Efficacy of sacral transcutaneous electrical nerve stimulation in patients with overactive bladder refractory to anticholinergic treatment: a prospective multi-center study

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ABSTRACT

Objective. To determine whether sacral transcutaneous electrical nerve stimulation (S-TENS) is an effective treatment in patients refractory to anticholinergic drugs (Achs).

Materials and methods. A prospective multi-center study of patients with overactive bladder (OB) refractory to Achs treated with S-TENS from 2018 to 2021 was carried out. S-TENS was applied over 3 months. Symptom progression was assessed using the voiding calendar and the Pediatric Lower Urinary Tract Symptoms Score (PLUTSS), excluding questions 3 and 4 –referring to enuresis– so that progression of daytime symptoms only (LUTS variable) was analyzed.

Results. 66 patients –50% of whom were female– were included, with a mean age of 9.5 years (range: 5-15). S-TENS significantly lowered PLUTSS (19.1 baseline vs. 9.5 final, p<0.001) and LUTS (13.1 baseline vs. 4.8 final, p<0.001). It also reduced the number of mictions (8.5 baseline vs. 6.4 final, p<0.001), while increasing urine volume in the voiding records (214 ml baseline vs. 258 ml final, p<0.001). Enuresis was the only variable refractory to S-TENS. Complication rate was 3% (2 patients with dermatitis in the S-TENS application area).

Conclusions. S-TENS is effective and safe in the short-term in patients with OB refractory to Achs. Further studies assessing long-term efficacy and potential relapses are required.

KEY WORDS: Overactive bladder; Cholinergic antagonists; Electrical stimulation therapy; Transcutaneous electric nerve stimulation.

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EFICACIA DE LA ELECTROESTIMULACIÓN TRANSCUTÁNEA SACRA EN PACIENTES CON VEJIGA HIPERACTIVA REFRACTARIOS A FÁRMACOS ANTICOLINÉRGICOS. ESTUDIO PROSPECTIVO Y MULTICÉNTRICO

RESUMEN

Objetivos. Determinar si la electroterapia nerviosa transcutánea a nivel sacro (TENS-S) es un tratamiento efectivo en pacientes refractarios a fármacos anticolinérgicos (Ach).

Material y métodos. Estudio prospectivo y multicéntrico: pacientes con VH refractaria a Ach tratados con TENS-S entre 2018-2021. El TENS-S se aplicó durante 3 meses. La evolución sintomática fue evaluada utilizando el calendario miccional y el cuestionario PLUTSS (*Pediatric Lower Urinary Tract Symptoms Score*), pero excluyendo sus preguntas 3 y 4 (referidas a la enuresis) para analizar solamente la evolución de la sintomatología diurna (variable LUTS).

Resultados. Fueron incluidos 66 pacientes (50% niñas), con una edad media de 9,5 años (rango: 5-15). El TENS-S disminuyó significativamente el PLUTSS (19,1 inicial *vs* 9,5 final, p<0,001) y el LUTS (13,1 inicial *vs* 4,8 final, p<0,001). Además, redujo el número de micciones (8,5 inicial *vs* 6,4 final, p<0,001) y aumentó el volumen de orina en los registros miccionales (214 ml inicial *vs* 258 ml final, p<0,001). La enuresis fue la única variable refractaria al TENS-S. La tasa de complicaciones fue del 3% (2 pacientes, dermatitis en el área de aplicación del TENS-S).

Conclusiones. El TENS-S es efectivo y seguro a corto plazo en pacientes con VH refractarios a los Ach. Deben realizarse estudios para evaluar la eficacia a largo plazo y posibles recaídas.

PALABRAS CLAVE: Vejiga hiperactiva; Fármacos anticolinérgicos; Electroterapia nerviosa transcutánea; TENS-S.

INTRODUCTION

Overactive bladder (OB) is the most frequent lower urinary tract (LUT) dysfunction in the pediatric population,

representing 40-50% of the total dysfunctions. Global OB incidence has progressively increased in the last years, with OB being one of the most common reasons for consultation at Pediatric Urology units.

The International Children's Continence Society (ICCS)[1], along with the European Society of Pediatric Urology (ESPU) and the European Association of Urology (EAU), recently standardized generic LUTS treatment guidelines. However, there is no guideline for the specific treatment of OB in the pediatric population. They all recommend individualized treatment for each patient, with a progressive approach, from less to more invasive strategies.

Initially, OB treatment involves standard urotherapy measures in order to rehabilitate and improve voiding. They provide with a good response in more than 70% of the patients, and they should be maintained in the long-term. Second-line treatment is drug therapy, namely with anticholinergic drugs (Achs), with a complete resolution rate of 40-50% and significant adverse effects (40-60%), which sometimes causes lack of treatment adhesion. Other therapeutic strategies described include pelvic floor rehabilitation or biofeedback –with low success rates for OB– and intravesical botulinum toxin puncture –an invasive technique finite in time. Sacral electrical therapy (S-TENS, or sacral transcutaneous electrical nerve stimulation) has been growing traction in the last years[2-10], especially in the treatment of OB, thanks to its high effectiveness rates (65-90%) and the few adverse effects caused.

According to the ICCS[1], S-TENS is the most recommended treatment for OB after urotherapy, with a 1a evidence level, and an A recommendation grade. In spite of this, there is no literature evidence today supporting the use of this therapy in patients where anticholinergic drugs have previously failed. Therefore, the objective of this study was to determine whether S-TENS is an effective treatment in pediatric patients with OB refractory to anticholinergic drugs.

MATERIALS AND METHODS

Study design

A prospective multi-center study of all patients diagnosed with OB refractory to anticholinergic treatment and treated with S-TENS in three hospitals (Donostia University Hospital, A Coruña University Hospital Complex, and Sant Joan de Déu Hospital in Barcelona, all of them in Spain) from 2018 to 2021 was carried out.

- *Inclusion criteria:* patients diagnosed with OB according to the ICCS definition with previous anticholinergic treatment failure; baseline Pediatric Lower Urinary Tract Symptoms Score (PLUTSS)[11] value higher than 8.5 points; pediatric age (5-16 years old).

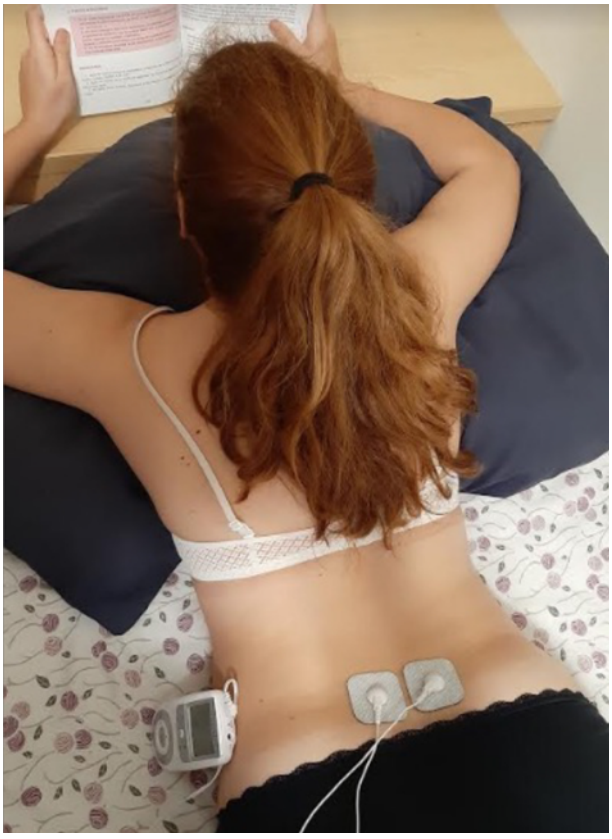

Figure 1. At-home S-TENS application while the patient is reading. Surface electrode placement in the sacral region, at the S2-S3 level.

- *Exclusion criteria:* change in diagnosis along follow-up; mixed LUT symptoms; patients with complete symptom resolution or PLUTSS value under 8.5 following baseline urotherapy measures; incomplete follow-up; lack of documentation; absence of informed consent for study participation.

Once OB diagnosis had been confirmed, the patients underwent urotherapy measures and constipation management for 2-3 months. All patients with persistent symptoms (PLUTSS> 8.5) in spite of these measures received S-TENS. Series patient follow-up was conducted at external consultations at treatment initiation and following 1 and 3 months of treatment.

S-TENS therapy

S-TENS is a form of electrical therapy applied with surface electrodes at the S2-S3 level. The application protocol was 10 Hz frequency and 200 μs. Intensity was individually regulated according to the maximum pain-free intensity tolerated by the patient, with a progressive increase over time according to adaptability, and with a maximum of 40mA. The therapy was applied at home, daily, for 15 minutes, over 3 months (Fig. 1).

Table 1. Results at baseline, 1 month, and 3 months of treatment.

	Baseline	*1 month*	*p*	*3 months*	*p*
Mean PLUTSS (0-35)	19.1	13.7	<0.0001	9.5	<0.0001
Mean LUTS (0-26)	13.1	8.2	<0.0001	4.8	<0.0001
Mean enuresis (0-6)	6	5.5	1.87	4.7	1.92
Mean no. of mictions	8.5	-	-	6.4	<0.0001
Mean maximum VV (ml)	214.3	-	-	258.2	<0.001
Mean EBC %	68.9%	-	-	85.5	<0.001

VV = voiding volume; EBC = expected bladder capacity [(age + 1) x 30]

Study variables

The variables studied included age, sex, body mass index (BMI), voiding calendar data –number of mictions and voiding volume–, and PLUTSS score.

PLUTSS questions 3 and 4 –specifically related to enuresis– were removed, thus obtaining the LUTS –daytime urinary symptoms– variable. This variable was numeric, with a maximum score of 26 points –with 26 being the greatest symptom severity. The enuresis variable was achieved by adding questions 3 and 4 values plus the PLUTSS score.

Statistical analysis

Statistical analysis was carried out using the Stata 14.2® software. A descriptive analysis of all study variables was conducted. Quantitative variables were expressed as mean ± standard deviation, whereas qualitative variables were expressed as absolute value and percentage. The association of quantitative variables was estimated by means of Student's t-test or Mann-Whitney U test. The association of qualitative variables was calculated using the Chi-squared test or Fisher's exact test.

Ethical approval

The study was approved by the relevant Clinical Research Ethics Committees (approval numbers: ICB-OXI-2018-01 and PIC-104-22). Patient confidentiality was ensured according to the European General Data Protection Regulation (EU 2016/679).

RESULTS

From January 2018 to December 2021, 66 patients with OB refractory to anticholinergic drugs were treated with S-TENS and included in the study. Of these patients, 33 were boys (50%) and 33 were girls (50%).

Mean age was 9.5 years, with a standard deviation (SD) of 5-15. Mean age was slightly lower in boys than in girls (8.57 years vs. 10.42 years, $p<0.01$). Mean BMI was 18.58 kg/m^2, with a SD of 12.8-31.2. Mean BMI was slightly lower in boys than in girls (16.9 kg/m^2 vs. 20.1 kg/m^2). 28% (19) had psychological history, with attention deficit hyperactivity disorder (ADHD) standing out (51%, 10/19).

All patients had previously received oxybutynin as a first-line treatment. 9% (6 patients) received solifenacin as a second-time treatment. The main cause of anticholinergic treatment discontinuation was lack of response (77%, 51). In the remaining patients, medication was discontinued as a result of adverse effects.

Most of the variables analyzed had a progressively favorable, statistically significant progression along follow-up. Table 1 features the results of the study's variable means. A decrease in PLUTSS, LUTS, and number of mictions was noted, with the resulting increase in voiding volume and expected bladder capacity (EBC).

At the end of the study, mean PLUTSS remained >8.5 points, i.e., above the threshold regarded as LUTS. However, the final LUTS value was lower than such cut-off point. This difference in the mean score achieved over time is explained by enuresis' capacity of being refractory to S-TENS. Mean score did not change throughout the study (Table 1, Fig. 2).

Mild complication rate was 3%, (2/66 patients). In both cases, it was dermatitis at the level of S-TENS application area. This complication did not interfere with therapy maintenance, since it was noted after completing the 3 months of treatment in both cases. No moderate or severe complications were recorded with the use of this device.

DISCUSSION

This work was carried out to identify whether sacral transcutaneous electrical therapy is effective for patients with overactive bladder refractory to anticholinergic treat-

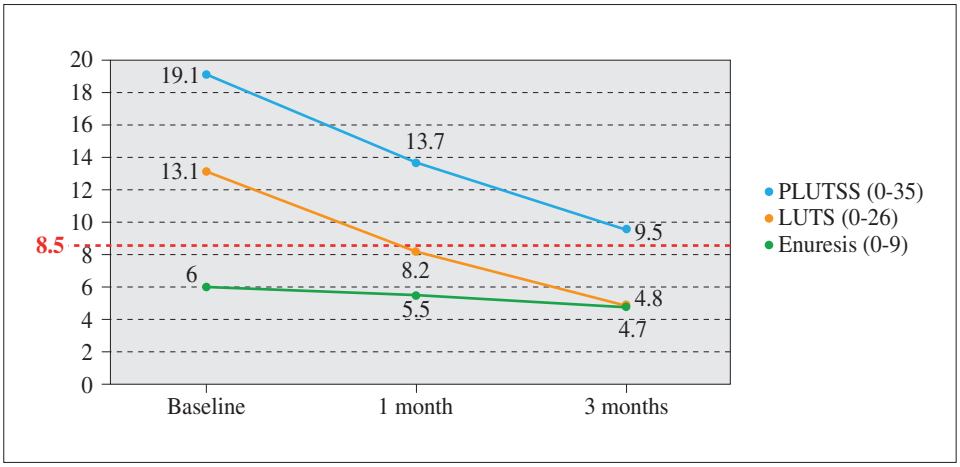

Figure 2. Progression of the PLUTSS, LUTS, and enuresis variables with time.

ment. The analysis revealed that S-TENS reduces the daytime symptoms of these patients in the first 3 months of treatment, apart from being a safe technique. This clinical improvement was particularly obvious, which means S-TENS could represent one of the main therapeutic alternatives in OB patients, even if OB has previously been refractory to anticholinergic treatment. However, there are no other studies in the literature assessing the use of S-TENS in OB patients as a single therapy once urotherapy and anticholinergic treatment have failed.

Various publications have analyzed the effect of TENS in OB patients, with some articles assessing the efficacy of TENS as a therapy combined with anticholinergic drugs[12-14]. In our work, the use of TENS as a single specific treatment, along with urotherapy, in patients previously treated with anticholinergics was studied. In addition, its sample size makes it one of the largest series regarding the use of TENS in pediatric OB published so far[9,15,16].

Consistent with most of the literature, our results confirm the main hypothesis that S-TENS proves beneficial in the treatment of OB in the pediatric population. However, some studies conclude that transcutaneous neuromodulation –at the sacral[10] or posterior tibial[17] levels– is not beneficial for these patients. Specifically, Sillen et al.[10] analyzed 24 OB patients treated with TENS, and found no statistically significant differences vs. the group treated with urotherapy only. Meanwhile, Boudaoud et al.[17] studied 11 OB patients treated with posterior tibial transcutaneous electrical nerve stimulation, and also found no statistically significant differences vs. the placebo –simulated electrical therapy– treated group.

Regarding enuresis in OB patients, our study concluded that enuresis is refractory to TENS treatment, consistent with previous publications[13,18]. Nevertheless, other articles conclude that TENS does help improve enuresis[19-21]. Most of these works do not differentiate between primary or secondary enuresis, which could cause the efficacy discrepancies found in terms of enuresis in OB patients. Therefore, these works are not comparable with ours.

Regarding the TENS application method and the measurement variables used to assess the efficacy of sacral electrical therapy, the studies published today are highly heterogeneous. In addition, there is still no universal and specific protocol accepted for application. Consequently, therapy duration, system activation parameters, and the application method vary widely among the various publications, which prevents comparisons from being made[22]. In our work, patients underwent at-home daily treatment for 15 minutes over 3 months. Casal et al.'s systematic review, which included 14 articles, shows that treatment duration ranged from 1 to 6 months, and the number of weekly applications varied from 2 daily to 2-3 days per week in all of them. Additionally, most of the patients were treated at hospital, whereas TENS was applied at home in 4 studies. Finally, the frequency (Hz) was the same in all studies analyzed, but there were differences in application intensity, which was mostly adapted to each patient's tolerance[22]. Therefore, new studies are required to analyze the effect of TENS administered less often and over a shorter period of time to facilitate patient adhesion.

Neuromodulation's efficacy assessment method is also very heterogeneous among the publications reviewed. In the literature, the use of different variables –both objective and subjective– as a TENS efficacy measurement tool has been described. Most of the studies use subjective scales, with the Visual Analog Scale (VAS) –which evaluates the presence of symptoms according to parental perception– standing out. However, four articles use objective scales. Three of them[4-6] use the Dysfunctional Voiding and Incontinence Scoring System (DVISS), and one of them[7] employs the Nonneurogenic Lower Urinary Tract Dysfunction/Dysfunctional Elimination Syndrome Questionnaire (NLUTD/DES). In our work, PLUTSS –a numerical, objective scale[11]– was used. PLUTSS is the

only scientifically validated, DVISS culturally adapted score that can be used in Spain in Spanish. Given that PLUTSS does not differentiate between primary and secondary enuresis –which could distort final study results–, decision was made to remove questions 3 and 4 regarding enuresis in order to assess daytime symptoms only. By including the remaining questions –which refer to daytime symptoms only–, the LUTS variable was obtained. This variable allowed for a more objective and reliable analysis of TENS efficacy for OB patients.

Finally, no symptom recurrences following the use of S-TENS were noted in our work. However, one of the study limitations is the fact follow-up was short, which means further studies are required to assess long-term efficacy. Up until now, four articles analyzing TENS have reported a relapse rate below 28%. In three of them, follow-up was longer. Lordelo et al.[8] conducted a 2-year follow-up, and reported a relapse rate of 16%, but with good results being maintained in 73% of the cases. Hoebeke et al.[3] carried out a 1-year follow-up, and reported a relapse rate of 17%, with good results being maintained in 51% of the patients.

In conclusion, S-TENS is effective and safe in the short-term in patients with OB refractory to anticholinergic treatment. The enuresis experienced by these patients is refractory to S-TENS. However, further studies are required to assess long-term efficacy and potential relapses.

REFERENCES

1. Austin PF, Bauer SB, Bower W, Chase J, Franco I, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn. 2016; 35: 471-81.
2. Bower WF, Moore KH, Adams RD. A pilot study of the home application of transcutaneous neuromodulation in children with urgency or urge incontinence. J Urol. 2001; 166: 2420-2.
3. Hoebeke P, Van Laecke E, Everaert K, Renson C, De Paepe H, Raes A, et al. Transcutaneous neuromodulation for the urge syndrome in children: A pilot study. J Urol. 2001; 166: 2416-9.
4. Barroso U, de Azevedo AR, Cabral M, Veiga ML, Braga AANM. Percutaneous electrical stimulation for overactive bladder in children: a pilot study. J Pediatr Urol. 2019; 15: 38.e1-38.e5.
5. Veiga ML, Queiroz AP, Carvalho MC, Braga AANM, Sousa AS, Barroso U. Parasacral transcutaneous electrical stimulation for overactive bladder in children: An assessment per session. J Pediatr Urol. 2016; 12: 293.e1-e5.
6. Quintiliano F, Veiga ML, Moraes M, Cunha C, De Oliveira LF, Lordelo P, et al. Transcutaneous parasacral electrical stimulation vs oxybutynin for the treatment of overactive bladder in children: A randomized clinical trial. J Urol. 2015; 193: 1749-53.
7. Stephany HA, Juliano TM, Clayton DB, Tanaka ST, Thomas JC, Adams MC, et al. Prospective evaluation of sacral nerve modulation in children with validated questionnaires. J Urol. 2013; 190: 1516-22.
8. Lordêlo P, Soares PVL, Maciel I, Macedo A, Barroso U. Prospective study of transcutaneous parasacral electrical stimulation for overactive bladder in children: Long-term results. J Urol. 2009; 182: 2900-4.
9. Hagstroem S, Mahler B, Madsen B, Djurhuus JC, Rittig S. Transcutaneous electrical nerve stimulation for refractory daytime urinary urge incontinence. J Urol. 2009; 182: 2072-8.
10. Sillén U, Arwidsson C, Doroszkiewicz M, Antonsson H, Jansson I, Stålklint M, et al. Effects of transcutaneous neuromodulation (TENS) on overactive bladder symptoms in children: A randomized controlled trial. J Pediatr Urol. 2014; 10: 1100-5.
11. Somoza-Argibay I, Méndez-Gallart R, Rodríguez-Ruíz M, Vergara I, Pértega S, Akbal C, et al. Validación de la versión española de la escala de síntomas de malfunción del tracto urinario inferior en población pediátrica (PLUTSS). Arch Esp Urol. 2017; 70: 645-53.
12. Borch L, Hagstroem S, Kamperis K, Siggaard C V, Rittig S. Transcutaneous electrical nerve stimulation combined with oxybutynin is superior to monotherapy in children with urge incontinence: A randomized, placebo controlled study. J Urol. 2017; 198: 430-5.
13. Pedersen N, Breinbjerg A, Thorsteinsson K, Hagstrøm S, Rittig S, Kamperis K. Transcutaneous electrical nerve stimulation as add-on therapy in children receiving anticholinergics and/or mirabegron for refractory daytime urinary incontinence: A retrospective cohort study. Neurourol Urodyn. 2022; 41: 275-80.
14. Zhang Y, Wang S, Zu S, Zhang C. Transcutaneous electrical nerve stimulation and solifenacin succinate versus solifenacin succinate alone for treatment of overactive bladder syndrome: A double-blind randomized controlled study. PLoS One. 2021; 16: e0253040.
15. Tugtepe H, Thomas DT, Ergun R, Kalyoncu A, Kaynak A, Kastarli C, et al. The effectiveness of transcutaneous electrical neural stimulation therapy in patients with urinary incontinence resistant to initial medical treatment or biofeedback. J Pediatr Urol. 2015; 11: 137.e1-5.
16. Malm-Buatsi E, Nepple KG, Boyt MA, Austin JC, Cooper CS. Efficacy of transcutaneous electrical nerve stimulation in children with overactive bladder refractory to pharmacotherapy. Urology. 2007; 70: 980-3.
17. Boudaoud N, Binet A, Line A, Chaouadi D, Jolly C, Francois Fiquet C, et al. Management of refractory overactive bladder in children by transcutaneous posterior tibial nerve stimulation: A controlled study. J Pediatr Urol. 2015; 11: 138.e1-10.
18. Jørgensen CS, Kamperis K, Borch L, Borg B, Rittig S. Transcutaneous electrical nerve stimulation in children with monosymptomatic nocturnal enuresis: A randomized, double-blind, placebo controlled study. J Urol. 2017; 198: 687-93.
19. Lordêlo P, Benevides I, Kerner EG, Teles A, Lordêlo M, Barroso U. Treatment of non-monosymptomatic nocturnal enuresis by transcutaneous parasacral electrical nerve stimulation. J Pediatr Urol. 2010; 6: 486-9.
20. Kajbafzadeh AM, Sharifi-Rad L, Mozafarpour S, Ladi-Seyedian SS. Efficacy of transcutaneous interferential electrical stimulation in treatment of children with primary nocturnal enuresis: a randomized clinical trial. Pediatr Nephrol. 2015; 30: 1139-45.

21. De Oliveira LF, De Oliveira DM, Da Silva De Paula LI, De Figueiredo AA, De Bessa J, De Sá CA, et al. Transcutaneous parasacral electrical neural stimulation in children with primary monosymptomatic enuresis: A prospective randomized clinical trial. J Urol. 2013; 190: 1359-63.

22. Casal Beloy I, García-Novoa M, García González M, Somoza Argibay I. Update on sacral neuromodulation and overactive bladder in pediatrics: A systematic review. Arch Esp Urol. 2021; 74: 699-708.