Role of Posterior Tibial Nerve Stimulation in the Treatment of Refractory Monosymptomatic Nocturnal Enuresis: A Pilot Study

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**Abbreviations and Acronyms**

DO = detrusor overactivity
EBC = expected bladder capacity
MCC = maximum cystometric capacity
MNE = monosymptomatic NE
MVV = maximum voided volume
NE = nocturnal enuresis
PTNS = posterior tibial nerve stimulation
PVR = post-void residual urine volume

Purpose: We evaluated the early clinical and urodynamic results of posterior tibial nerve stimulation in patients with refractory monosymptomatic nocturnal enuresis.

Materials and Methods: We randomly assigned 28 patients with refractory monosymptomatic nocturnal enuresis to 2 equal groups. Group 1 received a weekly session of posterior tibial nerve stimulation for 12 weeks and group 2 was the placebo group. Evaluation was performed in each group at baseline and after posterior tibial nerve stimulation to compare clinical and urodynamic findings. Another clinical assessment was done 3 months after the first followup.

Results: The 2 groups were comparable in baseline clinical and urodynamic data. Overall, 13 patients (46.4%) had detrusor overactivity and 14 (50%) had decreased bladder capacity. After treatment 11 group 1 patients (78.6%) had a partial or full response to posterior tibial nerve stimulation but only 2 (14.3%) in group 2 had a partial response (p < 0.002). Also, the average number of wet nights in group 1 was significantly lower than at baseline (p = 0.002). All urodynamic parameters significantly improved in group 1. In contrast, the number of wet nights and urodynamic parameters did not change significantly in group 2. At 3-month followup the number of patients with a partial or full response in group 1 had decreased from 11 (78.6%) to 6 (42.9%). No change was evident in group 2.

Conclusions: Posterior tibial nerve stimulation can be a viable treatment option in some patients with refractory monosymptomatic nocturnal enuresis. However, deterioration in some responders with time suggests the need for maintenance protocols.

Key Words: urinary bladder, nocturnal enuresis, transcutaneous electric nerve stimulation, urodynamics, treatment outcome

Nocturnal enuresis is usually associated with severe psychological and social distress to children and their families.1 In recent years several treatment modalities emerged to treat NE, such as behavioral therapy,2 alarm treatment,3 medical therapy with desmopressin, oxybutynin and imipramine, and combination therapy.4–6 However, none has been completely successful and the relapse rate of all of them is significant.7–9 Therefore, there is a great need to find other treatments that could be more effective and durable than current therapy.

The pathogenesis of refractory NE was discussed in many studies and attributed to decreased bladder capacity and/or DO.10–14

PTNS was introduced with early promising results as neuromodulative therapy for diseases that involve the
lower urinary tract and for refractory conditions in adults and children. These beneficial effects of PTNS for controlling various bladder disorders led us to try it in patients with refractory primary MNE.

MATERIALS AND METHODS

A total of 28 patients were included in this prospective, randomized, placebo controlled, single blind study from January 2010 to March 2012 at the urology department at Tanta University Hospital. The study protocol was reviewed and approved by the Tanta University institutional review board. Informed consent was obtained from all participants or from parents if the patient was younger than 18 years.

We recruited patients with severe (3 or more wet nights per week) primary MNE at least 6 months in duration in whom available conventional and combination therapies had failed, including desmopressin, anticholinergics and an alarm. We excluded those with secondary NE, nonMNE, nocturnal polyuria and any neurological abnormality.

All patients provided a detailed history and underwent complete physical examination, urinalysis, x-ray of the lumbo-sacral spine and ultrasound of the urinary system. All patients were asked to keep a nocturnal enuresis diary for 2 weeks, which included the time of sleep and arousal, and whether they had a dry or wet bed in the morning. Nocturnal urinary output was measured as the total urine volume collected in the diaper after voiding during the last night (assessed by weighing the diaper in the morning) plus the first morning urine volume. Nocturnal polyuria was defined as nocturnal urine output 130% or greater of EBC for age.20

The Arabic version of a 2-day frequency-volume chart (adapted from the Pan Arab Continence Society, www.pacsoffice.com) was obtained from all patients to confirm that the problem was MNE. Daytime functional bladder capacity was considered the recorded MVV. EBC for age was calculated by the formula, $30 + (age \times 30)$. Children with MVV less than 65% of EBC for age were considered to have a small bladder.20

All patients also underwent urodynamic tests, as performed by the same urodynamicist using a Delphis-KT device (Laborie, Toronto, Ontario, Canada), including 1) uroflowmetry with PVR estimation by ultrasound for at least 2 voids and 2) cystometrogram, including 1 filling cycle using an 8Fr double lumen urethral catheter with the patient supine and a slow filling rate of 10 ml per minute.

 Patients were randomly divided into 2 equal groups by method. Randomization was done blindly by having an independent nurse randomly take a card from an envelope containing 14 cards for group 1 and 14 for group 2. Group 1 received active PTNS treatment sessions using the Urgent® PC Neuromodulation System, while group 2 underwent a sham procedure.

Treatment Protocol

We applied the technique described by Stoller.21 The patient lay supine with the soles of the feet together, and the knees abducted and flexed (frog position). A 34 gauge needle was inserted percutaneously approximately 2 inches (5 cm) cephalad to the medial malleolus and 1 cm from the posterior margin of the tibia at an angle of 60 degrees from the skin surface and the lead wire attached to it. The surface electrode was placed on the same leg near the arch of the foot over the calcaneus bone. The device was turned on and amplitude was slowly increased until the largest toe of the patient began to curl, the digits fanned or the entire foot extended, indicating proximity to the nerve bundle (see figure). If this response was not achieved or pain occurred near the insertion site, the device was turned off and the procedure was repeated.

For the sham procedure we tested only the foot response to the electrical impulse and then turned off the apparatus during the whole session. To avoid patient identification of the type of procedure all participants were informed that they may or may not feel a sensory stimulus in the lower extremities during the treatment sessions.

Groups 1 and 2 underwent 12 weekly outpatient treatment sessions. All participants were advised to stop all medical treatment for NE at least 1 month before starting PTNS but to continue behavioral therapy, including fluid
restriction at night, complete bladder emptying before sleep and awakening 2 hours after sleep to void.

**Patient Assessment**

The first patient evaluation was done in the first 2 weeks after the last session. This evaluation involved repeating the clinical and urodynamic assessments. The clinical part included a nocturnal enuresis diary for 2 weeks in which the number of wet nights/week was reported as well as a 2-day frequency-volume chart.

The clinical response to treatment was assessed as outlined by the International Children’s Continence Society, including no response—less than a 50% decrease in the total number of wet nights, partial response—50% to 89% decrease, response—90% or greater decrease and full response—100% decrease.\(^2\) Urodynamic assessment included uroflowmetry, PVR measurement and cystometry.

The second evaluation was done 3 months after the last session. This evaluation involved clinical assessment and baseline characteristics of each group.

**Statistical Analysis**

All statistical analysis was performed using SPSS® 17. Data are shown as the mean ± SD unless otherwise specified. The Student t and paired sample t tests were used for comparison between groups and in the same group, respectively. Nonparametric data were compared by the Wilcoxon signed ranks or Mann-Whitney U test. Statistical significance was considered at p < 0.05.

**RESULTS**

Recruited for this study were 28 patients with refractory NE who met inclusion criteria. Initial assessment and baseline characteristics of each group showed no significant difference in clinical and urodynamic parameters (table 1). Overall, in the 2 groups DO was present in 13 patients (46.4%) and 14 (50%) had decreased bladder capacity.

The procedure was performed easily with no adverse effects in all cases. No patient discontinued the planned sessions.

At the end of the PTNS sessions clinical assessment revealed significant improvement in the average number of wet nights per week in group 1 (decrease from 4.7 to 2.6, p = 0.002, table 2). Compared to the placebo group, the number of wet nights after treatment was significantly lower in group 1 (p = 0.041, table 2). At that time 4 group 1 patients (28.6%) had a complete response to PTNS, 7 (50%) had a partial response and 3 were nonresponders. However, in group 2 there were 2 patients (14.3%) with a partial response, while the remainder did not respond. When we compared the 2 groups, the difference in this response rate was statistically significant (p = 0.002, table 2).

At first evaluation after the end of treatment, the active group showed significant improvement in all urodynamic parameters compared to baseline, including first and strong desire to void, and MCC (p = 0.002, 0.01 and 0.000, respectively, table 2). In group 2 these parameters did not significantly differ compared to baseline (table 2). Also, DO disappeared in 2 of 7 group 1 patients but this improvement was not noted in the sham treated group (table 2). Statistical analysis revealed that the difference be-

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**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Placebo</th>
<th>p Value</th>
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</thead>
<tbody>
<tr>
<td>No. boys/girls</td>
<td>8/6</td>
<td>9/5</td>
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<tr>
<td>Mean ± SD age (yrs)</td>
<td>13.7 ± 2.8</td>
<td>14 ± 2.8</td>
<td>0.8</td>
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<tr>
<td>Mean ± SD body mass index (kg/m²)</td>
<td>24.95 ± 4.40</td>
<td>26.27 ± 4.23</td>
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</tr>
<tr>
<td>Mean ± SD max urine flow (ml/sec)</td>
<td>26.85 ± 6.74</td>
<td>23.28 ± 5.49</td>
<td>0.13</td>
</tr>
<tr>
<td>Mean ± SD PVR (ml)</td>
<td>6.21 ± 7.11</td>
<td>5.86 ± 5.48</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean ± SD daytime frequency</td>
<td>3.9 ± 0.67</td>
<td>4.29 ± 0.64</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean ± SD MV (ml)</td>
<td>266.57 ± 82</td>
<td>288.93 ± 106.29</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean ± SD No. wet nights/wk</td>
<td>4.7 ± 1.3</td>
<td>5.1 ± 1.4</td>
<td>0.42</td>
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<tr>
<td>No. detrusor overactivity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>Mean ± SD void desire (ml):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>148.46 ± 25.89</td>
<td>153.50 ± 21.65</td>
<td>0.59</td>
</tr>
<tr>
<td>Strong</td>
<td>260.43 ± 84.18</td>
<td>271.79 ± 75.43</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean ± SD MCC (ml)</td>
<td>291.21 ± 86.82</td>
<td>322.21 ± 76.04</td>
<td>0.32</td>
</tr>
</tbody>
</table>

**Table 2. Intragroup and intergroup comparisons of clinical and urodynamic findings after PTNS at first evaluation**

<table>
<thead>
<tr>
<th></th>
<th>Active Baseline</th>
<th>After Treatment</th>
<th>p Value</th>
<th>Placebo Baseline</th>
<th>After Treatment</th>
<th>p Value</th>
<th>Posttreatment p Value</th>
</tr>
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<tbody>
<tr>
<td>Mean ± SD void desire (ml):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1st</td>
<td>177.71 ± 35.48</td>
<td>153.50 ± 21.65</td>
<td>0.002</td>
<td>154.14 ± 20.71</td>
<td>0.59</td>
<td>0.041</td>
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<tr>
<td>Strong</td>
<td>283.64 ± 72.03</td>
<td>271.79 ± 75.43</td>
<td>0.01</td>
<td>271.6 ± 72.8</td>
<td>0.94</td>
<td>0.67</td>
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<tr>
<td>Mean ± SD MCC (ml)</td>
<td>322.21 ± 76.04</td>
<td>323.57 ± 77.44</td>
<td>0.57</td>
<td>0.97</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. detrusor overactivity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7</td>
<td>6</td>
<td>0.44</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Absent</td>
<td>7</td>
<td>9</td>
<td>0.44</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD MV (ml)</td>
<td>280.14 ± 71.81</td>
<td>289.93 ± 106.29</td>
<td>0.022</td>
<td>291.07 ± 96.84</td>
<td>0.73</td>
<td>0.6</td>
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<tr>
<td>Mean ± SD No. wet nights/wk</td>
<td>4.7 ± 1.3</td>
<td>5.1 ± 1.4</td>
<td>0.002</td>
<td>4.7 ± 2.1</td>
<td>0.08</td>
<td>0.041</td>
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<tr>
<td>No. response:</td>
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<td>Full</td>
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<td>0</td>
<td></td>
<td></td>
<td>0.002</td>
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<td>7</td>
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<td>12</td>
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</table>
between the 2 groups in this regard was not statistically significant (p = 0.7, table 2). Furthermore, in this evaluation urodynamic parameters showed that bladder volume at first desire to void was significantly higher in group 1 than in group 2 (p = 0.041). On the other hand, bladder volume at strong desire to void and MCC did not significantly differ between the groups (p = 0.67 and 0.97, respectively, table 2). Five of the 8 group 1 patients with decreased EBC showed improved capacity. MVV also significantly increased after treatment from a mean of 266.57 ± 82 to 280.14 ± 71.81 cc (p = 0.022, table 2).

When we studied the relationship between the response to PTNS and initial urodynamic findings, we noted that all 10 group 1 patients with small bladder capacity and/or DO showed a good response to treatment, including 4 and 6 with a full and partial response, respectively. However, when we compared the type of response in those with normal vs abnormal urodynamic results, the 4 patients with normal urodynamic findings in this group had a poor response to the sessions, including 3 with no response and 1 with only a partial response. This difference was significant (p = 0.007).

Clinical results at 3 months after the last session showed some deterioration in early results in the active group. In this group the number of patients with a full response decreased from 4 to 2 and the number of those with a partial response decreased from 7 to 4. No change was detected in the other group. However, when we compared the response rate in the 2 groups at this time, we detected no significant difference (p = 0.13). In addition, the average number of wet nights per week at that time was 2.9 in group 1 and 4.2 in group 2, which did not significantly differ (p = 0.07).

**DISCUSSION**

This study demonstrates that PTNS could be of value in some patients with primary MNE in whom previous conventional therapies failed. To our knowledge this treatment modality has not been tried before in such cases but it has been successfully used for overactive bladder syndrome,22,23 lower urinary tract dysfunction in adults and children,15,18 refractory overactive bladder,16 refractory vesical dysfunction19 and refractory nonneurogenic bladder sphincter dysfunction.17

Absent daytime lower urinary tract symptoms in patients with NE does not necessarily mean that the bladder functions well because DO and/or decreased bladder capacity was previously reported in such patients.10,11 The clinical response to desmopressin therapy is less satisfactory when NE is associated with decreased bladder capacity and/or DO.12–14 In our study we detected DO and decreased bladder capacity in 46.4% and 50% of patients, respectively, although patients with MNE only were included in analysis. These values agree with previous reports showing bladder overactivity24 and small bladder capacity25 in 49% and 50% of children with MNE, respectively. These findings may partially explain the mechanism of resistance to the previous treatment trials in our patients.

Our results and those of others reveal that PTNS can be applied easily and safely in children.18,19 After the 12 PTNS sessions in our series, patients showed a significant increase in MVV and urodynamic parameters, including first and strong desire to void, and MCC, compared to the placebo group. These results agree with those in previous reports demonstrating that PTNS increased cystometric capacity from 197 to 252 cc26 and from 243 to 340 cc,27 and increased MVV by 39 cc, which was statistically significant.23

However, at 3-month followup we detected some deterioration in the response rate compared to early results. The overall number of full and partial responders decreased from 11 (78.6%) to 6 (42.9%) in group 1. This deterioration during followup suggests that PTNS may have temporary efficacy and its effect decreases gradually with time. This finding was also noted in patients with overactive bladder treated with PTNS. van der Pal reported that 7 of 11 patients with an initially good response had evidence of subjective and objective deterioration after PTNS.28 They suggested the need for maintenance treatment.

The early promising results of this study encouraged us to suggest that PTNS might be effective in patients with refractory primary MNE in whom nocturnal polyuria is not an etiological factor but in whom the main underlying pathological condition is decreased bladder capacity and/or DO. However, the exact mechanism that could explain the mode of action of this treatment modality is still unknown. PTNS may induce some inhibitory effects on DO. The existence of this functional abnormality in the bladder implies that the detrusor is not completely relaxed between voids. Therefore, the capacity of the overactive bladder is usually smaller than that of the bladder with a normal detrusor. Consequently, the clinical response usually occurs when bladder capacity increases and DO improves after PTNS. This explanation may be supported by the improvement in bladder capacity (functional and cystometric) and the disappearance of DO in patients who responded to PTNS in our study.

The main limitations of this study are the small sample size and the short 3-month followup. In addition, we did not repeat urodynamic tests at the second followup at 3 months to avoid patient discomfort but depended only on the patient clinical response. However, this information could be important for assessing the cause of the deterio-
ration in PTNS efficacy after treatment was stopped.

CONCLUSIONS

PTNS appears to be a viable treatment option in some patients with refractory primary MNE. However, deterioration in the response rate with time raises important questions about the long-term efficacy of this therapy and the need for further maintenance sessions. More studies are needed to support our findings and select patients who would be good candidates for this therapy.

REFERENCES


