The Effect of Pulse Rate Changes on the Clinical Outcome of Sacral Neuromodulation

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Purpose: We evaluated the effect of pulse rate changes on the clinical response to and stimulation related pain symptoms of sacral neuromodulation treatment.

Materials and Methods: In this pilot study we evaluated the effect of 4 pulse rates, including 5.2, 10, 21 and 40 Hz, in patients with a suboptimal response to sacral neuromodulation. The effect of each frequency was evaluated during a 6-day test period. To avoid the carryover effect stimulation was discontinued for 24 hours between consecutive test periods. On the last 3 days of each test period a voiding diary and questionnaire were completed. Changes in the clinical response and pain symptoms were compared between the 4 pulse rates using multivariate analysis.

Results: Of the 50 patients included in the study 40 (80%) were female. Mean ± SD age was 55.5 ± 12.3 years. Of the patients 41 (82%) had overactive bladder symptoms and 9 (18%) were in chronic nonobstructive urinary retention. No significant difference was found in clinical outcome on the voiding diary and questionnaire between the pulse rates and none of the 4 rates was significantly related to sacral neuromodulation associated pain. However, individuals appeared to benefit from changing the pulse rate in terms of treatment efficacy and stimulation related pain.

Conclusions: On the group level none of the 4 pulse rates appeared to have a significantly different effect on clinical outcome or sacral neuromodulation related pain. However, an individualized approach to optimize treatment efficacy by changing the pulse rate appears to be useful.

Key Words: urinary bladder, overactive; urinary incontinence; electric stimulation; pulse; pain

Abbreviations and Acronyms

OAB = overactive bladder

SNM = sacral neuromodulation

Submitted for publication September 2, 2010.

Study received institutional review board approval.

Supported by the Urological Research Foundation of Maastricht (Novartis, Medtronic, GlaxoSmithKline, Coloplast, AstraZeneca, Astellas and Abbot, partners).

Supplementary material for this article is available at s.de.wachter@mumc.nl.

* Equal study contribution.

† Financial interest and/or other relationship with Medtronic, Astellas and Ferring.

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PATIENTS with refractory OAB symptoms with or without urgency incontinence and nonobstructive urinary retention who do not respond to conservative treatment, such as pharmacotherapy or pelvic floor training, can achieve symptom relief by SNM therapy.[1–4] The implantable neurostimulator can have various settings. The waveform that the stimulator produces is a square wave pulse. The pulse rate can be set between 2.1 and 130 Hz, pulse width can be set between 60 and 450 μseconds, and amplitude can be changed from 0.05 to 10.55 V.

At most centers where patients with SNM are treated a pulse rate between 10 and 16 Hz is commonly used.[5–7] This choice is based on the optimal setting by measuring urethral closure pressure.[8] Data from animal studies sug-

0022-5347/11/1855-1781/0
THE JOURNAL OF UROLOGY®

Vol. 185, 1781-1785, May 2011
Printed in U.S.A.
DOI:10.1016/j.juro.2010.12.089

gest that the pulse rate should not exceed 50 Hz since this may be detrimental to the stimulated nerve due to early axonal degeneration.[9,10] Currently patients with apparently opposite dysfunctions of the lower urinary tract (OAB vs urinary retention) are treated using the same stimulation parameters because to our knowledge no available studies have clearly evaluated the clinical response to different stimulation parameters.

A parameter that may have an influence is the pulse rate. We evaluated the impact of pulse rate changes during SNM on the clinical outcome. We also evaluated the effect of changing the pulse rate on sensory responses and SNM related pain symptoms.

METHODS

This pilot study included patients with a suboptimal effect of SNM treatment using the standard parameter settings. Ethical approval for the study was granted and all patients provided written informed consent before the study started. Patients with urgency urinary incontinence and those in chronic nonobstructive urinary retention were recruited during followup at our outpatient clinic. All patients had an implantable pulse generator and had received SNM therapy for at least 6 months based on a good response during test stimulation, defined as more than 50% improvement in key voiding diary variables compared to baseline.

A suboptimal effect was defined in patients with incontinence as the persistence of some degree of incontinence, and in patients with retention as the need for catheterization to evacuate post-void residual urine. Only patients with a suboptimal effect were included in analysis, accepting the hypothesis that no symptom improvement can be expected in those who already experience a full clinical response (patients with no more symptoms). Patients who experienced decreased treatment efficacy since implantation were evaluated for technical malfunction or lead migration. Restoration of treatment efficacy was attempted by changing the polarity.

Initial baseline settings were amplitude just above the sensory threshold, frequency 10 Hz and pulse width 210 μseconds. Patients were asked to maintain a voiding diary for 3 days and complete a questionnaire. During the experimental protocol 4 pulse rates were used, each for a 6-day stimulation period. To avoid the carryover effect stimulation was discontinued for 24 hours between the different test periods. For each test period patients were asked to complete a voiding diary on days 4 to 6 of the period and answer the questionnaire on day 6. Pulse rates tested during the experimental protocol were 5.2, 10 (control setting), 21 and 40 Hz. The sequence was determined by randomization and blinded for each patient. Pulse width was not changed during the whole protocol (210 μseconds) and patients controlled the amplitude to just above sensory threshold.

The primary outcome was the change in voiding diary parameters among the 4 settings (5.2 vs 10 vs 21 vs 40 Hz). In patients with urinary incontinence the parameters were the number of voids daily, voided volume per void, daily incontinence episodes and daily pad use. In patients in urinary retention the parameters were the number of catheterizations daily, catheterized volume per catheterization, voided volume per void and the number of voids daily. A change of 20% or more in the relevant voiding diary parameters compared to baseline was considered clinically significant.

Secondary outcomes were derived from the questionnaire. Part 1 consisted of questions on stimulation related pain symptoms. At each pulse rate the site of the sensory response and the occurrence of pain or discomfort were documented. Part 2 consisted of 7 questions to evaluate subjective voiding symptoms using a visual analogue score of 0—worst to 100—best.

Statistical Analysis

Since this pilot study was 1 of the first to analyze the effect of the 4 pulse rate settings on the response of patients to SNM therapy, it was difficult to perform power analysis without knowing in advance the strength of the associations of the predictors used. Thus, we used a tentative initial number of 50 patients to gauge the sensibility of test settings. The paired t test was used to compare baseline (control) and 10 Hz outcomes to assess the validity of diary results. Repeated measures ANOVA was done to test results between the 4 pulse rates. The effects of the patient age and complaint type (OAB and nonobstructive urinary retention) subgroups on pulse rate settings were analyzed. If age had a statistically significant effect, optimal dichotomous categorizing was done to determine age cutoffs. Statistical significance was considered at $p < 0.05$. For all data analysis SPSS® PC, version 16.0 was used.

RESULTS

Clinical Outcome

Of the 50 patients 40 were female (80%). Mean ± SD age was 55.5 ± 12.3 years. A total of 41 patients (82%) had urinary incontinence and 9 (18%) were in urinary retention. Mean followup after implantation was 6.2 ± 4.8 years. Comparison of the baseline 10 Hz voiding diary with the experimental 10 Hz voiding diary showed no statistically significant differences in any outcome parameter (see table).

Of the patients 38 (76%) experienced clinical improvement, defined as a greater than 20% change in voiding diary parameters, for at least 1 of the 4 pulse rate settings. Part *A* of the figure shows the number of patients with clinical improvement for each pulse rate. Eight of the 41 patients (20%) with OAB were completely dry for at least 1 setting and 2 of the 9 (22%) in retention had no more need for catheterization.

When comparing the effect of the 4 pulse rates, no significant relation was found between any rate and a change in voiding diary parameters on univariate analysis. Multivariate analysis of voiding diary data, controlled for age and complaint type, revealed a significant difference in the number of voids daily at the 40 Hz setting ($p = 0.036$) but only in younger patients. For rates other than 40 Hz this effect was not found.