

Good results with transcutaneous tibial nerve stimulation for advanced chronic constipation treatment

Transkutaninė blauzdinio nervo stimuliacija – efektyvus lėtinio vidurių užkietėjimo gydymo metodas

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Background

Chronic constipation is a common complaint with a big impact on the quality of life, which may be difficult to treat. The aim of this prospective pilot study was to assess the efficiency of transcutaneous posterior tibial nerve stimulation in the treatment of constipation in the medium term and to investigate the potential predictors of treatment success.

Materials and methods

Forty nine patients with constipation resistant to maximal conservative therapy were treated by transcutaneous posterior tibial nerve stimulation twice a week for six weeks. If the treatment was successful, patients were proposed to continue the treatment for six months. The Knowles–Eccersley–Scott Symptom Score, the number of the bowel movements per two weeks and the Gastrointestinal Quality of Life index were evaluated pre- and post-treatment. The evaluation of constipation was performed at the baseline and after six weeks.

Results

The effect was seen in 53.1% of patients. The mean Knowles–Eccersley–Scott Symptom Score improved significantly (from 20.88 ± 5.19 to 15.61 ± 7.19 , $p < 0.001$) after six weeks. The two-week stool frequency increased from the mean of 4.65 ± 2.48 pre-treatment to 7.47 ± 3.51 post-treatment ($p < 0.001$). The use of laxatives decreased ($p < 0.001$). The Gastrointestinal Quality of Life index improved in all subscales ($p < 0.05$). The therapy was well tolerated, and no participant experienced any adverse event. No potential predictors of treatment success were found.

Conclusions

Transcutaneous posterior tibial nerve stimulation may be a new safe therapeutic option in patients with constipation, who have failed to respond to the maximal conservative treatment.

Key words: transcutaneous electric nerve stimulation, constipation, tibial nerve

Įvadas

Lėtinis vidurių užkietėjimas – dažnas virškinimo trakto sutrikimas, kuris labai blogina gyvenimo kokybę ir paprastai yra sunkiai gydomas. Šio perspektyviojo klinikinio tyrimo tikslas – įvertinti transkutaninės blauzdinio nervo stimuliacijos efektyvumą gydant lėtinį vidurių užkietėjimą ir nustatyti sėkmingo gydymo veiksnius.

Tyrimo medžiaga ir metodai

Transkutaninė blauzdinio nervo stimuliacija buvo atlikta 49 lėtinio vidurių užkietėjimu sergantiems pacientams, kuriems maksimalus konservatyvus gydymas buvo neveiksmingas. Stimuliacija buvo atliekama du kartus per savaitę šešias savaites. Vertinti *Knowles–Eccersley–Scott* vidurių užkietėjimo klausimyno balų, tuštinimosi dažnio ir gastrointestinio gyvenimo kokybės klausimyno balų pokyčiai prieš gydymą ir po jo.

Rezultatai

Poveikis gautas 53,1 % pacientų. Po 6 gydymo savaičių *Knowles–Eccersley–Scott* klausimyno balų vidurkis sumažėjo nuo $20,88 \pm 5,19$ iki $15,61 \pm 7,19$ ($p < 0,001$). Tuštinimosi dažnis per dvi savaites padidėjo nuo $4,65 \pm 2,48$ iki $7,47 \pm 3,51$ ($p < 0,001$). Sumažėjo vartojamų laisvinamųjų medikamentų kiekis ($p < 0,001$). Nustatytas akivaizdus teigiamas pokytis pagal visas gastrointestinio gyvenimo kokybės klausimyno skales ($p < 0,05$). Pacientai gerai toleravo gydymą ir nepasitaikė jokių šalutinių poveikių. Galimų sėkmingo gydymo prediktorių nenustatyta.

Išvada

Transkutaninė blauzdinio nervo stimuliacija yra naujas, saugus gydymo metodas, kuris gali būti taikomas vaistams atspariam lėtiniam vidurių užkietėjimui gydyti.

Reikšminiai žodžiai: transkutaninė elektrinė nervo stimuliacija, vidurių užkietėjimas, blauzdinis nervas

Introduction

Constipation is the most common digestive complaint affecting around 14% of adults worldwide [1, 2]. Chronic severe constipation has a significant, even debilitating, effect on the quality of life [1–4]. The disease is frequently multifactorial and can result from systemic or neurogenic disorders or medications, but the majority of patients suffer from idiopathic constipation [5]. A number of patients remain resistant to the maximal conservative therapy. However, the surgical treatment of constipation carries a significant risk of complications [6, 7]. Even if it often improves defecation frequency, symptoms of abdominal pain persist in the majority of patients, reflecting the panenteric motility disorder [8].

Currently, the modulation of the sacral plexus with sacral nerve stimulation (SNS) is widely used in clinical practice for the treatment of urinary incontinence and retention, fecal incontinence and constipation (slow transit constipation as well as obstructive defecation) with reported good results [5, 9–11]. SNS is a modera-

tely invasive therapy with a significant risk of complications and a high financial cost [7, 12].

An alternative to SNS is tibial nerve stimulation, a peripheral neuromodulation of the sacral nerve plexus, which is used to treat urinary incontinence and the overactive bladder syndrome as well as fecal incontinence [13–15]. Various stimulation parameters and regimens through percutaneous (using needle electrodes) or transcutaneous (adhesive electrodes) methods are used. Tibial nerve stimulation is a simple, well-tolerated and low-cost technique. There is a limited evidence that percutaneous (PTNS) and transcutaneous posterior tibial nerve stimulation (TTNS) are beneficial in treating slow transit constipation [8, 16]. To our knowledge, there are no data about the effect of TTNS or PTNS on obstructive defecation and normal transit constipation.

This prospective pilot study aimed to evaluate the efficacy of transcutaneous tibial nerve stimulation for constipation in the medium term and to investigate the potential predictors of treatment success.

Materials and methods

Study population

From November 2011 to June 2013, 49 patients with constipation, who were referred to a specialized centre and satisfied the inclusion and exclusion criteria, were prospectively enrolled in the consecutive cohort study. Constipation was defined as fewer than two bowel movements per week and/or straining or incomplete evacuation in more than 25% of all visits to the toilet [11]. Inclusion criteria were age over 18 years, symptoms present for a minimum of one year, psychological stability, failed conservative therapy, and an adequate motor and/or sensory response to the treatment. Exclusion criteria were any organic pathology causing constipation, previous large-bowel surgery, inflammatory bowel disease, erratic bowel habit (alternating constipation and diarrhea, or the irritable bowel syndrome), congenital anorectal malformations, stoma *in situ*, neurologic diseases causing constipation, a significant psychological element to the patient's symptoms (as judged by a physician), pregnancy or intention to become pregnant, implanted pacemaker or defibrillator, diabetes mellitus, severe distal venous insufficiency, and severe cutaneous local lesion.

Assessment

Pretreatment evaluation included a detailed history, physical examination, colonoscopy and colorectal physiological assessment: colonic transit study, anorectal manometry, rectal sensation, and defecography.

Constipation was assessed by the Knowles–Eccersley–Scott Symptom scoring system (KESS) [17] at the baseline before the first treatment session and after six weeks (primary outcome measure).

The improvement in the patients' symptoms was also assessed by using a two-week diary of the number of bowel movements, laxatives, suppositories and enemas used before and after six weeks of treatment. The effect of treatment on the quality of life was assessed using the Gastrointestinal Quality of Life Index (GIQLI) [18].

The KESS constipation score was used to rate constipation severity. This score ranges from 0 to 39, with 0 indicating no symptoms and 39 indicating severe constipation [17]. The GIQLI questionnaire consists of

36 questions that assess the impact of the disease on the physical, social, and mental status [18].

The colonic transit time was measured by a validated method of performing abdominal radiography 24, 72, and possibly 96 hours after the patient had ingested radiopaque markers. During this study, the patient was instructed not to use laxatives or enemas. The retention of markers for more than 72 hours indicated a prolonged transit time [5, 19].

Defecography was performed by a retrograde infusion of the radiopaque contrast and assessing rectal configuration and perineal descent while the patient was resting, contracting the anal sphincter, and straining to defecate [20].

Anorectal physiology included rectal sensory testing and the rectoanal inhibitory reflex. Rectal sensory testing was performed by distending the rectum with an air-filled balloon. Rectal volumes to distension for the first sensation of urge, sensation of the desire to defecate, and the maximum tolerated were recorded in milliliters [21].

Every patient served as his or her own control. The study was approved by the Ethics Committee of the Vilnius University, and every patient signed a written informed consent.

Procedure

TTNS was done with a stimulating Neuro Track TENS unit (Verity Medical, UK). Stimulation was done on the posterior tibial nerve route using a self-adhesive surface stimulation electrode [15, 22]. A negative electrode was placed on the ankle skin behind the internal malleolus with the positive electrode being placed 10 cm above the negative one. The adequate position of the electrode was determined by slowly increasing the electric current until sensory and/or motor responses were evident. Typical responses included foot sole sensation and/or great toe flexion [14]. The appropriate electric current intensity level was determined based on the intensity immediately under the threshold motor contraction and varied from 18 to 38 mA. The fixed pulse width of 200 μ s and a frequency of 20 Hz were applied in a continuous mode for 30 min. TTNS was done in the outpatient department twice weekly for six weeks (12 procedures) [14].

Statistical analysis and sample size

A reduction of 5 points in the KESS score was predefined to be clinically significant. It was estimated that nine subjects were required for the study to detect a 5-point difference with a 5% significance level and 90% power.

Continuous variables were checked for the normal distribution by the Shapiro–Wilk test. Normally distributed data were expressed as mean and standard deviations, and nonparametric data were expressed as a median and the range. Paired tests were used to compare data at baseline and after the treatment: a paired t-test for parametric and the Wilcoxon signed-ranks test for nonparametric variables. The Mann–Whitney U test was used to compare unpaired data at baseline and after the treatment. A p-value <0.05 was considered statistically significant.

Results

Between 2011 and 2013, 49 patients (45 women) with a mean age of 52.41 years (SD±17.73) underwent TTNS for constipation. All patients completed 12 sessions of TTNS in six weeks, filled in bowel diaries, KESS and GIQOL questionnaires. The effect was seen in 53.1% (26 out of 49) of patients. The overall mean KESS score improved significantly with treatment after six weeks (from 20.88 ± 5.19 to 15.61 ± 7.19 ; $p < 0.001$). In the subgroup analysis, 26 patients with a successful treatment had a mean baseline KESS score of 20.58 ± 5.22 ,

which improved to a mean score of 11.27 ± 5.78 after six weeks of TTNS ($p < 0.001$) (Figure 1).

The overall mean two-week stool frequency increased from 4.65 ± 2.48 pre-treatment to 7.47 ± 3.51 post-treatment ($p < 0.001$). In the effect subgroup, a mean of 4.65 ± 2.62 bowel motions per two weeks at baseline increased to a mean of 9.69 ± 2.74 after six weeks of treatment ($p < 0.001$). The median number of laxative tablets, suppositories and enemas used two weeks before treatment was 4 (range, 0–44), and it decreased to a median of 0 (range, 0–16) after the treatment ($p < 0.001$).

There was an improvement in the symptoms associated with constipation. A significant improvement on the subjective rating of the overall severity of abdominal pain and bloating was observed with TTNS (Figure 2).

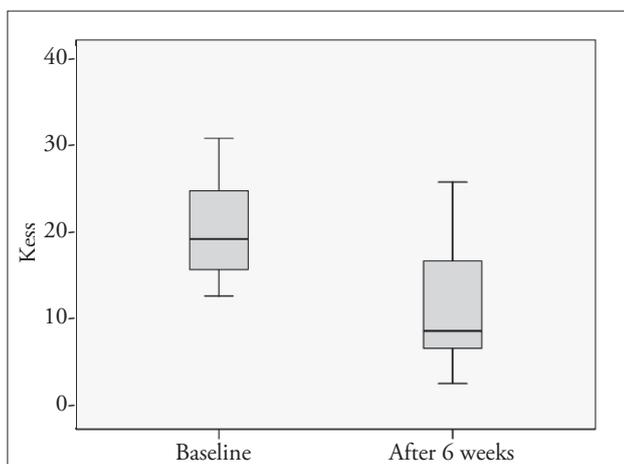
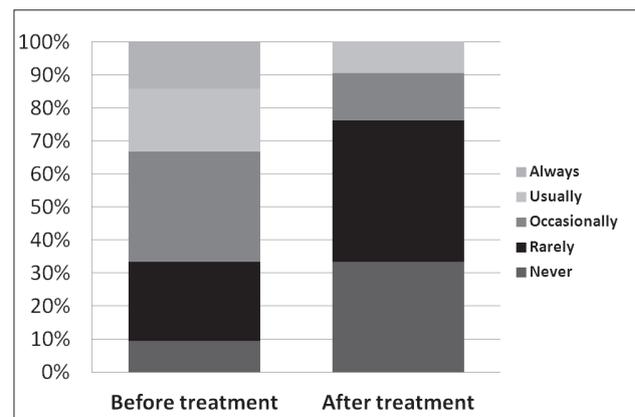
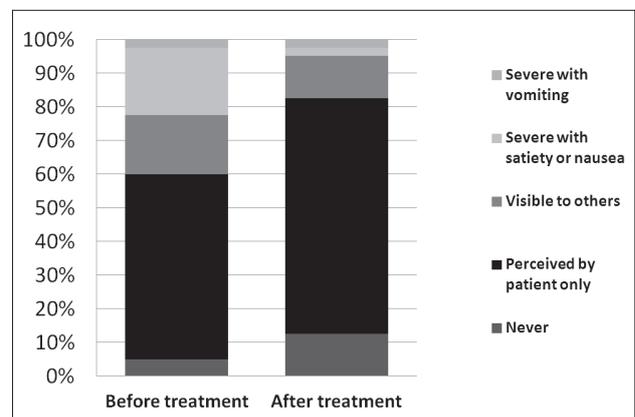


Figure 1. The KESS score changes before and after the treatment in the effect group



a)



b)

Figure 2. Subjective rating of (a) abdominal pain and (b) abdominal bloating at baseline and after six weeks of treatment as recorded by the KESS questionnaire

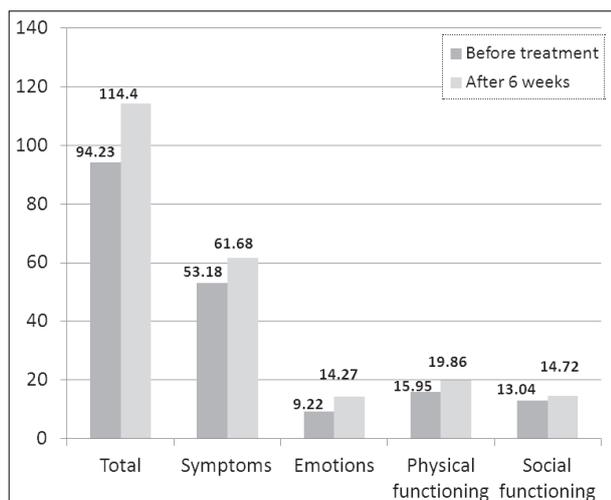


Figure 3. The GIQLI score and subscales before and after six weeks of treatment in the effect subgroup ($p < 0.05$)

The overall mean GIQLI score improved from 92.98 ± 16.06 to 104.76 ± 18.38 ($p < 0.001$) after six weeks ($p < 0.001$). There was a statistically significant improvement in all four GIQLI subscales as compared with the baseline level ($p < 0.001$) (Figure 3).

A colonic transit study was performed at baseline and after six weeks of treatment in case of slow transit constipation and TTNS effect. Four out of 10 patients with slow colonic transit benefited; however, two of them refused to repeat the transit study because of

radiation. Colonic transit normalized in the other two patients.

A comparison between success and failure groups did not help to define the initial conditions predictive of a symptomatic improvement. Both groups had a similar age, symptom duration, the KESS score, stool frequency, laxative consumption and the GIQLI scores at referral. The baseline measures of constipation in relation to success or failure of TTNS are shown in Table 1.

The success rate of TTNS was similar in patients with a slow and a normal transit time as well as in patients with complete and incomplete evacuation in defecography. Both groups had similar rectal sensation volumes.

The therapy was well tolerated, and no participant experienced any adverse event.

Discussion

The results of this study have shown that TTNS may be efficacious in patients with constipation, who have failed to respond to maximal conservative treatments.

To our knowledge, this is the first study evaluating the efficacy of TTNS for patients with all forms of constipation, including patients with obstructive defecation.

The TTNS effect, defined as a reduction in the KESS score of 5 points or more, was achieved in more than

Table 1. Baseline measures of constipation in relation to success or failure of TTNS

	All patients	TTNS failure	TTNS success
Colonic transit study			
Normal, n (%)	39	17 (43.6)	22 (56.4)
Slow transit, n (%)	10	6 (60)	4 (40)
Defecography			
Complete evacuation, n (%)	16	7 (44)	9 (56)
Incomplete evacuation, n (%)	33	16 (48.5)	17 (51.5)
Rectal sensation threshold (ml), median (range)			
First sensation volume,	40 (10–250)	45 (10–250)	40 (10–250)
Urge volume,	125 (40–350)	120 (40–350)	130 (50–350)
Maximum volume,	200 (80–500)	225 (80–500)	200 (90–500)

a half of patients. In the effect group, a considerable reduction (of almost 10 points) of the mean KESS score was seen after six weeks of treatment with TTNS. A significant increase was seen in stool frequency, and a marked decrease was observed in the use of laxatives as well as in abdominal pain and bloating. The quality of life also increased after the treatment. There was a statistically significant improvement in all four GIQLI subscales.

Since different outcome measures and inclusion criteria have been used, a comparison with the results of other studies is complicated. The most common outcome measured in the studies evaluating the SNS effect on constipation was a change in the frequency of defecation [8]. However, the number of defecations is not the only sign of constipation. According to the Rome III criteria, two or more symptoms must be present for six months or more. These include straining at stool, passing hard stools, sensation of incomplete emptying, sensation of anorectal obstruction, self-dilatation and defecation frequency of less than three times per week [23]. Therefore, the primary outcome in our study was a change in the KESS score and not an increase in the number of defecations. Currently, neither a standard of criteria exists as to which scoring system should be used nor there are universally accepted standardized inclusion criteria for patients undergoing clinical trials for constipation [11, 24]. The KESS score was used in this study, because we find it informative and useful and use it in our daily practice. Abdominal pain and bloating are usually present together with constipation. Therefore, we analyzed not only the whole KESS score before and after the treatment, but also assessed separate particular symptoms. An improvement in the sensation of bloating and abdominal pain was seen after the treatment with TTNS.

Baseline assessments of transit time and incomplete evacuation on defecography were not related to the outcome of TTNS, suggesting that this treatment method may be effective not only for those with constipation but also for those with evacuation difficulties. Similar results have been reported from SNS for constipation studies [11].

The success rate of our six week treatment period can be comparable with the percutaneous nerve evaluation

phase in SNS studies. The success rate of the percutaneous nerve evaluation phase for constipation in adults in published SNS studies ranged from 42% to 73% [8, 11]. In our study, the overall effect was seen in 53.1%. In 2011, Collins et al. published results on 18 patients with a slow transit constipation treated with PTNS, using needle electrodes. However, a predetermined criterion for success was achieved only by a third of participants, and colonic transit normalized only in three patients (16.6%) [16]. The result in our patients with a slow-transit constipation was very similar. The effect was seen in 40% of patients, although the group was very small (only ten patients). Better results were seen in patients with obstructive defecation (51.5%) and normal transit constipation (56.4%). The reported efficacy of PTNS and TTNS in fecal incontinence studies varies from 54% to 84.3% [14, 15, 22, 25–27]. Nevertheless, these are small, uncontrolled trials with different outcome measures and heterogeneous patient populations.

In TTNS studies with fecal incontinence patients, the stimulation was performed every day by patients themselves. Moreover, in some studies the treatment course lasted longer – about three months and more [22, 26]. Presumably, a better effect might be observed after three months of daily stimulation. In order to avoid bad patient compliance and to perform the procedure in a correct standardized manner, TTNS in our study was done in the outpatient department twice a week for six weeks.

As in TTNS studies with fecal incontinence patients [15, 22, 26], no adverse effects were seen in our study. The procedure was well-tolerated, and the compliance of the patients was very good. Whereas, PTNS is a minimally invasive technique, and mild and rare adverse effects have been reported in several studies, which include gastrodynia, paraesthesia or numbness and bleeding from the needle site [7, 14, 28].

Our study had several limitations. There was no control group with sham TTNS, which would allow to eliminate the placebo effect. However, blinding in such treatment method is difficult, because correct electrode placement and current amplitude is confirmed by sensory and/or motor response of the foot. There is a close association between severe constipation and psychological disorders [8]. Thus, the risk of a placebo

effect in our study is high, particularly in patients with normal colonic transit. PTNS has been shown to be significantly more effective than sham stimulation in urinary incontinent patients [29]. Effects beyond placebo suggest findings that PTNS modulates ascending spinal pathways [30] and long-term latency somatosensory-evoked potentials [7, 31, 32].

Non-standardized treatment with laxatives was another drawback. Patients were asked to continue medications and/or rectal irrigation used before the study and to alter the dose if needed. In case of TTNS efficiency, the doses decreased or the medications and/or irrigations were withdrawn.

Another limitation was radiological examinations. In order to avoid big amounts of radiation, we decided to repeat the transit study only in case of a good effect in patients with a slow transit constipation. However, some patients refused to perform it after the treatment. For the same reasons we decided not to repeat proctography.

A lot of questions remain unanswered about the TTNS and PTNS effect on defecation disorders. Larger studies with a better design and control groups are

needed to rule out the placebo response. It remains unclear how long and how often the stimulation should be done, and which patients are most likely to benefit from the therapy.

Conclusions

The first results of this study are encouraging. TTNS may be a new therapeutic option in patients with constipation (slow transit constipation as well as obstructive defecation) who have failed to respond to the maximal conservative treatment. It is a safe, noninvasive, technically simple procedure which can be easily performed in an outpatient setting or at home.

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The authors declare that they have no conflict of interests.

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