VILNIUS UNIVERSITY

Ieva Stundienė

TRANSCUTANEOUS TIBIAL NERVE STIMULATION: NEW TREATMENT METHOD EVALUATION FOR DEFECATION DISORDERS AND INVESTIGATION OF POTENTIAL PREDICTORS OF TREATMENT SUCCESS

Summary of Doctoral Dissertation

Biomedical Sciences, Medicine (06 B)

Vilnius, 2014

The dissertation was prepared at Vilnius University during the period of 2010–2014.

Research supervisor:

Prof. habil. dr. Jonas Valantinas (Vilnius University, Biomedical Sciences, Medicine – 06 B).

Dissertation is defended at the Board of Medical Sciences of Vilnius University Faculty of Medicine:

Chairman:

Prof. habil. dr. Algimantas Irnius (Vilnius University, Biomedical Sciences, Medicine – 06 B).

Members:

Prof. habil. dr. Limas Kupčinskas (Lithuanian University of Health, Biomedical Sciences, Medicine – 06 B);

Prof. dr. Vytautas Kasiulevičius (Vilnius University, Biomedical Sciences, Medicine – 06 B);

Assoc. prof. dr. Danutė Speičienė (Vilnius University, Biomedical Sciences, Medicine – 06 B);

Assoc. prof. dr. Riina Salupere (Tartu University, Biomedical Sciences, Medicine – 06 B).

The public defence of doctoral dissertation will be held at the open session of the Board of Medical Sciences on the 16th of December 2014, at 3:00 p.m. in the Conference Hall of Vilnius University Hospital Santariškių Klinikos. Address: Santariškių str. 2, LT-08661, Vilnius, Lithuania.

The summary of doctoral dissertation was sent out on 14 of November 2014.
The doctoral dissertation is available in the Library of Vilnius University (Universiteto str. 3, LT-01122 Vilnius, Lithuania), www.vu.lt/lt/naujienos/ivykiu-kalendorius.

VILNIAUS UNIVERSITETAS

Ieva Stundienė

TRANSKUTANINĖ BLAUZDINIO NERVO STIMULIACIJA: NAUJO TUŠTINIMOSI SUTRIKIMŲ GYDYMO METODO EFEKTYVUMO ĮVERTINIMAS IR GALIMŲ SĖKMINGO GYDYMO RODIKLIŲ PAIEŠKA

Daktaro disertacijos santrauka

Biomedicinos mokslai, medicina (06 B)

Vilnius, 2014

Disertacija rengta 2010–2014 metais Vilniaus universitete.

Mokslinis vadovas:
Prof. habil. dr. Jonas Valantinas (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B).

Disertacija ginama Vilniaus universiteto Medicinos mokslo krypties taryboje:

Pirmininkas:

Prof. habil. dr. Algimantas Irnius (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B).

Nariai:

Prof. habil. dr. Limas Kupčinskas (Lietuvos sveikatos mokslų universitetas, biomedicinos mokslai, medicina – 06 B)

Prof. dr. Vytautas Kasiulevičius (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

Doc. dr. Danutė Speičienė (Vilniaus universitetas, biomedicinos mokslai, medicina – 06 B)

Doc. dr. Riina Saupere (Tartu universitetas, biomedicinos mokslai, medicina – 06 B).

Disertacija bus ginama viešame Medicinos mokslo krypties tarybos posėdyje 2014 m. gruodžio 16 d. 15 val., Vilniaus universiteto ligoninės Santariškių klinikų auditorijoje.
Adresas: Santariškių g. 2, LT-08661, Vilnius, Lietuva.
Disertacijos santrauka išsiuntinėta 2014-11-14

Disertaciją galima peržiūrėti Vilniaus universiteto bibliotekoje (Universiteto g. 3, LT-01122 Vilnius, Lietuva), VU interneto svetainėje adresu: www.vu.lt/lt/naujienos/ivykiu-kalendorius.

ABBREVIATIONS

FI	–	faecal incontinence
FIQL	–	faecal incontinence quality of life
FIQL l	–	faecal incontinence quality of life lifestyle subscale
FIQL c	–	faecal incontinence quality of life coping subscale
FIQL d	–	faecal incontinence quality of life depression subscale
FIQL e	–	faecal incontinence quality of life embarrassment subscale
GIQLI	–	Gastrointestinal Quality of Life Index
GIQLI s	–	Gastrointestinal Quality of Life Index symptom subscale
GIQLI e	–	Gastrointestinal Quality of Life Index emotion subscale
GIQLI pf	–	Gastrointestinal Quality of Life Index physical functioning subscale
GIQLI sf	–	Gastrointestinal Quality of Life Index social functioning subscale
KESS	–	Knowles–Eccersley-Scott Symptom scoring system
PTNS	–	percutaneous tibial nerve stimulation
SNS	–	sacral nerve stimulation
TTNS	–	transcutaneous tibial nerve stimulation

INTRODUCTION

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

FI is a common problem, especially in older population, leading to physical and psychological disability and social isolation. The estimated prevalence of FI vary from 0.5% to 28%. However, the true prevalence is unknown because of embarrassment and isolation. Considering the problem of aging population, FI is likely to be even a greater burden in the future. Treatment of FI is challenging, because conservative treatment measures have lasting success in approximately 50 % of patients. Surgical treatment options carry significant risk of complications and have well established high long-term failure rates.

Currently, neuromodulation is one of the fastest growing areas of medicine. It is an intermediary therapy between conservative and surgical treatment methods. At present modulation of the sacral plexus with SNS is widely used in clinical practice for the treatment of urinary incontinence and retention, FI and constipation (slow transit constipation as well as obstructive defecation) with reported good results. SNS is a moderately invasive therapy with significant risk of complications and a high financial cost.

An alternative to SNS is tibial nerve stimulation, a peripheral neuromodulation of sacral nerve plexus, used to treat urinary incontinence and overactive bladder syndrome as well as FI. Tibial nerve stimulation is simple, well-tolerated and low-cost technique.

Various stimulation parameters and regimens through percutaneous (using needle electrodes) or transcutaneous (adhesive electrodes) methods are used. Many different regimens form once daily to once weekly of PTNS have been reported. In most TTNS studies the stimulation was performed once daily.

There is limited evidence that PTNS and TTNS is beneficial in treating slow transit constipation. To our knowledge there is no data about the effect of neither TTNS, nor PTNS for obstructive defecation and normal transit constipation.

Aim and objectives of the study

The aim of this prospective study is to evaluate the efficacy and effect on quality of life of TTNS for constipation and FI patients and to investigate potential predictors of treatment success.

Objectives of the study:

1. To evaluate the efficacy of TTNS done twice weekly for 6 weeks for patients with constipation, who have failed to respond to maximal conservative treatment.
2. To evaluate the efficacy of TTNS done twice weekly for 6 weeks for the patients with FI, who have failed to respond to maximal conservative treatment.
3. To determine the TTNS effect on the changes of quality of life of the patients with constipation and FI.
4. To determine the TTNS effect on the results of the functional colorectal investigations of the patients with constipation and FI.
5. To investigate potential predictors of TTNS treatment success.

Scientific novelty of the study

1. This is the first study evaluating the efficacy of TTNS for patients with all forms of constipation, including patients with obstructive defecation.
2. TTNS was done using different stimulation parameters and regimen: 20 Hz frequency, suprasensory stimulation, procedures were done twice a week for 6 weeks.

Principal arguments for defence

1. TTNS done twice a week for 6 weeks is effective for half of patients with constipation, who have failed to respond to maximal conservative treatment.
2. TTNS done twice a week for 6 weeks is effective for half of patients with FI, who have failed to respond to maximal conservative treatment.
3. TTNS improves quality of life in patients with constipation and FI.

MATERIALS AND METHODS

Study population

Some 69 patients (49 patients with constipation, 20 with FI) who were referred to specialized centre and satisfied the inclusion and exclusion criteria were prospectively enrolled in this consecutive cohort study from November 2011 to June 2013. Inclusion criteria: FI with solid and/or liquid stool or functional constipation (as defined by Roma III criteria), psychological stability, failed conservative therapy and adequate motor and/or sensory response during treatment, symptoms present for a minimum of one year.

Exclusion criteria were any organic pathology causing constipation or FI, major internal and/or external anal sphincter defect (>120 degrees of circumference), inflammatory bowel disease, erratic bowel habit (alternating constipation and diarrhoea), stoma in situ, neurologic diseases causing constipation or FI, 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 detailed history, physical examination, colonoscopy or barium enema, defecography, anorectal manometry and rectal sensation. Colonic transit study with radiopaque markers was done

for patients with constipation. Patients with FI also underwent endoanal ultrasound for anal sphincter evaluation.

Constipation was assessed by KESS score at baseline before the first treatment session and during follow up at 6 weeks, 3 months and 6 months. The primary outcome measure was KESS score reduction after 6 weeks of treatment. The improvement in patients' symptoms was also assessed by using a 2-week diary recording the number of bowel movements, laxatives, suppositories and enemas used before and after a 6 week treatment.

FI was assessed by 2 week bowel habit diaries at baseline before the first treatment session and during follow up at 6 weeks, 3 and 6 months. Primary outcome measure was the reduction in incontinence episodes per 2 weeks. We also assessed the Cleveland Clinic Florida FI Score (CCF-FI score) and Wexner FI score at baseline, after 6 weeks, 3 months and 6 months.

The effect of treatment on quality of life was assessed using the GIQLI at baseline, after 6 weeks and after 6 months of treatment. GIQLI questionnaire consists of 36 questions that assess the impact of disease on physical, social and mental status. For patients with FI disease specific FI quality of life questionnaire (FIQL) was used additionally. The FIQL questionnaire is disease specific for FI and measures quality of life in four domains (lifestyle, coping / behaviour, depression and embarrassment) on a scale of 1–4. Defecography was performed by retrograde infusion of radiopaque contrast and assessing rectal configuration and perineal descent while the patient was resting, contracting the anal sphincter, and straining to defecate. Anorectal physiology included rectal sensory testing and rectoanal inhibitory reflex. Rectal sensory testing was performed by distending the rectum with an air-filled balloon. Rectal volumes to distension for first sensation of urge, sensation of desire to defecate and maximum tolerated volume were recorded in millilitres. Study protocol and evaluation intervals are shown in Figure 1.

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

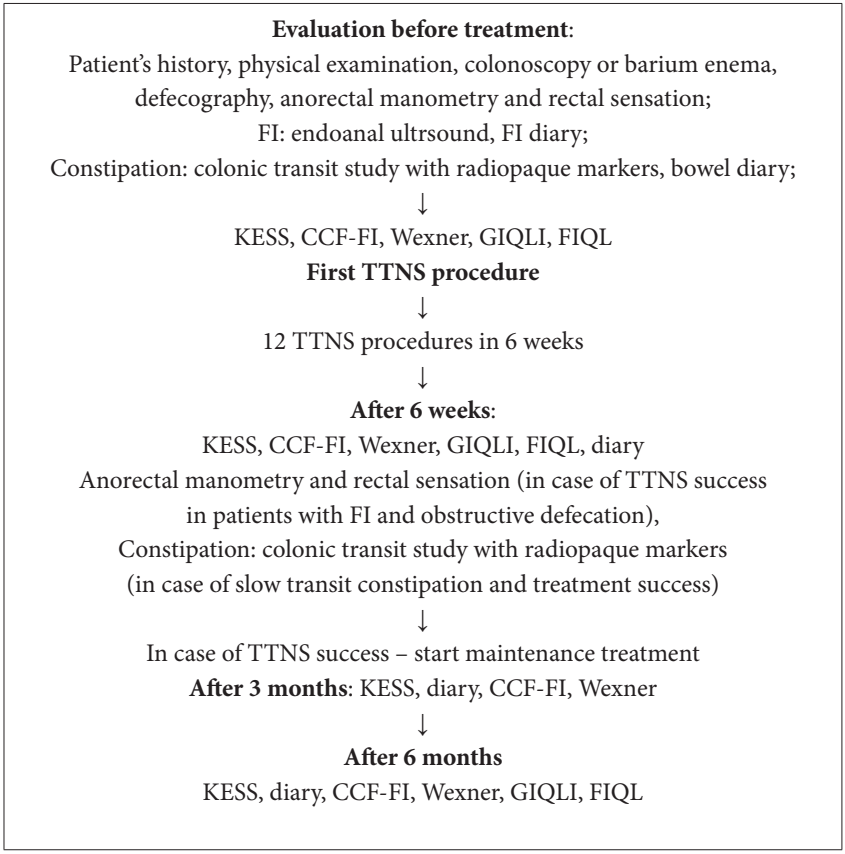

Figure 1. Study protocol and evaluation intervals.

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. Negative electrode was placed on the ankle skin behind the internal malleolus with the positive electrode being placed 10 cm above the negative one (Figure 2). 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. The appropriate electric current intensity level was determined based on the intensity on the threshold motor contraction and varied from 18 to 38 mA. The fixed pulse width of 200 μs and a frequency of 20 Hz were applied in continuous mode for 30 min. TTNS was done in outpatient department twice a week for 6 weeks (12 procedures). After 6 weeks in case of positive treatment effect, the maintenance treatment was started. The frequency of sessions was then slowly reduced from six sessions weekly to six sessions every 2 weeks.

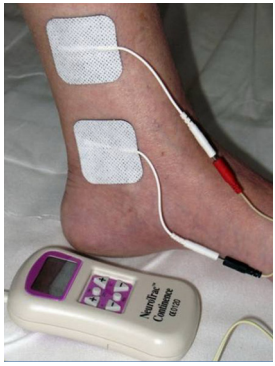

Figure 2. Placement of TTNS electrodes.

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 5 points difference with a 5% significance level and 90% power.

With reference to previous studies and initial data of our study, we estimated that 20 patients would be necessary to detect an improvement of FI in 50% with a power of 90% at a significance level of 0.05.

Continuous variables were checked for normal distribution by Shapiro-Wilk test. Normally distributed data were expressed as mean and standard deviations, and nonparametric data were expressed as median and range. Paired tests were used to compare data at baseline and after the treatment: paired t-test for parametric, Wilcoxon signed-ranks test for nonparametric variables. 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

Patients with constipation

Between 2011 and 2013, 49 patients underwent TTNS for constipation. All patients completed 12 sessions of TTNS in 6 weeks, filled in bowel diaries, KESS and GIQOL questionnaires. Patients' characteristics are shown in Table 1.

Table 1. Patients' characteristics.

Baseline demographics:	
Age (years)	Average – 52.41 ± 17.73; Median – 52 (25–82)
Gender (male/female)	4/45
Duration of constipation (years)	Average – 13.78 ± 9.53; Median – 12 (1-50);
Anorectal manometry:	
Resting pressure (mmHg)	Average – 48.23 ± 14.93; Median – 50 (15-78);
Squeeze pressure (mmHg)	Average – 104.76 ± 25.08; Median – 105.5 (50-160);
Dyssynergic defecation	21 (42.86 %)
Rectal sensation thresholds:	
First sensation volume (ml)	Median – 40 (10-250); Average – 63.47 ± 63.71;
Urge volume (ml)	Median – 125 (40-350); Average – 138.67 ± 81;
Maximum tolerable volume (ml)	Median – 200 (80-500); Average – 232.14 ± 98.24;
Rectal hypersensitivity	9 patients (18.37 %)
Rectal hyposensitivity	15 patients (30.61 %)
Defecography	
Incomplete rectal evacuation	33 patients (67.3 %)
Slow transit	10 (20.4 %)

Clinical outcome

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 subgroup analysis, 26 patients with successful treatment had a mean baseline KESS score of 20.58 ± 5.22 (median 19.5 (13-31)), which improved to a mean score of 11.27 ± 5.78 (median 9 (3-26)) after 6 weeks of TTNS ($p < 0.001$) (Figure 3). This group of patients started maintenance treatment. During evaluation after 3 months of TTNS mean KESS score was 11.1 ± 5.24 (median 9 (3-20)) ($p < 0.001$), after 6 months - 11.78 ± 6.18 (median 10 (3-25) ($p < 0.001$) (Figure 4).

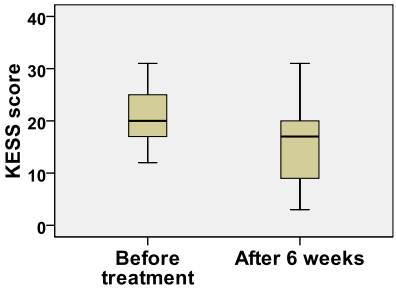

Figure 3. KESS score before and after 6 weeks of treatment

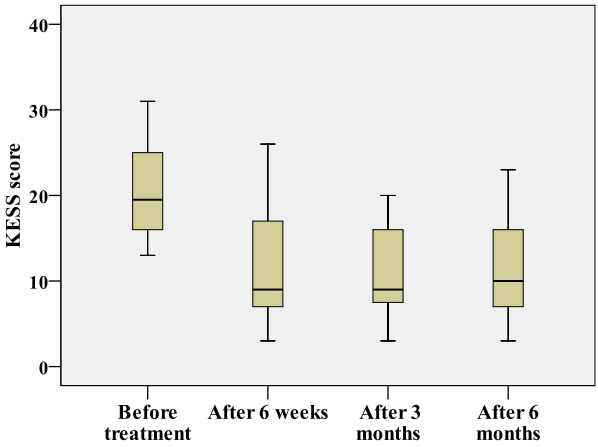

Figure 4. KESS score changes in treatment success subgroup before and after 6 weeks, 3 and 6 months of TTNS.

Two patients stopped maintenance treatment because of no further benefit (one after 3 months, another after 5 months). One patient had improvement, but found travel to the hospital too difficult. One woman with successful treatment decided to get pregnant, so she stopped the treatment after 3 months. Flow of patients through the study is shown in Figure 5.

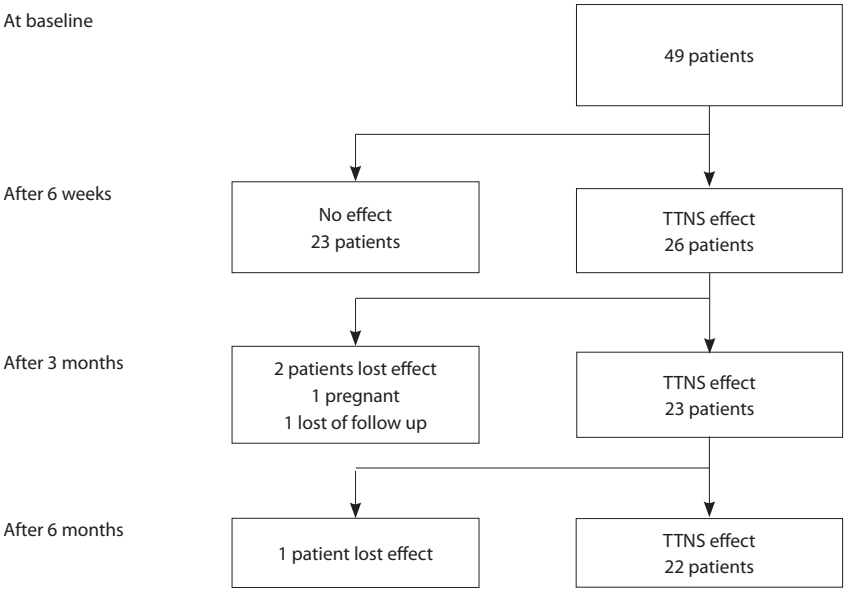

Figure 5. Flow of patients through the study.

Overall mean two week stool frequency increased from 4.65 ± 2.48 (median 4 (1-12)) pre-treatment to 7.47 ± 3.51 (median 7 (1-14)) post-treatment ($p < 0.001$). In the TTNS success subgroup a mean of 4.65 ± 2.62 (median 4 (2-12)) bowel motions per two-weeks at baseline increased to a mean of 9.69 ± 2.74 (median 10 (4-14)) after 6 weeks of treatment ($p < 0.001$). The median number of laxative tablets, suppositories and enemas used combined two weeks before treatment was 4 (range 0–44) (mean 8.85 ± 10.5) and it decreased to a median of 0 (range 0-16) (mean 3 ± 5.25) after the treatment ($p < 0.001$).

There was an improvement in the symptoms associated with constipation. A significant improvement on subjective rating of the overall severity of abdominal pain and bloating was observed with TTNS (Figure 6).

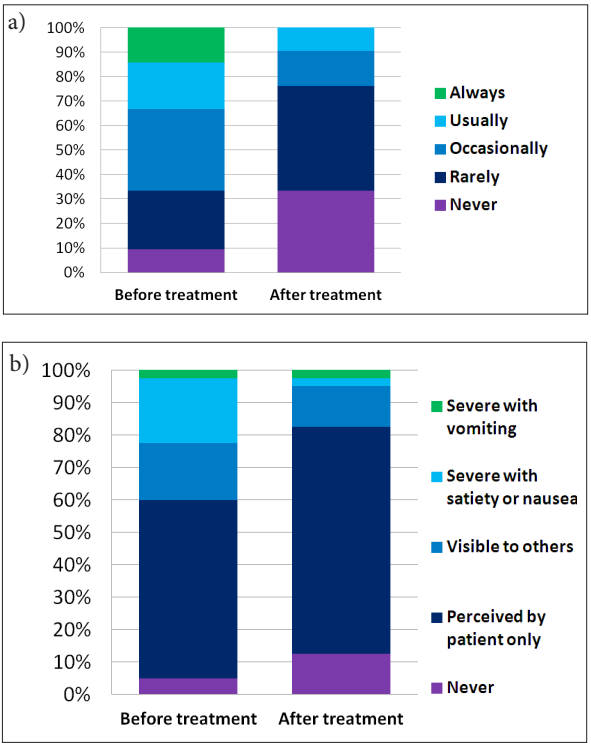

Figure 6. Subjective rating of (a) abdominal pain and (b) abdominal bloating at baseline and after 6 weeks of treatment as recorded by KESS questionnaire.

Overall mean GIQLI score improved from 92.98 ± 16.06 (median 94 (60–124)) to 104.76 ± 18.38 (median 105 (60-136)) ($p < 0.001$) after 6 weeks and to 116.27 ± 13.93 (median 116 (92-137)) after 6 months ($p < 0.001$). There was a statistically significant improvement in all four GIQLI subscales compared with baseline ($p < 0.001$) (Table 2).

Table 2. GIQLI score before and after 6 weeks of treatment with TTNS in patients with constipation.

	Before treatment			After 6 weeks of treatment			P value
	Average	Median (IQR)	Min.-Max.	Average	Median (IQR)	Min.-Max.	
GIQLI s	52.78 ± 7.16	53 (7)	32–69	57.86 ± 8.5	57 (12)	32–75	< 0.001
GIQLI e	9.55 ± 4.56	10 (8)	1–18	12.41 ± 4.04	12 (5)	3–20	< 0.001
GIQLI pf	15.47 ± 5.57	15 (9)	2–25	17.82 ± 5.67	18 (10)	2–26	< 0.001
GIQLI sf	12.41 ± 2.86	13 (5)	5–16	13.35 ± 2.63	14 (4)	7–16	0.001

IQR – interquartile range.

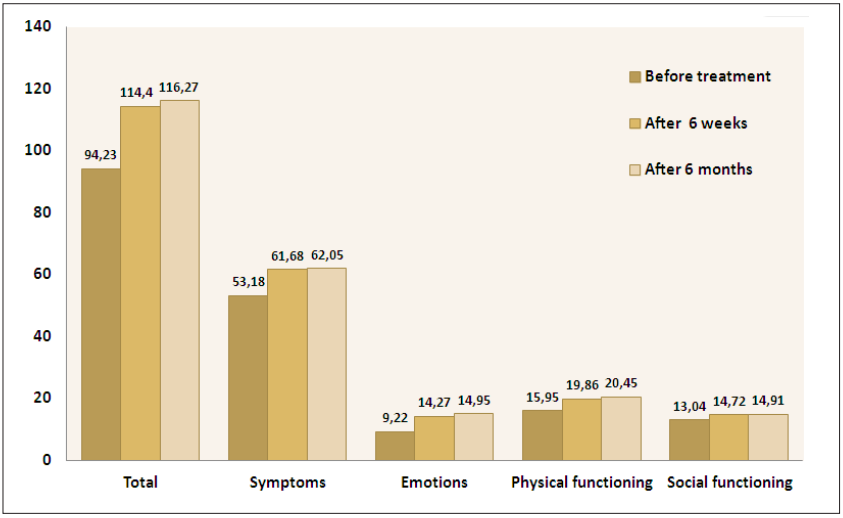

Figure 7. GIQLI score changes in the effect subgroup before and after 6 weeks and 6 months of TTNS treatment in patients with constipation.

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

Patients with slow transit constipation

Colonic transit study was performed at baseline and after 6 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 transit study. Colonic transit normalized in other two patients.

Patients with obstructive defecation

As many as 31 patients (all women) matched obstructive defecation criteria (Rome III). The effect of TTNS was seen in 17 patients (54.8 %) with obstructive defecation. The data of this group of patients before and after 6 weeks of TTNS is shown in Table 7.

Table 7. The data of the patients with obstructive defecation before and after 6 weeks of TTNS.

	Before treatment			**After 6 weeks of treatment**			**P value**
	Average ± SD	Median (IQR)	Min-max.	Average ± SD	Median (IQR)	Min-max.	
Age (years)	50.81 ± 18.13	50 (35)	25–80	–	–	–	–
Duration of constipation	13.1 ± 10.49	10 (15)	1–50	–	–	–	–
Stool frequency	5.19 ± 2.8	4 (4)	2–12	7.77 ± 3.39	7 (5)	2–14	< 0.001
KESS score	21.13 ± 5.33	20 (8)	12–31	15.61 ± 6.59	17 (11)	4–29	< 0.001
Laxatives	6.48 ± 6.16	4 (4)	0–28	3.58 ± 4.15	3 (5)	0–14	< 0.001
GIQL t	92.61 ± 15.87	94 (28)	67–124	104.03 ± 17.8	105 (27)	67–136	< 0.001
GIQL s	53.45 ± 7.11	54 (7)	37–69	57.84 ± 7.08	57 (9)	44–70	< 0.001
GIQL e	9.35 ± 4.13	10 (7)	3–18	12.19 ± 4.21	12 (5)	3–20	0.001
GIQL pf	14.77 ± 5.68	14 (9)	2–24	17.32 ± 6.05	17 (11)	2–26	< 0.001
GIQL sf	11.9 ± 2.94	12 (5)	5–16	13.03 ± 2.79	14 (5)	7–16	0.003

In case of TTNS effect anorectal manometry was performed in patients with obstructive defecation after 6 weeks of treatment. There was no statistically significant difference when comparing manometric and rectal sensitivity findings before and after 6 weeks of treatment (Table 8).

Table 8. Anorectal manometry findings in effect group of patients with obstructive defecation before and after 6 weeks of treatment.

	Before treatment	After 6 weeks of treatment	P value
Anorectal manometry:			
Resting pressure (mmHg)	Average – 50.49 ± 14.55 Median – 50 (18.74-78)	Average – 50.13 ± 13.76 Median 50 (20–74.5)	0.819
Squeeze pressure (mmHg)	Average – 110.72 ± 22,23 Median – 110 (75-160)	Average – 112.294 ± 21.32 Median – 113 (75-157)	0.616
Rectal sensation thresholds:			
First sensation volume (ml)	Median – 50 (10 - 250) Average 75.29 ± 73.83	Median 50 (20-200) Average 68.23 ± 61.57	0.223
Urge volume (ml)	Median – 160 (50-350) Average – 154.7 ± 88.47	Median – 150 (50-320) Average – 145 ± 81.28	0.224
Maximum tolerable volume (ml)	Median – 220 (100-500) Average – 240.59 ± 108.83	Median – 220 (120-470) Average – 232.35 ± 92.43	0.330

Investigation of potential predictors of TTNS treatment success in patients with constipation

Comparison between success and failure groups did not help to define initial conditions predictive of a symptomatic improvement. Both groups had similar age, symptom duration, KESS score, stool frequency, laxative consumption and GIQLI scores at referral. Baseline measures of constipation in relation to success or failure of TTNS are shown in Table 9. The success rate of TTNS was similar in patients with slow and normal transit time as well as in patients with complete and incomplete evacuation in defecography. Both groups had similar rectal sensation volumes (Table 10).

Table 9. Baseline measures of constipation in relation to success or failure of TTNS.

Baseline measures	TTNS success			TTNS failure			P value
	Average ± SD	Median (IQR)	Min.-max.	Average ± SD	Median (IQR)	Min. –max.	
Age	50.5 ± 15.92	51 (23.75)	27-82	54.57 ± 19.73	54 (37)	25-80	0.496
Duration of symptoms (years)	13.77 ± 8.98	10 (13.5)	1-30	13.78 ± 10.32	15 (15)	1-50	0.904
Stool frequency	4.65 ± 2.62	4 (65)	2-12	4.65 ± 2.37	4 (65)	1-12	0.734
KESS score	20.58 ± 5.22	19.5 (9)	13-31	21.22 ± 5.26	20 (9)	12-31	0.581
Laxatives	8.85 ± 10.5	4 (11)	0-44	6.13 ± 6.5	4 (4)	0-28	0.761
GIQLI	91.65 ± 16.45	87.5 (28.25)	67-124	94.48 ± 15.83	96 (22)	60-123	0.541
GIQLI s	52.65 ± 7.22	53.5 (9)	37-69	52.91 ± 7.25	53 (6)	32-67	0.809
GIQLI e	8.73 ± 4.91	8.5 (9.25)	1-18	10.48 ± 4.04	10 (4)	3-18	0.202
GIQLI ff	15 ± 5.9	14 (11)	4-25	16 ± 5.26	17 (7)	2-24	0.405
GIQLI sf	12.5 ± 3.17	12.5 (6)	5-16	12.3 ± 2.53	13 (4)	7-16	0.606

Table 10. Baseline measures of functional colorectal investigations of patients with constipation in relation to success or failure of TTNS.

	All patients	TTNS failure	TTNS success	P value
Colonic transit				
Normal, n (%)	39	17 (43.6)	22 (56.4)	
Slow, n (%)	10	6 (60)	4 (40)	0.483
Defecography				
Complete evacuation, n (%)	16	7 (44)	9 (56)	
Incomplete evacuation, n (%)	33	16 (48.5)	17 (51.5)	0.75
Rectal sensation thresholds (ml), median (min - max)				
First sensation,	40 (10-250)	45 (10-250)	40 (10-250)	0.813
Urge volume,	125 (40-350)	120 (40-350)	130 (50-350)	0.613
Maximum tolerable volume,	200 (80-500)	225 (80-500)	200 (90-500)	0.508
Dyssinergic defecation in anorectal manometry	21	11	10	0.324

Patients with FI

Between 2011 and 2013 twenty patients underwent TTNS for FI. All patients completed 12 sessions of TTNS in 6 weeks, filled in bowel diaries, FIQL and GIQLI questionnaires. Patient's characteristics are shown in Table 11.

Table 11. Patients' characteristics.

Baseline demographics:	
Age (years)	Average – 64.1 ± 14.32, Median – 68.5 (30–84)
Gender (male/female)	4/16
Duration of incontinence (years)	Average – 6.03 ± 5.44 Median - 4 (1-18)
Anorectal manometry:	
Resting pressure (mmHg)	Average – 36.61 ± 19.74 Median - 35 (15-94)
Squeeze pressure (mmHg)	Average – 75.31 ± 23,87 Median - 75 (40–109)
Rectal sensation thresholds:	
First sensation volume (ml)	Median – 35 (10-80); Average – 40 ± 19.67;
Urge volume (ml)	Median – 109 (40-200); Average – 109 ± 43.27;
Maximum tolerable volume (ml)	Median – 185 (100-400); Average – 191 ± 74.68;
Rectal hypersensitivity	4 patients (20 %)
Rectal hyposensitivity	3 patients (15 %)
Endoanal ultrasound:	
Intact sphincter complex	15
External sphincter defect	2 (partial)
Internal sphincter defect	3

Clinical outcome

Of the 20 patients, 11 (55 %) had a 50 % or greater reduction in incontinence episodes at 6 weeks of follow up. The overall median two week FI episodes decreased from 4 (range 2-84) (15.15 ± 23.4) pre-treatment

to median 2 (range 0-56) (mean 6.75 ± 12.47) after 6 weeks of treatment (p = 0.002). In the effect subgroup a median of 4 (range 2-70) (mean 16.4 ± 22.86) FI episodes per two weeks at baseline decreased to a median of 1 (0-10) (mean 2.5 ± 3.75) after 6 weeks (p = 0.005) the treatment. The overall mean Wexner score improved significantly with treatment from 10.95 ± 3.73 (median 11 (2-19)) to 7.85 ± 3.76 (median 7 (2-17)) (p = 0.002) after six weeks (Figure 8). Mean CCF-FI score decreased from 10.9 ± 4.34 (median 9.5 (5-20)) to 7.8 ± 3.96 (median 7 (2-18)) (p = 0.002) (Figure 9).

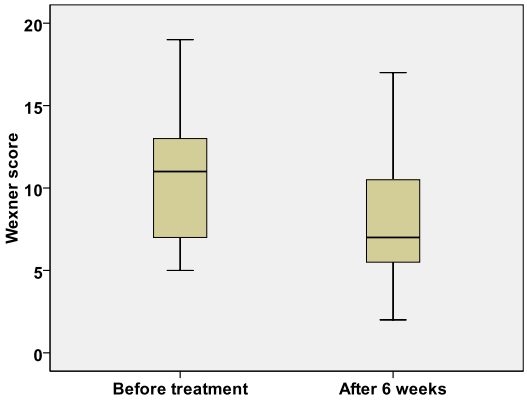

Figure 8. Wexner score before and after 6 weeks of treatment with TTNS.

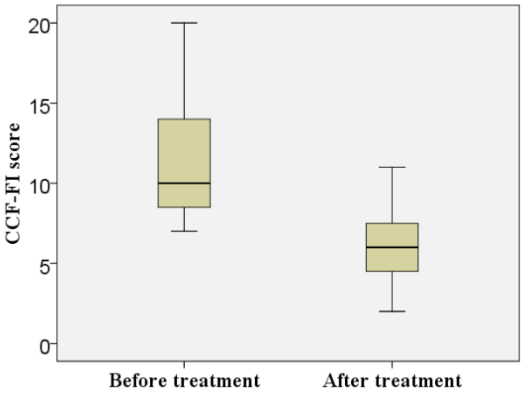

Figure 9. CCF-FI score before and after 6 weeks of treatment with TTNS.

Despite TTNS effect two patients stopped maintenance treatment. One patient found a job (after 6 weeks) and had no time to attend treatment. Another one stopped the treatment because of the suspected kidney tumour during sonography after 3 months of successful treatment. Flow of patients with FI through the study is shown in Figure 10.

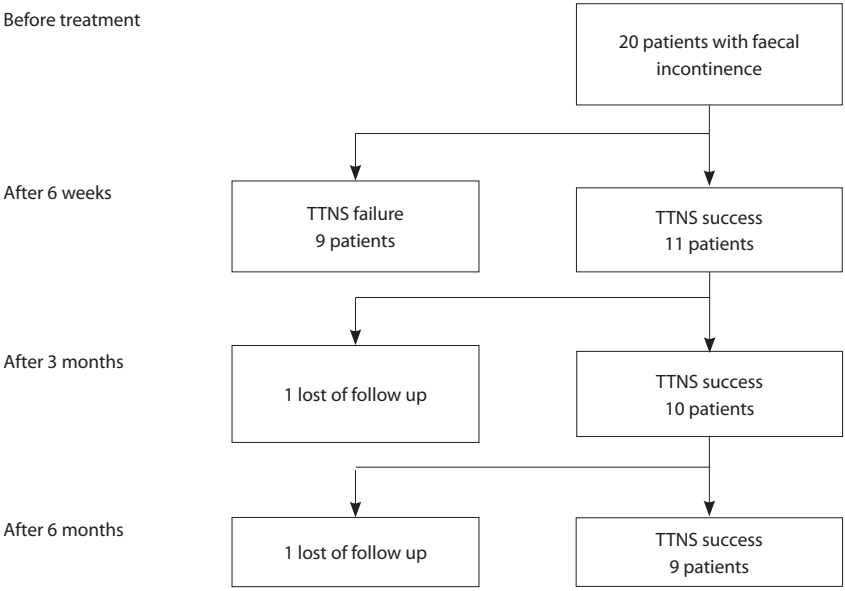

Figure 10. Flow of patients with FI through the study.

In subgroup analysis, patients with successful treatment had a mean baseline Wexner score of 11.4 ± 4.03 (median 11 (7-19)), which improved to a mean score of 5.7 ± 2.95 (median 6 (2-12)) (p = 0.005) after 6 weeks, to 5.6 ± 2.27 (median 5.5 (3–11), p = 0,004) after 3 months and to 5.5 ± 2.4 (median 5(3-11), p = 0,004) after 6 months (Figure 11). Mean CCF-FI score improved from 11.1 ± 4.48 (median 9.5 (7-20)) to 5.7 ± 2.58 (median 5.5 (2-11)) after 6 weeks (p = 0.005), to 5.6 ± 2.27 (median 5.5 (3–11), p = 0,004) after 3 months and to 5.5 ± 2.4 (median 5 (3-11), p = 0,004) after 6 months of TTNS (Figure 12).

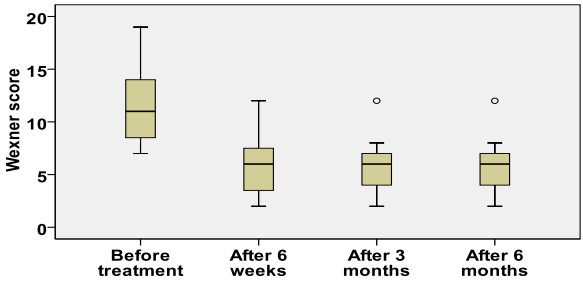

Figure 11. Wexner score changes before and after the treatment in the effect group.

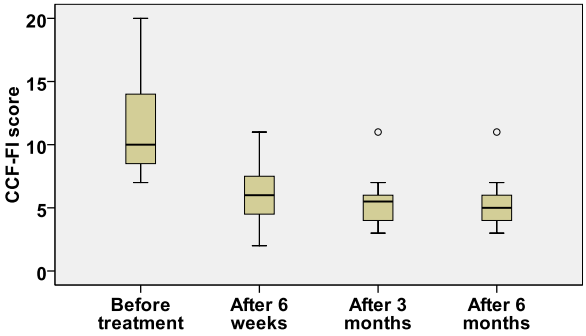

Figure 12. CCF-FI score changes before and after the treatment in the effect group.

Overall mean GIQLI score improved from 88.9 ± 19.02 (90.5 (55-121)) to 101.9 ± 18.03 (median 104 (75-132)) ($p < 0.001$) after 6 weeks. The GIQLI improved significantly in all domains (Table 12).

Table 12. GIQLI score changes in patients with FI before and after 6 weeks of treatment.

	Before treatment			After treatment			P
	Average ± SD	Median (IQR)	Min.–max.	Average ± SD	Median (IQR)	Min.-max.	
GIQLI	88.9 ± 19.02	90.5 (28.75)	55 – 121	101.9 ± 18.03	104 (30.25)	75 – 132	< 0.001
GIQLI s	49.35 ± 10.16	48 (15.25)	28 – 66	56.5 ± 9.36	56.5 (18.5)	43 – 71	0.001
GIQLI e	10.05 ± 3.05	10.5 (5.5)	5 – 17	12.6 ± 3.41	12.5 (6)	5 – 18	< 0.001
GIQLI pf	14.3 ± 5.92	14.5 (8)	5 – 24	16.05 ± 5.57	18 (10.75)	7 – 23	0.037
GIQLI sf	12.1 ± 3.4	12.5 (6.5)	4 – 16	13.6 ± 2.84	14.5 (4.75)	7 – 16	0.005

In the response subgroup mean GIQLI score improved from 91.4 ± 21.82 (median 93.5 (55–121)) to 109.6 ± 18.15 (median 112.5 (75–132)) after 6 weeks (p = 0.005) and to 112.55 ± 18.3 (median 116 (78–132)) after 6 months (p = 0.04). The mean score of symptom subscale from 49.8 ± 10.32 (median 50.5 (36–63)) increased to 60.2 ± 9.16 (median (63 (43–71)) (p = 0.005) after 6 weeks and to 62.67 ± 8.29 (median 64 (44–71)) (p = 0.04) after 6 months. The mean score of emotion subscale from 10.5 ± 3.6 (median 11.5 (6–17)) increased to 13.9 ± 3 (median 15 (9–18)) (p = 0.005) after 6 weeks and to 14.78 ± 3.03 (median 15 (10 – 18)) (p = 0.04) after 6 months. Physical functioning score increased from 15.6 ± 6.62 (median 17 (5–24)) to 18.1 ± 5.9 (median 21 (7-23)) (p = 0.017) after 6 weeks and to 18.11 ± 5.78 (median 21 (8–23)) (p = 0,031) after 6 months. Social functioning score from 12.2 ± 3.82 (median 13.5 (4–16)) increased to 14.1 ± 3.03 (median 16 (7–16)) (p = 0.017) and to 13.89 ± 3.48 (median 14 (7–19)) (p = 0.016) respectively (Figure 13).

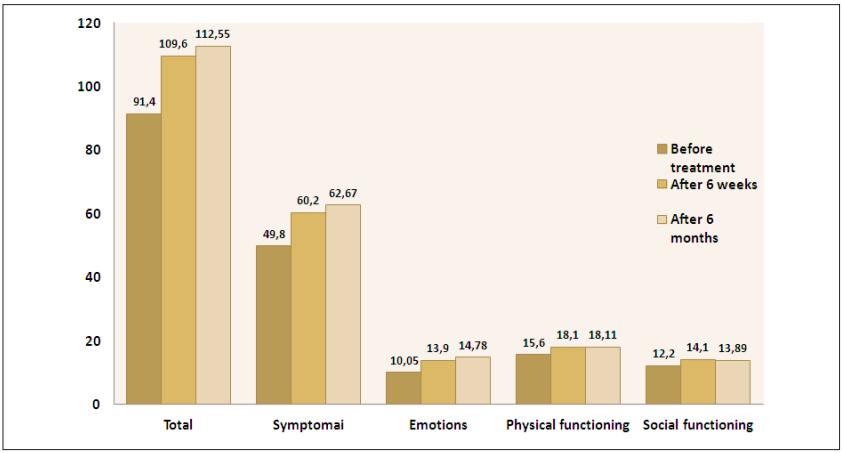

Figure 13. GIQLI changes in patients with FI and TTNS success before and after the treatment.

The disease-specific assessment with FIQL questionnaire showed improvements in all four domains (Table 13).

Table 13. FIQL score changes before and after 6 weeks of treatment.

	Before treatment			After 6 weeks of treatment			P
	Average ± SD	Median (IQR)	Min.–max.	Average ± SD	Median (IQR)	Min.–max.	
FIQL l	2.56 ± 0.8	2.55 (1.5)	1.2–3.75	2.92 ± 0.83	3.1 (1.34)	1.3–4	0.001
FIQL c	2.05 ± 0.7	2.05 (1.19)	1-3.25	2.49 ± 0.75	2.62 (1.5)	1.125-3.57	0.003
FIQL d	2.76 ± 0.56	2.67 (0.82)	2-3.8	3.08 ± 0.65	3 (1.12)	2.17-4.14	0.007
FIQL e	1.83 ± 0.62	2 (1.02)	1-2.67	2.2 ± 0.66	2.5 (1.01)	1–3	0.003

In the response group mean score of FIQL lifestyle domain increased from 2.56 ± 0.78 (median 2.8 (1.5–3.7)) pre-treatment to 23.18 ± 0.77 (median 3.39 (1.9–4)) post-treatment (p = 0.005) and to 3.17 ± 0.72 (median 3.2 (1.9–4)) after 6 months (p = 0.04). The mean score of coping domain increased from 2.13 ± 0.76 (median 2.12 (1.11–3.25)) to 2.81 ± 0.63 (median 2.88 (1.5–3.57)) (p = 0.005) after 6 weeks and to 2.8 ± 0.61 (median 2.87 (1.5–3.58)) after 6 months (p = 0.04). The score of depression domain increased from 2.9 ± 0.62 (median 2.93 (2–3.8)) to 3.48 ± 0.55 (median 3.6 (2.57–4.14)) after 6 weeks (p = 0.005), and to 3.52 ± 0.5 (median 3.5 (2.57–4.14)) after 6 months (p = 0.04). The score of embarrassment domain increased from 1.67 ± 0.61 (median 1.67 (1–2.67)) to 2.27 ± 0.66 (2.5 (1–3)) (p = 0.007) and to 2.22 ± 0.67 (median 2.66 (1–3)) (p = 0.08) respectively. The changes of FIQL score in the effect subgroup are shown in Figure 14.

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

In case of TTNS effect anorectal manometry was performed after 6 weeks in patients with FI. There was no statistically significant difference when comparing manometric and rectal sensitivity findings before and after 6 weeks of treatment (Table 14).

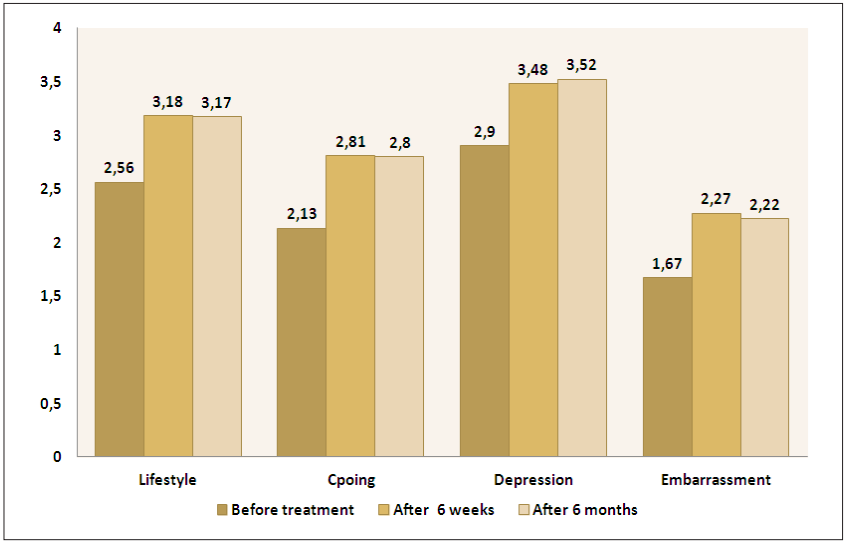

Figure 14. FIQL score changes before and after the treatment in effect group.

Table 14. Anorectal manometry findings in effect group of patients with FI before and after 6 weeks of treatment.

	Before treatment	After 6 weeks of treatment	P value
Anorectal manometry:			
Resting pressure (mmHg)	Median – 40 (20-94) Average – 43.45 ± 20.66	Median 40 (25-95) Average – 44.45 ± 19.85	0.375
Squeeze pressure (mmHg)	Median - 80 (51-120) Average – 82.72 ± 20.98	Median - 80 (55-120) Average - 83.18 ± 19.27	0.508
Rectal sensation thresholds:			
First sensation volume (ml)	Median - 40 (10-80) Average 39.09 ± 21.54	Median 40 (20-70) Average 40 ± 15.49	0.813
Urge volume (ml)	Median – 120 (40-200) Average – 104.54 ± 47.4	Median - 110 (50–180) Average – 107.27 ± 37.71	0.613
Maximum tolerable volume (ml)	Median - 150 (100-400) Average – 184.54 ± 83.35	Median - 150 (110-350) Average – 182.72 ± 66.34	0,508

Investigation of potential predictors of TTNS treatment success in patients with FI

Comparison between success and failure groups did not help to define initial conditions predictive of a symptomatic improvement. Both groups were of similar age, symptom duration, CCF-FI score, Wexner score, number of FI episodes, FIQL and GIQLI scores at referral (Table 15).

Table 15. Baseline measures of FI in relation to success or failure of TTNS.

	TTNS success			TTNS failure			p value
	Average ± SD	Median (IQR)	Min.-max.	Average ± SD	Median (IQR)	Min.-max.	
Age	63.5 ± 17.78	70 (25.25)	30-82	64.7 ± 10.76	66 (17.75)	52-84	0.623
Duration of symptoms (years)	4.1 ± 3.9	2 (8.25)	1-10	7.95 ± 6.26	4.5 (11.75)	1,5-18	0.062
CCF-FI score	11.1 ± 4.48	9.5 (5.75)	7-20	10.7 ± 4.42	9.5 (9)	5-18	0.731
Wexner score	11.4 ± 4.03	11 (7.5)	7-19	10.5 ± 3.57	10.5 (5.5)	5-17	0.674
FI episodes	16.4 ± 22.86	4 (27.5)	2-70	13.9 ± 25.11	4.5 (12)	2-84	0.699
GIQLI	91.4 ± 21.82	93.5 (32.5)	55-121	86.4 ± 16.53	86.5 (27.5)	57-110	0.496
GIQLI s	49.8 ± 10.32	50.5 (21.75)	36-63	48.9 ± 10.54	47.5 (13.75)	28-66	0.791
GIQLI e	10.5 ± 3.6	11.5 (6)	6-17	9.6 ± 2.5	9.5 (3.5)	5-13	0.703
GIQLI ff	15.6 ± 6.62	17 (10.5)	5-24	13 ± 5.14	11 (8.5)	7-23	0.270
GIQLI sf	12.2 ± 3.82	13.5 (5)	4-16	12 ± 3.13	11.5 (7)	8-16	0.760
FIQL l	2.56 ± 0.78	2.8 (1.4)	1.5-3.7	2.55 ± 0.87	2.5 (1.42)	1.2-3.75	1.000
FIQL c	2.13 ± 0.76	2.12 (1.47)	1.11-3.25	1.97 ± 0.66	1.81 (0.97)	1-3.25	0.545
FIQL d	2.9 ± 0.62	2.93 (1.15)	2-3.8	2.62 ± 0.48	2.62 (0.62)	2-3.67	0.211
FIQL e	1.67 ± 0.61	1.67 (1.08)	1-2.67	2 ± 0.61	2 (1.35)	1-2.67	0.246

DISCUSSION

The results of this study proved that TTNS twice a week for 6 weeks may be efficacious in patients with constipation and FI 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.

TTNS effect, defined as a reduction in KESS score of 5 points or more, was achieved in more than a half of patients with constipation. In the effect group the considerable reduction of almost 10 points of the mean KESS score was observed after 6 weeks of treatment with TTNS. 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.

TTNS effect, defined as 50 % or greater reduction in incontinence episodes in two weeks, was achieved in more than a half of patients (55 %) with FI. Significant decrease was seen in FI episodes and in CCF-FI score. The quality of life increased after the treatment in both groups of patients.

Since different outcome measures and inclusion criteria have been used, the comparison with other studies is complicated. The most common outcome measures in the studies evaluating SNS effect on constipation was a change in the frequency of defecation. However, the number of defecations is not the only symptom of constipation. According to Rome III criteria, two or more symptoms must be present for 6 months or more. These include straining at stool, passing hard stools, sensation of incomplete emptying, sensation of anorectal obstruction, digitation and defecation frequency of less than three times a week. Therefore, the primary outcome in our study was the change in KESS score, and not an increase in the number of defecations. Currently, neither there are standard criteria as to which scoring system should be used, nor universally accepted standardized inclusion criteria for patients undergoing clinical trials for constipation. KESS score was used in this study because we find it informative and useful, and we 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 sensation of bloating and abdominal pain was seen after the treatment with TTNS.

The success rate of our 6 week treatment period in patients with constipation can be comparable with the percutaneous nerve evaluation phase in SNS studies. The success rate of percutaneous nerve evaluation phase for constipation in adults in published SNS studies ranged from 42 % to 73 %. In our study the overall effect was seen in 53.1 %. In 2011 Collins et al. published results of 18 patients with 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 3 patients (16.6 %). The result in patients with 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 %).

The reported efficacy of PTNS and TTNS in FI studies varies from 54 % to 84.3 %. Nevertheless, these are small, uncontrolled trials with different outcome measures and heterogeneous patient populations. The comparison with results of other TTNS and PTNS studies is complicated, because of different outcome measures used. In several studies a FI score or even a visual analogue score, not a change in incontinence episodes was used as a primary endpoint. Furthermore, various stimulation parameters and regimens have been used. Primary outcome measure of our study was the reduction of incontinence episodes in 2 weeks. The decrease of FI episodes per unit of time was the most frequently used measure in SNS studies and is considered to be least affected by subjective reporting. However, being a count this variable has a Poisson distribution and a greater variability than expected. This raises major difficulties in defining a clinically significant mean reduction in FI episodes within a population of patients with widely dispersed initial FI frequencies. To counter this problem, contemporary studies have adopted a primary outcome for 'success', using a categorical measure of percentage reduction (the proportion of patients who have a 50 per cent or greater reduction in FI episodes per week).

The treatment with TTNS and PTNS is not standardized and the optimal regimen is not known. Various different frequencies have been described in

the literature varying from twice daily for 3 months to every other day for 4 weeks. In most TTNS studies the stimulation was performed every day by patients themselves. Moreover, in some studies the treatment course lasted longer, about 3 months and more. In order to avoid bad patient compliance and to perform procedure in a correct standardized manner, TTNS in our study was done in the outpatient department twice a week for 6 weeks, like in the most PTNS studies. Presumably a better effect might be observed after 3 months of daily stimulation.

The TTNS was well tolerated; the compliance of the patients was very good, no adverse events occurred. The same results were seen in other TTNS studies. It is noteworthy that adverse effects such as gastrodynia, paraesthesia or numbness and bleeding from the needle site have been reported in several PTNS studies.

Our study had several limitations. Firstly, the group of patients with FI was considerably small. Nevertheless, most published TTNS and PTNS studies with FI patients are small, uncontrolled and with heterogeneous patient populations. Only 15–45 % of those suffering from FI consult medical services, owing to embarrassment and lack of knowledge about potential treatments.

Another limitation was heterogeneous group of patients with constipation. The majority suffered from obstructive defecation, other 10 patients were with slow transit constipation and the rest 8 with normal transit constipation. In SNS studies on constipation different types of constipation are also evaluated together. Constipation, especially obstructive defecation, can originate from different reasons, therefore it is a very heterogeneous pathology itself.

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

CONCLUSIONS

1. TTNS done twice weekly for 6 weeks is effective for 53.1% of patients with constipation, who have failed to respond to maximal conservative treatment.
2. TTNS done twice weekly for 6 weeks is effective for 55% of patients with FI, who have failed to respond to maximal conservative treatment.
3. TTNS improves quality of life in patients with constipation and FI.
4. Findings of anorectal manometry and rectal sensitivity did not change significantly before and after 6 weeks of treatment with TTNS in patients with constipation and FI.
5. Potential predictors of TTNS treatment success were not defined.

SUGGESTIONS FOR CLINICAL PRACTICE AND FURTHER RESEARCH

We suggest using TTNS in clinical practice in the treatment of patients with FI and constipation, who have failed to respond to maximal conservative treatment.

Larger randomised controlled studies are needed to evaluate TTNS effect on constipation. The evidence about long term effects is needed. It remains unclear how long and how often the stimulation should be done, and which patients are most likely to benefit from the therapy.

SUMMARY IN LITHUANIAN

ĮVADAS

Tiriamoji problema ir darbo aktualumas

Vidurių užkietėjimas yra dažniausiai pacientų įvardijamas virškinimo sistemos skundas, kuris vargina net iki 27,2 % populiacijos ir labai blogina pacientų gyvenimo kokybę. Daliai pacientų maksimalus konservatyvus lėtinio vidurių užkietėjimo (LVU) gydymas yra neveiksmingas. Chirurginis gydymas dažnai sukelia komplikacijų, be to, dažnai neefektyvus.

Išmatų nelaikymas (IN) – viena iš sunkiausiai sprendžiamų būklių koloproktologijoje, kuri sukelia fizinių ir psichologinių problemų, socialinę izoliaciją ir reikšmingai pablogina gyvenimo kokybę. IN gydymas yra sudėtingas, nes tiek konservatyvūs, tiek chirurginiai gydymo metodai dažnai būna neveiksmingi. Šiuo metu klinikinėje praktikoje šlapimo bei išmatų nelaikymui bei vidurių užkietėjimui gydyti gan plačiai taikoma nuolatinė žemos amplitudės kryžmeninių nervų moduliacija (KNM). KNM yra minimaliai invazinė procedūra, bet implantuojant neurostimuliatorių yra infekcijos bei kitų komplikacijų rizika, šio metodo taikymas yra brangus. Periferinę kryžmeninio nervinio rezginio neuromoduliaciją galima atlikti ir neinvaziniu, techniškai paprastesniu neuromoduliacijos būdu – stimuliuojant blauzdinį nervą, t. y. atliekant transkutaninę blauzdinio nervo stimuliaciją (TBNS). TBNS yra paprastas, gerai toleruojamas ir pigus gydymo metodas. Jis gali būti atliekamas ambulatoriškai arba pacientas gali jį taikyti namuose savarankiškai. Literatūroje daug diskutuojama dėl šio metodo efektyvumo išmatų nelaikantiems pacientams ir nėra duomenų apie jo veiksmingumą LVU sergantiems pacientams.

Tyrimo tikslas ir uždaviniai

Tyrimo tikslas – perspektyviojo tyrimo būdu įvertinti TBNS efektyvumą išmatų nelaikančių ir LVU sergančių pacientų gydymui bei poveikį šių pacientų gyvenimo kokybei, taip pat nustatyti sėkmingo gydymo rodiklius.

Tyrimo uždaviniai:

Nustatyti:

1. TBNS, atliekamos du kartus per savaitę 6 savaites, efektyvumą LVU sergantiems pacientams, kuriems maksimalus konservatyvus gydymas yra neveiksmingas;

2. TBNS, atliekamos du kartus per savaitę 6 savaites, efektyvumą išmatų nelaikantiems pacientams, kuriems maksimalus konservatyvus gydymas yra neveiksmingas;
3. Kaip dėl TBNS poveikio kinta IN ir LVU sergančių pacientų gyvenimo kokybė;
4. Kaip dėl TBNS poveikio kinta IN ir LVU sergančių pacientų funkcinių storosios žarnos tyrimų duomenys;
5. Galimus sėkmingo TBNS gydymo rodiklius.

Tyrimo naujumas ir praktinė reikšmė

Naujumas:

1. Pirmą kartą ištyrėme TBNS poveikį LVU sergantiems pacientams.
2. Vertinome TBNS poveikį išmatų nelaikantiems pacientams, naudodami kitokius stimuliacijos parametrus ir dažnumą: 20 Hz dažnį ir sukeliantį motorinį atsaką intensyvumą (suprasensorinė stimuliacija), procedūras atlikome 2 kartus per savaitę 6 savaites.

Ginamieji disertacijos teiginiai

1. TBNS, atliekama du kartus per savaitę 6 savaites, yra efektyvus gydymo metodas pusei LVU sergančių pacientų, kuriems maksimalus konservatyvus gydymas yra neveiksmingas.
2. TBNS, atliekama du kartus per savaitę 6 savaites, yra efektyvus gydymo metodas pusei IN sergančių pacientų.
3. TBNS gerina IN ir LVU sergančių pacientų gyvenimo kokybę.

TYRIMO MEDŽIAGA IR METODAI

Nuo 2011 metų lapkričio iki 2014 metų birželio Vilniaus universiteto ligoninėje „Santariškių klinikos“ atliktas prospektyvusis tyrimas, kuriame IN ir LVU sergantys pacientai buvo gydomi TBNS. Pacientų įtraukimo į tyrimą kriterijai: kietų ir (ar) skystų INs arba funkcinis vidurių užkietėjimas (remiantis Romos III kriterijais), stabili psichika, nesėkmingas konservatyvus gydymas, pakankamas motorinis ir (ar) sensorinis atsakas

į TBNS, simptomų trukmė – mažiausiai vieneri metai. Neįtraukimo kriterijai: didelis vidinio ir (ar) išorinio išangės rauko defektas (>120 laipsnių), organiniai tiesiosios žarnos pakitimai, lemiantys išmatų nelaikymą ar vidurių užkietėjimą, tiesiosios žarnos iškritimas, neurologinės ligos, lemiančios LVU ar IN, uždegiminės žarnų ligos, nepastovus tuštinimosi pobūdis, stoma, sunkus kojų veninis nepakankamumas ir (ar) dideli odos pokyčiai, implantuotas širdies stimuliatorius ar defibriliatorius, cukrinis diabetas, nėštumas arba planuojamas nėštumas.

TBNS buvo atliekama naudojant išorinį elektrostimuliacijos aparatą *NeuroTrack TENS* (*Verity Medical*), kurio elektrodai priklijuoti pagal blauzdinio nervo eigą. Stimuliacijos parametrai: 200 μs, 20 Hz, 10–38 mA, stimuliacijos intensyvumas – vos sukeliantis motorinį atsaką. Vienos procedūros trukmė – 30 minučių. TBNS buvo atliekama ambulatoriškai 2 kartus per savaitę 6 savaites. Jei po 6 savaičių (12 gydymo procedūrų) nustatytas teigiamas TBNS poveikis, gydymas pratęstas palaikomąja terapija, o nesant poveikio – gydymas nutrauktas. Palaikomoji terapija: 1 kartą per savaitę 6 savaites, vėliau po kartą kas 2 savaites 6 kartus (6 kartai per 12 savaičių).

TBNS poveikis LVU sergantiems pacientams buvo vertinamas naudojant KESS (*Knowles Eccersley Scott Symptom Scoring System*) vidurių užkietėjimo sunkumo klausimyną. Teigiamu TBNS poveikiu vidurių užkietėjimu sergantiems pacientams buvo laikomas ≥ 5 balų KESS klausimyno balo sumažėjimas po 6 gydymo savaičių. Naudojant LVU sergančių pacientų tuštinimosi dienoraštį, vertinti tuštinimosi dažnio, naudojamų laisvinamųjų vaistų ir (ar) klizmų skaičiaus pokyčiai prieš ir po 6 savaičių gydymo.

TBNS poveikis išmatų nelaikantiems pacientams buvo vertinamas naudojant dviejų savaičių tuštinimosi dienoraštį prieš gydymą ir po 6 gydymo savaičių. Teigiamu TBNS poveikiu išmatų nelaikymu sergantiems pacientams buvo laikoma ≥ 50 % išmatų nelaikymo epizodų per dvi savaites sumažėjimas po 6 gydymo savaičių. Prieš pradedant TBNS, po 6 savaičių ir esant efektui – po 3 bei 6 mėnesių IN sergantiems pacientams taip pat vertinti Klivlando klinikos išmatų nelaikymo skalės (KKIN) (*Cleveland Clinic Florida Faecal Incontinence Score*) ir *Wexner* išmatų nelaikymo skalės įverčiai.

TBNS poveikis vertintas ir pacientų gyvenimo kokybei: prieš pradedant gydymą, po 6 savaičių ir esant poveikiui – po 6 mėnesių visi IN ir

LVU sergantys pacientai pildė Gastrointestininį gyvenimo kokybės klausimyną (GIGK) (*Gastrointestinal Quality of Life Index*), IN sergantys pacientai – ir Išmatų nelaikymo gyvenimo kokybės klausimyną (INGK) (*Fecal Incontinence Quality of Life)*.

Vertinant anamnezės, klausimynų ir anorektalinės fiziologijos duomenis, buvo bandoma nustatyti rodiklius, kurie leistų tiksliau atrinkti pacientus, tinkamus šiam gydymo metodui, ir pasiekti geresnių gydymo rezultatų.

TYRIMO REZULTATAI

Tyrime dalyvavo tuštinimosi sutrikimų turintys 69 pacientai, iš jų 20 pacientų nelaikė išmatų, 49 sirgo LVU.

Lėtiniu vidurių užkietėjimu sergančių pacientų grupės rezultatai

Teigiamas TBNS poveikis (KESS balo sumažėjimas ≥ 5) nustatytas 26 iš 49 (53,1 %) LVU sergančių pacientų. Visų tyrime dalyvavusių LVU sergančių pacientų KESS klausimyno balo vidurkis po 6 savaičių gydymo labai pagerėjo – nuo 20,88 ± 5,19 iki 15,61 ± 7,19 (mediana – nuo 20 (12–31) iki 17 (3–31)) ($p < 0,001$). Vertinant pokyčius efekto grupėje, KESS klausimyno balo vidurkis po 6 savaičių gydymo TBNS sumažėjo nuo 20,58 ± 5,22 iki 11,27 ± 5,78 (mediana nuo 19,5 (13–31) iki 9 (3–26)) ($p < 0,001$). Šie pacientai tęsė palaikomąjį gydymą. Po 3 mėnesių gydymo TBNS KESS balo vidurkis buvo 11,1 ± 5,24 (mediana 9 (3–20)) ($p < 0,001$) po 6 mėnesių – 11,78 ± 6,18 (mediana 3–25) ($p < 0,001$).

Pacientų, kuriems gautas teigiamas TBNS poveikis, tuštinimosi kartų per dvi savaites vidurkis po 6 savaičių gydymo padidėjo nuo 4,65 ± 2,62 (mediana 4 (2–12)) iki 9,69 ± 2,74 (mediana 10 (4–14)) ($p < 0,001$). Šios grupės pacientų naudotų laisvinamųjų vaistų per dvi savaites skaičiaus mediana po 6 savaičių gydymo sumažėjo nuo 4 (0–44) (vidurkis 8,85 ± 10,5) iki 0 (0–16) (vidurkis 3 ± 5,25), ($p < 0,001$). Po 6 savaičių 12 pacientų (24,5 %) visai nevartojo laisvinamųjų vaistų. Po 6 savaičių gydymo TBNS akivaizdžiai sumažėjo ir su vidurių užkietėjimu susiję simptomai: pilvo skausmas ir pūtimas.

Pagerėjo TBNS gydytų LVU sergančių pacientų gyvenimo kokybė: bendras GIGK klausimyno balo vidurkis po 6 savaičių gydymo padidėjo nuo 92,98 ± 16,06 iki 104,76 ± 18,38 (mediana nuo 94 (60–124)) iki 105

(60–136)) ($p < 0,001$), po 6 mėnesių – iki 116,27 ± 13,93 (mediana 116 (92–137)) ($p < 0,05$). Statistiškai reikšmingai pagerėjo visų keturių GIGK klausimyno skalių įverčiai.

Efekto grupėje po šešių savaičių GIGK klausimyno balai nuo 94,22 ± 16,25 (mediana 96 (67–124)) prieš gydymą padidėjo iki 114,4 ± 14 (mediana 117,5 (89–136)) ($p < 0,001$), po 6 mėnesių – 116,27 ± 13,93 (mediana 116 (92–137)) ($p = 0,04$). Simptomų skalės balas nuo 53,18 ± 7,4 (mediana 54 (37–69)) padidėjo iki 61,68 ± 6,58 (mediana (62,5 (45 – 71)) ($p < 0,001$), po 6 mėnesių – 62,04 ± 6,7 (mediana 61 (55–73)) ($p = 0,04$). Emocijų skalės balas nuo 9,22 ± 4,75 (mediana 9,5 (1–18)) padidėjo iki 14,27 ± 3,13 (mediana 15 (9–20)) ($p < 0,001$), po 6 mėnesių – 14,95 ± 3,13 (mediana 15 (9–20)) ($p = 0,04$). Fizinio funkcionavimo skalės balas nuo 15,95 ± 5,7 (mediana 14,5 (7–25)) padidėjo iki 19,86 ± 5,15 (mediana 21,5 (10–26)) ($p < 0,001$), po 6 mėnesių – 20,45 ± 5,13 (mediana 22 (11–27)) ($p = 0,031$). Socialinio funkcionavimo skalės balas padidėjo nuo 13,04 ± 3,01 (mediana 14 (5–16)) iki 14,72 ± 1,86 (mediana 16 (11–16)) ($p = 0,001$), po 6 mėnesių – 14,91 ± 1,6 (mediana 16 (12–16)) ($p = 0,016$).

Obstrukcinės defekacijos kriterijus atitiko 31 pacientė, iš jų efektas gautas 17 pacienčių (54,8 %). Šioms pacientėms po 6 savaičių gydymo TBNS pakartotas anorektalinės manometrijos ir tiesiosios žarnos jautrumo tyrimas. Duomenys palyginti su prieš pradedant gydymą gautais duomenimis, statistiškai patikimo slėgių ir tiesiosios žarnos jautrumo skirtumo nenustatyta.

Prognozinių sėkmingo gydymo rodiklių LVU sergantiems pacientams nenustatėme.

Išmatų nelaikančių pacientų grupės rezultatai

Po 6 savaičių 11 iš 20 IN sergančių pacientų (55 %) pastebėtas teigiamas TBNS efektas, t. y. 50 % ar didesnis IN epizodų per 2 savaites sumažėjimas. IN epizodų skaičius po 6 savaičių gydymo sumažėjo nuo medianos 4 (2–84) (vidurkis 15,15 ± 23,4) iki 2 (0–56) (vidurkis 6,75 ± 12,47) ($p = 0,002$). Pacientams, kuriems buvo teigiamas TBNS poveikis, IN epizodų skaičiaus mediana po 6 savaičių sumažėjo nuo 4 (2–70) (vidurkis 16,4 ± 22,86) iki 1 (0–10) (vidurkis 2,5 ± 3,75) ($p = 0,005$).

Po 6 savaičių gydymo labai pagerėjo *Wexner* balo vidurkis nuo 10,95 ± 3,73 (mediana 11 (2–19)) iki 7,85 ± 3,76 (mediana 7 (2–17)) ($p = 0,002$) ir

KKIN skalės balo vidurkis nuo 10,9 ± 4,34 (mediana 9,5 (5–20)) iki 7,8 ± 3,96 (mediana 7 (2–18)) (p = 0,002). Teigiamo poveikio grupėje po 6 savaičių gydymo reikšmingai sumažėjo *Wexner* skalės balų vidurkis nuo 11,4 ± 4,03 (mediana 11 (7–19)) iki 5,7 ± 2,95 (mediana 6 (2–12)) (p = 0,005), po 3 mėnesių išliko 5,4 ± 2,9 (mediana 4,7 (2–12)) (p = 0,004), po 6 mėnesių – 5,7 ± 3,03 (mediana 6 (2–12), p = 0,004). KKIN skalės balų vidurkis nuo 11,1 ± 4,48 (mediana 9,5 (7–20)) po 6 savaičių sumažėjo iki 5,7 ± 2,58 (mediana 5,5 (2–11)) (p = 0,005), po 3 mėnesių – 5,6 ± 2,27 (mediana 5,5 (3–11), p = 0,004), po 6 mėnesių – 5,5 ± 2,4 (mediana 5 (3–11), p = 0,004).

Pagerėjo TBNS gydytų IN sergančių pacientų gyvenimo kokybė: bendras GIGK klausimyno balo vidurkis po 6 savaičių gydymo padidėjo nuo 88,9 ± 19,02 (90,5 (55–121)) iki 101,9 ± 18,03 (mediana 104 (75–132)) (p < 0,001). Po 6 savaičių visų keturių GIGK klausimyno skalių balai statistiškai reikšmingai pagerėjo. Efekto grupėje po šešių savaičių GIGK klausimyno balai nuo 91,4 ± 21,82 (mediana 93,5 (55–121)) prieš gydymą padidėjo iki 109,6 ± 18,15 (mediana 112,5 (75–132)) (p = 0,005), po 6 mėnesių – 112,55 ± 18,3 (mediana 116 (78–132)) (p < 0,004). Simptomų skalės balas nuo 49,8 ± 10,32 (mediana 50,5 (36–63)) padidėjo iki 60,2 ± 9,16 (mediana (63 (43–71)) (p = 0,005), po 6 mėnesių – 62,67 ± 8,29 (mediana 64 (44–71)) (p = 0,04). Emocijų skalės balas nuo 10,5 ± 3,6 (mediana 11,5 (6–17)) padidėjo iki 13,9 ± 3 (mediana 15 (9–18)) (p = 0,005), po 6 mėnesių – 14,78 ± 3,03 (mediana 15 (10–18)) (p = 0,04). Fizinio funkcionavimo skalės balas nuo 15,6 ± 6,62 (mediana 17 (5–24)) padidėjo iki 18,1 ± 5,9 (mediana 21 (7–23)) (p = 0,017), po 6 mėnesių – 18,11 ± 5,78 (mediana 21 (8–23)) (p = 0,031). Socialinio funkcionavimo skalės balas padidėjo nuo 12,2 ± 3,82 (mediana 13,5 (4–16)) iki 14,1 ± 3,03 (mediana 16 (7–16)) (p = 0,017), po 6 mėnesių – 13,89 ± 3,48 (mediana 14 (7–19)) (p = 0,016).

Ligai specifinio INGK klausimyno visų skalių balai po 6 savaičių gydymo pagerėjo, pokytis statistiškai reikšmingas. Efekto grupėje INGK klausimyno gyvenimo būdo skalės balų vidurkis nuo 2,56 ± 0,78 (mediana 2,8 (1,5–3,7)) po 6 savaičių padidėjo iki 3,18 ± 0,77 (mediana 3,39 (1,9–4)) (p = 0,005), po 6 mėnesių – iki 3,17 ± 0,72 (mediana 3,2 (1,9–4)) (p = 0,04). Elgesio skalės balų vidurkis nuo 2,13 ± 0,76 (mediana 2,12 (1,11–3,25)) po 6 savaičių gydymo padidėjo iki 2,81 ± 0,63 (mediana 2,88 (1,5–3,57)) (p =

0,005), po 6 mėnesių – iki 2,8 ± 0,61 (mediana 2,87 (1,5–3,58)) (p = 0,04). Depresijos skalės balų vidurkis nuo 2,9 ± 0,62 (mediana 2,93 (2–3,8)) po 6 savaičių gydymo padidėjo iki 3,48 ± 0,55 (mediana 3,6 (2,57–4,14)) (p = 0,005), po 6 mėnesių – 3,52 ± 0,5 (mediana 3,5 (2,57–4,14)) (p = 0,04). Drovėjimosi skalės balų vidurkis nuo 1,67 ± 0,61 (mediana 1,67 (1–2,67)) padidėjo iki 2,27 ± 0,66 (2,5 (1–3)) (p = 0,007), po 6 mėnesių – iki 2,22 ± 0,67 (mediana 2,66 (1–3)) (p = 0,08).

Išmatų nelaikantiems pacientams, kuriems nustatytas efektas, po 6 savaičių gydymo TBNS pakartotas anorektalinės manometrijos ir rektalinio jautrumo tyrimas. Duomenys palyginti su prieš pradedant gydymą gautais duomenimis, statistiškai patikimo skirtumo nepastebėta.

Prognozinių sėkmingo gydymo rodiklių išmatų nelaikantiems pacientams nenustatėme.

IŠVADOS

1. TBNS, atliekama du kartus per savaitę 6 savaites, yra efektyvi 53,1 % LVU sergančių pacientų, kuriems maksimalus konservatyvus gydymas yra neveiksmingas.
2. TBNS, atliekama du kartus per savaitę 6 savaites, yra efektyvi 55 % IN sergančių pacientų.
3. Dėl TBNS poveikio gerėja IN ir LVU sergančių pacientų gyvenimo kokybė.
4. Anorektalinė manometrija ir rektalinio jautrumo duomenys prieš gydymą ir po 6 savaičių gydymo TBNS statistiškai reikšmingai nesiskyrė nei IN, nei LVU sergančių pacientų.
5. Sėkmingo TBNS gydymo rodikliai lieka neaiškūs.

PASIŪLYMAI KLINIKINEI PRAKTIKAI

TBNS siūlome naudoti klinikinėje praktikoje išmatų nelaikančių bei LVU sergančių pacientų gydymui, jei jiems maksimalus konservatyvus gydymas yra neveiksmingas.

SCIENTIFIC ACTIVITY ON THE TOPIC OF THE DISSERTATION

Publications

1. Ieva Stundienė, Paulius Žeromskas, Jonas Valantinas. Perkutaninė blauzdinio nervo stimuliacija: naujas išmatų nelaikymo gydymo metodas. Literatūros apžvalga. Medicinos teorija ir praktika. 2011; 17 (3): 369–375.
2. Ieva Stundienė, Paulius Žeromskas, Jonas Valantinas. Transcutaneous tibial nerve stimulation for the treatment of faecal incontinence: results of a prospective study. Acta Medica Lituanica. 2014; 21 (2): 91–98.
3. Ieva Stundienė, Paulius Žeromskas, Johann Pfeifer, Jonas Valantinas. Good results with transcutaneous tibial nerve stimulation for advanced chronic constipation treatment. Lietuvos chirurgija, 2014; 13 (3): 192–199.

Thesis in international conferences

1. Ieva Stundienė, Paulius Žeromskas, Jonas Valantinas. Tibial nerve stimulation – a new treatment method of defecation disorders. Evolutionary medicine: new solutions for the old problems, 12–15 of June 2012 (poster presentation).
2. Ieva Stundienė, Paulius Žeromskas, Jonas Valantinas. Transcutaneous posterior tibial nerve stimulation in the treatment of functional constipation. European Society of Coloproctology, 8th Anual and Scientific Meeting, Belgrad, Serbia, 25–27 of September 2013 (poster presentation).
3. Ieva Stundienė, Paulius Žeromskas, Jonas Valantinas. Peripheral Transcutaneous Neuromodulation in the Treatment of Idiopathic Constipation: Preliminary Results of a Pilot Study. 21st United European Gastroenterology Week, 12–16 of October 2013, Berlin, Germany (poster presentation). National Scholar Award, Poster of Excelence.

BRIEF INFORMATION ABOUT THE AUTHOR

1997–2003	Vilnius University Faculty of Medicine (medical doctor)
2003–2004	Primary residency programme at Vilnius University Faculty of Medicine
2004–2010	Residency programme in gastroenterology at Vilnius University Hospital "Santariskiu Klinikos"
2010–present	Vilnius University Hospital "Santariskiu Klinikos", Centre of Hepatology, Gastroenterology and Dietetics, consulting gastroenterologist, endoscopist
2010	Traineeship in functional coloproctology, Graz University Hospital, Austria, duration – 2 weeks.
2012–present	Vilnius University, Medical faculty, Clinic of Gastroenterology, Nephrourology and Surgery, lecturer.