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Parasacral Transcutaneous Electrical Nerve Stimulation for the Treatment of Children and Adolescents with Bladder and Bowel Dysfunction: A Randomized Clinical Trial

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Purpose: Parasacral transcutaneous electrical nerve stimulation has been used to manage lower urinary tract symptoms refractory to standard urotherapy. Nevertheless, its actual effectiveness in treatment of bladder and bowel dysfunction remains to be established. We sought to evaluate the effectiveness of parasacral transcutaneous electrical nerve stimulation in the treatment of children with bladder and bowel dysfunction.

Materials and Methods: This was a randomized clinical trial conducted with children and adolescents of 5–17 years of age diagnosed with bladder and bowel dysfunction. Patients with neurological or anatomical abnormalities of urinary or digestive tracts, those unable to attend treatment sessions 3 times a week, individuals with diabetes mellitus or diabetes insipidus and those using anticholinergic drugs or laxatives were excluded from the study. The sample was divided into 2 groups: a control group submitted to standard urotherapy plus sham electrotherapy applied to the scapular region and a treatment group submitted to urotherapy plus parasacral transcutaneous electrical nerve stimulation. All the patients were submitted to 3, 20-minute electrotherapy (parasacral transcutaneous electrical nerve stimulation or sham) sessions/week for a total of 20 sessions.

Results: Forty patients were evaluated, 20 in the control group and 20 in the treatment group. Mean age (±standard deviation) was 8.4±2.8 years and 52.5% were male. In 15 patients (37.5%), rectal diameter was ≥3 cm. Lower urinary tract symptoms improved in both groups following treatment, with no statistically significant differences in Dysfunctional Voiding Scoring System score, lower urinary tract symptoms or uroflowmetry patterns between the groups. Intragroup evaluation showed a significant improvement in enuresis in the treatment group. There was a significant improvement in functional constipation post-intervention in treatment group compared to control group (70% vs 20%, p=0.004).

Conclusions: Parasacral transcutaneous electrical nerve stimulation is effective for treatment of bladder and bowel dysfunction in children and adolescents, particularly insofar as functional constipation is concerned.

Key Words: constipation, lower urinary tract symptoms, child, adolescent, transcutaneous electric nerve stimulation

Abbreviations and Acronyms

BBD = bladder and bowel dysfunction
CG = control group
DVSS = Dysfunctional Voiding Scoring System
FC = functional constipation
LUTS = lower urinary tract symptoms
PTENS = parasacral transcutaneous electrical nerve stimulation
Q_{max} = maximum flow rate
TG = treatment group
VAS = visual analogue scale

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In children with bladder and bowel dysfunction, treatment of lower urinary tract symptoms is based principally on urotherapy, biofeedback, anticholinergics, and electrical nerve stimulation.[1] Treating functional constipation is known to be an essential step when treating children with

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LUTS and can lead to an improvement in or even complete resolution of urinary symptoms.[2,3] Nevertheless, despite success rates of 40%–50% for LUTS, standard urotherapy may be insufficient for the management of FC. Approximately 50% of children with FC experience at least 1 recurrence of the condition in the first 5 years after their initial recovery and in 25%–30% of children FC will remain present even after puberty, irrespective of treatment given.[4,5] Some factors that may influence response to treatment include age, child's motivation, often affected by cognitive and behavioral disorders, caregivers' motivation and the need for a team of dedicated therapists well trained in managing cases of BBD.[6] Biofeedback, the form of physiotherapy used in cases of dysfunctional voiding, has yielded conflicting results in cases of FC.[7,8] In addition, anticholinergics that improve symptoms of urinary urgency and daytime incontinence may exert a negative effect on colonic transit, making FC worse.[9]

Transcutaneous electrical nerve stimulation has been used as an alternative treatment for patients with LUTS refractory to standard urotherapy, and this treatment has also been reported to exert an effect on FC.[10,11] A pilot study has already shown that parasacral transcutaneous electrical nerve stimulation is able to simultaneously improve LUTS and FC in children with BBD, possibly reducing the duration of treatment and the associated costs.[12] Nevertheless, despite these promising results studies with a greater level of evidence have yet to be conducted on the effectiveness of PTENS in patients with BBD. Therefore, the objective of the present clinical trial was to evaluate the effectiveness of PTENS in the treatment of LUTS and FC in children with BBD. To the best of our knowledge, this is the first randomized clinical trial to evaluate PTENS in patients with BBD.

METHODS

This was a randomized, prospective, and blind clinical trial. Data collection took place between October 2017 and December 2019.

Selection of Sample

Inclusion criteria included patients who were seeking treatment from urology of 5–17 years of age with BBD, defined as the presence of FC associated with LUTS, with no previous treatment. Patients with neurological and/or anatomical abnormalities of the urinary and/or digestive tracts, those unable to attend treatment sessions 3 times a week, individuals with diabetes mellitus and/or diabetes insipidus and those taking anticholinergic drugs or laxatives were excluded from the study.

Instruments

Some instruments evaluated LUTS prior to and following the intervention: 1) a structured questionnaire evaluated LUTS; 2) Dysfunctional Voiding Scoring System evaluated LUTS intensity (scores of 6 for girls and 9 for boys being the cutoff points); and 3) a 2-day bladder diary recorded urinary frequency, mean voided volume, and maximum voided volume. A visual analogue scale measured the improvement in daytime urinary symptoms at the end of the treatment, with response being classified as no response—<50%, partial response—50%–99%, or complete response—an improvement of 100%.

Rome IV criteria evaluated FC for children of 4–18 years of age, in which patients who had at least 2 positive items of the 6 listed criteria for more than a month were constipated. A modified constipation score for children and adolescents based on an 8-item structured questionnaire on symptoms associated with FC was used to evaluate its intensity (1. frequency of bowel movements; 2. difficulty or pain on defecation; 3. sensation of incomplete evacuation; 4. abdominal pain; 5. time spent on the toilet >5 minutes; 6. use of laxatives or digital assistance; 7. failed evacuation attempts per 24 hours; and 8. constipation symptoms' duration; This score has a maximum score of 30 points). The Bristol Stool Scale was also applied, and types 1 and 2 were associated with FC.

Ultrasonography evaluated post-void residual urine and rectal diameter. The rectum was considered distended when its transverse diameter was ≥3 cm. All patients were submitted to uroflowmetry prior to and following the intervention, including evaluation of maximum flow rate, time to Q_{max}, average flow rate, voided volume, duration of flow and flow curve pattern.

Intervention

Randomization was performed by shuffling blocks of 4 sealed, sequentially numbered brown envelopes. The patients were divided into 2 groups: treatment group (standard urotherapy plus PTENS) and control group (standard urotherapy plus sham electrotherapy). All patients were submitted to PTNS at 20-minute sessions held 3 times a week for a total of 20 sessions at a frequency of 10 Hz and pulse width of 700 μs, with intensity varying according to patient's tolerance level and without reaching the motor threshold. Four electrodes were placed on each patient, 2 in the parasacral region (TG) and 2 in the scapular region (CG) (fig. 1).

All patients received urotherapy consisting of the following instructions: not to wait longer than 3 hours between voids; not to ingest foods such as coffee, tea, carbonated drinks, chocolate or citric fruits during treatment; to void before going to sleep; to drink more fluids during the day (around 5 to 8×200 ml glasses/day depending on age), with those complaining of enuresis to avoid drinking fluids for at least 2–3 hours before going to sleep; and to avoid postponing voiding when urinary urgency was present. Instructions were also given regarding the appropriate consumption of fiber-rich foods for all patients; however, neither fiber supplements nor specific nutritional diets were recommended for either group. All patients were instructed to sit appropriately on the toilet for 5–10 minutes 3 times a day after their main meals.

Parents, patients, and post-treatment evaluator were blinded to group allocation. The endpoints were evaluated 7 to 14 days after the last PTENS session.

The study was registered in the Brazilian Clinical Trials Registry (ReBEC) under number RBR-58c63h. The

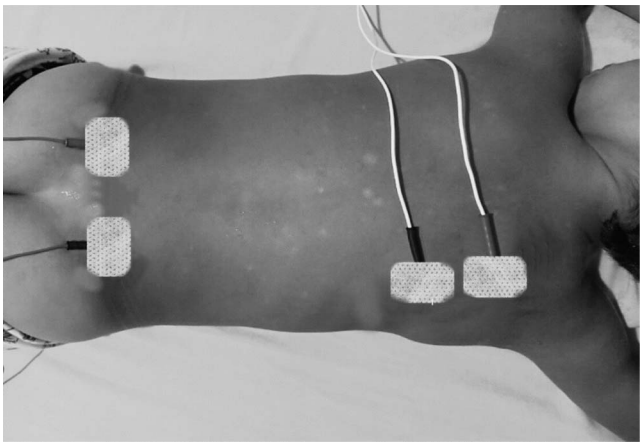

Figure 1. Position of electrodes during PTENS and scapular electrotherapy

institute's internal review board approved the study protocol under reference 683884517.5.0000.5544. Patients were only admitted to the study after their parents/guardians had signed an informed consent form or patient, if over 6 years of age, had signed an assent form.

Statistical Analysis

Descriptive and comparative analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS® Statistics), version 21 for Windows®. The sample size needed for a power of 80% (2-tailed alpha=5%), with a 95% confidence interval, was estimated using the WINPEPI calculator.[13] Taking into consideration an expected rate of resolution of voiding symptoms of 75% in the TG and 31.3% in the CG, as suggested by previous studies,[14,15] a total of 20 patients would be required in each group.

For intergroup analysis, Student's t-test compared the following variables between TG and CG: rectal diameter, constipation score$_{log10}$, Qmax$_{log10}$, voided volume$_{log10}$ and duration of flow$_{log10}$. DVSS, number of positive Rome IV criteria, time to Q_{max}, and average flow criteria were analyzed using the Mann-Whitney test. The Fisher test compared categorical variables: LUTS, flow curve patterns, VAS score and FC.

For the intragroup analysis, the McNemar test was used to evaluate all categorical variables prior to and following interventions evaluated in the intergroup analysis except for the variables FC in both groups and urinary urgency in the TG, since these were present in all patients prior to intervention. Wilcoxon signed-rank test evaluated the following numerical variables prior to and following the intervention: average flow, time to Q_{max}, and DVSS score while the paired Student's t-test was used to analyze duration of flow$_{log10}$, Qmax$_{log10}$, voided volume$_{log10}$ and constipation score$_{log10}$. p Values <0.05 in the bivariate analysis were considered statistically significant in all cases.

RESULTS

Forty patients with BBD were included in the study (fig. 2). The mean age of the participants was 8.4±2.8

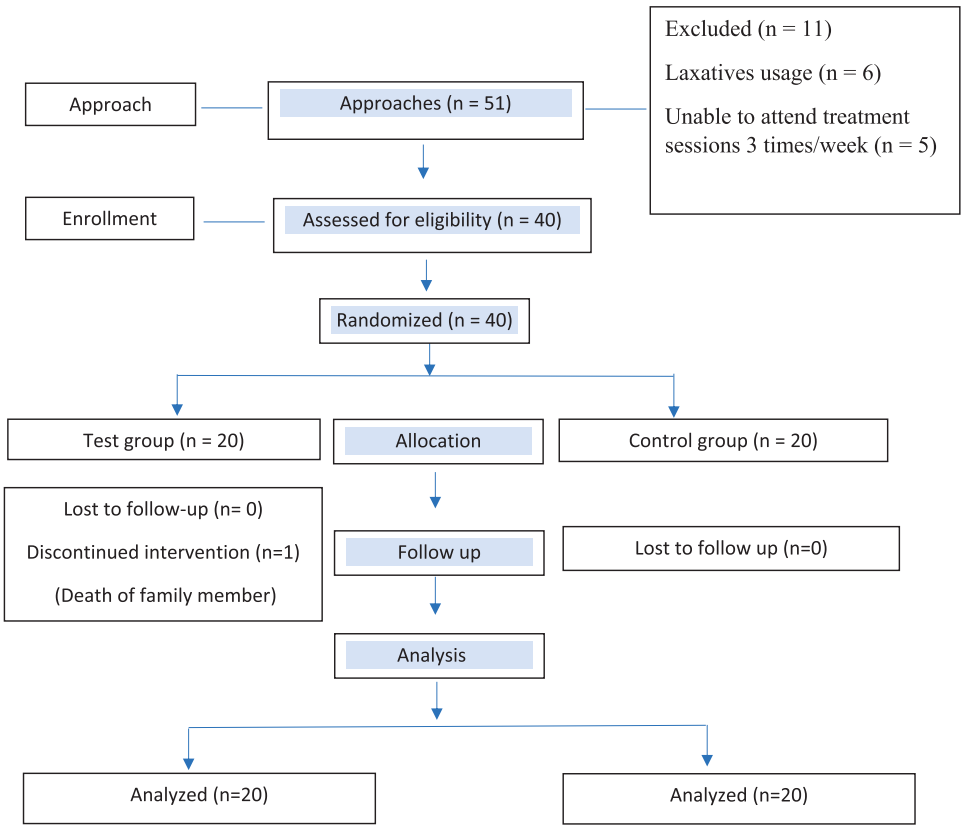

Figure 2. Consort flowchart

Table 1. *Intragroup comparison: urinary symptoms and uroflowmetry patterns in control and treatment groups*

	Control Group			Treatment Group (PTNS)		
	Baseline	Post-Intervention	p Value	Baseline	Post-Intervention	p Value
Median DVSS (IQR)	13.5 (11–16)	6 (0.25–10)	**< 0.001***	13 (8.25–16.75)	2 (0–9)	**< 0.001***
No. urinary urgency (%)	19 (95)	7 (35)	**< 0.001†**	20 (100)	7 (35)	-
No. daytime incontinence (%)	18 (90)	8 (40)	**0.002†**	17 (85)	7 (35)	**0.002†**
No. holding maneuvers (%)	16 (80)	6 (30)	0.01†	17 (85)	6 (30)	0.001†
No. frequent urination (%)	11 (55)	2 (10)	0.004†	12 (60)	4 (20)	0.008†
No. nocturia (%)	4 (20)	4 (20)	1.00†	7 (35)	2 (10)	0.06†
No. enuresis (%)	17 (85)	15 (75)	0.50†	15 (75)	9 (45)	0.03†
Mean duration of $flow_{log10}$ (±SD)	1.35 ± 0.2	1.36 ± 0.24	0.97‡	1.33 ± 0.2	1.22 ± 0.16	0.07‡
Median time to Q_{max} (IQR)	9 (6.2–18)	9.05 (6–13)	0.89*	8.5 (7–12.3)	7 (5.75–8.25)	0.007*
Mean $Q_{max\ log10}$ (±SD)	1.18 ± 0.27	1.21 ± 0.3	0.55‡	1.1 ± 0.21	1.25 ± 0.22	<0.001‡
Median av flow (IQR)	6 (3.25–10.38)	9.4 (6–11.4)	0.35*	5 (3–9.73)	8.5 (7–12.29)	0.001*
Mean voided vol_{log10} (±SD)	2.21 ± 0.3	2.26 ± 0.37	0.84‡	2.17 ± 0.28	2.21 ± 0.21	0.37‡

* Wilcoxon test.
† McNemar test.
‡ Student's paired t-test.

years; mean body mass index was 18.57±5.8 kg/m^2; mean rectal diameter was 2.9±0.9 cm and 52.5% of the sample was male. Rectum was distended (≥3 cm) in 15 patients (37.5%) prior to treatment, with a mean diameter of 3.84±0.6 cm (supplementary table 1, https://www.jurology.com). Baseline urinary and intestinal symptoms are shown in supplementary tables 2 and 3 (https://www.jurology.com), respectively.

In the intragroup analysis, all daytime urinary symptoms improved in both groups. With respect to nighttime symptoms, enuresis improved only in the TG. Some uroflowmetry patterns changed significantly in the TG alone, with an increase in average flow and in Q_{max}, and a reduction in time to Q_{max} (table 1).

Intergroup evaluation showed no difference between the groups in relation to LUTS or in uroflowmetry patterns. LUTS resolved completely in 12 patients in the sample (30.8%), as expressed by a post-intervention DVSS score of 0. Five of these patients (25%) were in the CG and 7 (36.8%) were in theTG (table 2).

In the intragroup analysis, despite an improvement of constipation $score_{log10}$ in the CG, there was an improvement in only 1 Rome IV criteria (fecal incontinence; p=0.02). There was a reduction in number of positive Rome IV criteria in the CG; however, the median indicated the persistence of FC (median=2; IQR 0.25–3; table 3).

Intergroup analysis showed an improvement in FC in the TG, with only 4 patients in this group (20%) requiring laxatives following treatment. When each of the Rome IV criteria was evaluated individually, a significant improvement was found in frequency of bowel movements and in retentive posturing in the TG. Following treatment, there was a greater reduction in the number of positive Rome IV criteria in the TG (table 4).

Evaluating the measures of association regarding the magnitude of the effect of PTENS on FC, values to relative risk, absolute reduction of risk and number necessary to treat were 0.29%, 50% and 2, respectively. The effect size for constipation $score_{log\ 10}$ was 0.79 (Cohen's d).

DISCUSSION

In the present study, PTENS plus behavioral therapy was an effective approach for FC in children and adolescents with BBD. An improvement in LUTS was found in both groups, showing that

Table 2. *Intergroup comparison following intervention: urinary symptoms and uroflowmetry patterns*

	Post-Intervention		
	Control Group	Treatment Group (PTNS)	p Value
Median DVSS (IQR)	6 (0.25–10)	2 (0–9)	0.23*
No. urinary urgency (%)	7 (35)	7 (35)	1.00†
No. daytime incontinence (%)	8 (40)	7 (35)	1.00†
No. holding maneuvers (%)	6 (30)	6 (30)	1.00†
No. frequent urination (%)	2 (10)	4 (20)	0.66†
No. nocturia (%)	4 (20)	2 (10)	0.66†
No. enuresis (%)	15 (75)	9 (45)	0.11†
Mean duration of $flow_{log10}$ (±SD)	1.36 ± 0.24	1.22 ± 0.22	0.08‡
Median time to Q_{max} (IQR)	9.05 (6–13)	7 (5.75–8.25)	0.13*
Mean $Q_{max\ log10}$ (±SD)	1.21 ± 0.31	1.25 ± 0.22	0.59‡
Median average flow (IQR)	9.4 (6.6–11.4)	8.5 (7–12.29)	0.6*
Mean voided vol_{log10} (±SD)	2.26 ± 0.37	2.21 ± 0.21	0.64‡
No. flow curve patterns (%):			0.72†
Bell-shaped	15 (78.9)	16 (88.9)	
Staccato	1 (5.3)	0 (0)	
Tower-shaped	1 (5.3)	1 (5.6)	
Intermittent	2 (10.5)	1 (5.6)	
No. VAS score (%):			0.75†
No response (VAS <50%)	1 (5)	2 (10)	
Partial response (VAS 50% –99%)	12 (60)	10 (50)	
Complete response (VAS =100%)	7 (35)	8 (40)	

* Mann-Whitney test.
† Fisher test.
‡ Student's t-test.

Table 3. *Intragroup comparison: bowel symptoms pre-intervention and post-intervention in control and treatment groups*

	Control Group			Treatment Group (PTNS)		
	Baseline	Post-Intervention	p Value	Baseline	Post-Intervention	p Value
No. constipation (%)	20 (100)	14 (70)	-	20 (100)	4 (20)	-
Median pos Rome IV criteria (IQR)	3 (2—3)	2 (0.25—3)	0.03*	2.5 (2—3)	0 (0—1)	<0.001*
No. Rome IV criteria (%):						
<2 Bowel movements/wk	9 (45)	7 (35)	0.63†	6 (30)	1 (5)	0.06†
Episode of fecal incontinence	11 (55)	4 (20)	0.02†	11 (55)	2 (10)	0.004†
Retentive posturing	10 (50)	9 (45)	1.00†	11 (55)	2 (10)	0.01†
Pain/straining at evacuation	15 (75)	10 (50)	0.18†	14 (70)	6 (30)	0.01†
Lumpy or hard stools	4 (20)	1 (5)	0.37†	3 (15)	1 (5)	0.63†
Stools that may block toilet	8 (40)	8 (40)	1.00†	11 (55)	4 (20)	0.04†
Median constipation $score_{log10}$ (±SD)	1.02±0.2	0.78 ± 0.37	0.002‡	0.91 ±0.2	0.5 ± 0.34	<0.001*
No. stool types 1 + 2 of Bristol stool scale (%)	8 (40)	10 (50)	0.63†	9 (45)	5 (25)	0.29†

* Wilcoxon test.
† McNemar test.
‡ Student's paired t-test.

standard urotherapy, although relatively ineffective for FC, can be beneficial in reducing LUTS in BBD patients. An interesting finding was that there was an improvement in enuresis only in the PTENS group.

Although standard urotherapy is considered the only measure initially required for many children with LUTS, PTENS in association with urotherapy can be particularly beneficial in children with BBD, as FC is a symptom that is always present in BBD. In this group of patients, the advantage of PTENS in improving FC and reducing the need for laxatives should be emphasized, since it is well known that the treatment of FC is vital if LUTS are to be resolved. Another important aspect to be taken into consideration is the marked improvement in fecal incontinence and pain following PTENS, which were found in the intragroup evaluation. Both symptoms are known to be a symptom that greatly distresses children and is often associated with a reduction in quality of life.[16] Since PTENS reduced FC rate by 50%, with the magnitude of the effect demonstrating the need to treat 2 patients to have a positive effect on 1 patient, we observed that neuromodulation was beneficial when compared to standard urotherapy. Thus, it is estimated that this is the first study to show the efficacy of PTENS on FC in BBD patients, not only using a control group, but through a randomized clinical trial.

Table 4. *Intergroup comparison: bowel symptoms*

	Post-Intervention		
	Control Group	Treatment Group	p Value
No. constipation (%)	14 (70)	4 (20)	0.004*
No. Rome IV criteria (%):			
<2 Bowel movements/wk	7 (35)	1 (5)	0.04*
Episode of fecal incontinence	4 (20)	2 (10)	0.66*
Retentive posturing	9 (45)	2 (10)	0.03*
Pain/straining at evacuation	10 (50)	6 (30)	0.33*
Lumpy or hard stools	1 (5)	1 (5)	1.00*
Stools that may block toilet	8 (40)	4 (20)	0.30*
No. stool types 1 + 2 of Bristol stool scale (%)	10 (50)	5 (25)	0.19*
Mean constipation $score_{log10}$ (±SD)	0.78 ±0.37	0.5 ±0.34	0.02†
Median pos Rome IV criteria (IQR)	2 (0.25—3)	0 (0—1)	0.002‡
No. use of laxatives following treatment (%)	13 (65)	4 (20)	0.01*

* Fisher test.
† Student's t-test.
‡ Mann-Whitney test.

Another relevant finding is enuresis improvement in the PTENS group. This result suggests that by improving FC, PTENS produces a positive effect on enuresis. An association between enuresis and FC has been reported in the literature[20] and another recent study found that FC could interfere negatively in the patient's response to desmopressin.[21] A

previous study conducted by our research team showed that PTENS can be useful in children with nonmonosymptomatic nocturnal enuresis.[22] Interestingly, in children with BBD enuresis can also improve with PTENS. We observed that BBD affected more boys than girls. We believe that this sample was distributed in this way at random. Nevertheless, sex maybe not have affected our results since we had already observed in previous studies that sex does not affect PTENS results.[23]

The use of laxatives is the most recommended treatment for FC, yielding good outcomes, particularly with the use of polyethylene glycol.[24] Nevertheless, due to the risk of a recurrence of bowel dysfunction, the need for prolonged use of these drugs can be quite expensive, often constituting a reason for the patient to abandon treatment. Fear of episodes of fecal incontinence resulting from reduced fecal consistency and even fear of bowel damage due to their prolonged use could also be a cause of treatment discontinuation.[5,25] Therefore, the use of PTENS could prove a promising alternative in cases of BBD, since in addition to improving LUTS it also results in a significant improvement in FC. In other words, its use may be particularly beneficial in children and adolescents with BBD, perhaps enabling the dose of laxatives to be reduced, decreasing the time of use of these drugs or helping control FC when anticholinergics are necessary.

The short followup time is a limitation, which is insufficient to allow us to affirm that PTENS results in a lasting improvement in FC. The improvement in FC in the immediate evaluation is a promising finding; however, a long-term analysis is required to enable this finding to be confirmed. The fact that it was impossible to blind the professionals who administered PTENS and that there were doubts regarding the effectiveness of the blinding procedure in the families may have led to some biases, a situation that may have been attenuated by blinding the final evaluator and same weekly electrotherapy regimen. Nevertheless, the use of previously validated evaluation instruments such as the DVSS and the Rome IV criteria may have resulted in a slightly more precise analysis of the results.

CONCLUSIONS

PTENS is effective as a therapeutic approach on FC in patients with BBD. Although PTENS leads to an improvement in LUTS, this result is no different from that obtained with standard urotherapy.

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EDITORIAL COMMENT

This interesting study adds to the literature evaluating effectiveness of PTENS on BBD studied in a randomized controlled trial. Unfortunately, no randomized controlled trial can provide absolute proof of effectiveness of a treatment as even randomized controlled trials can be biased. Evidence should be viewed as an ongoing process that evolves over time. This study should be followed by larger studies or aggregate data analysis in order to strengthen the evidence for transcutaneous electrical nerve stimulation as treatment for BBD.

The current study has some limitations: remote computerized randomization is preferred over block randomization with concealed envelopes. Blinding of patients, parents and clinicians in a study on transcutaneous electrical nerve stimulation is challenging. One can imagine that smart parents might be able to unblind treatment allocation and therefore introduce a placebo effect. Conscious or unconscious differential attention and emphasis on the urotherapeutic advice could be a source of bias introduced by the therapist.

Another limitation might be the sample size. Transcutaneous electrical nerve stimulation might have only marginal additional effects to urotherapy.[1] For a treatment with low effect size, high power is needed. A sample size of 40 might be too small. Interestingly, the authors found a significant effect on constipation, but could not reproduce significant improvement of LUTS. This could be a type II error. I encourage the authors to continue their research with more studies and more power to confirm the beneficial effect of transcutaneous electrical nerve stimulation on BBD.

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