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Neuromodulation Therapy in Chronic Pain and Clinical Outcomes: A Single-Center Experience

Kronik Ağrıda Nöromodülasyon Tedavileri ve Klinik Sonuçlar: Tek Merkez Deneyimi

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ABSTRACT

Objective: Neuromodulation therapies are successful treatment options for pain raised from a variety of etiologies. Careful patient selection and multidisciplinary evaluation are essential to achieve the best outcome. We aimed to discuss the common indications of neuromodulation therapies, efficacy, and clinical outcomes of patient follow-up to 3 and 6 months.

Methods: Twentytree patients completed the 6-month follow-up: four underwent cervical spinal cord stimulation (SCS), sixteen had thoracic SCS, and three had sacral neuromodulation (SNS). Outcome measures were pain (visual analog scale[VAS]), quality of life (36-Item Short Form Survey [SF-36]), Oswestry Disability Index [ODI]), and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) neuropathic pain scale questionnaire. The overactive bladder assessment form and the pelvic pain impact questionnaire were performed on patients who would undergo SNS.

Results: A significant difference was shown in regards to the scores of the VAS, SF-36 parameters, ODI, and LANSS between admission and the third and sixth-month follow-ups ($p<0.001$). Visual Analog Scale, ODI, and LANSS sixth-month scores were also lower than the third-month scores ($p=0.001$). There were no significant differences between the groups in terms of sex.

Conclusion: Neuromodulation therapies provide short and long-term pain relief and quality-of-life improvements in patients with refractory chronic pain syndromes.

Keywords: Spinal cord stimulation, sacral neurostimulation, failed back surgery syndrome, quality of life

ÖZ

Amaç: Nöromodülasyon terapileri, çeşitli etiyolojilerden kaynaklanan ağrılar için etkili tedavi seçenekleridir. Titiz bir deneme süresi ve multidisipliner değerlendirmeyi içeren dikkatli hasta seçimi esastır. Bu makale, nöromodülasyon terapilerinin ortak endikasyonlarını, etkinliğini ve 3 ile 6 aya kadar olan hasta takiplerinin klinik sonuçlarını tartışmaktadır.

Yöntem: Dört servikal omurilik stimülasyonu (SCS), onaltı torasik SCS ve üç sakral nöromodülasyon (SNS) olmak üzere toplam 23 hastanın 6 aylık klinik takipleri yapıldı. Sonuç ölçütleri ağrı (görsel analog skala [VAS]), yaşam kalitesi (36 Maddelik Kısa Form Anketi [SF-36]), Oswestry Engellilik İndeksi (ODI) ve Leeds Nöropatik Semptomlar ve Belirtiler Değerlendirmesi (LANSS) Nöropatik Ağrı Ölçeği Anketi idi. Aşırı aktif mesane değerlendirme formu ve pelvik ağrı etkisi anketi SNS uygulanacak hastalarda ayrıca değerlendirildi.

Bulgular: Başvuru ile üçüncü ve altıncı ay takipleri arasında SF-36 parametreleri, VAS, ODI ve LANSS puanları açısından anlamlı fark vardı ($p<0,001$). Visual Analog Scale, ODI ve LANSS altıncı ay puanları da üçüncü ay puanlarından daha düşüktü ($p=0,001$). Cinsiyet açısından gruplar arasında anlamlı fark bulunmadı.

Sonuç: Nöromodülasyon tedavileri, dirençli kronik ağrı sendromlu hastalarda kısa ve uzun süreli ağrı kesici etkilidir ve yaşam kalitesinde iyileşme sağlar.

Anahtar sözcükler: Spinal kord stimülasyonu, sakral nörostimülasyon, başarısız bel cerrahisi sendromu, yaşam kalitesi

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INTRODUCTION

Chronic pain is defined as persistent pain lasting more than 3–6 months and impacts all dimensions of health-related quality of life and healthcare expenditures. Neurostimulation therapies in chronic pain have become increasingly popular. They are approved for chronic neuropathic pain disorders of the trunk and extremities, including failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), painful diabetic peripheral neuropathy (DPN), radiculopathy, refractory angina pectoris, and peripheral limb ischemia. The most frequent indications for neuromodulation therapies are post operative chronic low back and radicular pain (grade B recommendation), CRPS (grade B), and peripheral neuropathy pain (grade D) (1,2). Spinal cord stimulation (SCS) involves the application of electrodes to the spinal dorsal columns, which modulate pain signals relayed by ascending pain pathways to the brain. Although its precise mechanisms are complex and not fully understood, the concept derives from the gate control theory, first described by Melzack and Wall (3). In neuropathic pains tates, it is thought to alter the local neurochemistry of the dorsal horns, thereby reducing the hyperexcitability of neurons. There is experimental evidence that GABA and serotonin levels are increased and excitatory amino acid levels are suppressed. The stimulation electrode is implanted, percutaneously or surgically, in the posterior epidural space, in contact with the spinal cord. A trial stimulation phase is mandatory to assess the efficacy of the therapy (pain intensity decrease >40-50%) before connecting the electrode to a subcutaneous stimulator. Formerly, only tonic (50-90 Hertz) continuous stimulation, inducing perceptible paresthesia, has been used. Recently, new stimulation modalities such as burst stimulation, high frequency (>1000 Hertz) stimulation or high intensity stimulation have been proposed to prevent the perception of paresthesia or reduce pain. In our clinic, we prefer the most appropriate type of lead and wave form patterns for neuromodulation according to the clinical condition of the patient (4). The mechanism of action in ischemic pain is thought to involve modulation of the sympathetic nervous system, levels of prostaglandin, and nitric oxide production (2). Sacral neurostimulation (SNS) is an also effective treatment method that can be used in the treatment of chronic pelvic pain resistant to many treatments such as overactive bladder (OAB), chronic urinary retention, interstitial cystitis, fecal incontinence, and chronic constipation. There are many theories regarding the mechanisms of action of SNS; activation of spinal inhibitory pathways through somatic afferent inputs in the S3 root, activation of gate control in the dorsal horn nucleus, inhibition of neurotransmitter pathways such as GABA and adenosine can be counted among these theories. It has also been shown that the SNS increases the somatosensory cortical responses to evoked potentials in the posterior tibial nevre or pudendal nerve (5). Consequently, neuromodulation applications, which can be performed easily with the right indication, are both minimally invasive and effective treatment options. They should be handled with a multidisciplinary approach and a treatment plan should be made. Other advantages of neuromodulation are that it has been well tolerated by patients and has a low adverse effect profile compared with pharmacotherapy (e.g. narcotic analgesics) and other pain therapy modalities (e.g injections and ablations) (6). This article aims to discuss the common indications for neuromodulation therapies, efficacy, and clinical outcomes at 3 and 6 months follow-up of patients after treatment.

MATERIAL and METHODS

Design and Study Population

Ethical approval of the current study was obtained from the Local Ethics Committee (Number: 2021/07-21 Date: 14/04/2021). A total of 23 patients who were treated with neuromodulation therapies were enrolled in the study between January 2020 and January 2021. A flowchart diagram of the 23 patients is summarized in Figure 1. All neuromodulation interventions were administered by the same experienced pain physician. In our clinic, in pre and post treatment follow-up, we routinely use a visual analog scale (VAS) for pain, the Oswestry Disability Questionnaire (ODI), the Short Form-36 (SF-36) questionnaire, and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) neuropathic pain scale to all patients who are planned to undergo neuromodulation treatment. In addition, we use the OAB assessment form and the pelvic pain impact questionnaire (PPIQ) for patients who will undergo SNS. In this study, we evaluated the results of the questionnaires from the medical archive that we routinely used preprocedure, and at the 3rd and 6th month follow-ups, of our patients who underwent neurostimulation therapy between April 2020 and September 2021. Patients who did not have survey data in the medical archive and did not benefit during the trial period were excluded from the study.

Intervention

A typical SCS/SNS device contains four parts: a pulse generator, a lead, an extension cable, and a remote controller to turn the system on/off and to regulate the degree of stimulation. The SCS/SNS implantation usually consists of two stages. Patients who will be treated with SCS/SNS implantation should pass a trial stimulation by using externalized leads to mimic the effects of a real neurostimulator. After a successful trial stimulation, permanent implantation can be performed. The T1-T2 interspinous space was preferred with the paramedian

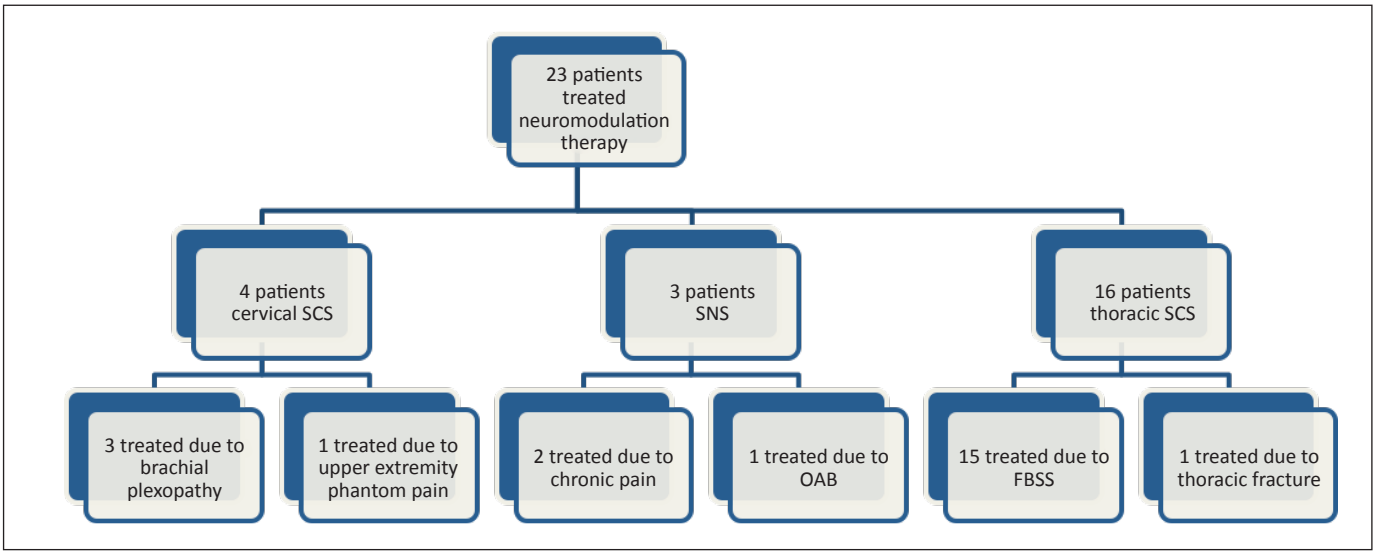

Figure 1. Flowchart diagram of the distribution of the patients who underwent neuromodulation therapy in the study. **SCS:** Spinal cord stimulation, **SNS:** Sacral neurostimulation, **OAB:** Overactive bladder, **FBSS:** Failed back surgery syndrome.

approach for cervical leads. For lumbar applications, T12-L1 was used for patients with prominent low back pain (LBP), and the L1-L2 interspinous space was preferred for patients with prominent leg pain. The lead placement was at the T9-T10 level in patients with LBP and the T10-T11 level in patients with leg pain. All lead placements were fixed after being adjusted to cover at least 70% of the original pain with perioperative sensory stimulation. All sacral leads were placed sacral root through the S3 transforaminal space. Sacral leads were fixed after observing contraction in the anal sphincter and a foot plantar flexion response with stimulation (Figure 2).

Statistical Analysis

The statistical analyses in the current study were performed using the Number Cruncher Statistical Systems version 2007 software package (Kaysville, Utah, USA). Quantitative variables are presented as frequency and percentage. Along with the Shapiro-Wilk test, visual inspection of histograms, normal Q-Q plots, and box plots showed that the majority of the continuous variables, except the age, 3rd and 6th month physical functioning (PF) variables, did not reveal normal distribution. Thus, all the continuous variables were presented as median (minimum-maximum) values and non-parametric tests were applied. The comparison of median values between two and more than two related samples was performed using Wilcoxon's signed-rank test and the Friedman test,respectively ($p<0.05$ was considered statistically significant).

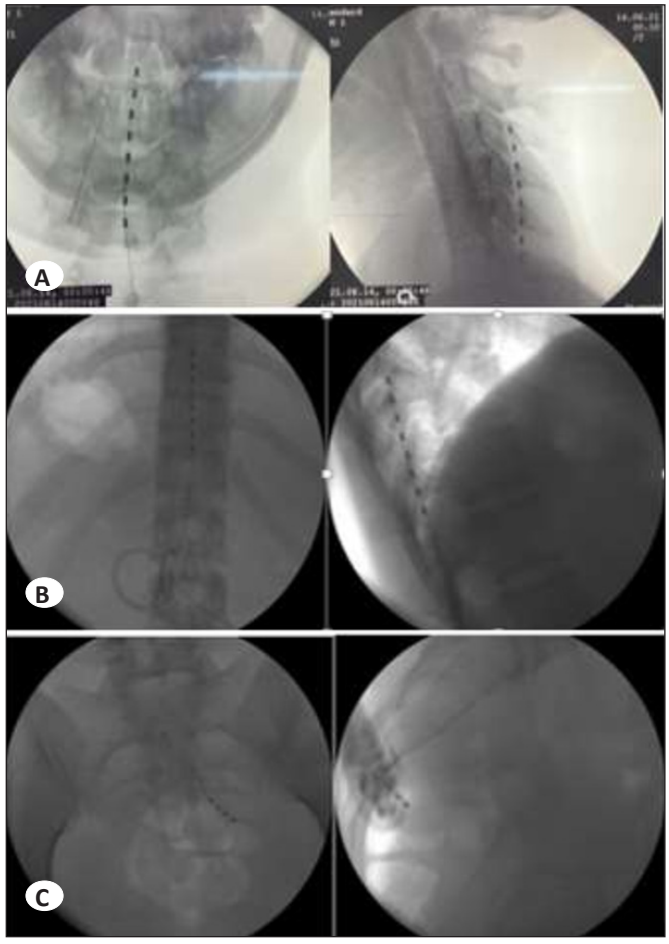

Figure 2. Flouroscopic AP and lateral views. **A)** Cervical, **B)** Thoracic, **C)** Sacral electrodes.

RESULTS

The median age of the cohort was 49 (38-60) years. Fourteen (60.9%) patients were male with 15 (65.2%) patients, FBSS was the most common diagnosis. Other than cervical plexopathy in 3 (13%) patients, there was pelvic pain in 2 (8.7%) patients, phantom pain in 1 (4.3%), thoracic vertebra fracture in 1 (4.3%), and neurogenic bladder in 1 (4.3%) patient. The median duration of the diagnosis at the time of intervention was 7 (4-10) years. The anatomic location of the intervention was thoracic in 16 (69.6%), cervical in 4 (17.4%), and sacral in 3 (13%) patients. The demographic and clinical characteristics of the cohort are presented in Table I.

Table I. The Demographic and Clinical Characteristics of the Cohort

Variables	n (%) – Median (min-max)
Age, *years*	49 (38 – 60)
Male	14 (60.9)
Duration of pain, *years*	7 (4 – 10)
Diagnosis	
Failed back surgery syndrome	15 (65.2)
Brachial plexopathy	3 (13)
Pelvic pain	2 (8.7)
Phantom pain	1 (4.3)
Thoracic vertebra fracture	1 (4.3)
Overactive bladder	1 (4.3)
Anatomic location	
Cervical	4 (17.4)
Thoracic	16 (69.6)
Sacral	3 (13)

The SF-36 parameters of the patients on admission and at the 3rd and 6th month follow-ups after the intervention are revealed in Figure 3. As revealed in Table II, there was a significant difference in regards to the scores of the SF-36 parameters between admission and the 3rd and 6th month follow-ups (p<0.001). This significant difference very likely resulted from the increase of the SF-36 parameter scores in 3rd and 6th month follow-ups, which were confirmed in a further subgroup analysis (Table II).

The median scores of the entire cohort on the LANNS pain scale at admission, and the 3rd and 6th month follow-ups were 19 (16-24), 16 (11-19), and 11 (9-14), respectively. This steady decrease in LANNS pain scores was statistically significant (p<0.001). Although the LANSS pain scores at the 3rd and 6th month follow-ups were statistically lower than the score on admission, the 6th month score was also found to be considerably lower than that of the 3rd month (p<0.001) (Figure 4).

The median ODI score of the 16 patients who received thoracic SCS was 76 (72-82), 32 (30-40), and 30 (26-32) on admission, and the 3rd and 6th month follow-ups, respectively (Figure 5). The gradual decrease of the ODI score was significant (p<0.001). Moreover, the ODI scores at the 3rd and 6th-month follow-ups were considerably lower than that at admission (p<0.001 and p<0.001, respectively), and the 6th month score was also lower than the 3rd month (p=0.001). Among the 3 patients who received SNS, the median PPIQ scores on admission and at the 3rd and 6th month follow-ups were 29 (29-32), 17 (16-18), and 9 (8-10), respectively, the median OAB scores were 8 (7-40), 6 (4-15), and 3 (3-8). Statistical analyses in regards to PPIQ and OAB were not performed because of the limited number of patients.

The median VAS scores on admission, and at the 3rd and 6th-month follow-up were 9 (8-10), 4 (4-6), and 3 (2-4),

Table II. Comparison of the Median SF-36 Parameters of the Patients on Admission, and the 3rd-6th Month Follow-Up

Variable	Admission	3rd month	6th month	p-value[a]	p-value[b] (admission vs. 3rd month)	p-value[b] (admission vs. 6th month)	p value[b] (3rd vs. 6th month)
PF	15 (0 – 60)	70 (50 – 90)	70 (50 – 90)	**<0.001**	**<0.001**	**<0.001**	**0.006**
RP	0 (0)	50 (25 – 100)	75 (50 – 100)	**<0.001**	**<0.001**	**<0.001**	**0.048**
EP	0 (0)	66.7 (33 – 100)	66.7 (67 – 100)	**<0.001**	**<0.001**	**<0.001**	**0.003**
E/F	30 (0 – 40)	45 (40 – 60)	55 (40 – 65)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
EWB	25 (16 – 36)	52 (48 – 68)	60 (52 – 76)	**<0.001**	**<0.001**	**<0.001**	**0.003**
SF	25 (0 – 38)	62.5 (50 – 75)	62.5 (63 – 88)	**<0.001**	**<0.001**	**<0.001**	**0.007**
PAIN	22.5 (0 – 55)	67.5 (45 – 78)	90 (68 – 90)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
GH	25 (15 – 30)	55 (45 – 60)	60 (55 – 75)	**<0.001**	**<0.001**	**<0.001**	**<0.001**

E/F: Energy/fatigue, **EP:** Emotional problems, **EWB:** Emotional well-being, **GH:** General health, **PAIN:** Pain, **PF:** Physical functioning, **RP:** Physical health, **SF:** Social functioning. Note that; [a]indicates Friedman test result and [b] indicates Wilcoxon signed-ranked test.

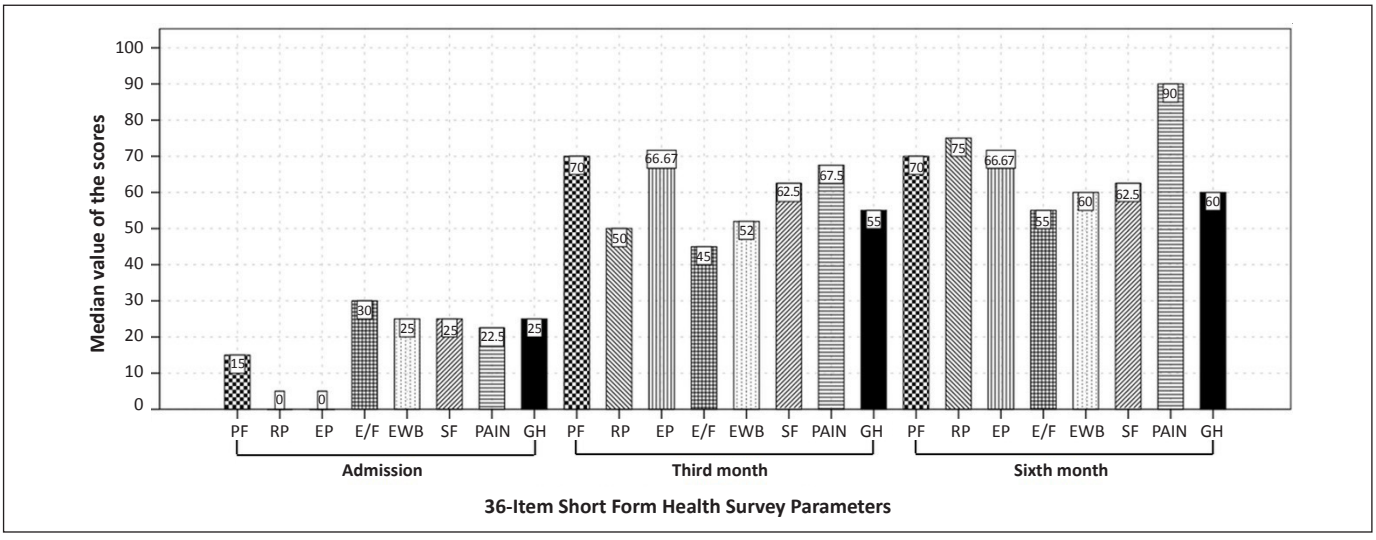

Figure 3. 36-Item Short-Form Health Survey (SF-36) parameters of the cohort on admission and the 3rd and 6th month follow-ups.

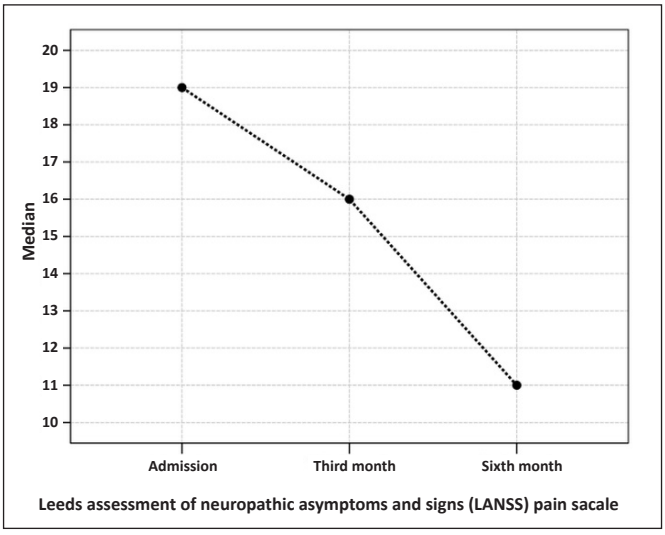

Figure 4. The LANNS pain scale on admission, on the 3rd and 6th month follow-ups. **LANNS:** Leeds assessment of neuropathic symptoms and signs.

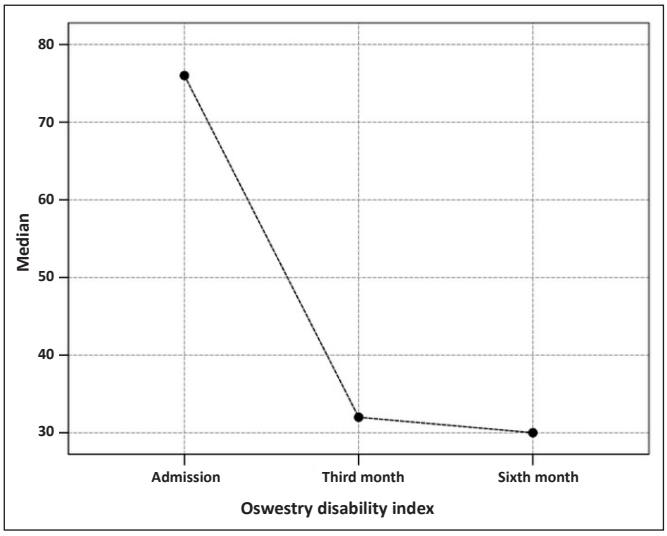

Figure 5. The Oswestry disability index of the cohort on admission, and the 3rd and 6th month follow-ups.

respectively (Figure 6), and there was a significant difference among them (p<0.001). In subgroup analysis, the difference between the VAS scores of the 3rd and 6th months were significantly lower than the score on admission (p<0.001 and p<0.001, respectively), and the score at the 6th month was also lower than that of the 3rd month (p<0.001).

The statistical comparison results based on sex are presented in Table III. Except for the energy/fatigue (E/F) and the emotional well-being (EWB) scores at the 3rd month, where the E/F score was significantly higher in females (p=0.011) and the EWB score was higher in males (p=0.004), none of the 36-SF parameters showed a significant difference between males and females.

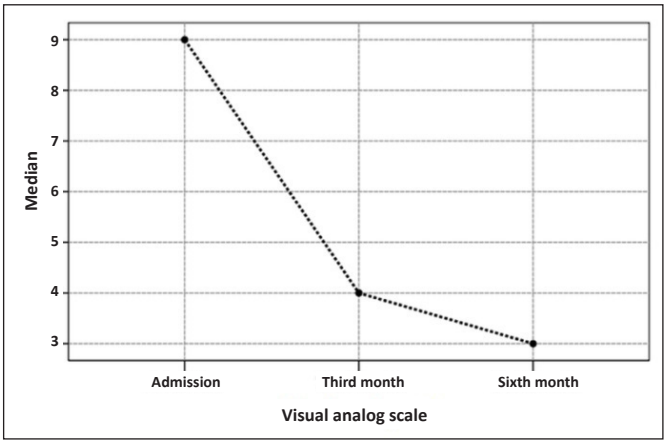

Figure 6. The visual analogue scale of the cohort on the admission, the 3rd and 6th month follow-ups.

DISCUSSION

Neuromodulation therapies are an expanding field of pain medicine. The most frequent indications remain as FBSS, CRPS, and peripheral neuropathy. Similar to the literature, FBSS was the most common diagnosis in our study. In a recent study from French, SCS has been suggested as a third-line treatment for chronic neuropathic pain after the failure of first line drugs such as gabapentinoids and antidepressants (7). The efficacy of SCS has been reported in several randomized controlled trials (RCT). There is low-to-moderate quality evidence that SCS is superior to resurgery or conventional

Table III. Further Subgroup Analysis Results Between Males and Females

	Gender		
Variables	**Male (n= 14)**	**Female (n= 9)**	**p-value[c]**
Age, *years*	49 (38 – 60)	49 (38 – 54)	0.877
Duration of pain, *years*	6.5 (5 – 10)	8 (4 – 10)	0.477
PF, admission	15 (0 – 50)	10 (0 – 60)	0.516
RP, admission	0 (0 – 0)	0 (0 – 0)	0.999
EP, admission	0 (0 – 0)	0 (0 – 0)	0.999
E/F, admission	30 (0 – 35)	30 (13 – 40)	0.688
EWB, admission	26.5 (16 – 36)	24 (20 – 36)	0.516
SF, admission	25 (0 – 38)	25 (13 – 38)	0.600
PAIN, admission	22.5 (0 – 55)	22.5 (13 – 45)	0.975
GH, admission	25 (15 – 25)	25 (15 – 30)	0.781
PF, 3rd month	70 (50 – 90)	65 (55 – 90)	0.557
RP, 3rd month	50 (25 – 100)	50 (25 – 100)	0.403
EP, 3rd month	66.7 (33-100)	66.7 (33 – 67)	0.734
E/F, 3rd month	40 (40 – 50)	50 (45 – 60)	**0.011**
EWB, 3rd month	60 (52 – 68)	52 (48 – 60)	**0.004**
SF, 3rd month	56.2 (50 – 75)	62.5 (50 – 75)	0.643
Pain, 3rd month	66.3 (55 – 78)	67.5 (45 – 78)	0.999
GH, 3rd month	55 (45 – 60)	55 (50 – 60)	0.516
PF, 6th month	72.5 (50 – 85)	70 (65 – 90)	0.877
RP, 6th month	75 (50 – 100)	75 (50 – 100)	0.643
EP, 6th month	83.3 (67- 100)	66.7 (67 – 100)	0.829
E/F, 6th month	55 (40 – 65)	55 (50 – 60)	0.477
EWB, 6th month	64 (52 – 76)	60 (52 – 76)	0.600
SF, 6th month	62.5 (63 – 88)	62.5 (63 – 88)	0.643
PAIN, 6th month	90 (68 – 90)	77.5 (68 – 90)	0.369
GH, 6th month	62.5 (55-70)	60 (55 – 75)	0.829
VAS, admission	9 (8 – 10)	9 (8 – 10)	0.477
VAS, 3rd month	4.5 (4 – 5)	4 (4 – 6)	0.999
VAS, 6th month	3 (2 – 4)	3 (2 – 3)	0.999
ODI, admission	78 (72 – 80)	76 (72 – 82)	0.408
ODI, 3rd month	32 (30 – 36)	32 (30 – 40)	0.408
ODI, 6th month	30 (26 – 32)	30 (26 – 32)	0.536
LANNS, admission	19 (16 – 24)	19 (16 – 19)	0.072
LANNS, 3rd month	16 (13 – 19)	16 (11 – 16)	0.877
LANNS, 6th month	11 (9 – 14)	11 (9 – 14)	0.781

E/F: Energy/fatigue, **EP:** Emotional problems, **EWB:** Emotional well-being, **GH:** General health, **PF:** Physical functioning, **RP:** Physical health, **SF:** Social functioning, **LANNS:** Leeds assessment of neuropathic symptoms. Note that [c]indicates the Mann-Whitney U test.

medical therapy for FBSS. And there are conflicting results about the superiority of classic tonic SCS over different SCS modalities (8). It has been reported that SCS is most effective in 62% of patients with FBSS who have intense neuropathic pain in the lower extremities (9,10). Heteren et al. showed that peripheral nerve field stimulation (PNFS) in addition to SCS provided parallel long term pain relief and quality of life improvement in patients with FBSS with chronic back and leg pain. Therefore, they recommend adding PNFS in patients with refractory LBP who do not respondto SCS alone (11). We did not divide our patients with FBSS into subgroups, but all of them had both LBP and leg pain. We observed significant improvement in pain, quality of life assessment, and ODI scores in all of our 16 patients with FBSS at 3rd and 6th month follow-up. In an international multicenter RCT, the addition of a multicolumn SCS leads to optimal medical management (OMM) that provides statistically significant improvements in pain relief, quality of life, and function compared with OMM alone in FBSS patients with predominant LBP (12). All of our patients with FBSS were unresponsive to optimal medical and conservative treatment, thus SCS was performed. After SCS, the dose of narcotic analgesics and gabapentinoids decreased in each patient. Regarding cervical SCS, in a review, it is suggested that using the cervical SCS was an effective modality of pain that satisfied and improved the quality of life of most patients. The authors commented the use of SCS could reduce the high cost of medical expenses, as well as increase the productivity of patients(13). In a SCS study of 100 patients treated with cervical or cervicomedullary spinal cord stimulation, SCS was found as an effective treatment option for neuropathic pain that is not adequately controlled by analgesics and may contribute more significant relief along the upper extremities than axially. We found similar results with cervical SCS performed on patients with plexopathy. The clinical outcomes of our one phantom limb pain patient are consistent with the literature showing that SCS is a good treatment modality in phantom limb pain which was not relieved by pharmacological treatment alone (14). Besides these effects of SCS, a recent study demonstrated that shortterm pain improvement induced by sham stimulation was safe and efficacious and provided relief along the upper extremities (15). Considering the effect of SCS on phantom pain (phantom pain is a form of chronicpainthat can be seenwith a rate of 38%), it should be considered that the placebo effect of SCS is not negligible (16). Sacral neurostimulation therapy has become a minimally invasive treatment option for refractory OAB, non-obstructive urinary retention, and fecal incontinence, with more than 300,000 implants worldwide (6). Considering the rate of continuation of OAB medical treatment after SNS application, it was determined that more than 80% of patients who underwent SNS did not need medical treatment and continued with SNS treatment only. Accordingly, SNS emerges as an effective treatment method for patients who can not tolerate medical treatment or who have drug adverse effects in resistant OAB (17). All three of our patients who underwent SNS benefited significantly from the treatment, in line with the literature. Spinal cord stimulation applied to the dorsal column may have neuromodulatory effects at cortical levels, but the mechanism is very complex to understand. In a review of animal and human studies, central hypersensitivity was explained as an exaggerated response in the presence of minimal nociceptive input from minimally damaged tissues, with a common peripheral and supraspinal mechanisms (18). Long term potentiation (LTP) and long term depression (LTD) in the spinal dorsal horn induce synaptic plasticity and central responsiveness in chronic pain. Tetanic high frequency stimulation usually induces LTP. However, primary afferent nerves usually characterize low frequency, rhythmic burst discharges in painful situations. In a study investigating how theta burst stimulation (TBS) of primary afferents affect plasticity and nociception in mice, the authors commented that TBS-induced LTP at primary afferent-dorsal neuron synapses was an suitable cellular model for understanding chronic pain mechanism (19). A recent functional magnetic resonance imaging (fMRI) study using a peripheral neuropathic pain model in rats showed that the higher centers of the pain perception system were modulated by the SCS by interactions in multiple pain pathways (20). Spinal cord stimulation-stimulated brain areas reverse the lowered mechanical threshold due to nerve damage but improve the cognitive motivational aspects of pain (20). Similarly, an assessment of cortical function using fMRI showed decreased cortical communication between the somatosensory cortex and limbic areas using SCS in patients with peripheral neuropathic pain (e.g CRPS) (21). The limitations of our study can be listed as being retrospective, single-centered, and therefore the relatively small number of cases.

CONCLUSION

Neuromodulation therapy appears to be a minimally invasive and costeffective treatment, effective on pain, neuropathic pain, and quality of life, with no adverse effects. In the results of our study, it was determined that quality of life, pain, and neuropathic pain parameters improved significantly at the 6th month follow-ups compared with the 3rd month. It may be considered that neuromodulation treatments are more effective in the long term and may be due to their effect on central sensitization. Therefore, future studies are needed to evaluate the longterm effectiveness of all neuromodulation modalities and investigate the specific cortical areas which are activated with SCS.

AUTHOR CONTRIBUTIONS

Conception or design of the work: DG, CE

Data collection: DG, OY, BOH

Data analysis and interpretation: DG, BOH, OY, CE

Drafting the article: DG, BOH

Critical revision of the article: DG, BOH, CE

All authors (DG, BOH, OY, CE) reviewed the results and approved the final version of the manuscript.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication else where.

Sponsor's Role: There is no sponsor contribution.

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