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ORIGINAL ARTICLE

PROGETTO DIAMANTE

Efficacy of sacral neuromodulation on urological diseases: a multicentric research project

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Introduction and aim of the study: *Sacral neuromodulation has been used as a safe, effective treatment option for patients with lower urinary tract dysfunction (LUTD). Several clinical studies demonstrated its positive effects on refractory urge incontinence, non-osbstructive urinary retention, urgency frequency syndrome, as well as on other non- urological disorders, such as fecal incontinence and chronic constipation. The aim of this research project was to evaluate the efficacy and safety of sacral neuromodulation on the management of LUTD refractory to the standardized first line treatment options.*

Materials and methods: *We retrospectively collected and evaluated data from patients undergoing sacral neuromodulations between September 2001 and November 2010 in 4 Urological Centres of North-Eeast Italy. The patients were affected by Overactive Bladder Syndrome (OAB), Urinary Retention (UR), Fecal Incontinence (FI), Constipation (CO), Chronic Pelvic Pain (CPP). All the patients were evaluated with voiding diaries, before and after implantation.*

Patients included in the present evaluation were followed up in a network of 4 Italian urological centres, which participate to in the Italian Clinical Service project - a national urological database and medical care project aiming at describing and improving the use of implantable urological devices in the Italian clinical practice.

Continuous normally distributed variables were reported as the mean value±standard deviation (SD). Continuous non-normally distributed variables were presented as the median values and an interquartile range (IQR).

The t-test and Wilcoxon test were used to compare continuous variables, as appropriate. A two-sided p <0.05 was considered statistically significant.

Results: *Overall, 157 patients underwent implantation of sacral neuromodulator during the period under review. Eighty-three out of 157 (53%) patients complained of OAB; 52 (33%) of UR; 5 (3%) of faecal incontinence; 4 (2%) of chronic constipation; 12 (8%) of CPP. The median follow- up was 11 months (IQR 1 – 91 months). In patients treated for OAB, we documented a statistically significant reduction in the mean number of: incontinence episodes/die, pads/die, daily micturitions, nocturnal micturitions and global micturitions. In patients treated for UR, we observed a statistically significant reduction in the mean post- voiding residual volume and in the number of self catheterization.*

Interpretation of results: *It is difficult to translate into quantifiable data the subjective perception of improvement of the symptos expressed by the patients, as they are frequently subjective perceptions, not always numeric data.*

This subjective perception makes it difficult to the clinician to evaluate the real outcomes of this

procedure, and makes it difficult to achieve a complete follow-up.
Conclusions: *This multicenter research project confirmed the midterm safety and effectiveness of sacral neuromodulation in the treatment of refractory overactive bladder syndrome and urinary retention, showing high cure rates and low complication rates.*

Key words: *Sacral neuromodulation, Overactive bladder, Urinary retention*

Parole chiave: *Neuromodulazione sacrale, Vescica iperattiva, Rietenzione urinaria*

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INTRODUCTION AND AIM OF THE STUDY

The sacral nerve stimulation or sacral neuromodulation (SNM) is based on the research by Schmidt and Tanagho, and since 1988 it has gradually become a second line treatment for refractory lower urinary tract dysfunction (LUTD), such as wet and dry overactive bladder syndrome, fecal incontinence and chronic bladder pain syndrome (1, 2, 3).
Actually, the mechanism underlying sacral neuromodulation is not completely understood, but probably this technique stimulates the afferents and thereby it probably restores the correct balance between excitatory and inhibitory impulses from and to the pelvic organs at a sacral and supra-sacral level (4).
Sacral neuromodulation has been used as a safe and effective treatment option for patients with LUTD. Several clinical studies demonstrated its positive effects on refractory urge incontinence, non-osbstructive urinary retention and urgency frequency syndrome and, in addition to urological disorders, for faecal incontinence and chronic constipation.
In 1997 and in 1999, the FDA has approved the use of SNM for the management of overactive bladder and urinary retention.
The long-term success rate varies from 50% up to 86%, according to the different underlying LUTD (5 -12).
At the present time, more than 35000 patients haves been treated with this technique worldwide (14) .
The aim of this multicenter research project was to evaluate the efficacy and safety of sacral neuromodulation on the management of LUTD.

MATERIALS AND METHODS

We retrospectively collected and evaluated data from patients who underwent sacral neuromodulation (SNM) between September 2001 and November 2010 in 4 Iitalian Urological Centres (Policlinico G.B. Rossi, Verona; Ospedale Santa Maria della Misericordia, Pordenone; Ospedale San Maurizio, Bolzano; Ospedale Sacro Cuore, Negrar).
We collected the demographic and clinical characteristics of the patients, including age, gender, indications to the sacral neuromodulation (overactive bladder syndrome, urinary retention, faecal incontinence, chronic constipation, chronic pelvic pain), age at diagnosis, primary and secondary diagnosis, comorbidities, previous surgery and presence of neurological diseases. The overactive bladder syndrome (OAB) was defined as the complaint of involuntary leakage accompanied by or immediately preceded by urgency; urinary retention (UR) was defined as the inability to void without an anatomical or neurological disease; chronic pelvic pain syndrome (CPP) was defined as persistent o recurrent episodic pelvic pain associated with symptoms suggesting lower urinary tract, sexual, bowel or gynaecological dysfunction, in the absence of proven infection or other obvious pathology.
In all patients the standard pharmacological and conservative treatment hads failed.
The pulse generator was implanted in the outer part of the buttock using the standard technique; and since 2005 we have used a percutaneous approach with the tined lead (13).
Patients who showed 50% or greater improvement in the symptoms were scheduled to receive the permanent SNM implant.
The patients included in the present analysis were evalu-

ated pre-operatively with history, physical evaluation, voiding diaries, urodynamic studies and were followed up in a network of 4 Italian urological centers, which participated in to the Italian Clinical Service project - a national urological database and medical care project aiming to describe and improve the use of implantable urological devices in the Italian clinical practice. In each center the follow-up was performed with global clinical evaluation and voiding diaries at 3, 6 and 12 months after the implantation.

A clinical improvement $\geq$ 50% of the symptpoms was considered as a positive outcome, with a joint decision between patient and surgeon, and with the evaluation of the voiding diaries and the post- voiding residual volumes after self catheterization.

The usual stimulation parameters were amplitude 0.5 to 10 V, rate 10 to 40 Hz, width 180 to 210 milliseconds with continuous stimulus.

All adverse events and complications or surgical re-intervention were recorded and evaluated.

Continuous parametric variables were reported as the mean value±standard deviation (SD). Continuous non-parametric variables were presented as the median values and an interquartile range (IQR).

The t-test and Wilcoxon test were used to compare continuous variables, as appropriate. A two-sided $p < 0.05$ was considered statistically significant.

RESULTS

A total of 157 patients underwent the implantation of a sacral neuromodulator in the period under review. Patients' characteristics were as follows: 122/156 (78%) were female; the mean age at symptoms presentation was 51±18 years; the mean age at implantation was 58±15 years (Table I). The primary diagnosis was OAB in 83/157 (53%) patients; UR in 52/157 (33%) patients; fecal incontinence (FI) in 5/157 (3%), and chronic constipation (Co) in 4/157 (2%). Twelve 12 (8%) patients suffered from CPP. Forty-nine (31%) patients presented a secondary diagnosis: OAB in 7 (5%) patients; UR in 6 (4%); FI in 7(5%); Co in 27 (17%), and CPP in 6 (4%) (Table I). The etiology of the primary symptom was idiopathic in 59 (44%) patients; neurogenic in 36 (27%), and surgery-related in 39 (29%). Seventy-five patients (58%) underwent previous surgery, with hysterectomy in 35 patients (27%) and cystopexy in 9 (7%) as the most frequent. The other surgical treatments were rectopexy (5%), radical prostatec-

TABLE I - DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Variable	N	
Female gender, no. (%)	156	122 (78%)
Age at PNE, mean±SD	157	58±15
Age at onset of symptoms, mean±SD	109	51±18
Primary diagnosis, no. (%)	157	
Overactive bladder syndrome (OAB)		83 (53%)
Urinary retention (UR)		52 (33%)
Fecal incontinence (FI)		5 (3%)
Constipation (Co)		4 (2%)
Chronic pelvic pain (CPP)		12 (8%)
Other		1 (1%)
Secondary diagnosis, no. (%)	157	49 (31%)
Overactive bladder syndrome (OAB)		7 (5%)
Urinary retention (UR)		6 (4%)
Fecal incontinence (FI)		7 (5%)
Constipation (Co)		27 (17%)
Chronic pelvic pain (CPP)		6 (4%)
Other		2 (1%)
Etiology of the primary symptom, no. (%)	134	
Idiopathic		59 (44%)
Neurogenic		36 (27%)
Surgery-related		39 (29%)
Diabetes, no. (%)	100	11 (11%)
Previous surgery, no. (%)	130	75 (58%)
Hysterectomy		35 (27%)
Cystopexy		9 (7%)
Rectopexy		7 (5%)
Prostatectomy		6 (5%)
Hemorroidectomy		2 (2%)
Sphincterotomy		1 (1%)
Other		41 (32%)
Neurological disease, no. (%)	138	38 (28%)
Multiple sclerosis		7 (5%)
Spinal lesion		8 (5%)
Stroke		4 (3%)
Parkinson's disease		3 (2%)
Other		20 (14%)

tomy (5%), hemorrhoidectomy (2%), and other procedures (32%). Of the 38 patients affected from a neurological disease (28%), 7 (5%) had multiple sclerosis, 8 (5%) spinal lesion, 4 (3%) stroke, and 3 (2%) Parkinson's disease (Table I). One hundred and fifty-seven patients underwent a percutaneous nerve evalutation (PNE) test; a total of 120 patients (76 %) received a permanent SNM implant. The median time elapsed between the PNE test and the permanent implant was 43.5 days (IQR: 23.8-65.3 days). The median term follow- up was 11 months (range 1 – 91 months), and 81 (68%) patients were eligible at follow- up. All patients completed at least 11 months of follow- up. Table II shows the baseline clinical characteristics of the evaluated patients. We included in the follow- up the voiding diaries of 50 eligible patients affected by OAB and 30 affected by UR. In the patients treated for OAB, we documented a statistically significant reduction (p <0.001) in the mean number of incontinence episodes/die (1.5± 2.1 VS 4.1±2.7), number of pads used (1.3±1.4 VS 3.4±2.4), and number of daytime urination [1.3 micturition (8.1±2.7 VS 13.0±5.3)] (Table III). In the patients treated for UR, we observed a statistically significant reduction (p <0.001) in the post-voiding residual volume (87.2±96.9 VS 321.4±153.5) and in the number of self- catheterization (1.3±1.3 vs.VS 3.8±1.4). The reduction in the daily, nocturnal and global micturition was not statistically significant (Table IV); 86% of the patients with complete urinary retention (8) achieved a voided volume >120 cc.

TABLE II - BASELINE CLINICAL VARIABLES

Variable	OAB (No. = 90)°		UR (No. = 58)#	
	No.		No.	
Incontinence episode/day, mean±SD	63	4.4±3.1		---
Pads/day, mean±SD	60	3.4±2.2		---
Voided volume, mean±SD	63	147.7±70.3		---
Post void residual urine, mean±SD		---	50	322.6±151.2
Self-catheterization/day, mean±SD		---	51	4.2±2.7
Daily micturition, mean±SD	64	10.6±4.2	49	5.0±4.6
Nightly micturition, mean±SD	63	3.0±3.1	49	0.8±1.5
Global micturition, mean±SD	63	13.6±6.3	49	5.8±5.3

°65 baseline voiding diaries; #51 baseline voiding diaries

TABLE III - OAB PATIENTS

Variable	No.	Baseline	FU	P-value
Incontinence episode/day, mean±SD	48	4.1±2.7	1.5±2.1	<0.001°
Pads/day, mean±SD	44	3.4±2.4	1.3±1.4	<0.001°
Voided volume, mean±SD	45	143.6±69.9	206.7±88.5	<0.001*
Daily micturition, mean±SD	48	10.4±4.2	7.4±2.5	<0.001°
Nightly micturition, mean±SD	48	2.6±1.8	0.8±0.9	<0.001°
Global micturition, mean±SD	48	13.0±5.3	8.1±2.7	<0.001°

*T-Test; ° Wilcoxon test

TABLE IV - UR PATIENTS

Variable	No.	Baseline	FU	P-value
Post void residual urine, mean±SD	30	321.4±153.5	87.2±96.9	<0.001°
Self-catheterization/day, mean±SD	30	3.8±1.4	1.3±1.3	<0.001°
Daily micturition, mean±SD	29	4.7±3.8	5.4±2.0	0.159°
Nightly micturition, mean±SD	29	0.7±1.3	0.7±1.1	0.886°
Global micturition, mean±SD	29	5.4±4.6	6.1±2.5	0.328°

*T-Test; ° Wilcoxon test

During the observation time, 24 adverse events occurred in 20 patients (13%), with the lost of efficacy as the most frequent (10 cases). Only six patients (5%) discontinued the treatment, with a median time of 18 months (IQR: 7 – 30 months). Only 11 patients (9%) have replaced at least once the impulse generator (IPG) battery. The mean time between the permanent implant and the battery change was 3.4±2.0 years (range 1-8).

INTERPRETATION OF RESULTS

The physiological mechanisms underlying the mode of action of SNM on urinary and fecal incontinence are still barely understood. Several studies evaluated the efficacy and the long- term results of SNM.

In five studies with a long**-** time follow**-** up, evaluated by Van Kerrebroeck in a recent review of the literature, the satisfaction degree of the patients was variable between 60 to 77% (15). Moreover, the results of 17 centres worldwide (163 patients), with a minimum follow**-**up of 5 years, showed 5-year success rates of 68%, 56%**,** and 71% for the management of urge urinary incontinence**,** urgency frequency**,** and urinary retention, respectively (6).

In all these studies, the success of treatment was defined as the percentage of patients who had a successful outcome at last follow-up visit (more than 50% improvement in the voiding diary variables).

In our study, we documented a statistically significant reduction in the mean number of incontinence episodes/die, pads used and daytime urination in the patients treated for OAB, and a statistically significant reduction in the post-voiding residual volume and in the self catheterization number in the patients treated for UR, demonstrating that sacral NMS is an effective treatment. Patients undergoing sacral neuromodulation can also achieve improvements of their sexual life, as demonstrated by Signorello et al (17). Considering the relative young age of our patients, sexual life may represent and important aspect of the well-being of our patients. Unfortunately, we do not have data about the impact of NMS on the health-related quality of life domains. Limitations of our study are as follows: the patients' evaluation of the patients was performed retrospectively, without validated questionnaires, with a short-term follow-up. The patients' retrospective evaluation of the patients can not allow us to obtain all necessary information and, unfortunately, we could evaluate the follow-up of about half the patients. Moreover, because of the lack of information of the impact of SNM on patients' quality of life, it was difficult to translate into quantifiable data the subjective perception of symptoms improvement of the as expressed by the patients, as they are frequently subjective perceptions, not always numeric data. The evaluation of the patients' perceptions may be arbitrary and problematic. This subjective perception makes it hard to evaluate the real outcomes of this procedure and makes it difficult to achieve a complete follow-up. The median follow- up of our study was 11 months, and this may represent a further bias, considering that the length of follow- up is considered one of the parameters predictive of explantation and revision of the neuromodulator. We need further well- designed large, prospective and randomized studies, in order to identify the real efficacy of this treatment.

CONCLUSIONS

This multicenter research project demonstrated that sacral

neuromodulation is a mid-term safe and effective treatment of refractory overactive bladder syndrome and urinary retention, with high cure rates and low complication rates.

RIASSUNTO

La neuromodulazione sacrale è un'opzione terapeutica efficace e sicura per i pazienti affetti da disfunzioni del basso apparato urinario, dimostrata e validata da numerosi studi clinici.
Sono stati raccolti retrospettivamente i dati di tutti i pazienti affetti da sindrome della vescica iperattiva (OAB), ritenzione urinaria (UR), incontinenza fecale (FI), stipsi cronica (CO), dolore pelvico cronico (CPP), sottoposti a neuromodulatione sacrale tra Settembre 2001 e Novembre 2010 in 4 centri urologici del Nord-Est, nell'ambito del progetto italiano Clinical Service. Quest'ultimo ha lo scopo di costituire una banca dati nazionale urologica con il fine di descrivere e migliorare l'uso dei dispositivi impiantabili nella pratica clinica. Tutti i pazienti sono stati valutati con diario minzionale, prima e dopo l'impianto.
Complessivamente sono stati analizzati 157 pazienti sottoposti a impianto di neuromodulatore sacrale nel periodo di valutazione; 83 (53%) soggetti erano affetti da vescica iperattiva (OAB), 52 (33%) da ritenzione urinaria cronica (UR), 5 (3%), incontinenza fecale, 4 (2%) da stipsi, 12 (8%) da dolore pelvico cronico. Il follow-up mediano è stato di 11 mesi (IQR 1-91 mesi). Per quanto riguarda i pazienti trattati per OAB, abbiamo documentato una riduzione statisticamente significativa nel numero medio di episodi giornalieri di incontinenza urinaria, il numero di pannolini/die utilizzati, il numero di minzioni diurne, di minzioni notturne e di minzioni globali. Per quanto riguarda i pazienti trattati per UR, abbiamo documentato una riduzione statisticamente significativa del volume residuo dopo svuotamento e del numero di auto cateterismi/die.
Questo progetto di ricerca multicentrico ha confermato che la neuromodulazione sacrale è a medio termine un trattamento sicuro, ed efficace per i pazienti affetti da sindrome della vescica iperattiva e ritenzione urinaria.

Conflict of interest

All the authors declare not to have any that we have no conflict of interest.

The data presented in this study are part of a multicentric database operated by Medtronic, as part of a multicenter project, the Italian Clinical Service project.

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