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Usefulness of sacral nerve modulation in a series of multiple sclerosis patients with bladder dysfunction

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ABSTRACT

Objective: Bladder dysfunctions are common in multiple sclerosis (MS) often causing the most distressing symptoms. The aim of this paper was to evaluate the effectiveness of sacral nerve modulation (SNM) in this disease.
Methods: We conducted an observational retrospective survey in 17 patients treated with SNM in the north-east of Italy, all complaining of bladder symptoms (storage in 41%, voiding in 24%, mixed in 35%) unresponsive to conventional therapies, with a mean follow-up of 52 ± 26 months and mean Expanded Disability Status Scale score of 5.8 ± 1.8.
Results: 75% of patients reported significant and lasting improvement in bladder symptoms and in quality of life. We observed a statistically significant improvement in frequency, urgency, number of pads, residual volumes, number of catheterizations and in the voided volumes.
In 5 out of 6 cases with mixed symptoms the stimulation was discontinued (device totally explanted or turned off) after a mean time of 66 months (range 10–84 months) after the implant, for disease progression or loss of efficacy.
Conclusion: SNM could be an option in very selected cases of storage and voiding symptoms refractory to conservative treatments caused by a stable or slowly progressive MS considering its minimal invasiveness and reversibility. The poor results observed suggest avoiding this therapy in mixed symptoms and in cases of advanced disability.

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1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, neurodegenerative disorder affecting the central nervous system (CNS) with unknown etiology [1] and it represents the commonest progressive neurological disease affecting young people.

Bladder dysfunctions are common in people with MS, occurring in up to 75% of patients during the course of the disease; they can cause some of the most distressing symptoms, with a great impact on the quality of life (QoL), and are often associated with significant morbidity [2]. Urinary symptomatology is polymorphic and, like its incidence, subject to change over time, but it tends to increase with disease progression and it is mainly the result of spinal cord involvement. The most frequent are storage symptoms (urinary frequency, urgency, and urge incontinence) while voiding symptoms (hesitancy, incomplete voiding and urinary retention) exist to a lesser degree [3]. Therapeutic options

for storage symptoms vary and they include, with or without associated clean intermittent self-catheterization, conservative treatments such as anticholinergic drugs — although the published data provide limited evidence for their efficacy in MS [4,5]. In patients with severe bladder overactivity unresponsive to anticholinergics there is evidence for the use of bladder injections of botulinum toxin A [6,7] and also emerging evidence on the use of cannabinoids [8] and tibial nerve stimulation [9]. Surgical procedures, which have been advocated with varying success [10], are a last resort being irreversible, with a risk of major operative morbidity and long-term consequences; they include augmentation cystoplasty [11], in which the bladder is transected and repaired with a patch of ileum isolated from the small intestine, and urinary diversion [12].

Sacral nerve modulation (SNM) is a safe and minimally invasive treatment and it has become an option in refractory low urinary tract symptoms (LUTS) from different underlying diseases [13–16]; a number of prospective trials and numerous case series have provided an evidence base that has confirmed the efficacy and durability of SNM [17]. Despite the documented clinical benefit, the exact underlying neurophysiological mechanism of action of SNM is complex and not fully

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understood. However, evidence supports an emerging consensus that it exerts its effect through afferent pathways that modulate the activity in other neural pathways within the spinal cord and higher centers [18]. Some studies have just investigated the effects of SNM on the higher centers. Braun et al. [19] performed serial electroencephalograms (EEG) in 10 patients with both neurogenic and idiopathic bladder dysfunction who had permanent implants of SNM in S3, using an on–off paradigm with 1.5 s with stimulation "on" followed by a 10 second stimulation "off". They demonstrated in all patients a cortical potential complex following stimulation with an early electronegative component at 50 ms followed by a late potential component with a mean latency of 253 ms, both with a maximum in the post-central gyrus. These findings occurred irrespective of patients' reports of actually feeling the SNM being switched on and off, whereby the authors concluded that, although these potentials are similar to cognitively mediated "event-related potentials", they are clearly distinct from any subjective sensory or even painful response and support the potential role of suprasacral centers in SMN, most probably in the sensory cortex areas [19].

Blok et al. [20] used positron emission tomography (PET) to study the brain effects of SNM in patients with urge incontinence comparing chronic (in whom SNM was switched on for >6 months) and acute patients (neurostimulator activated for the first time in PET scanner). They observed different modifications in cerebral blood flow in different areas during the chronic and acute stimulations. On the basis of these findings, the authors suggested that chronic SNM influences, presumably via the spinal cord, brain areas previously implicated in bladder overactivity, awareness of bladder filling, the urge to void and the timing of micturition and, furthermore, areas involved in alertness and awareness. On the other hand acute SNM modulates predominantly areas involved in sensorimotor learning, which might become less active during the course of chronic SNM [20].

Since few data are available about this treatment for LUTS in MS [21–23], in the present retrospective evaluation we wanted to determine whether SNM benefits patients with LUTS caused by this disease and unresponsive to first line conservative treatment and to assess if there is any difference in the responsiveness degree of different symptoms.

2. Materials and methods

In July 2008, we proposed to the Departments of Urology in the north-east of Italy performing SNM a retrospective survey about the effectiveness of SNM in MS patients. Only in 3 departments was SMS used in MS patients and all the MS patients implanted in these centers were included in the survey. A questionnaire has been filled for each included subject, enquiring about general data, MS features, perceived changes in micturition symptoms after SNM and changes coming from micturition-diaries. The post-voiding residual volume was evaluated by the clean intermittent catheterization which is usually performed by patients with voiding and mixed symptoms.

A visual analogic scale (VAS) was used to assess the improvement of the QoL and the symptom urinary urgency. Outcome data were obtained from the periodic follow-up as usually conducted.

For statistical analysis the following tests were applied: Cramer's V test, Kruskal Wallis test, univariate ANOVA, true Fisher test.

The clinical practice followed with uniformity by all the Departments required that the candidates for surgical implantation were selected on the basis of informed consent, prolonged failure of the conservative treatments with severe impact on QoL, no abnormality of upper urinary tract and kidney function. The pre-operative assessment included a 5 day voiding diary, the post-void residual evaluation, serum creatinine determination, urine culture, kidney ultrasound and videourodynamics. In the voiding diaries were recorded also the leakage episodes, degree of urgency and the pad used. The SNM implant procedure was performed as previously described [24].

The test period lasted for at least 3 weeks and the stimulation parameters (pulse width, frequency and amplitude) were individually chosen for each patient on the basis of the best responses, with stimulation below threshold. Eligibility criteria for the definitive implant were represented by a positive neuroanatomical response to the stimulation with clinical improvement in the symptoms and no side effects.

3. Results

17 subjects agreed to complete the survey during a follow-up visit, 13 females and 4 males, mean age 49.8 ± 10.9 years. The disease duration before implant ranged from 4 to 40 years (mean 13.5 ± 9.2 years); 10 subjects (59%) had the relapsing remitting, 2 (12%) the secondary progressive and 5 (29%) the primary progressive forms of the disease, with a mean Expanded Disability Status Scale (EDSS) score of 5.8 ± 1.8 [25]. Thirteen subjects (77%) were paraparetic. Regarding LUTS, 4 patients (24%) had voiding symptoms, 7 (41%) storage symptoms and 6 (35%) mixed symptoms; 6 patients reported simultaneous constipation. No statistical differences were identified among these three groups in baseline characteristics except for the anal tone, which resulted hypertonic in 83% of patients with mixed symptoms ($p = 0.032$). The mean baseline EDSS score was worse in mixed and voiding LUTS than in the storage ones. The mean time from the implant was 52 ± 26 months (range 12–97 months). The electrical parameters have been individually programmed and the number of reprogramming during the period of observation ranged from an average of 0.9, in patients with storage symptoms, to 3.0, in those with mixed LUTS. In five out of 6 cases with mixed symptoms the stimulation has been discontinued after a mean time of 66 months (range 10–84 months) for disease progression in 2 cases and for loss of efficacy in 3. The mean EDSS score didn't change significantly from baseline to the last follow-up evaluation, but patients complaining of mixed symptoms presented a quicker progressive MS (Table 1).

Regarding the subjective improvements, 75% of the total population (100% of patients with storage, 75% with voiding and 40% with mixed symptoms) replied positively to the question "After SNM did you detect any significant and lasting improvement in your bladder symptoms?"

The change in QoL was evaluated by the VAS after the question "How much has your QoL changed?" with a score ranging from 0 (not at all) to 5 (very much). The average score reported was 2.9 ± 1.5 for the whole population, 1.8 ± 1.4, 3.3 ± 1.0 and 3.6 ± 1.4 for patients respectively with mixed, storage and voiding symptoms (Fig. 1). Furthermore, there was a statistically significant reduction in subjective urgency level evaluated by the VAS – ranging from 0 (no urgency at all) to 5 (severe urgency) – in patients with storage and mixed symptoms; they passed from an average score of 3.6 ± 1.1 before SNM to 2.0 ± 1.3 during SNM ($p = 0.014$) (Fig. 2).

Analyzing the subgroups, there was a statistically significant reduction in the number of micturitions/day (from 14.3 ± 9.6 to 8.1 ± 3.7; $p = 0.012$) and number of pads/day (from 3.5 ± 1.8 to 1.9 ± 2.4; $p = 0.033$) in patients with storage and mixed symptoms. In subjects with voiding and mixed symptoms was found a statistically significant reduction in number of catheterizations/day (from 3.1 ± 2.0 to 0.9 ± 1.0; $p = 0.017$) and residual volumes (from 195.0 ± 9.0 to 71.5 ± 63.3 ml; $p = 0.018$) and a statistically significant increase in

Table 1
EDSS score in different LUTS, at baseline and during SNM.

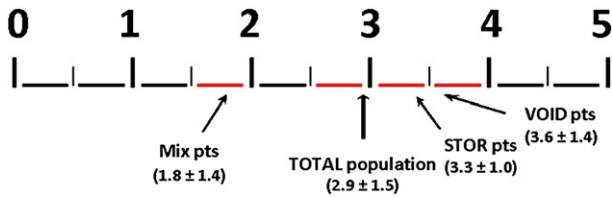|	N	Baseline EDSS	Follow-up EDSS
All patients, mean (SD)	17	5.8 (1.8)	6.3 (2.1)
Voiding symptom, mean (SD)	4	6.5 (1.8)	6.5 (1.9)
Storage symptoms, mean (SD)	7	5.1 (2.1)	5.4 (2.2)
Mixed symptoms, mean (SD)	6	6.8 (0.5)	7.9 (0.9)

Fig. 1. Quality of life changes with SNM at the time of survey compilation. Score ranging from 0 (not at all) to 5 (very much).

spontaneous voided volumes (from 131.9 ± 36.7 to 209 ± 90.0 ml; p = 0.016). In Figs. 3, 4, 5, 6 and 7 are shown these changes.

4. Discussion

Schmidt et al. introduced SNM for the treatment of different kinds of LUTS refractory to conservative treatments [26]. In 2000 a multicenter, international and prospective study of 581 patients found that SNM reduced by more than 50% the voiding frequency, incontinence episodes and retention symptoms in patients with such intractable conditions, but the study excluded patients with underlying neurologic disorders [27].

SNM has been also used in some cases of neurogenic bladder [14,16, 28] and also in neurogenic bladder caused by MS, though the few references usually regard a small number of patients and mainly with a short or median follow-up [21–23,29]. Furthermore the use of SNM is discouraged in MS for the progressive features of the disease [4] and a limitation to the use of this therapy in MS patients is its contraindication to magnetic resonance (MRI) examination.

In many MS patients the demyelination of the dorsal columns, which determines the interruption of normal inhibitory signals coming from sacral parasympathetic outflow tracts, can result in neurogenic detrusor overactivity, which represents the most common problem experienced during the course of the disease. Also voiding symptoms can be experienced by MS patients when the urethral sphincter fails to relax in a picture of detrusor-sphincter dyssynergia [3] or in case of detrusor hypocontractility, reported in 20% of cases [30].

Another problem is the fact that MS nervous system lesions tend to resolve and then recur in different patterns, resulting in unpredictable changes in symptoms over time, and in any case this disease is generally progressive, and hence the therapeutic response can vary. Therefore patients have to be clearly informed that the results of SNM may be altered by the evolution of their underlying disease.

Notwithstanding these considerations, many authors do not consider MS a contra-indication for SNM. The few studies published on this topic regard mainly urinary incontinence; only Marinkovic and Gillen investigated pure urinary retention, reporting remarkably good results [22].

Bosch and Groen observed in 4 MS women with refractory urge-incontinence a reduction in incontinence episodes – from a mean of 4 to 0.3 per day – with SNM. Two women were completely dry and 1 improved significantly during the two year follow-up; in the last case the urinary symptoms worsened with clinical progression of the disease [21]. Subsequently their 4 cases were included in a series of 9 patients [14] with neurogenic urge-incontinence resistant to conservative therapies, due to MS in overall 5 cases. At 6 months, SNM resulted in all of

Fig. 2. Subjective urgency level at baseline (retrospective) and at the time of survey compilation. Score ranging from 0 (no urgency at all) to 5 (severe urgency).
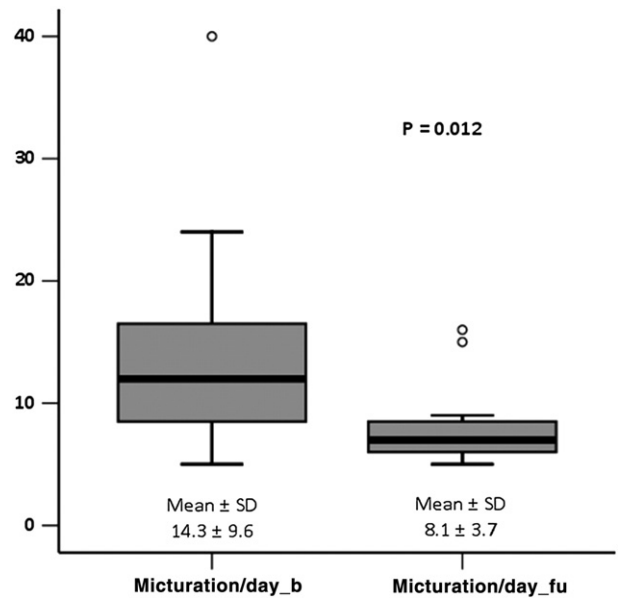

Fig. 3. Micturition number/day at baseline (b) and last follow-up visit (fu).*Strong outlier values; °outlier value.

them having a marked symptomatic improvement in incontinence with positive changes in everyday life: frequency improved from 16.1 to 8.2 voids per day and the mean volume per void correspondingly increased from 115 to 249 ml with six patients completely dry. These results remained stable for an average of 43.6 months except that in two MS patients. Moreover another MS patient had a short follow-up (11 months). In conclusion 2 out of 5 subjects with MS have had a long-lasting benefit from SNM with a follow-up of 60 and 72 months.

Wallace et al. implanted 28 patients with neurogenic bladder complaining of incontinence and/or urinary retention and among them there were 13 MS. At a mean follow-up of 12.4 months they observed a statistically significant improvement in all the usual items regarding detrusor overactivity and also a reduction of 58% in the number of self-catheterizations. Unfortunately MS patients are not distinguishable from other patients [16].

Recently Marinkovic and Gillen reported complete success in 86% of 14 MS females complaining of urinary retention: the pre-operative
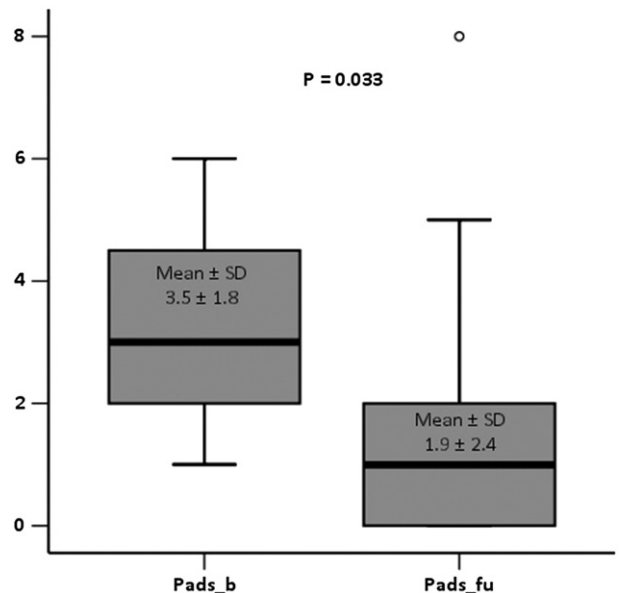

Fig. 4. Number of pads/day at baseline (b) and last follow-up visit (fu). °Outlier value.
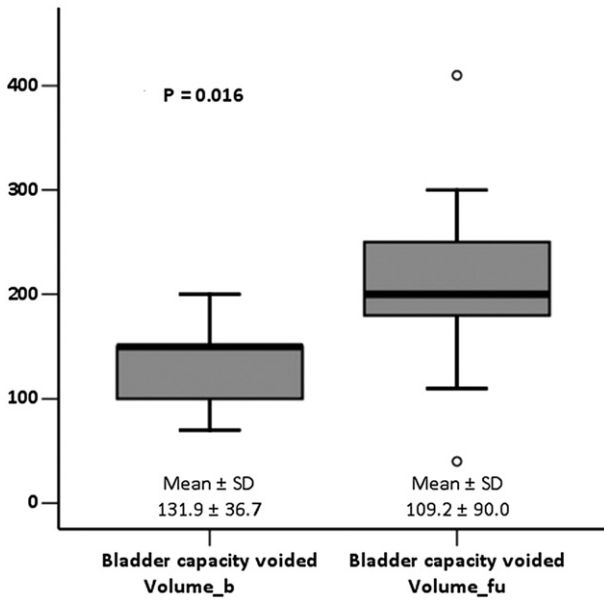
Fig. 5. Voided volume (ml) at baseline (b) and last follow-up (fu). °Outlier value.

Fig. 7. Residual volume (ml) at baseline (b) and last follow-up visit (fu).

mean post-void residual of 308 ml fell to 50 ml and 12 women went on to void without intermittent catheterization at a follow-up of 4.3 years. The authors outlined that the only 2 patient non-responders to SNM were wheelchair-bound [22].

Minardi and Muzzonigro treated 15 patients and found that urinary retention due to detrusor underactivity is not a good indication for SNM while it should be offered in the case of refractory urge-incontinence or urinary retention due to detrusor sphincter dyssynergia [23].

Most of these studies are included in a meta-analysis about neurogenic bladder dysfunction treated with SNM which confirms the low number of MS patients investigated and their heterogeneity, with 50 MS cases out of 357 patients [29].

In none of the above studies reported have there been significant complications.

Also if the literature concerning SNM in MS is small, SNM seems to have an inhibitory effect on neurological detrusor overactivity also if the proportion of patients whose LUTS improved is much less than in non-neurological pathologies.
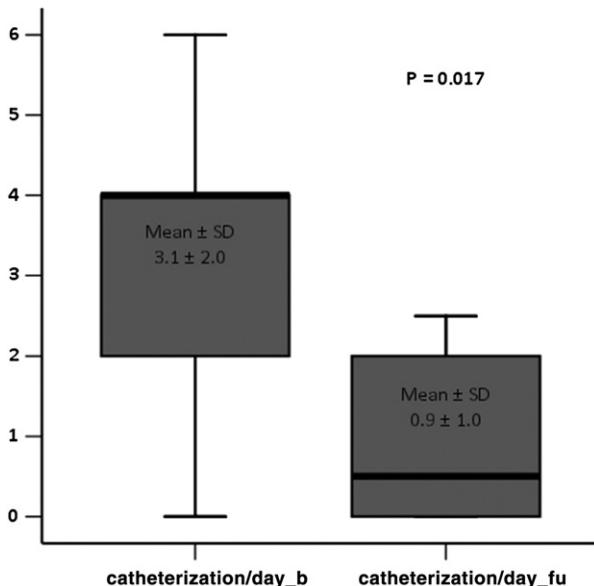

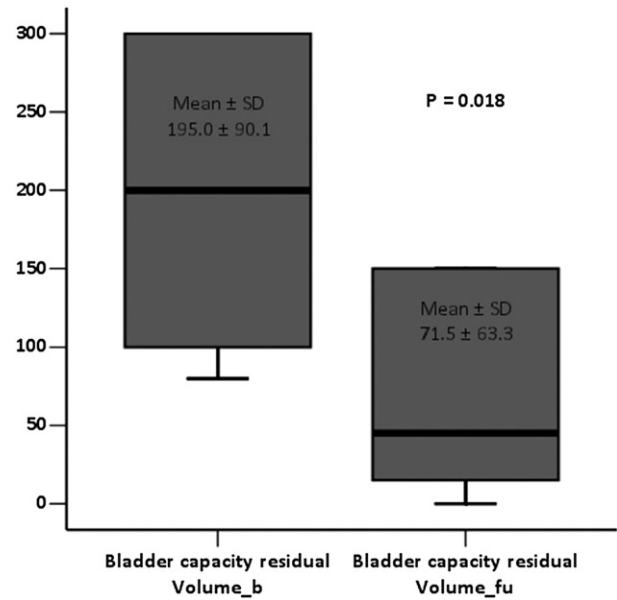**Fig. 6.** Catheterization number/day at baseline (b) and last follow-up visit (fu).

Our observational retrospective survey, regarding patients treated with SNM for every type of LUTS, is the largest MS series studied to date. SNM has been performed in a minority of Urology Units – some of those more trained in neuro-urology – and overall has been rarely used considering that only 17 patients had been implanted in a wide geographic area.

In our experience, SNM has been a quite effective therapy for LUTS with improvement in QoL in MS with lower EDSS. In fact, SNM has worked better in patients with less severe motor impairment as reported in previous studies [22,29]. In the present report the lack of a validated questionnaire on QoL could be a limitation but a VAS evaluation was easier to perform, equally reliable and supported by objective urinary data (reduction of leakage episodes and residual volume).

Moreover these results have been maintained over time in most of patients and they have been detected in all the items at a medium follow-up. The best responses have been observed in storage LUTS, followed by the voiding ones. Poor and short-lasting benefits have been reported in the mixed LUTS, in connection with a quicker and more aggressive form of the disease (EDSS score worsened in the course of time compared to the other cases), and this could explain the decrease of SNM efficacy over time observed in the majority of these patients (five out of six patients).

There is a significant feature in our series of patients: it is not a selected cohort but represents the real MS population. Regarding the gender, our casuistry – with 4 men out of 17 patients – reflects the gender prevalence ratio of MS, while in others reports are mainly analyzed with only female patients. Furthermore we have analyzed every type of LUTS whereas others authors focused only on incontinence or retention [12,21–23,29].

5. Conclusion

In our experience SNM has obtained objective and subjective improvement of LUTS in most of the cases of MS with long-lasting benefit. Therefore it could be a therapeutic option in very selected cases of storage and voiding symptoms, refractory to conservative treatments, caused by a stable or slowly progressive MS without severe motor impairment.

Storage LUTS have the best chance of amelioration, followed by the voiding ones. SNM should be avoided in mixed symptoms and in cases

of advanced disability, in order to maximize the cost–benefit of this therapy.

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