Transcutaneous Tibial Nerve Stimulation as Therapy for Functional Constipation

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ABSTRACT

Background: *Functional constipation is a common disorder that is difficult to treat on occasion. Symptoms of this condition can persist despite dietary modification, exercise, and medication. Results of neuromodulation with nerve stimulation have been promising in terms of efficiency for treatment-resistant patients. This study aimed to investigate the efficacy of bilateral transcutaneous tibial nerve stimulation as a noninvasive treatment method for functional constipation.*

Methods: *We evaluated 105 patients with functional constipation diagnosed using the Rome IV criteria. Bilateral transcutaneous electrical nerve stimulation was utilized for transcutaneous tibial nerve stimulation for 6 weeks; 3 sessions were conducted every week, with each session lasting for at least 30 minutes. The Constipation Severity Instrument was used before treatment, at the end of 6 weeks, and at 12 weeks (6 weeks after the end of treatment). The effects of transcutaneous tibial nerve stimulation on the time spent in the toilet and the use of softeners were investigated.*

Results: *Of the 105 patients included in the study, 41 (39%) were male. The mean age was 43.1 (range, 19-64 years). Transcutaneous tibial nerve stimulation was found to reduce the time patients spent in the toilet. The use of softeners decreased from 76.2% to 20% ($P < .001$). Obstructive defecation ($P < .001$), colonic inertia ($P < .001$), pain ($P < .001$), and Constipation Severity Instrument total score ($P < .001$) improved after the 6-week treatment period. The treatment effect persisted until the 12th week.*

Conclusion: *Bilateral transcutaneous tibial nerve stimulation is a noninvasive, easily applicable, and effective treatment for functional constipation, without major adverse effects. Large randomized controlled trials are required so that transcutaneous tibial nerve stimulation can be established as an alternative treatment for functional constipation that is resistant to standard care and laxative agents.*

Keywords: *Constipation, functional, neuromodulation, stimulation, tibial nerve*

INTRODUCTION

Chronic constipation is a frequent and important problem that reduces the quality of life.[1] Recent reviews on chronic constipation have reported the frequency of this condition as being very low (2.6%) in some patient groups and up to 30% in some others. The main reasons for such a difference in frequency may be the population variation, in terms of sex, age, and geographic region, in studies and differences in constipation diagnostic criteria.[2,3] These include infrequent bowel movements, hard or lumpy stool, excessive straining, sensation of incomplete evacuation, and the use of manual maneuvers to facilitate evacuation in some instances.[4] Functional constipation (FC) is a functional bowel disorder that is characterized by difficult, infrequent, or incomplete defecation.[5] Functional constipation is one of the most common causes of chronic constipation and accounts for approximately three-quarters of patients with chronic constipation.[6]

The diagnosis of FC is based on the Rome criteria.[5] Parameters such as clinical history, physical examination, laboratory tests, and colonoscopy (in patients with alarm symptoms) are used for the diagnosis of FC. Tests such as colonic transit time test and anorectal motility studies are indispensable in the diagnosis of FC. Patients with chronic constipation without metabolic and structural causes should be evaluated for FC.[3] Functional constipation affects the quality of life of patients more severely than many other organic diseases and creates additional financial burden on the health system.[1,7]

Despite the availability of many treatment methods, certain patients with chronic constipation remain unresponsive to such approaches. Therefore, neuromodulation has been increasingly used in recent years as an alternative treatment for treatment-resistant constipation.[8-10] Only few cases demonstrating the efficacy of transcutaneous

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tibial nerve stimulation (TTNS) are available. However, the number of patients included in our study was much higher. Because the patients included in this study were blinded to the protocol, the placebo effect was believed to have been minimal. Studies have been conducted to investigate the effect of neuromodulation with sacral nerve stimulation (SNS) on colonic functions. Sacral nerve stimulation is effective against chronic constipation because it increases pancolonic antegrade propagating waves.[11] However, SNS is an invasive and expensive method that is not widely available. An alternative neuromodulation method is posterior tibial nerve stimulation (PTNS). Posterior tibial nerve stimulation has been suggested to modulate the sacral roots via multiple afferent pathways because the posterior tibial nerve originates from the L4–S3 roots.[8] It is effective in the treatment of chronic pelvic pain and constipation.[9,12] Transcutaneous tibial nerve stimulation is effective in a manner that is similar to that observed for PTNS.[13] Not only is this method cheaper than SNS and PTNS and easily accessible but it also can be applied at home by patients after little training.

The primary aim of our study was to investigate the improvement in the Constipation Severity Instrument (CSI) scores of patients who were resistant to FC treatment (resistant to standard care or laxatives) using bilateral TTNS. We also investigated the effect of TTNS on the symptoms of defecation, anal pain, and inability to completely evacuate the rectum, as well as time spent in the toilet in patients with FC. The hypothesis of our study is that TTNS may be an alternative treatment for FC patients unresponsive to standard medical treatment.

MATERIALS AND METHODS

This prospective study included 105 patients with FC between June 2018 and February 2019. Functional constipation was diagnosed based on the Rome IV criteria. All the patients completed the CSI before undergoing TTNS, at the end of the 6-week treatment, and at 12 weeks (6 weeks after treatment).[14] We used the culturally adapted version of CSI.[15] All patients were provided with a form and maintained a diary to keep track of their defecation. The patients were asked to bring these diaries along for the test, and this test was conducted 3 times altogether. The forms contained the main topics of our test. The time spent by the patients in the toilet was accepted as the duration of defecation. The test consisted of 3 subgroups, namely obstructive defecation, colonic inertia, and pain. A minimum of 2 and a maximum of 73 points can be obtained in the test, with higher scores indicating a greater constipation severity. To evaluate the effect of TTNS on the defecation time, the patients were asked about each time they went to the toilet for defecation, before the treatment, at the end of the 6-week treatment, and 6 weeks after treatment. The patients were divided into 3 groups according to defecation duration as follows: <5 minutes (group 1), 5-11 minutes (group 2), and >11 minutes (group 3). Thus, we attempted to determine the efficacy of the TTNS treatment in reducing the defecation time. The change in the requirement of stool softeners and/or herbal tea use was evaluated using TTNS.

Inclusion criteria for the study included patients with FC who were non-responders to diet modification and standard medical treatment (stool softener), patients who had not undergone PTNS treatment in the last 1 year, and those who had not started laxative or other drug therapy in the last 1 month. Exclusion criteria included the presence of obstruction on colonoscopy (colonoscopy within the past 5 years), diabetes mellitus, cerebrovascular disease, dementia, history of gastrointestinal cancer, histories of intra-abdominal and anorectal surgeries, neurodegenerative disease, inflammatory bowel disease, and spinal cord injury. Geriatric patients (age ≥ 65 years), patients under the age of 18 years, pregnant women, and patients who had previously participated ın TTNS sessions were excluded from the study. We aimed to maintain a large sample size to increase the reliability of the study. The study was conducted in accordance with the Declaration of Helsinki and approved by a local ethics committee. Informed consent was obtained from all the patients and their relatives.

Main Points

- *Bilateral transcutaneous tibial nerve stimulation is a non-invasive, easily applicable and effective treatment for functional constipation, without major adverse effects.*
- *Large randomized controlled trials are required so that transcutaneous tibial nerve stimulation can be established as an alternative treatment for functional constipation that is resistant to standard care and laxative agents.*

Transcutaneous Tibial Nerve Stimulation Procedure

Bilateral transcutaneous electrical nerve stimulation (TENS) was applied in all the patients for TTNS for 6 weeks, 3 times per week, with each session lasting for at least 30 minutes. Four bilateral electrodes were placed on the medial malleolus, approximately 15 cm above the malleolus, to stimulate the sacral plexus via the tibial

nerve using TENS electrodes. Stimulation parameters were set at a pulse width of 200 μs and frequency of 10 Hz. The procedure was performed by trained personnel at the hospital. The patients who did not comply with or missed the sessions were excluded from the study.

Assessments

Data pertaining to the age, sex, and medical history of all patients included in the study were recorded. As presented in Table 1, patients with several comorbidities or multiple drug use were excluded from the study.

Statistical Analysis

Among the continuous variables, the mean, minimum, median, and maximum values were presented because of their non-normal distributions. Therefore, a nonparametric Friedman *k*-related sample test was used to determine the significance among the periods (0, 6, and 12 weeks). Related two-level comparisons were performed using the Wilcoxon nonparametric test. Significant differences between the periods were labeled using different letters on the basis of a .05 level of significance. For the categorical variables, frequencies and percentages are presented. A chi-squared test was used for the associations, and gamma statistics was used for the ordered cross-table correlations between the 2 categorical variables.

Table 1. Evaluation of Patients-Questioning in Terms of Chronic Diseases

Diabetes mellitus
Cerebrovascular disease
Dementia
History of gastrointestinal cancer
Histories of intra-abdominal and anorectal surgeries
Neurodegenerative disease
Inflammatory bowel disease
Spinal cord injury
Antihypertensive drugs

If the *P* value was <.05, then the statistical result was evaluated as significant. All the analyses were performed using the Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA).

RESULTS

Altogether, 105 patients were included in the study. New patients were included in the study instead of the 12 older patients who could not complete all sessions. There were 41 (39%) male and 64 (61%) female patients in the study. The mean age was 43.1 (range, 19-64 years). According to the defecation duration, 61.9% (n = 65) of the patients were included in group 1, 35.2% (n = 37) in group 2, and 2.9% (n = 3) in group 3 before treatment. At the end of the TTNS treatment (at the end of 6 weeks), 82.9% of the patients were transferred to group 1, 15.2% to group 2, and only 1.9% to group 3 ($P < .001$). At the 12-week follow-up, 67.6% of the patients were still in group 1 and 28.6% in group 2. The defecation time of the patients continued to decrease in comparison with that at the beginning of treatment ($P < .001$). Comparison of the defecation time at the end of treatment (6th week) and at the 12th week showed that the defecation time had increased in some patients ($P = .038$; Table 2).

Before TTNS treatment, 76.2% (n = 80) of the patients were found to be using stool softeners to help in defecation. At the end of the treatment, softener use decreased to 20% (n = 21; $P < .001$). In the follow-up after the end of the TTNS treatment (12th week), the frequency of softener use showed no increase (Table 3).

At the end of the 6-week TTNS treatment, obstructive defecation (22.4 vs 8.4; $P < .001$), colonic inertia (19.6 vs 6.6; $P < .001$), anal pain (9.4 vs 4.1; $P < .001$), and total CSI score (51.4 vs 19.1; $P < .001$) showed significant reduction. In the 12-week follow-up, although the scores were increased as compared with those at the 6th week, the beneficial effect of the treatment continued when compared with the baseline scores (Table 4). The effect of

Table 2. Change in Time of Defecation with Treatment

	Patient Groups According to Defecation Time			Test		
Week	Group 1	Group 2	Group 3	Week	Chi-Square (Sig.)	Gamma (Sig.)
0	3 (2.9%)	37 (35.2%)	65 (61.9)	0-6	145.960 (<.001)	−0.975 (<.001)
6	87 (82.9%)	16 (15.2%)	2 (1.9%)	0-12	117.145 (<.001)	−0.947 (<.001)
12	71 (67.6%)	30 (28.6%)	4 (3.8%)	6-12	6.548 (.038)	0.386 (.009)

Table 3. Use of Stool Softener

	Softener Use			
Week	No	Yes	Week	Chi-Square (Sig.)
0	25 (23.8%)	80 (76.2%)	0-6	66.401 (<.001)
6	84 (80.0%)	21 (20.0%)	0-12	81.213 (<.001)
12	90 (85.7%)	15 (14.3%)	6-12	1.207 (<.272)

TTNS treatment on the total CSI score (male vs female, 19 ± 8 vs 20 ± 9; $P = .67$) and the subgroup scores showed no sex-related differences.

No serious side effects that could cause discontinuation of treatment were observed, although side effects such as local erosion, hyperemia, and itching were noted. Side effects were not at a level that required treatment and regressed spontaneously. These local side effects were reported in 8/105 (7.6%) patients.

DISCUSSION

Among the patients with FC, some show persistent symptoms despite lifestyle/dietary changes and medical treatments. Therefore, neuromodulation is being studied as an alternative treatment. In this study, we investigated the efficacy of bilateral TTNS performed noninvasively using a transdermal patch. As a result, we found that patients benefited from 6 weeks of treatment. In addition, at the end of the 6-week follow-up period without treatment, the effect of the treatment persisted; there was a significant reduction in the time spent in the toilet. A study of 45 patients who underwent SNS showed that the time spent in the toilet was reduced with neuromodulation.[16] However, SNS is an invasive and difficult procedure that can cause serious complications. Kamm et al.[16] reported that 11 patients had serious complications. Moreover, they reported that 15.5% (7/45) of patients discontinued participating in the study. In our study, neuromodulation was performed with TTNS. None of the patients experienced any serious adverse effects and discontinued the treatment for this reason. Therefore, compared with SNS, TTNS has more ease of applicability and accessibility, is a more noninvasive approach, and has a lower risk of serious complications.

Our study showed a decrease in the requirement of laxative and/or softener use with TTNS treatment. In a previous study, percutaneous tibial nerve stimulation was evaluated in 18 patients, and similar to the results of our study, a decrease in laxative use was observed among the patients.[9] The number of patients in this study was small, and a needle was used for percutaneous nerve stimulation. In our study, the use of transdermal patches for nerve stimulation is important in terms of patient comfort, for patients to perform the procedure by themselves at home, and for protection against infectious diseases.

The CSI was administered to all the patients in our study. The total scores at the end of the treatment and at follow-up significantly decreased in comparison with those at baseline, meaning that the patients had better constipation symptoms. In addition, the incidence of obstructive defecation and colonic inertia and the pain scores

Table 4. Change of Constipation Severity Instrument and Its Subscores by Treatment

CSI Subscale	Week	n	Mean	SD	Chi-Square	Sig.
Obstructive defecation	0 (a)	105	22.4	3.64	179.404	<.001
	6 (c)	105	8.4	4.15		
	12 (b)	105	10.7	5.55		
Colonic inertia	0 (a)	105	19.6	3.37	169.871	<.001
	6 (c)	105	6.6	3.85		
	12 (b)	105	8.4	5.36		
Pain	0 (a)	105	9.4	3.07	163.157	<.001
	6 (c)	105	4.1	2.00		
	12 (b)	105	4.7	2.75		
Constipation Severity Instrument Total Score	0 (a)	105	51.4	8.17	173.688	<.001
	6 (c)	105	19.1	8.66		
	12 (b)	105	23.8	12.81		

decreased. A similar study evaluated the efficacy of PTNS in 36 patients with rectal evacuation disorders. The Modified Obstructed Defecation and Patient Assessment of Constipation–Quality of Life questionnaire scores improved significantly with tibial nerve stimulation.[10] In contrast, another study concluded that transcutaneous SNS was ineffective in the treatment of FC.[8] In this study, only 20 patients were evaluated, and a different nerve stimulation method was used. Nerve stimulation was attempted by placing patch electrodes on the sacrum. As a result, the patients were not benefitted from the treatment. In general, SNS appears to be effective for constipation. However, some studies have claimed that it is useless. Differences in outcomes may be associated with the type of stimulation applied, localization, duration, patient selection, and patient compliance.

A limitation of this study was that patients did not undergo tests such as colonic transit time test and anorectal motility studies, which are indispensable in the diagnosis of FC, at the diagnosis stage. The strength of our study is that the treatment approach is of a noninvasive nature that has no significant side effects. As a result, bilateral TTNS was found to be effective for reducing the complaints of patients with treatment-resistant FC. As a noninvasive, easily applicable, and accessible method with low risk of serious complications, it can be considered as an alternative treatment for FC unresponsive to classic therapies. Single-blinded randomized controlled studies are required before considering bilateral TTNS as a treatment alternative.

Ethics Committee Approval: The study was approved by the medical ethics committee of İstanbul Education and Research Hospital (KAEK 50 No: 1264).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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