when compared to preoperative scores (p < 0.001).

Conclusion: Rescue-therapy with combination of multiple waveforms, including tonic, burst, 1.2 kHz-HFS, and DHHFS, was associated with a significant pain relief in patients with failed conventional SCS. This approach is a safe and efficient and should be considered before explantation of the SCS-system.

Keywords: Chronic pain, complex regional pain syndrome, failed back surgery syndrome, high-frequency stimulation, neuromodulation, spinal cord stimulation

INTRODUCTION

Spinal cord stimulation (SCS) has shown to be an effective therapy for various chronic pain conditions, improving the quality of life of patients, and reducing medication intake on the long term (1,2). However, to date, the precise mechanism of action of this therapy has not been fully elucidated. In this respect, the pain gate control theory by Melzack and Wall has been suggested as a possible model to explain how SCS functions (3). Following this concept, the goal of SCS would be to deliver an electrical stimulus at the level of the dorsal columns, where large-diameter sensory fibers are located, which will eventually modulate the passage of nociceptive signals to subcortical and cortical areas of the brain (4). Another mechanism that has been proposed involves the activation of the inhibitory descending pathway, which will ultimately modulate the cholinergic system and decrease pain intensity (5). However, how these pathways interact in the context of SCS is still not fully understood.
not completely understood. Nevertheless, since its beginning, the modulation of these fibers, particularly the dorsal columns, through standard (low frequency tonic stimulation, 40–90 Hz) and novel (burst and high-frequency stimulation [HFS] at 10 kHz) SCS has shown to be an efficient method to provide pain relief (6–9). Moreover, long-term data in disorders like complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS), and painful diabetic peripheral neuropathy has shown that patients with this therapy still profit from the effect of SCS after many years (10–12). Nevertheless, the clinical outcome with SCS may not always be satisfactory for all patients. Even patients who initially achieved sufficient pain relief through these SCS paradigms may experience a loss of efficacy over the course of time. In some cases, a novel and more flexible treatment algorithm may be required. Ultimately, SCS systems may be explanted in refractory cases where multiple new programming sessions show unsatisfactory results. In order to cope with the dynamic nature of this disorder, new different waveforms and modalities of neurostimulation are needed, especially systems that could provide a broad option of stimulation waveforms (13). In recent years, SCS systems have been developed that have the capacity to deliver diverse patterns of frequencies, multiple waveforms, customizable field shapes within the same hardware, and to target different neural anatomical targets (14). This flexibility in the programming may avoid the potential explantation of already implanted electrodes in SCS refractory cases, regardless of the hardware was implanted after an anatomical or paresthesia-guided approach.

A recent randomized controlled trial has shown that among these new stimulation algorithms, frequencies of 1 kHz with the appropriate adjustment of pulse-width and amplitude are as effective in pain relief as SCS with higher frequencies (e.g., 10 kHz) (15). These findings may prove to be of crucial importance not only for the longevity of the device, but particularly on the potential reduction of tolerance after SCS, by chronically delivering a smaller charge. Furthermore, another randomized controlled trial showed that subperception SCS under 1.2 kHz was an effective treatment in patients previously implanted with a SCS system under paresthesia stimulation (16). Moreover, patients reported an additive effect with multiple waveforms compared to only one paradigm, regardless of whether the stimulation was with or without paresthesias. Recent technological advances of the hardware allow clinicians not only to deliver new frequencies or to offer multiple waveforms, but also to provide these stimuli through customized field shapes (17,18). These new configurations of the electrical fields allow to target different anatomical structures within the spinal cord. In particular, the use of these customized field shapes to directly reach structures like the dorsal horn may provide new insights for an optimized strategy into SCS mediated pain relief. This novel form of stimulation is based on preclinical computational, electrophysiological, and immunohistochemical findings after the application of subperception SCS (17,18). These novel geometry waveforms are generated after a specific contact configuration that may selectively activate in the depth dorsal roots, afferent terminals over dorsal columns.

This study aims to investigate the efficacy of new stimulation algorithms including 1.2 kHz HFS and dorsal horn high frequency stimulation (DHHFS) in patients who initially benefited from conventional SCS and lost the effect after months/years of stimulation.

### MATERIALS AND METHODS

#### Participants and Pain Assessment

We retrospectively analyzed the records of SCS patients who presented themselves to our department from January 2014 until December 2019, experiencing refractory chronic pain and loss of efficacy of their conventional SCS therapy, and who consented in trying new stimulation paradigms after lead externalization. All these patients underwent externalization of the implanted SCS leads in the context of a rescue-therapy. In all patients, a SCS system with one or multiple epidural electrodes and one generator was previously implanted months or years before the trial. We included patients with hardware from different companies (Nevro, Abbott, Boston Scientific, and Medtronic). In every case, the complete systems had initially been implanted because of a significant pain reduction of at least 50% in the numeric rating scale (NRS) scores during the testing phase. All patients remained postoperatively satisfied with the stimulation and remained like that for months or years. However, all patients developed a loss of efficacy phenomenon at different time points. Loss of efficacy was defined as a complete loss of effect with similar pain scores in stimulation ON and OFF conditions or a reduction of pain scores under 50% during ON periods. In case of loss of efficacy, lead position was verified with x-rays and/or CT-scans. In case of correct lead position, similar to the result of immediate postoperative imaging one day after initial surgery, multiple sessions in the outpatient clinic followed with reprogramming of the stimulation parameters according to the capabilities of each system. If the patients showed no clinical improvement in spite of extended trials with all stimulation options possible with the implanted hardware, the case was considered as a persistent failure to chronic SCS. Each patient was offered the possibility of three options: continue with the previous SCS parameters, have the complete SCS-system explanted, or undergo an invasive trial with new stimulation paradigms (e.g., 1.2 kHz HFS and/or field shaping algorithm [DHHFS]) after the lead externalization. All patients who chose the third option and decided to have a new trial were included in the study. All procedures in this study were approved by the University Hospital of Cologne Ethics Committee, following the principles outlined in the Declaration of Helsinki. All patients signed and gave their informed consent for every procedure included in this study.

#### Surgical Procedures and Pain Assessment

Externalization of the implanted SCS leads was performed under sedation protocol. During the procedure, the implanted electrodes were disconnected from the implantable pulse generator (IPG) and reconnected with an extension cable at the subcutaneous pocket and externalized through the skin at an adequate distance to avoid surgical site infections. The testing phase was initiated at the same day of the surgical procedure. The length of the trial varied according to the clinical response of each patient, with a maximum of 20 days. Criteria for a successful trial and thus reimplantation of a new IPG were the following: a reduction of at least 50% in the NRS scores, as well as a positive response to a temporary withdrawal stimulation test defined as a recurrence of the preoperative pain intensity after the IPG was switched OFF for at least two hours. Antibiotics were administered only in cases where the trial lasted longer than seven days, until the end of the externalization phase. During this externalization phase, multiple waveforms were tested patient either alone (burst, tonic, 1.2 kHz
HFS, and DHHFS) or in combination (tonic, burst, and 1.2 kHz HF stimulation, or burst and 1.2 kHz HFS, or 1.2 kHz HF and DHHFS), until all stimulation options were exhausted. One or two different types of external pulse generators (from different companies) were used for stimulation. Patients who could not be improved with the rescue trial were considered nonresponders and were given the option to get their previous SCS system either reconnected or fully explanted.

Patients were evaluated using the NRS scale from 0 to 10 points to assess their overall level of pain at different time points (0 = no pain, 10 = worst pain). All patients had their pain scores evaluated at baseline (the day before lead externalization procedure) and on a daily-basis during the trial phase period. Patients in the responder group had their pain scores assessed at 1, 3, 6, and 12 months after the new IPG was implanted.

**Statistics**

Data obtained from NRS scores before and after surgery were statistically tested using the IBM® SPSS® Statistics, Version 26 (IBM Corp., Armonk, NY, USA) software. A p value <0.05 was considered as significant. Group differences comparing preoperative pain scores to postoperative scores at different follow-up points were evaluated individually by a Student’s t-test. The same test was applied for comparison between responders and nonresponders before and after the testing phase. Differences between all groups together and the use of multiple waveforms were analyzed by means of an analysis of variance test.

**RESULTS**

**Patients and Clinical Outcome**

In total, 37 patients (18 females, 19 males) with recurrence of refractory pain after chronic SCS stimulation underwent externalization of intraspinal leads. Indication for initial SCS was chronic back and leg pain after FBSS in 26 cases, followed by degenerative back and leg pain, foot pain, posttraumatic back pain, CRPS II, diabetic foot syndrome, pelvic pain syndrome, postsurgical cervical pain, and back pain after tethered cord syndrome. Demographic and clinical data from all patients are presented in Table 1. The mean age of patients was 58.81 years (SD ± 12.16), ranging from 32 to 81 years. Mean duration of stimulation before lead externalization was 2.89 years (SD ± 4.18, from one month to 25 years), with a mean duration of the testing phase of 7.97 days (SD ± 3.42, n = 36). In only one case, no externalization of the electrodes was performed. Instead, upon request of the patient, this patient was immediately reimplemented with the new IPG and tested postoperatively with the new stimulation algorithms at the ward.

NRS score one day before surgery ranged from 6.0 to 9.5 points, with a mean of 8.1 points (SD ± 0.9, n = 37) during stimulation. The postoperative scores at the end of the trial ranged from 0.0 to 8.5 points, with a mean of 3.8 points (SD ± 2.5, n = 37) for the ON stimulation period. Delta improvement in the NRS score at the end of the trial ranged from 0 to 8 points (median of 4.5 points), expressed in percentage from 0.0 to 100% (mean of 48.0%). This analysis showed a significant difference between the preoperative NRS scores for the whole cohort compared to the postoperative scores (p < 0.001). At this point, eight patients reported an improvement under 50% on the NRS scores (mean of 1.4%, p > 0.05), while 29 patients reported an improvement above 50% on the NRS scores (mean of 66.6%, p < 0.001) (Fig. 1). The patients that were considered as nonresponders (n = 8) after testing all possible combinations of waveforms, all underwent full explantation of the SCS-system. Contrarily, the remaining 29 patients who were considered as responders were implanted with new generators that had the capacity to deliver the new algorithms. After the second surgery, all patients were discharged from the hospital. The patients who continued with the new SCS paradigms reported mean NRS scores of 2.7 points (SD ± 1.0, n = 29) one month after the surgery, 3.7 points (SD ± 1.7, n = 29) six months after the surgery, and 3.5 points (SD ± 1.7, n = 29) 12 months after the surgery. At the last follow-up assessment, the delta improvement in the NRS scores still showed a significant reduction of 43.3% when compared to preoperative scores (p < 0.001) (Fig. 2). No statistical differences in pain intensity of responder patients were observed throughout all postoperative follow-up time points (p > 0.05), meaning that the clinical improvement achieved in the early assessments was sustained at the long term.

No correlation was found between age, gender, duration of test trial, duration of previous SCS history, indication for the SCS, and the reported clinical outcome in responders and nonresponders (p > 0.05). No major complications were documented during the follow-up.

**Effect of Stimulation Waveforms**

Before lead externalization, 91% of the cases (n = 37) were stimulated with a single waveform, while 89% (n = 37) reported a better clinical outcome with a combination of multiple waveforms thereafter (Fig. 3a, b). Most patients (responders and nonresponders) were stimulated with tonic waveforms (n = 23), followed by 10 kHz HFS (n = 11), and tonic and burst waveforms combination (n = 3) (Fig. 3c) before externalization of the leads. After the permanent IPG implanta-

No correlation was found between age, gender, duration of test trial, duration of previous SCS history, indication for the SCS, and the reported clinical outcome in responders and nonresponders (p > 0.05). No major complications were documented during the follow-up.
Table 1. Demographic Data of the Cohort.

| Pat. number | Age | Gender | Indication                  | Duration of previous stimulation | Testing days |
|-------------|-----|--------|------------------------------|----------------------------------|--------------|
| 1           | 57  | M      | Back and leg pain—degenerative | 3 years                          | 7            |
| 2           | 32  | M      | Back pain—FBSS               | 1 month                          | 8            |
| 3           | 58  | F      | Back pain—tethered cord syndrome | 25 years                         | NA           |
| 4           | 51  | M      | Back pain—posttraumatic      | 7 years                          | 7            |
| 5           | 55  | M      | Cervical pain—postsurgical   | 1 year                           | 13           |
| 6           | 67  | M      | Back and leg pain—FBSS       | 4 months                         | 6            |
| 7           | 40  | F      | Back pain—degenerative      | 3 years                          | 8            |
| 8           | 59  | M      | Back and leg pain—FBSS       | 8 months                         | 9            |
| 9           | 51  | F      | Back and leg pain—FBSS       | 3 years                          | 5            |
| 10          | 76  | F      | Back and leg pain—FBSS       | 8 years                          | 5            |
| 11          | 45  | F      | CRPS II                      | 9 months                         | 16           |
| 12          | 39  | F      | Back pain—degenerative      | 1 month                          | 13           |
| 13          | 52  | F      | Back and leg pain—FBSS       | 2 years                          | 17           |
| 14          | 38  | F      | Back and leg pain—FBSS       | 2 years                          | 14           |
| 15          | 65  | F      | Back and leg pain—FBSS       | 8 years                          | 9            |
| 16          | 79  | M      | Back and leg pain—FBSS       | 2 years                          | 7            |
| 17          | 75  | M      | Back pain—posttraumatic      | 1 month                          | 6            |
| 18          | 75  | F      | Back pain—FBSS               | 1 year                           | 5            |
| 19          | 61  | F      | Back and leg pain—degenerative | 4 years                         | 6            |
| 20          | 64  | F      | Pelvic pain syndrome         | 4 years                          | 12           |
| 21          | 59  | F      | Back and leg pain—FBSS       | 3 years                          | 5            |
| 22          | 69  | M      | Back and leg pain—FBSS       | 1 year                           | 1            |
| 23          | 53  | F      | Back and leg pain—FBSS       | 2 years                          | 7            |
| 24          | 60  | M      | Back pain—FBSS               | 1 year                           | 7            |
| 25          | 62  | M      | Foot pain                    | 2 years                          | 9            |
| 26          | 57  | F      | Back and leg pain—FBSS       | 3 years                          | 6            |
| 27          | 52  | M      | Back and leg pain—FBSS       | 1 year                           | 10           |
| 28          | 54  | F      | Back and leg pain—FBSS       | 2 years                          | 7            |
| 29          | 52  | F      | Back and leg pain—FBSS       | 1 year                           | 8            |
| 30          | 50  | M      | Foot pain                    | 10 months                        | 7            |
| 31          | 74  | F      | Back pain—degenerative      | 4 years                          | 6            |
| 32          | 58  | M      | Back and leg pain—degenerative | 15 months                        | 6            |
| 33          | 48  | M      | Back pain—degenerative      | 8 months                         | 9            |
| 34          | 75  | M      | Back and leg pain—degenerative | 2 years                         | 5            |
| 35          | 74  | M      | Back pain—FBSS               | 16 months                        | 11           |
| 36          | 59  | M      | Leg and foot pain—diabetic PNP | 4 years                         | 6            |
| 37          | 81  | M      | Back and leg pain—FBSS       | 2 years                          | 4            |

CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; PNP, polyneuropathy.

Figure 1. NRS scores reported before the externalization and at the end of the testing phase in responder (gray bars, n = 29) and nonresponder (white bars, n = 8) patients. ***p < 0.001.

Figure 2. NRS scores obtained before surgery (black bars, n = 37), at the end of trial (white bars, n = 37), and one month (dark gray bars, n = 29), six months (white and black bars, n = 29), and 12 months after surgery (light gray bars, n = 29). *p < 0.05; ***p < 0.001.
Lead placement. Many of these patients have undergone multiple spine operations in the past, and thus have an increased risk of complications with each additional surgery. In particular in cases with implanted leads for many years, where lead replacement is made more difficult due to scarring (19,20).

The loss of efficacy in SCS after initial sustained pain relief has been extensively reported (21,22). This phenomenon is the main reason for SCS systems explantation at the long term, followed by infections (23). Previous studies have reported an explantation rate of up to 23.9% at long-term follow-up (23), being accompanied by high financial costs for patients as well as health-care systems. The most cited explanation for this loss of therapeutics effect is habituation after chronic stimulation (24,25). However, from a pathophysiological perspective, currently there is not enough evidence to support this hypothesis. At present, there is no strategy to avoid this problem of habituation. Our strategy presented in this study is one solution in order to deal with this habituation and its consequent (e.g., financial) problems once it has occurred. Nevertheless, as we have mentioned before, it is important to remark that the majority of patients that undergo SCS still benefit from this therapy on the long term with conventional stimulation paradigms (10–12). On the other hand, there is no long-term data on the most novel stimulation paradigms, like many included in this study. The benefit of these paradigms will still require to be documented after many years of follow-up.

In regard to the waveforms, it is important to mention that the documented stimulation algorithms in our study were the last parameters used by the patients, where they achieved their maximal clinical benefit after several reprogramming sessions, which still delivered an insufficient pain relief. This is relevant in the context that these patients profited initially from various waveforms for a long period of time, until they developed a loss of therapeutics effect. Moreover, we reported that patients described no clinical benefit when they were exposed to these waveforms, except when they were used combined with other waveforms postoperatively. However, these observations still require a standardized double-blinded randomized control trial in order to corroborate them. Our results corroborate previous findings from previous randomized controlled studies (SENZA-RCT and WHISPER-RCT) of chronic pain patients treated with HFS, with 10 kHz and 1.2 kHz, respectively, that were previously implanted for SCS (16,26). Along with these findings, we also observed a significant pain relief in patients that were programmed with multiple waveform options compared to single waveform settings. In the case of the WHISPER trial, the use of high frequencies under 1.2 kHz may prove to be highly relevant, in order to reduce the charging frequency and extend the battery life. Differently to the WHISPER trial (16), we included patients with hardware from different commercial companies that were compatible to the new paradigm settings. As a consequence, we were able to reach a larger cohort of patients. On the other hand, some patients lost the assurance of magnetic resonance imaging compatibility, since the use in parallel of two systems. The most cited explanation for this loss of therapeutic effect is habituation after chronic stimulation (24,25). However, from a pathophysiological perspective, currently there is not enough evidence to support this hypothesis. At present, there is no strategy to avoid this problem of habituation. Our strategy presented in this study is one solution in order to deal with this habituation and its consequent (e.g., financial) problems once it has occurred. Nevertheless, as we have mentioned before, it is important to remark that the majority of patients that undergo SCS still benefit from this therapy on the long term with conventional stimulation paradigms (10–12). On the other hand, there is no long-term data on the most novel stimulation paradigms, like many included in this study. The benefit of these paradigms will still require to be documented after many years of follow-up.

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structures probably involves the activation of the inhibitory descending pathway, in order to eventually reduce, so they may not differ on their mechanism of action (27,28). Further studies are still required to confirm if these findings will be sustained on a longer or even permanent basis.

CONCLUSION

Rescue therapy with combination of multiple waveforms including dorsal column tonic, burst, 1.2 kHz HFS, and DHHFS stimulation was associated with a significant pain reduction in patients with a recurrence of pain after initial beneficial conventional chronic SCS. This approach is safe and efficient and should be considered before explantation of the SCS system.

Authorship Statement

Pablo Andrade, Veerle Visser-Vandewalle, and Georgios Matis were responsible for the conceptualization and design of the study. Pablo Andrade and Petra Heiden were responsible for the methodology and preparing the original draft of the manuscript. Pablo Andrade, Petra Heiden, and Georgios Matis were responsible for the data collection and data analysis. Pablo Andrade, Veerle Visser-Vandewalle, and Georgios Matis were responsible for writing, reviewing, and editing the manuscript. All authors approved the final version of the manuscript.

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COMMENTS

This clinical study could be beneficial for patients who are experiencing refractory chronic pain and loss of efficacy of their conventional spinal cord stimulation therapy.

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This is a nice and interesting paper. Results of the study with the use of this new spinal cord stimulator technology are promising, as it could potentially reduce the incidence of therapy failure.

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