ORIGINAL ARTICLE

Subcutaneous Target Stimulation (STS) in Chronic Noncancer Pain: A Nationwide Retrospective Study

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■ **Abstract:** Stimulation of primary afferent neurons offers a new approach for the control of localized chronic pain. We describe the results with a new neurostimulation technique, subcutaneous target stimulation (STS), for the treatment of chronic focal noncancer pain. STS applies permanent electrical stimulation directly at the painful area via a percutaneous-placed subcutaneous lead. We reported the clinical outcomes of 111 patients with focal chronic, noncancer pain treated with STS in this first nationwide, multicenter retrospective analysis. The indications for STS were low back pain ($n = 29$) and failed back surgery syndrome (back pain with leg pain) ($n = 37$), cervical neck pain ($n = 15$), and postherpetic neuralgia ($n = 12$). Pain intensity was measured on a numerical rating scale (NRS) before and after implantation. Data on analgesic medication, stimulation systems, position, and type of leads and complications were obtained from the patients' records. After implantation, the mean pain intensity improved by more than 50% (mean NRS reduction from 8.2 to 4.0) in the entire patient group ($P = 0.0009$). This was accompanied by a sustained reduction in demand for analgesics. In all the patients, the STS leads were positioned directly at the site of maximum pain. Lead dislocation occurred in 14 patients (13%), infections in 7 (6%), and in 6 cases (5%), lead fractures were observed. The retrospective

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data analysis revealed that STS effectively provided pain relief in patients suffering from refractory focal chronic noncancer pain and that STS is an alternative treatment option. Prospective controlled studies are required to confirm these retrospective findings. This article presents a new minimally invasive technique for therapy-resistant focal pain. ■

Key Words: chronic focal pain, neuropathic pain, neuromodulation, subcutaneous target stimulation

INTRODUCTION

Chronic pain refractory to systemic medical therapies has a significant impact on quality of life.[1,2] Such conditions include low back pain (LBP), failed back surgery syndrome (FBSS), typically presenting as radicular pain mixed with focal pain in the paravertebral area,[1] cervical neck pain, tension headache, and postherpetic neuralgia (PHN).

Spinal cord stimulation (SCS) has been successfully used for the treatment of chronic neuropathic pain[1] since 1967, and the development of programmable stimulators and multicontact leads, as well as the refinements in surgical techniques, have made SCS particularly successful for the treatment of FBSS, low back, and cervical pain syndromes.[3–6] FBSS patients commonly suffer from both nonradicular axial LBP and pain in the lower extremities, which is mostly of radicular origin.[7,8] While SCS is particularly successful for radicular pain, it does not appear to be similarly effective for axial LBP mainly because of the technical difficulty of achieving paresthetic coverage of the painful area in the lower back.[9–11] It has been demonstrated in the past that continuous stimulation of peripheral nerves by subcutaneously placed leads can reduce the severity of focal neuropathic pain,[12] and stimulation of primary afferent neurons has widely been used for reduction of chronic pain in the last 42 years.[6]

A new peripheral neurostimulation technique for the treatment of certain chronic pain conditions, the so-called subcutaneous target stimulation (STS), has been described in 2 recently published case series,[13,14] including localized pain in nondermatomal areas. STS delivers permanent electrical stimulation directly at the site of maximum pain via subcutaneously inserted leads. So far, no prospective controlled trials with STS have been published. This retrospective, first nationwide multicenter study from 111 Austrian patients, is the largest series to date.

METHODS

Data Collection and Outcome Measures

Records were analyzed from all patients (119) treated with STS between June 1999 and February 2007 at the 7 sites in Austria that were using STS.

Pain intensity was evaluated by means of a self-reported 11-point (0 to 10) numerical rating scale (NRS). NRS scores were documented prior to STS implantation and every week thereafter for at least 3 months after implantation of the permanent neurostimulation system. During the same period, systemic pain medication was documented before the trial phase and for 3 months after STS implantation. Systemic medication was categorized according to the World Health Organization (WHO) classification as 0 = no oral medication, I = nonopioids, II = weak opioid, and III = strong opioid. Furthermore, the use of antidepressants and anticonvulsants was recorded. The patient records were distributed and collected by clinical staff. Every center had 1 or 2 medical doctors who took care of these implanted patients. One investigator (K.F.) collected the data from the patient records at the 7 participating centers by using a standardized data sheet in compliance with local review board regulations. Data collection was conducted according to accepted ethical principles as defined by International Conference on Harmonization (www.emea.europe.eu) and good clinical practice.

Indications for STS

To be eligible for STS, the patients had to meet the following criteria: prior failure of systemic or less invasive treatments (comprehensive systemic medication alone or in combination with other treatment modalities such as psychological methods, physical rehabilitation, temporary nerve blocks, or additive methods) [15–17] and no indication for further surgery. Prior to an obligatory trial stimulation, the patients had to undergo a thorough multidisciplinary evaluation, including a neurological and psychological assessment. Exclusion criteria for STS are listed in Table 1.

Trial Period

A trial period of 1 to 2 weeks was obligatory before implantation of a permanent neurostimulation system.

During the trial period, the patients who use a pain diary for numerical rating of pain intensity and reporting of changes in physical activity recorded pain relief. The decision for definitive implantation was based on

Table 1. Subcutaneous Target Stimulation: Exclusion Criteria

1. A pathophysiologic contraindication (eg, a chief complaint of mechanical low back pain)
2. Abnormal pain behavior
3. Unresolved psychiatric illness
4. Unresolved issues of secondary gain
5. Another coexisting chronic pain problem or chronic neurologic disease
6. A coexisting condition that would increase procedural risk (eg, sepsis, coagulopathy)
7. Inappropriate use of medication
8. Patients who applied for litigation

patient self-reported pain relief and a minimum of at least 50% pain relief during the trial period.

Implantation Procedure

Before implantation of the permanent leads, all the patients received a single dose antibiotic prophylaxis (cephalosporin or penicillin). The leads were subcutaneously inserted, using a Tuohy needle, with the active electrode contacts (poles) localized in the center of the painful area. It was deemed essential that the area of maximum pain was covered by the paresthesia induced by electrical stimulation.[18] One or 2 leads were implanted. The lead position was routinely documented using fluoroscopy or X-ray imaging.

In majority of the cases, the implanted permanent stimulating systems were from Medtronic neurostimulation systems (Medtronic, Inc., Minneapolis, MN, U.S.A.), and the others were from ANS (ANS, Advanced Neuromodulation Systems, Inc., Plano, TX, U.S.A.). A programming device enabled the patients to adjust the stimulation intensity within ranges defined by the physician. Position and type of leads, the stimulation system and the respective individual stimulation parameters (frequency, pulse width, active poles) were recorded, as were complications.

Statistical Analysis

SPSS 14 (SPSS Inc. 2005, Chicago, IL, U.S.A.) was used for statistical analysis. Continuous variables were described by median and range or by arithmetic means (standard deviation) and were compared between subsequent assessments of the same patients using the sign test. Multiple subgroup testing was corrected by computing Bonferroni–Holm corrected P values.[19] Post-treatment assessments were compared between the groups of patients using analysis of covariance, adjusting for baseline value. Categorical variables were described by frequencies and percentages and compared using McNemar's test. Two-sided P values lower than 5% were considered statistically significant.

RESULTS

Demographics

From 7 Austrian centers, 119 patients (57 female, 48%; 62 men, 52%) were included in the study. A minimum of at least 50% pain relief during the trial period was recorded in 111 patients (53 female, 48%; 58 men, 52%). Mean patient age was 59 years (31 to 87). Median duration of chronic pain was 13 years (3.0 to 31.6), and median number of previous surgeries was 2.7 (1 to 5). The indications for STS could be categorized by using a total of 7 International Classification of Diseases (ICD)-10 Codes[20]: (1) FBSS with predominant LBP and persistent radicular pain equaling or exceeding axial LBP in pain intensity as some patients had evidence of lumbar radiculopathy or root injury, or neurologic deficit or EMG change, (2) local, predominantly axial back pain, (3) cervical neck pain, (4) thoracic back pain, (5) tension-type headache, (6) trigeminal neuralgia, and (7) PHN (Table 2). No patients also have spinal cord stimulators. The respective painful areas are schematically depicted in Figure 1A,B.

Pain Intensity before and after Implantation

Analysis of covariance revealed that neither age, duration of disease nor number of previous surgeries had any significant effect on NRS scores 1 week before and 3 months after STS implantation. Also, no difference in gender could be observed (Figure 2).

The overall mean pain intensity before implantation was 8.2 ± 1.0. After STS implantation, a significant improvement in pain intensity was observed, with a mean reduction of NRS to 4.0 ± 2.1 ($P = 0.0009$) (Figure 3). Pain intensity decreased in 102 (92%) patients. In 9 patients (8%), NRS scores remained unchanged after STS implantation (6 patients with FBSS, 1 patient with thoracic back pain, and 2 patients with cervical pain). Four patients (4%), 3 of whom suffered from FBSS, reported complete pain relief (NRS = 0) following STS.

Significant improvements were observed in each of the diagnostic groups (Table 2, Figure 4).

Average NRS pain intensity in the group of FBSS was 8.0 ± 1.4 before implantation and decreased significantly to 3.3 ± 2.1. The patients with tension headache

Table 2. Diagnostic Classification According to International Classification of Diseases (ICD)-10-Code (WHO)[20] and Average Pain Intensity (Numerical Rating Scale [NRS]) before and after Implantation of Patients Included into the Analysis.

Diagnosis	ICD-10-Code	*N* = 111	Mean (SD) NRS before Implantation	Mean (SD) NRS after Implantation	Corrected *P* Value
Failed back surgery syndrome	M96.1	37	8.0 (1.4)	3.3 (2.1)	<0.0001
Low back pain	M54.5	29	8.3 (0.9)	4.2 (2.2)	<0.0001
Chronic cervical or neck pain	M54.92	15	8.4 (0.9)	4.9 (2.2)	0.0313
Postherpetic neuralgia	B02.2	12	8.2 (1.0)	4.5 (2.7)	0.0059
Tension headache	G44.2	10	8.3 (0.7)	5.4 (1.6)	0.0313
Trigeminal neuralgia	G50.0	4	8.0 (0.0)	3.0 (2.0)	0.7500
Thoracic back pain	R07.4	4	8.8 (1.5)	2.5 (0.6)	0.7500

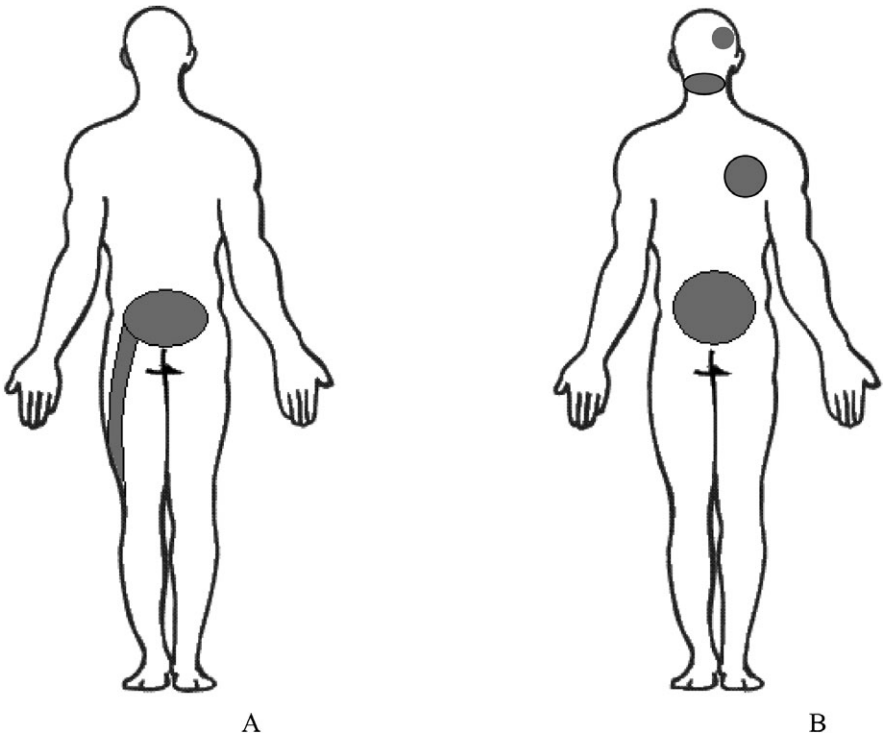

Figure 1. (A) Axial low back pain with radicular leg pain, (B) cervical neck, thoracic back and axial low back pain, tension headache, trigeminal neuralgia or postherpetic neuralgia.

showed the smallest decrease in pain intensity from 8.3 ± 0.7 before implantation to 5.4 ± 1.6 thereafter (Table 3, Figure 4).

Analgesic Medication

Prior to the trial stimulation, 82 (74%) patients chronically used strong opioids (WHO III), 16 (14%) used weak opioids (WHO II), 11 (10%) used only nonopioids (WHO I), and 2 (2%) used no medication at all (Figure 5). After STS implantation, a significant reduction in the use of the respective analgesics occurred (sign test $P < 0.001$) (Figure 5). Fourteen (13%) patients changed from WHO III to WHO II, 6 (5%) needed only WHO I after STS, and 13 (12%) of the patients stopped using any analgesic medication (Figure 5). The reduction in analgesic medication was most pronounced in the patients suffering from FBSS. Sixteen patients from the 37 FBSS patients changed from WHO III to WHO II, and 10 patients from WHO III changed to no medication (<0.001). In the LBP group, 5 patients switched from WHO III to WHO I, and 1 patient ceased to take analgesic medication after STS implantation.

Before implantation, 77 patients (69%) were taking antidepressants. After STS implantation, this number was reduced to18 patients (16%) ($P < 0.001$).

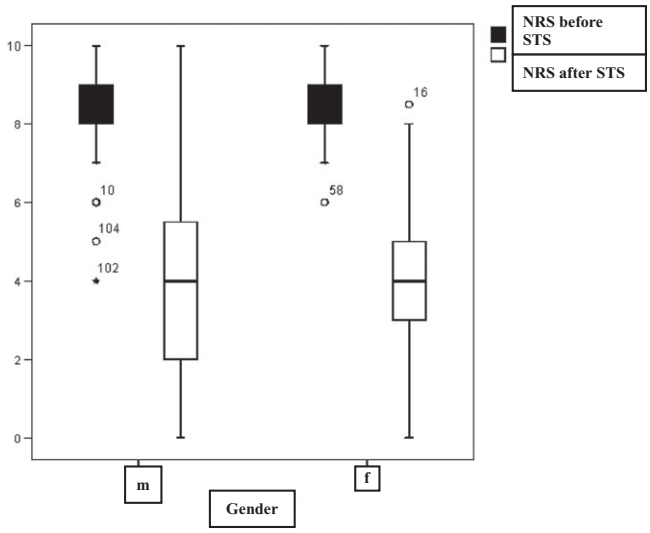

Figure 2. Pain intensity (numerical rating scale [NRS]; 0 = no pain, 10 = unbearable pain) in males and females before and after subcutaneous target stimulation (STS), baseline corrected ($P = 0.82$).

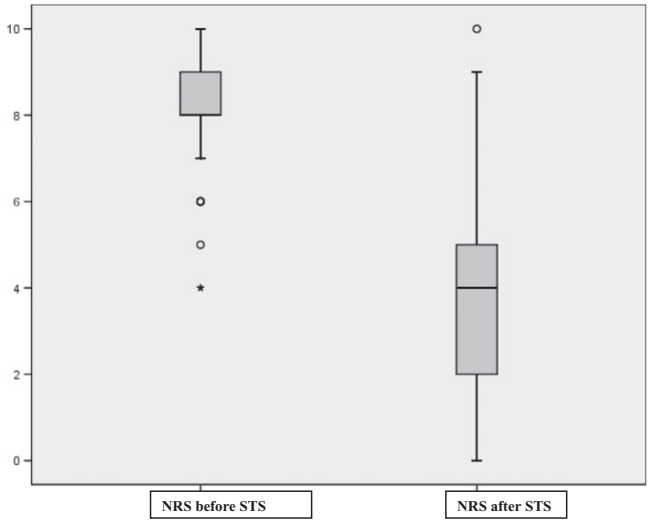

Figure 3. Pain intensity score before and after subcutaneous target stimulation (STS) stimulation for all 111 patients (numerical rating scale [NRS]; 0 = no pain, 10 = unbearable pain) (median; 8 before STS, 4 after STS), percentile 25 (8 before STS, 2 after STS), percentile 75 (9 before STS, 5 after STS). *$P < 0.001$.

Table 3. STS Stimulation Parameters ($N = 111$)

Poles active	Frequency in Hz (*n*)	Pulse Width in μsec (*n*)	Mean Duration of Daily Stimulation in hours per day (*n*)
0–3 + n = 106	30 (14)	120 (7)	24 (20)
2 + 3–n = 5	50 (71)	210 (69)	12 (41)
	100 (26)	340 (7)	10 (29)
		450 (28)	8 (21)

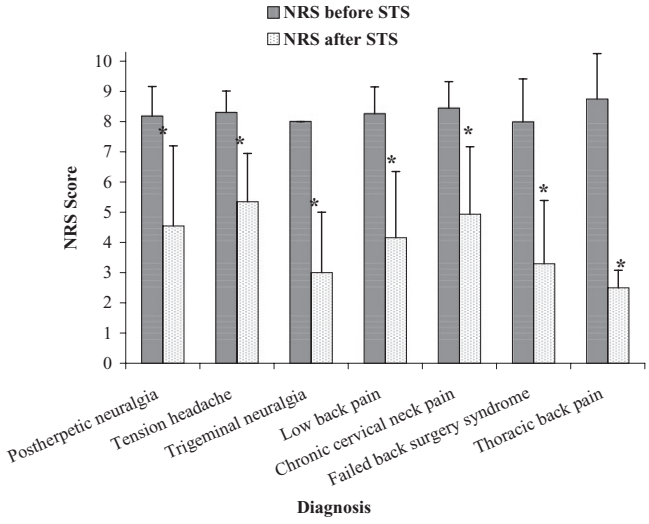

Figure 4. NRS Scores in the different diagnostic categories 1 week before and 3 months after STS (means ± SD). *$P < 0.001$.

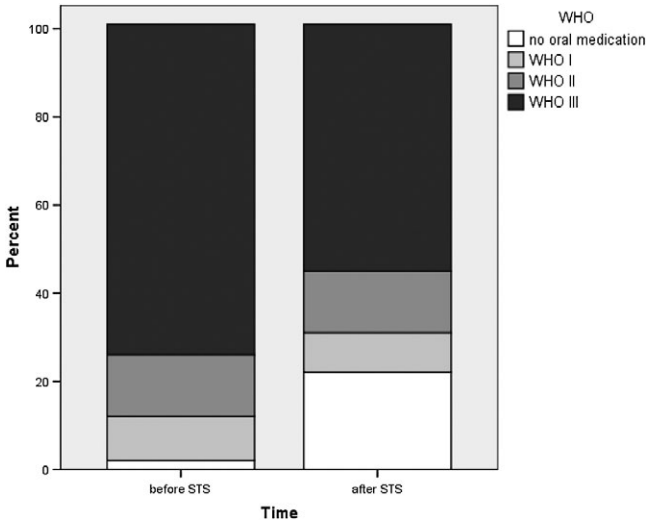

Figure 5. Analgesic medication according to World Health Organization (WHO) 3-step ladder (I to III) before and 3 months after implantation. Percentage of patients; WHO I (nonopioids), WHOII (weak opioids), WHO III (strong opioids).

Before STS stimulation, 75 patients (68%) chronically used anticonvulsants. After implantation, 62 patients (56%) needed no anticonvulsants anymore ($P = 0.023$).

Trial Stimulation

The average duration of the STS trial stimulation was 11.8 days, ranging from 5 to 60 days. Seven-day trial was reported in 13 individuals, 10 days in 42, and 14 days in 29 patients. One patient needed a trial period of 28 days, and 1 patient even of 60 days.

Only the patients with a reduction in pain intensity of ≥50% were permanently implanted.

Forty-three patients (39%) needed only 1 lead, 63 patients received 2 leads (57%), 2 patients needed 3 leads (2%), and 3 patients (3%) 4 leads.

Perioperative Antibiotics

All of the patients received a single dose of intravenous antibiotics preoperatively. Ninety-six patients (86%) received antibiotics during the whole trial phase until after the definitive implantation (6 to 21 days). Twenty patients (18%) received penicillins and 91 patients (82%) received cephalosporins.

Stimulation Systems and Stimulation Parameters

Two types of neurostimulators were implanted for subcutaneous nerve stimulation: conventional battery-driven neurostimulators and rechargeable devices.

Neurostimulation systems (Medtronic, Inc.) were implanted in 106 out of the 111 patients, with 102 patients receiving a Synergy (model 7427), 1 patient a Restore Advanced (Model 37713) and 3 patients a Versitrel (Model 7427V).

In 5 patients, ANS systems (Genesis [Model 3608], Advanced Neuromodulation Systems, Inc.) were implanted. Medtronic devices, Pisces Z Quad (Model 3890), and Pisces Z Quad Plus (Model 3892) leads were used, and the ANS Lead Kit (Model 3183) for ANS systems.

Data on the configuration of stimulation parameters were available from all the patients after implantation and follow-up at 3 months. The most often used frequency was 50 Hz in 71 patients (64%), followed by 100 Hz in 26 (24%) and 30 Hz in 14 (13%) patients. In 97 patients, the pulse widths ranged from 120 to 450 μs. The most frequently used pulse width was 210 μs in 69 (63%) patients, and 450 μs in 28 (25%) patients. Amplitude between 0.5 and 1.0 volts (36, 32%), 2.0 and 2.9 volts (73, 66%), and 3.0 and 3.9 volts (2, 2%) were used. These parameters did not change between the trial period and follow-up at 3 months.

Forty-one patients used their STS for 12 hours per day (h/d), 29 patients (26%) for 10 h/d, 21 (19%) for 8 h/d, and 20 (18%) patients used continuous STS for 24 h/d (stimulation parameters in Table 3).

Placement and Positions of the STS Electrodes

Details of target electrode placement were documented in 99 (89%) patients. The lead positions of all the patients were documented by X-ray imaging (Figure 6).

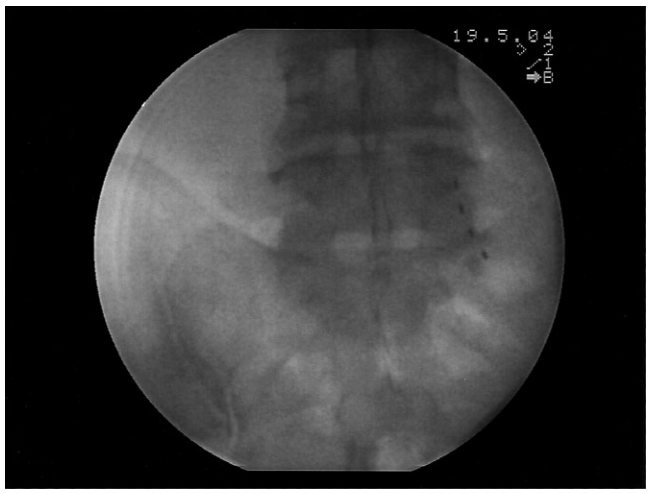

Figure 6. Implanted subcutaneous target stimulation lead, paravertebral in the right low back area.

The electrodes were placed in the low back area in 48 (44%) patients, in the sacral and iliosacral area in 12 patients (11%), in the occipital area in 21 patients (19%), in the thoracic in 11 patients (10%), and in the cervical region in 7 (8%).

One patient lived with the implanted STS since 1999, 2 since 2000, 4 since 2001, 5 since 2002, 6 since 2003, 20 since 2004, 20 since 2005, 21 since 2006 and 32 since 2007 (range 02/1999–07/2007).

Complications

No complications occurred in 84 patients (76%). Complications shortly after the surgical procedure developed in 27 (24%) patients. Infections of the implanted lead or neurostimulator (within the first to second week after implantation) occurred in 7 patients (6%). Fourteen (13%) patients experienced a dislocation of a lead (in 1 week up to 12 weeks after implantation), and 6 patients (5%) had a lead fracture (between 6 weeks and 6 months after implantation).

DISCUSSION

This large case series demonstrated for the first time that STS produces long-lasting and effective pain relief in chronic noncancer pain patients who are otherwise difficult to treat.

In this retrospective, nationwide multicenter study, 111 patients treated with STS experienced an average pain relief of more than 50% during the trial period. Following permanent STS implantation, these improvements were persistent during sustained regular follow-up

evaluations and were accompanied by a significant reduction in analgesic medication after 3 months.

In a multidisciplinary setting, neurostimulation techniques have been shown to contribute to the management of pain difficult to treat by conservative methods only. Currently, the most frequently used neuromodulation techniques include transcutaneous electrical nerve stimulation (TENS), electroacupuncture, peripheral nerve simulation, and SCS.

According to the generally accepted treatment algorithm of benign chronic pain, SCS is indicated when other, more conservative treatment options have failed [9]. Whereas radicular pain can be effectively treated with SCS, pain relief is not always sufficient for local nonsegmental chronic pain of the lumbar, cervical, or thoracic regions.[21,22] Particularly, in patients suffering from FBSS, it is effective for the radicular pain component[7] but often fails to reduce the axial pain. One reason might be that nociceptive pain components with FBSS are not as responsive to SCS as neuropathic pain.[9]

In contrast, the new STS was reported to be effective in more localized, nonsegmental musculoskeletal pain. The implantation of a stimulation lead directly at the site of the peripheral pain proved to be effective and safe. Compared with other invasive techniques for back pain treatment, such as spine surgery or SCS, the STS technique is less invasive[11] and easily reversible. In contrast to SCS, the subcutaneous insertion of the STS leads directly toward painful areas but is a much simpler and safer procedure.[13,14] However, up to now, only 1 small series (3 patients) and 1 review of chronic pelvic pain patients were published on the use of STS in intractable chronic pain.[13,14] STS apparently improves the recruitment of peripheral nerve fibers when compared with the less invasive but also less effective TENS.[2,23] Compared with the more invasive and surgically more demanding technique of peripheral nerve stimulation, the procedural risk of STS is small.

The majority of patients in our case series experienced a significant reduction in pain as well as in their analgesic medication. In only 9 of 111 patients, NRS pain scores remained unchanged after the STS implantation. Perhaps a longer trial period of more than 2 weeks could cover a placebo effect. On the other hand, 4 patients, all suffering from FBSS, reported NRS 0 (ie, they were pain-free) following STS implantation. Interestingly, a complete pain reduction was only observed in the FBSS patients. The patients with FBSS, LBP, and thoracic back pain experienced the greatest pain relief, whereas the patients with tension-type headache gained the least benefit. In all 7 diagnostic categories, STS significantly reduced the patients' systemic analgesic medication. A reduction in analgesic dosage in these chronic pain patients should also reduce adverse effects,[24,25] and by saving costs, even more cost-effectiveness in some patients.

In our patients, the safety of STS technique was demonstrated by the lower complication rates compared with those reported for SCS.[8,26–28] Infection rates, however, were similar to those reported in the literature for peripheral nerve stimulation and SCS; lead dislocation and fractures occurred more rarely.[29,30] Development of more advanced devices and further progress in miniaturization of leads will provide refinement and further simplification as well as increased safety of STS.

The present analysis has, of course, the limitations of a retrospective data collection. Complete follow-up data were not always available for every patient. This means that longitudinal effects could have been masked. Twenty patients lived for 3 years, 20 patients for 2 years, and 21 patients for 1 year with the implanted STS system. Another limitation was the variation in NRS scoring time intervals after implantation, which may have increased the variability in the[30] NRS changes with time. However, our data consistently showed relevant pain relief with STS during a follow-up of 3 months.

Unfortunately, functional and quality-of-life scores were not routinely recorded before and after STS implantation.

In conclusion, STS nevertheless proved to be a promising approach for the management of certain chronic noncancer pain syndromes. Our retrospective, nationwide study has shown the benefits of STS in a highly selected group of patients with chronic, localized, noncancer pain; those who experienced at least a 50% pain reduction in a 1- to 2-week trial period continued to experience this benefit for 3 months. It may be also an effective treatment modality for refractory neuropathic pain syndromes, but further prospective long-term evaluations are required to confirm these observations. Future clinical trials should also investigate the cost-effectiveness of STS vs. long-term systemic medication.[31] However, further prospective long-term evaluation are required to confirm these observations.

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