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Cycling Sacral Root Neuromodulation: Pilot Study to Assess the Effectiveness of This Mode in Neuromodulator Programming for the Treatment of Chronic Pelvic Pain Syndrome

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Abstract

Aim: There is lack of evidence of the role of sacral root neuromodulation (SNM) in the management of chronic pelvic pain syndrome (CPPS). We evaluated the effectiveness of cycling sacral root neuromodulation (CSNM) in the management of CPPS in patients non responders to conservative treatment.

Methods: A prospective, single center, cohort study was carried out on all patients with CPPS refractory to conventional treatment, who underwent test stimulation using the tined lead between February 2012 and March 2016. During test stimulation the tine lead was positioned along the third sacral nerve, on the side where they reported more pain. Success was defined as >50% improvement of pain and concurrent urinary symptoms. After a successful SNM test period of 4 weeks, patients received a permanent implant. We also included 9 more patients already with a permanent implant and partial responders to continuous mode in neuromodulator programming. To assess pain and quality of life, all patients filled-in a VAS scale and SF-36 and McGill questionnaires, at baseline, after the 4-week test period ad after the permanent implant.

Results: Overall 22 consecutive adult patients were suitable to undergo a cycling test stimulation; 19 out of them (86.3%) underwent a permanent implant after a satisfactory test phase, using a codified cycling mode of programming. Eighteen naive patients out of nineteen (94.7%) maintained the benefits of the test stimulation at a mean follow up of 21.3 months. VAS scale, McGill and SF-36 questionnaires scores improved significantly in all domains with a 95% satisfaction rate; 7 out of the 9 already implanted patients (77.7%) significantly improved their pain control.

Conclusion: CSRN appears to be effectiveness in treating CPPS in both naïve and previous implanted partial responder patients.

Keywords: Sacral root neuromodulation; Chronic pelvic pain syndrome; Cycling sacral root neuromodulation

Introduction

Failure to adequately diagnose and treat patients with pelvic pain often leads to the development of a chronic pelvic pain syndrome (CPPS).

These patients generally present undiagnosed, taking multiple medications including analgesics, anxiolytics and hypnotics. Electrical stimulation of peripheral nerves using implanted electrodes for the therapy of intractable pain has been used for the past 30 years [1].

In most cases, neuropathic pain is the cause of a CPPS, which is not only due to the entrapment of the pudendal nerve, as believed in the past, but also to an inflammation of this nerve and/or an alteration of pain receptors and central pain pathways [2].

Transcutaneous electrical nerve stimulation (TENS) has been the most commonly form of electrical modulation used in the past to treat chronic pain [3-6]. Actually there is lack of evidence of the role of sacral root neuromodulation (SNM) in the management of CPPS refractory to conventional treatment. Commonly SNM patterns provide for continuous stimulation [7].

However in the management of idiopathic urgency urinary incontinence in women, it has been shown an equivalent benefit between cyclic and continuous stimulation patterns [8]. The application of cyclic stimulation pattern to CPPS patients would bring benefits in terms of energy and consequently a reduction in both nerve

stress and fibrosis and a delay of re-intervention for neuromodulator battery replacement.

All these could result in a better cost-benefit balance with favourable effects on long-term efficacy and sanitary costs.

The first aim of our study was to evaluate the effectiveness of cycling stimulation pattern applied to the sacral nerve, named cycling sacral root neuromodulation (CSRN), using the same parameters utilized for TENS analgesia. This mode in SNM programming is innovative as only continuous mode of neuromodulator programming have been described in the literature.

Moreover, the parameters used during stimulation were not reported in most papers. The second aim was trying to further detect if CSRN can improve the outcome in CPPS patients with partial response to "conventional" SNM, as several articles in the treatment of CPP [9-12] reported an overall mean success rate of 60%.

Material and Methods

From February 2012 to March 2016, we carried out a prospective, single center, cohort study enrolling all patients with CPPS refractory to conventional treatment, candidate to a test stimulation of SNM.

All patients had a test stimulation using a tine lead inserted along the third sacral nerve root, on the side where they reported more pain; the lead positioning was guided by the evidence of somato-sensory evoked potentials (SSEP's), or the more exacerbating pain at pressure on Alcock canal (Tinel's sign +) (Table 1) [1].

All patients complained of one or more symptoms related to some pelvic floor dysfunction (urinary, fecal, and sexual).

Additionally, we included 9 more patients (3 male and 6 female, mean age 45 ± 1.3 years) with a SNM permanent implant (Table 1) for CPPS, partial responders to a continuous mode in neuromodulator programming, in order to evaluate if the new parameters of stimulation could improve their symptoms.

Both naïve and implanted patients had been weaned of their analgesic medication (drug wash out) for at least 21 days before the procedure, and pain intensity was evaluated by a VAS scale [13], in association with SF-36 questionnaire [14] before the procedure, after the test stimulation and after the permanent implant.

In addition all patients filled the McGill Pain questionnaire [15] for a more comprehensive evaluation. The VAS scale score ranges from 0 to 10. The SF-36 questionnaire scores range from 36 to 180.

The McGill Pain questionnaire scores range from 0 to 78. For the SF-36 questionnaire higher scores represent a better outcome on QoL. For the VAS scale and the McGil Pain questionnaire higher score means a higher level of symptoms or problems.

All patients received a unilateral implant at the root of S3, following the conventional technique described in the literature by Tanagho and Schmidt [16], modified in 2002 with the introduction of the tined lead [17].

The tined lead is a quadripolar in-line lead containing 4 cylindrical electrodes of equal length that are spaced equidistantly. An anchoring mechanism proximal to the electrodes forms an integral part of the lead body and comprises 4 tine elements with each tine element consisting of 4 flexible, pliant tines.

The system was studied to be implanted in and engage subcutaneous tissue, particularly muscle tissue, to inhibit axial movements of the lead body and consequent dislodgment of the stimulation electrodes

The apparatus consists of a directional guide wire, a metal dilator with a concentric plastic sheath and a dilator locking mechanism. The sheath is slightly tapered at the distal end to allow smooth transition to the dilator.

The dilator is made of stainless steel tubing tapered at the distal end for smooth insertion. The directional guide is made of stainless steel wire rounded at each end. It has depth markings etched into the surface along the distal end [17].

The patient is placed prone. Using local anesthesia a foramen needle is inserted in the S3 foramina, on the same pain side, which is then stimulated to ensure the correct sensory and motor response. The inner style of the needle is removed and replaced with the directional guide.

The foramen needle is removed, and the dilator and introducer sheath are placed over the directional guide and advanced into the foramen. The directional guide and dilator are removed, leaving the introducer sheath in place.

The lead is passed through the introducer sheath until the proximal electrode enters the foramen. Electrodes 0 to 3 are tested while the patient is observed for responses [17]. Simultaneous fluoroscopy is essential to place correctly and confirm the position of the tined lead in relation to optimal patient sensory responses (at least 3 poles of the tined lead working between 1.0 and 1.5 V or less).

We started to stimulate at the sensory threshold, using a 4-8 Hz pulse rate and a 30 minutes on and 3 hours off cycle. If not comfortable or effective we changed the parameters and cycling pattern, after one week interval, to obtain better comfort and effectiveness for the patients.

If non responders to low frequency stimulation patients underwent a new high frequency trial (using a 100 Hz pulse rate at 0.1 V below the sensory threshold and adapting the on-off cycle to the pain perception).

We advised them to switch on the device when the pain started and to switch off when it was relieved. All patients completed the test phase of SNM without side effects or complications.

After 4-week test stimulation, all patients were re-evaluated and those with an improvement of at least 50% in their main symptom (VAS) and in SF-36 and McGill questionnaires underwent permanent implant.

All previously implanted patients underwent the same trial protocol, with no requirement to implant a new neuromodulator.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS Inc, Chicago, IL) version 18.0. Continuous variables with normal distribution were reported as means and standard deviations; the Friedman test and the GLM Repeated Measures were used to compare the continuous variables as appropriate.

A $p \leq 0.05$ was considered statistically significant.

Patient initials	Sex	Side of pain	SSEP's	Tinel's sign	Main Pelvic floor dysfunction	1st stage	Initial Parameter Pattern (Hz)	Parameter Adjustment (Hz)
AL	F	Left	Pathologic	+	O.D.	+	6	100
DRG	F	Left	Pathologic	+	OAB	+	8	
RC	M	Right	Normal	+	-	-		
GG	M	Left	Pathologic	+	OAB	+	8	
FT	F	Left	Pathologic	+	Dy	+	5	100
GT	F	Left	Pathologic	+	Dy	+	5	
FC	F	Right	Pathologic	+	O.D.	+	7	
LD	F	Right	Pathologic	+	Dy	+	5	
RT	F	Left	Pathologic	+	OAB	+	8	
CM	M	Left	Pathologic	+	-	-		
GB	F	Left	Pathologic	+	O.D.	+	7	100
SF	F	Right	Normal	+	OAB	+	8	
AG	F	Left	Pathologic	+	OAB	+	8	
FR	F	Left	Pathologic	+	Dy	+	5	
PP	F	Left	Pathologic	+	O.D.	+	6	
PR	M	Left	Pathologic	+	-	-		
AR	F	Right	Pathologic	+	OAB	+	5	
CB	M	Left	Pathologic	+	-	+	Failure*	
CZ	F	Right	Pathologic	+	OAB	+	5	
GC	F	Left	Normal	+	O.D.	+	4	
AA	F	Left	Normal	+	Dy	+	6	
FZ	F	Left	Pathologic	+	O.D.	+	5	
Patient initials	**Sex**	**Side of pain**	**SSEP's**	**Tinel's sign**	**Main Pelvic floor dysfunction**	**New trial test mode**		
GM	M	Left	Pathologic	+	OAB	+	5	
FP	F	Left	Pathologic	+	-	-		
MC	F	Right	Normal	+	OAB	+	5	
FC	F	Left	Pathologic	+	Dy	+	4	100
GA	M	Left	Pathologic	+	OAB	+	8	
SDM	M	Right	Pathologic	+	-	-		
BL	F	Left	Pathologic	+	O.D.	+	4	
PR	F	Left	Normal	+	OAB	+	7	
GN	F	Right	Normal	+	Dy	+	6	

Table 1: Patient database (22 naive + 9 implanted pts).

Results

Overall 22 consecutive adult patients (5 male, 17 female), mean age 43 ± 2.4 years affected by CPPS and non-responders to conservative therapy, were suitable to perform a SNM test stimulation.

Nineteen patients out of twenty-two (86.3%) underwent a permanent implant after a satisfactory test phase (Table 1). We reviewed all implanted patients with a six months control protocol or as needed. VAS score and questionnaires were completed at each follow up visit.

Eighteen naive patients out of nineteen (94.7%) maintained the benefits of the first stage (Table 1) at a mean follow up of 21.3 months. Seven out of the nine already implanted patients (77.7%) improved their pain control in a definitive way, reducing it by 50% or eliminating adjuvant drugs (Table 1).

Neither complication nor collateral effects were observed during the follow up. Within a 6-month follow-up four patients out of the total twenty-five responders to CSRN (16%) required an adjustment of the parameters of stimulation (from 4-8 Hz to 100 Hz) with good outcomes.

VAS scale, McGill and SF-36 questionnaires improved consistently in all domains and patients reported an overall satisfaction rate of 95% when asked if they could recommend this therapy to a friend or a relative [18-21]. Tables 2 and 3 show VAS scale, McGill and SF-36 questionnaires scores in naïve and already implanted patients, respectively.

Instrument	Before 1st stage (mean ± SD)	During 1st stage (mean ± SD)	At follow up (mean ± SD)	P value
VAS scale	8.4 ± 0.9	2.1 ± 1.2	1.3 ± 0.7	0.02
McGill quest.	70.3 ± 3.2	12.2 ± 2.6	9.1 ± 1.1	0
SF-36 quest.	31.9 ± 2.8	157.7 ± 8.7	161.1 ± 3.4	0.003

Table 2: Naive patients, Pain and QoL evaluation in 18 naive patients.

Instrument	Before changing parameters (mean ± SD)	During Trial (mean ± SD)	At follow up (mean ± SD)	P value
VAS scale	4.1 ± 1.3	1.9 ± 0.6	1.2 ± 0.5	0.05
McGill quest.	36.4 ± 4.4	13.7 ± 2.2	11.3 ± 2.9	0.042
SF-36 quest.	80.2 ± 3.8	151.1 ± 6.4	159.7 ± 4.1	0.02

Table 3: Implanted patients, Pain and QoL evaluation in 7 previously implanted patients.

Pelvic floor dysfunction symptoms (mainly overactive bladder and dyspareunia) improved as pain was improving and disappeared within three to six months and even before the complete remission of pelvic pain itself.

Two out of the three non-responders patients to the test phase (Table 1), the patient who did not maintain the treatment benefit after the implant, and two out of nine already implanted non responders to the new neuromodulation course didn't show any associated pelvic floor dysfunction.

Later, all these non-responders had pain symptom relief with the inferior hypogastric plexus blockade.

Discussion

The trans-foraminal sacral nerve root stimulation, currently used to treat voiding dysfunction, is not specifically indicated for treatment of pelvic pain. However a number of publications stated the ability of such stimulation to relieve pain, as well as relieving voiding symptoms in pelvic pain patients treated for coinciding pelvic dysfunction [18-21]. This is the first study demonstrating the effectiveness of CSRN in the management of CPPS in patients refractory to conventional treatment or only partially responding to continuous sacral nerve stimulation, with more than 85% improvement in naïve patients and up to 77% in patients already implanted.

Siegel et al. [22] reported a 60% significant improvement in pelvic pain in 10 patients at a median follow-up of 19 months. Everaert et al. [23], treating a series of chronic pelvic pain, reported that success was inversely related to neuropathic pain, but that the 11 patients who responded appeared to have a lasting response up to 3 years. In both case seriers a continuous SNM was used for therapy resistant pain.

Taking into account the previously implanted patients group as a surrogate for a "control arm", the improvement of pain symptoms confirms that intermittent neuromodulation can offer better results than the conventional one used up to date.

In our study all the non-responders did not show any associated pelvic floor dysfunction. The absence of an associated pelvic floor dysfunction might be considered as a negative predictive sign for the good outcome of a neuromodulation therapy in CPPS, because of a potential visceral origin of pain, as they positively responded later to inferior hypogastric plexus blockade [21,24] .

Though the exact pathogenesis of CPPS remains unknown, in these patients pelvic floor hyperactivity and pelvic congestion are a common phenomenon [23,25].

CPPS is often interconnected to the dysfunction of the pelvic floor, with associated symptoms such as overactive bladder, urinary retention, constipation, dyschezia and dyspareunia. The pain cycle theory explains why pelvic floor spasms and pelvic pain are patho-physiologically linked [3,26].

One possible working mechanism for neuromodulation in the treatment of CCPS is based on the gate control theory. This theory states that pain perception depends on a pattern of peripheral nervous input. It is believed that there is a mechanism at the spinal segment level which regulates the interaction between afferent nerve signals and pain sensation [27,28].

Interneurons of the spinal cord dorsal horn create gating components and inhibition or facilitation of afferent fibers, modulating the input to the spinal transmission neurons. It's also believed that the impulses from the dorsal horn are controlled by a descending system containing fibers from the brainstem, thalamus and limbic lobes [27-28].

There are also suggestions that dysregulated central nervous system responses may have a major role in the etiology and persistence of CPP [28-29].

In CPPS, as in other chronic pain syndromes, brain alterations (e.g., reduction in relative gray matter volume) were recently detected ,

raising the question of whether they could be a new target in the treatment of the disease and explaining the unsatisfactory results of peripheral treatment concepts [30,31].

Neuromodulation supposed to restore the control at the spinal segmental gate as well as at supraspinal sites such as the brainstem and the limbic system nuclei.

TENS may be an effective and safe treatment for refractory CPPS in men [32].

Actually, because the pathogenesis of CPPS is poorly understood, numerous therapeutic approaches have been tried including antibiotics, analgesics, a1-blockers, 5a-reductase inhibitors, intravesical instillations, electrotherapies, and transurethral interventions. Novel concepts for the treatment of CPPS are percutaneous tibial nerve stimulation, electroacupuncture, high-frequency sacral magnetic stimulation, sacral neuro-modulation (SNM), and pudendal neuromodulation [33]. Yet another type of neuromodulation is TENS, which has been established for the treatment of chronic musculoskeletal pain and may also be a valuable option in pelvic pain [34]. Advantages of TENS include the fact that it is a noninvasive procedure, applicable at home, not expensive, and without adverse events.

CSNM works exactly like TENS, utilizing the same neurophysiological pathways and mechanisms of action, but only recruiting a larger number of fibers with a better result, avoiding the fatigue of muscles and overstimulation of nerves present with continuous SNM, and with less pelvic floor contracture, the latter being a fundamental part of pain persistence [35]. Recent research with PET scanning indicates that at the level of the brain, the activity of centers in the paraventricular grey matter can be enhanced or reduced by sacral nerve stimulation [36].

In the same way TENS-induced activity in small diameter muscle afferents (Aδ, GIII) leads to the activation of brainstem nuclei such as the periaqueductal grey (PAG) and nucleus raphe magnus (nRM). These nuclei form the descending pain inhibitory pathways [27]. Several neurophysiological mechanisms of action, following TENS, have been suggested in the past [5], these include simple blocking of pain transmission by a direct effect on the spinothalamic tracts, activation of descending inhibitory pathways, effect on central sympathetic systems, segmental inhibition through coarse fiber activation and brain stem loops; inhibition by increasing GABA levels in the dorsal horn and activation of a thalamo-cortical mechanism masking the nociceptive input.

The currently suggested mechanisms by which TENS produces neuromodulation include the following:

- Presynaptic inhibition in the dorsal horn of the spinal cord
- Endogenous pain control (via endorphins, enkephalin, and dynorphin)
- Direct inhibition of an abnormally excited nerve (gate control)
- Restoration of afferent input

Studies show marked increases in beta endorphin and met-enkephalin with low-frequency TENS and demonstrated reversal of the anti-nociceptive effects by naloxone [29]. These effects have been postulated to be mediated through micro-opioid receptors.

Pain relief by means of the pain gate mechanism involves activation (excitation) of the A beta (Aβ) sensory fibers, and by doing so, reducing the transmission of the noxious stimulus from the 'C' fibers, through the spinal cord and hence on to the higher centers. The Aβ fibres appear to appreciate being stimulated at a relatively high rate (in the order of 80 - 130 Hz or pps). It seems difficult to find a single frequency that works best for every patient, but this range appears to cover the majority of individuals [27].

A delta (Aδ) fibers respond preferentially to a much lower rate of stimulation (in the order of 2 - 5 Hz, even though some authors consider a wider range of 2 – 10 Hz), which will activate the opioid mechanisms, and provide pain relief by causing the release of an endogenous opiate (encephalin) in the spinal cord which will reduce the activation of the noxious sensory pathways. Again, it is unlikely that there is a single (magic) frequency in this range that works at the best for everybody [27].

Our study has important limitations. It is a nonrandomized, prospective analysis with a small sample size. Strengths include the use of standardized symptoms and QoL instruments and a clear description of the stimulation parameters. Advantages of CSRN are a reduction in both nerve stress and fibrosis and a delay of re-intervention for neuromodulator battery replacement.

Conclusion

The published literature on the effectiveness of TENS in a variety of medical conditions, and CPPP specifically, reports a wide range of outcomes. Generally TENS provides an initial relief of pain in 70-80% of patients, but the success rate decreases after a few months to around 20-30% [4].

CSRN is able, also, to increase the lifetime of the implanted neuromodulator battery, avoiding to the patient 1 or 2 more replacement during their life, with consequent improvement of satisfaction.

Furthermore, CSRN treatment relieved the symptoms of CPPS as well as one or more symptoms related to pelvic floor dysfunction (urinary, fecal, and sexual) with a great impact on patients' satisfaction rate.

Our preliminary data showed that CSRN gave better results than conventional treatments, also improving the outcome of those patients, already implanted, who were partial responders to continuous neuromodulation therapy.

Parameters and patterns of neuromodulation are very clear and easily applicable for whoever wants use this new procedure to improve the outcome of CPPS in patients non responder to conservative therapy. The results of our study should be confirmed in larger, prospective, well-designed studies.

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