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Clinical Effectiveness of Percutaneous Auricular Vagus Nerve Stimulation in Chronic Back Pain Patients - A Single-Centre Retrospective Analysis

Jozsef Constantin Széles[1], Stefan Kampusch[2,3], Van Hoang Le[2,3], David Philipp Enajat[2], Eugenijus Kaniusas[2,3] and Christoph Neumayer[1]*

[1]Department of General Surgery, Division of Vascular Surgery, Medical University of Vienna, Austria

[2]Institute of Electrodynamics, Microwave and Circuit Engineering, Vienna University of Technology, Austria

[3]SzeleSTIM GmbH, Austria

Abstract

Objectives: Chronic back pain is one of the biggest causes of disability today. The objective of this study was to evaluate the safety and effectiveness of percutaneous auricular Vagus Nerve Stimulation (pVNS) for chronic back pain patients in routine clinical practice.

Methods: Data were retrospectively sourced from a clinical database. Mean reduction in average and maximum pain intensity at three weeks as compared to baseline using Numeric Rating Scale (NRS) pain intensity was assessed. A patient responder was defined as having at least 50% improvement in average NRS pain intensity, assessed at 1-, 3- and 6-weeks, as well as 3 months. In addition, analgesic intake, subjective well-being and number and type of Adverse Events (AEs) were reported.

Results: A total of 148 patients underwent pVNS stimulation and met all inclusion criteria. Average NRS pain intensity significantly decreased from 6.36 ± 2.18 at baseline to 3.25 ± 1.83 ($p<0.001$) at three weeks of treatment. One week into treatment, the responder rate was 32.4%, while reaching a maximum of 58.8% at six weeks of treatment. 60% of patients taking opioid analgesics at baseline were able to decrease or stop their opioid usage. Reported AEs were mild and pVNS was well-tolerated.

Discussion: Our results suggest that pVNS may be a safe and effective adjunct treatment for difficult to treat chronic back pain patients. Given the retrospective nature of this study, further research is warranted to confirm these findings.

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Correspondence:

Jozsef Constantin Széles, Department of General Surgery, Division of Vascular Surgery, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria,

E-mail: jozsef.szeles@meduniwien.ac.at

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Introduction

Chronic pain conditions are by far the biggest cause of disability today [1]. Estimates suggest that every second person in the EU will suffer from back pain at some point in their life. 15% of these patients will be on sick leave for one month or longer because of their condition [2,3]. Besides the personal dimension, this generates costs to the European Union of up to 441 billion Euros each year [4]. For the US, the economic burden is in the range of €468 to €530 billion per year, including both the cost of healthcare and loss of productivity [5].

The current standard of care following international guidelines suggests as first-line therapy the use of acetaminophen and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) [6,7], and under specific conditions short courses of skeletal muscle relaxants or opioid analgesics, in conjunction with non-pharmacological strategies such as multidisciplinary rehabilitation, cognitive-behavioral therapy, or acupuncture. Given the fact that those therapies may often provide only mild symptomatic improvements [6], big efforts are currently put in towards finding adjunct, non-pharmacologic treatment options.

With the recent advances in bioelectronics, growing evidence suggests that neurostimulation of the vagus nerve may be used to modulate nociception and pain perception [8,9]. Vagus nerve stimulation using implantable neurostimulation devices is used for the treatment of refractory epilepsy and major depression [10,11]. Disadvantages of implantable systems are frequent Adverse Events (AEs) due to surgical procedure and stimulation of efferent vagus nerve fibers (e.g., hoarseness,

sore throat, shortness of breath and coughing). Non-invasive or minimally-invasive stimulation techniques can mitigate these disadvantages [12]. Percutaneous auricular Vagus Nerve Stimulation (pVNS) allows for a minimal-invasive electrical stimulation of the auricular branch of the vagus nerve [13]. Several small studies and randomized controlled trials have demonstrated safety and efficacy of pVNS in producing antinociceptive effects for various pain conditions [9]. These conditions include postoperative acute pain, chronic low back pain, or cervical syndrome. Sator-Katzenschlager et al. [14], conducted a randomized control trial in patients with chronic low back pain and found over 70% reduction in pain intensity in those patients receiving auricular electrical stimulation over six weeks as compared to sham. Pain reduction came along with reduced intake of opioid rescue medication (over 95% reduction in intake of tramadol), as well as improved quality of sleep, well-being, and physical activity. All positive effects sustained up to a 12 weeks' follow-up. Similarly, a high trial success rate was observed in patients with chronic cervical pain during a six-week therapy [15]. So far, there are no studies investigating the clinical safety and effectiveness of pVNS in a larger cohort of patients in clinical routine.

This retrospective study aims at evaluating the safety and effectiveness of pVNS in chronic back pain patients that had previously failed first-line therapy, in a real-world clinical setting.

Materials and Methods

Study design and procedures

This was a monocentric, retrospective data analysis study. Data for this study were drawn from medical records of all attending patients who were trialed and/or treated for pain with pVNS at the outpatient clinic for special pain therapy at the Medical University of Vienna, Department of Surgery (Vienna, Austria), from February 2002 to June 2010. Combined, a total of 349 patients underwent treatment with pVNS. The study was approved by the ethics committee at the Medical University of Vienna (1789/2020). All authors had full access to the study data.

Inclusion/Exclusion criteria

Patient data were included in an Intention-To-Treat (ITT) analysis if the patient met the following criteria: (1) Adult patients 18 years of age or older with a history of back pain, meeting the diagnostic criteria listed in ICD-10 M54 (2019); (2) have not had an adequate response to first-line pharmacological therapy with acetaminophen, NSAIDs, and/or opioid analgesics; (3) plausible pain diary documentation, i.e., Numeric Rating Scale (NRS) scorings higher or equal than 0 and smaller or equal 10, maximum > average > minimum NRS scorings; and (4) received at least one pVNS therapy, which included a minimum of two documented visits (baseline and one consecutive therapy visit, with a maximum of 21 days in between the two visits).

Patient data were included in a Per Protocol (PP) analysis if the patient additionally had: (1) At least four documented consecutive visits (baseline and three consecutive therapy visits); and (2) the interval between two visits was between three and eight days.

Stimulation procedure

pVNS was performed using P-STIM (Biegler Medizinelektronik GmbH, Mauerbach, Austria). P-STIM is a single-use miniaturized (Figure 1), battery-powered, percutaneous electrical stimulator with a pre-programmed amplitude (3.8 V), stimulation frequency (1 Hz), pulse width (1 ms), and duty cycle (3 h ON/3 h OFF). The procedure has been described previously in [14,15]. Needles were positioned in the cymba and cavity of concha as well as the crura of antihelix, i.e., regions partly or solely innervated by the auricular vagus nerve [16,17]. Positions were chosen close to local blood vessels, running in parallel or close to targeted nerve fibers [9,18-19]. Each patient received pVNS continuously over a period of four days a week. At each therapy visit, a new device was applied.

Data collection and outcome measures

Standardized data, collected by clinical personnel under supervision of the first author, at baseline and/or at each scheduled therapy visit, were retrieved retrospectively from medical records at the Medical University of Vienna. Baseline data refer to the data collected at the time of patient consent prior to pVNS treatment. These included: patient sex, age at start of the therapy, medical history, presenting pain symptoms, and pain severity on a NRS 11-point scale (from 0 = no pain to 10 = worst imaginable pain; [20]). From the last visit, additional variables were extracted related to number and type of AEs, demand for additional medication (i.e., increased, decreased or unchanged), and change in subjective well-being on a 6-point scale (from 0 = very good to 5 = very bad).

The primary endpoint of the study was the mean reduction in average and maximum NRS pain intensity at three weeks as compared to baseline in the PP analysis. Secondary endpoints were: (1) Percentage of patients achieving different thresholds of pain relief in maximum and average NRS pain intensity compared to baseline [21], i.e., ≥ 30% (moderate), ≥ 50% (substantial), and ≥ 80% (which we defined as extensive improvement), at one week, three weeks, six weeks, and three months; (2) percentage of patients decreasing or not requiring additional analgesic medication as a result of the treatment; (3) change in subjective well-being; and (4) number and type of AEs.

Statistical analysis

Analyses were conducted in both PP group (i.e., patients completing primary endpoint assessment) and ITT group (i.e., patients who were administered the treatment at least once).

For the PP analysis, if a patient visited the outpatient clinic more than once per week, the data from the last visit of that week was taken. All other data from that week were omitted. For the ITT analysis, only the baseline and the last visit of a patient were considered. If a patient visited the outpatient clinic irregularly with a break of more than 21 days between two consecutive visits, only the data up to this point were considered. All the data after the break were omitted. For the ITT analysis, missing data for time points after the last visit of a patient were imputed using last observation carried forward. A decrease of ≥ 50% in average NRS pain intensity was considered significant. Patients reaching this improvement were called responders. Responder analysis was performed for two time points, i.e., after one week and after three months of treatment.

NRS pain intensity is presented as mean ± standard deviation, unless otherwise stated. Comparison between baseline and therapy visits was performed using χ^2-tests and paired t-tests. To compare responders and non-responders, a Welch t-test and χ^2-test were performed. Threshold for significance of statistical comparisons was set to $p<0.05$. Bonferroni correction was used for multiple comparisons. AEs and medication usage were reported descriptively for all patients. Statistical analysis was done using Python 3.7.4 with NumPy 1.18.1 and SciPy 1.4.1.

Table 1: Patient characteristics at baseline.

	ITT group (n=148)	PP group (n=59)
Age (years)	62.9 ± 15.7	64.3 ± 13.9
Number of female/male patients	96/52	39/20
Dorsalgia (ICD-10, M54) (%)	100	100
Radiculopathy (M54.1)	5.4	8.5
Cervicalgia (M54.2)	18.2	16.9
Lumbago with sciatica (M54.4)	36.5	33.9
Low back pain (M54.5)	23.6	22.1
Dorsalgia, unspecified (M54.9)	16.3	18.6
NRS Max ± STD	7.49 ± 1.94	7.42 ± 1.88
NRS Mean ± STD	6.56 ± 2.15	6.40 ± 2.36
NRS Min ± STD	5.52 ± 2.60	5.27 ± 2.88

Data are expressed as n, mean ± STD or n (%). ITT: Intention-to-Treat group; PP: Per Protocol group; NRS: Numeric Rating Scale; STD: Standard Deviation

Results

Patients and baseline statistics

During the study period, a total of 349 patients were treated with pVNS at our institution. Patients presented to the outpatient clinic with a range of chronic pain conditions, including back pain (51%), abdominal pain (4.3%), pain localized to other parts of lower abdomen (3.2%), shoulder pain (3.7%), postoperative pain (3.7%), migraine (2.3%) and other complex pain patterns (31.8%, either different location or not sufficiently documented). Of the total 349 patients, 171 patients were excluded due to not meeting the diagnostic criteria listed in ICD-10 M54 (dorsalgia). From the remaining 178 chronic back pain patients, 30 had to be excluded due to a missing therapy visit within 21 days after the baseline visit. The remaining 148 patients met all inclusion criteria and constituted the ITT population. Of those patients, 59 (39.9%) met the PP criteria. Patient baseline characteristics and demographics are summarized in Table 1.

Patients for the ITT analysis were 62.9 ± 15.7 years of age, 64.9% female. Among these, 36.5% suffered from lumbago with sciatica, 23.6% from low back pain, 18.2% from cervicalgia, 16.3% from unspecified dorsalgia, and 5.4% from radiculopathy. The minimum, average and maximum NRS pain intensity at baseline was 5.52 ± 2.60, 6.56 ± 2.15, and 7.49 ± 1.94, respectively. Baseline characteristics for the PP population were comparable to those of the ITT population (Table 1).

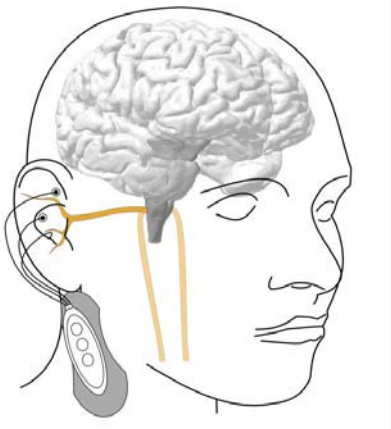

Figure 1: P-STIM® device.

Pain reduction and responder rates

Per protocol (PP) analysis: Maximum and average NRS pain intensity decreased significantly over the first three weeks of treatment in the PP analysis (n=59), as shown in Figure 2. Average NRS pain intensity decreased from 6.36 ± 2.18 at baseline to 4.31 ± 1.70 ($p<0.001$) at one week, to 3.68 ± 2.20 ($p<0.001$) at two weeks, and to 3.25 ± 1.83 ($p<0.001$) at three weeks. Similarly, the maximum NRS pain intensity decreased from 7.42 ± 1.88 at baseline to 6.41 ± 1.99 ($p=0.002$) at one week, 5.25 ± 2.58 ($p<0.001$) at two weeks, and 4.88 ± 2.55 ($p<0.001$) after three weeks.

Intention-to-treat (ITT) analysis: Pain intensity changes from baseline to the last therapy visit of each patient in the ITT analysis (n=148) were analyzed for four separate time points (one week, three weeks, six weeks, and three months), with regards to the percentage of patients experiencing an average and maximum NRS pain intensity reduction of ≥ 30%, ≥ 50% and ≥ 80%, respectively.

As shown in Table 2 and Figure 3, the percentage of patients achieving more than 30% reduction in average NRS pain intensity increased from 51.4% after one week to 70.3% at three weeks and remained relatively constant at six weeks (72.3%) and three months (75.0%). Similarly, 32.4% of all patients in the ITT population exhibited a ≥ 50% improvement of average NRS pain intensity after one week, 49.3% at three weeks and 58.8% at six weeks. The proportion of patients achieving a ≥ 80% improvement in average NRS pain intensity increase slower from 7.4% at one week to 20.3% at six weeks and 25% at three months. The ratio of patients with complete symptom remission increased from 3.4% at one week to 14.2% at three months. In contrast, ratio of patients not improving over the treatment decreases from 31.1% at one week to 11.5% at three months (Figure 2). A similar behavior could be seen for maximum NRS pain intensities, showing a smaller relative reduction from baseline to the last study visit (Table 2).

In this study, responders were defined as patients showing an average NRS pain intensity reduction of at least 50%. When comparing responders with non-responders for one week and six weeks of treatment, significant differences in the baseline NRS pain intensity values of these groups can be found (Table 3). Responders at six weeks had significantly higher minimum NRS pain intensities (6.10 ± 2.45 *vs.* 4.69 ± 2.57, $p=0.014$), average NRS pain intensities (7.06 ± 2.06 *vs.* 5.85 ± 2.07, $p=0.009$), and maximum NRS pain intensities (7.89 ± 1.89 *vs.* 6.92 ± 1.88, $p=0.003$) compared to non-responders. In contrast, this was not the case when comparing baseline values of responders and non-responders at one week of treatment.

Medication and adverse events

Patients were subject to various pharmacological therapies, prior to pVNS treatment, including the use of acetaminophen (4.3% of all reported medication), NSAIDs (48.7%), muscle relaxants (5.1%), anticonvulsants (4.3%), opioid analgesics (18.8%), and others (18.8%). In 45.3% of patients we had detailed reporting on concomitant medication. From these patients, 26.9% were able to discontinue their pain medication, 22.4% reduced intake, 40.3% did not change, and 10.4% increased their medication intake. Opioid analgesics were taken by 29.9% of patients at baseline. 60% of those patients were able to decrease or stop their opioid usage during pVNS treatment.

Subjective well-being was available for 36.5% of patients. On average, subjective well-being improved by 1.89 ± 1.66 points.

In general, reported AEs were mild and pVNS treatment was

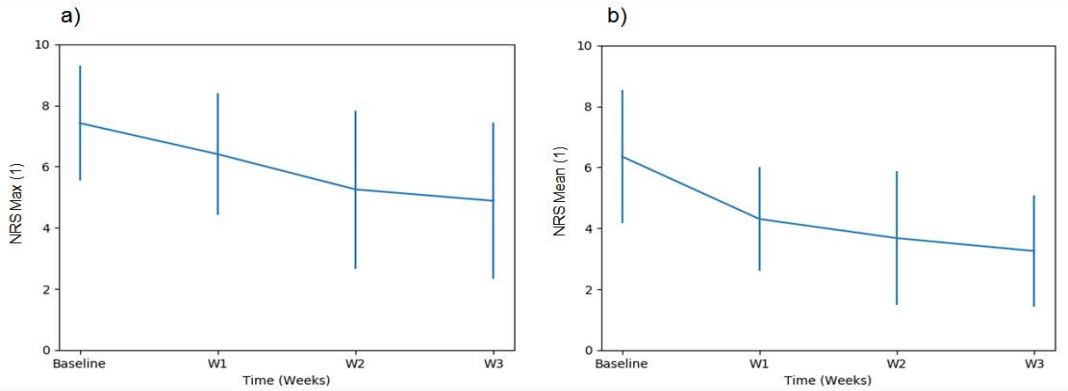

Figure 2: Longitudinal (a) maximum and (b) average NRS pain intensity for chronic back pain patients (n=59) over three weeks of pVNS treatment (mean ± standard deviation).

Table 2: Percentage of patients reaching a 30%, 50%, and 80% improvement in maximum and average NRS pain intensity at timepoints (one week, three weeks, six weeks, and three months) of pVNS treatment.

ITT group (n=148)	1 week	3 weeks	6 weeks	3 months
Max NRS 50% reduction (%)	13.5	32.4	41.2	46.6
Average NRS 50% reduction (%)	32.4	49.3	58.8	58.8
Max NRS 80% reduction (%)	3.4	12.8	14.9	17.6
Average NRS 80% reduction (%)	7.4	18.2	20.3	25
Max NRS 30% reduction (%)	29.7	47.3	55.4	56.1
Average NRS 30% reduction (%)	51.3	70.3	72.3	75

NRS: Numeric rating scale; ITT: Intention-to-Treat group

Table 3: Baseline NRS scores in the responder and non-responder groups (50% reduction in average NRS pain intensity) after 1 week and 6 weeks of pVNS treatment.

ITT group (n = 148)	NRS baseline responders		NRS baseline non-responders	
	1 Week (n=48)	6 Weeks (n=87)	1 Week (n=100)	6 Weeks (n=61)
NRS Max ± STD	7.81 ± 1.86	7.89 ± 1.89	7.33 ± 1.97 (p=1.84)	6.92 ± 1.88 (p=0.033)
NRS Mean ± STD	7.13 ± 1.90	7.06 ± 2.06	6.29 ± 2.21 (p=0.25)	5.85 ± 2.07 (p=0.009)
NRS Min ± STD	6.23 ± 2.29	6.10 ± 2.45	5.18 ± 2.67 (p=0.19)	4.69 ± 2.57 (p=0.014)

NRS: Numeric Rating Scale; STD: Standard Deviation; ITT: Intention-to-Treat group

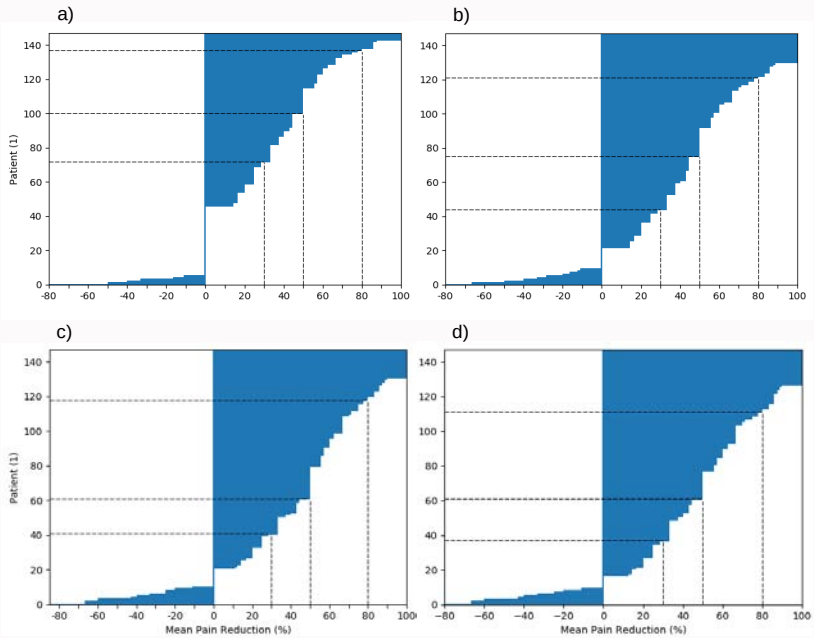

Figure 3: Percentage improvement of patients in average NRS pain intensity at the last therapy visit compared to baseline at (a) one week, (b) three weeks, (c) six weeks, and (d) three months of pVNS treatment. Lines indicate patient populations with improvements of ≥ 30%, ≥ 50%, and ≥ 80%.

well-tolerated. Twenty patients experienced an unwanted device disconnection during therapy requiring re-affixation, fifteen patients did not perceive the stimulation at some point of therapy, four patients developed skin irritations due to device application on the neck, and one patient each experienced decreased quality of sleep, dizziness, headache, and pain at stimulation site in the ear, all mild and transient. Twenty patients reported improved motility, three patients reported improved quality of sleep, and one patient reported reduced anxiety. No unexpected side effects were reported. Six patients discontinued therapy, four patients due to insufficient pain reduction, one due to skin irritations on the neck at device application site, and one due to cost of therapy.

Treatment duration and compliance

From 148 patients, 106 (71.6%) used the device regularly for three weeks, declining to 61 (41.2%) for six weeks, and 28 (18.9%) for three months. Considering the results presented above, with responder rates of roughly 30% at one week, 49% at three weeks, and 59% at six weeks, this indicates moderate compliance with treatment. The duration of therapy for individual patients varied greatly, from 1 day up to 568 days. However, in median each patient had 31 (14-56, 25th to 75th percentile) stimulation days with 8.05 ± 10.01 therapy visits. In addition, the mean interval between two therapy visits was 8.14 ± 3.25 days.

Discussion

This work constitutes the first study to date evaluating clinical safety and effectiveness of pVNS for patients with difficult to treat chronic back pain in a routine clinical setup. In a total of 148 patients we showed that 32.4% of patients experienced at least 50% improvement in average NRS pain intensity immediately after the first week of treatment, while the responder rate reached a maximum of 58.8% at six weeks of treatment. Additionally, several patients reached full symptom remission, decreased their analgesic usage, and increased their subjective well-being. Thus, pVNS may elicit fast and clinically meaningful responses with a low side-effect profile in this group of chronic back pain patients.

Comparison with other studies on pVNS in chronic pain conditions is difficult, because of inhomogeneous trial designs [9]. A reduction in average NRS pain intensity at six weeks of adjuvant pVNS treatment for chronic cervical pain patients could be shown in [15]. Similarly, a high trial success rate with pVNS was observed in patients with chronic low back pain [14], in comparison to traditional manual auricular acupuncture as sham treatment. The present data extends above findings and shows a clinically significant improvement in a rather inhomogeneous clinical cohort over a comparable timespan of several weeks.

Using the IMMPACT's benchmarks for identifying clinically important changes in pain intensity outcome measures [21], the maximum benefit for patients with a ≥ 30% and ≥ 50% response occurred at three or six weeks of therapy, respectively, and thereafter leveled off, which is in line with published data on Spinal Cord Stimulation (SCS; 22,23), but seems to contradict data on the slow accrual of clinical benefits over time reported in VNS studies in epilepsy, chronic migraine and depression [24-26]. Our data might suggest that participants, who do not achieve minimal or substantial improvement within the first six weeks of treatment, are likely to discontinue the pVNS treatment. In contrast, participants who continued treatment may represent self-identified responders for whom the device is effective, whereas a long-term use of pVNS in treatment responders would be fully justifiable (i.e., beyond 3 months or longer). Hence, a six weeks' timeframe might allow a physician to separate responders from non-responders and to decide on more accurate treatment strategies (i.e., continuing or switching the therapy).

The modulation of nociception and pain perception by pVNS is suggested to be highly dependent on the specific electrical stimulation pattern and localization of stimulation [9,13]. In this study, stimulation amplitude was fixed and mostly produced a tingling (but not painful) sensation at the stimulation region. In particular, pVNS targets Aβ-fibers responsible for cutaneous mechanoreception and touch sensation while avoiding activation of Aδ-fibers, which are involved in affective-emotional pain functions [9]. The frequency of stimulation of 1 Hz was used to interfere positively with the bodies' own cardiac rhythm, facilitating stimulation effects. For instance, the positive influence of the timing between pVNS and the respiratory cycle in pain reduction was demonstrated earlier [27-29].

Furthermore, several patients either substantially reduced or completely abolished analgesic intake, whereas some patients even reported that they stopped or cut down their use of opioid analgesics. Similar results have been described in the pVNS literature for opioid analgesics such as tramadol [14,15], remifentanil [36], morphine hydrochloride [30], naproxen and tramadol and morphine [31,32]. In addition, pVNS reduced anesthetic requirements in response to noxious electrical stimulation, as shown in a clinical trial in [33], and reduced analgesic medication intake after abdominal and accident/trauma surgery, as shown by a case series in Szeles et al. [34] and Qureshi et al. [35].

The lack of AEs typically seen with implantable VNS such as hoarseness, sore throat, shortness of breath, and coughing, might be a factor positively influencing patient's compliance, long-term pain control, and an improvement in function in patients who received pVNS therapy. Similar to our study, many studies have shown that pVNS is a safe therapy in treating chronic pain, with AEs being generally minor and transient [14,15,36-39].

Study Limitations

As a retrospective investigation of standard clinical practice, this study has several limitations. Since administration in clinical practice is less rigorous than in clinical trials, documentation of outcomes and data from patient follow-up were sometimes inconsistent. Because pain scores were self-reported and assessed in a non-blinded manner, there is a possibility that positive responses regarding the outcome of pVNS treatment were over-reported or under-reported and as such these results should be interpreted with caution. In addition, some patients had a full set of scores for pain, medication, and subjective well-being, whereas others did not. Both factors resulted in an inhomogeneous data set with a declining patient number throughout follow-up, which could hide a sub-cohort of non-responders, potentially biasing the presented outcome. An alternative explanation may be that, if a patient is doing well, they may not feel the need to attend more therapy sessions. In such scenario, there would be a significant potential for under reporting successful clinical outcomes. Whereas randomized controlled trials unquestionably hold many advantages over retrospective studies, the current study serves the purpose of assessing the clinical effectiveness of pVNS treatment in difficult to treat patients seen in general practice, contributing to previous knowledge.

Conclusion

pVNS treatment led to rapid clinically meaningful pain relieve in patients with chronic back pain that improved with time on treatment. Already after one to six weeks of treatment, substantial reductions in average and maximum pain intensity were observed, along with a decreased need for analgesic medication. Our results suggest that pVNS may be a safe and effective adjunct treatment for difficult to treat chronic back pain patients.

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Conflict of Interest

We have following conflicts of interest to disclose: J.C. Széles, S. Kampusch, E. Kaniusas are shareholders of SzeleSTIM GmbH. S. Kampusch, E. Kaniusas, V.H. Le are employed at SzeleSTIM GmbH. All other authors declare no competing interests.

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Author Contributions

JCS, SK, EK, and CN contributed to conception and design of the study. JCS and SK wrote the first draft of the manuscript. JCS, SK, VHL, and DPE performed data collection. JCS, SK, VHL, DPE, EK, and CN performed data analysis and interpretation. JCS, SK, and VHL performed statistical analysis of the data. All authors contributed to manuscript revision, read and approved the submitted version.

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