Further optimization of sacral neuromodulation therapy

Citation for published version (APA):

Leong, R. K. (2012). *Further optimization of sacral neuromodulation therapy*. [Doctoral Thesis, Maastricht University]. Off Page Amsterdam. <https://doi.org/10.26481/dis.20121217rl>

Document status and date:

Published: 01/01/2012

DOI:

[10.26481/dis.20121217rl](https://doi.org/10.26481/dis.20121217rl)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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Further optimization of Sacral Neuromodulation Therapy

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Further optimization of Sacral Neuromodulation Therapy
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Cover: Seroe Colorado, Aruba (photo by Freek Lanting)
Lay-out: Bilbo Schickenberg and Randall Leong
Printed by: Off Page, Amsterdam

ISBN: 978-94-6182-184-3

Further optimization of Sacral Neuromodulation Therapy

Proefschrift

**ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van Rector Magnificus, Prof. dr. L.L.G. Soete,
volgens het besluit van het College van Decanen
in het openbaar te verdedigen op
maandag 17 december 2012 om 14:00 uur**

door

Randall Kwong-Fei Leong

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Prof. dr. A.A.M. Masclee

The publication of this thesis was financially supported by:

WAMU (Abbott, Astellas, Astra Zeneca, GSK, Medtronic en Zambon)

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List of abbreviations

BTX	Botulinum Toxin A
EPG	External Pulse Generator
FSTLP	First Stage Tined-Lead Placement Test
FU	Follow-Up
IE	Incontinence Episodes
INS	Implantable Nerve Stimulator
I-OAB	Idiopathic Overactive Bladder Syndrome
MCC	Maximum Cystometric Capacity
PNE	Percutaneous Nerve Evaluation
QALY	Quality Adjusted Life Years
QoL	Quality of Life
S3	Third sacral nerve
SNM	Sacral Neuromodulation
UUI	Urgency Urinary Incontinence

Chapter 1

**General Introduction, Aim and Outline of
the Thesis**

General introduction

Sacral neuromodulation (SNM) therapy is a therapy that comprises the electrical stimulation of the sacral nerves that innervate most organs and structures of the pelvis including the bladder, urethral sphincter and pelvic floor muscles. For this therapy electrodes are placed at the level of the third sacral nerve (S3) and are connected to an implantable battery that is known as an Implantable Nerve Stimulator (INS). This treatment was developed in the early 1980s and since the FDA approval in 1997, an increasing number of patients have been treated with SNM. Within urology, SNM is an accepted treatment option for patients with idiopathic overactive bladder syndrome (I-OAB) or non-obstructive urinary retention and who are refractory to conservative treatment.

Idiopathic overactive bladder syndrome

Idiopathic overactive bladder syndrome (I-OAB) is a combination of urinary symptoms and is defined as urgency with or without urgency-incontinence, usually with frequency and nocturia [1]. The estimated prevalence is between 12-17% of which a third experiences urgency urinary incontinence (UUI) [2-5]. This syndrome significantly impacts on the patient's quality of life (QoL) and the costs for I-OAB management are estimated between 250 million and 4.2-billion euro in selected European countries [6-9]. Treatment of patients with I-OAB is complex and international guidelines suggest lifestyle interventions, pelvic floor muscle training, bladder retraining and medication (anti-muscarinics) as first line treatment options [1, 10, 11]. PTNS (Percutaneous Tibial Nerve Stimulation) is a non-surgical treatment option that has recently been included in the European Association of Urology Guidelines for Incontinence. It is considered as a possible treatment option for improvement of urgency urinary incontinence in women, but not in men, who have not benefited from antimuscarinic medication [10].

When first line therapy options fail or are unacceptable for patients, surgical options are available. These include SNM therapy, Botulinum toxin injection in the bladder (BTX) and bladder augmentation (Figure 1). SNM and BTX therapies are considered to be minimally invasive and should be tried first before bladder augmentation. Starting with SNM or BTX is usually based on the experience of the clinic and personal preference as well from the patient's perspective as from the doctor's point of view. There is no prospective study yet comparing these two treatment options and the long-term cost effectiveness is still unclear.

Figure 1: Algorithm derived from ‘evidence-based’ recommendations of the ICI from 2008

Non-obstructive urinary retention

Urinary retention is defined as the inability to empty the bladder completely. The causes of urinary retention can be divided into (mechanically) obstructive urinary retention and non-obstructive urinary retention. Non-obstructive urinary retention includes inability of outlet (e.g. sphincter) relaxation, detrusor underactivity or a combination of both, and can be neurogenic or non-neurogenic. Obstructive urinary retention is a mechanical or anatomical obstruction of the bladder outlet, such as a tumour, stone or urethral strictures, and can usually be treated by medication or by surgically removing the obstruction. However, few treatment options are available for non-obstructive urinary retention. Non-obstructive urinary retention (when not pharmacotherapeutically induced) is usually treated conservatively with intermittent self-catheterization or placement of an indwelling catheter suprapubically or transurethrally. SNM is a minimally invasive treatment option for patients with non-obstructive urinary retention. For practical purposes non-obstructive non-neurogenic urinary retention will be referred to as non-obstructive urinary retention.

Sacral neuromodulation therapy

Working mechanism

The precise mechanism of action of SNM therapy is still not entirely clear. SNM has been proven to work in patients with a seemingly contradictory condition, namely overactive bladder and underactive bladder, and the treatment comprises of continuous stimulation. This suggests that SNM affects the 'neuroaxis' and restores the balance between excitatory and inhibitory regulation at various locations within the peripheral and central nervous system [12]. The exact sites or pathways that are modulated are still unknown, however, several neurophysiological data suggest an effect on the afferent pathway. One study showed a reduction in the sensory threshold of the bladder during SNM treatment, but not of the urethra, which suggests afferent nervous system involvement through the pelvic plexus [13]. Another study showed a significant decrease in pudendal somatosensory evoked potential latency during SNM [14]. Studies with PET-scans on patients with SNM showed activation changes in the brain that also supports the hypothesis that SNM works by modulation through afferent nerves. One study with PET-scans compared acute with chronic SNM treatment on patients with overactive bladder and showed activation differences in the associative sensory cortex, premotor cortex and the cerebellum [15]. The other study with PET-scans compared patients with non-obstructive urinary retention with and without SNM and showed activation differences in the midbrain and limbic cortical regions [16].

Treatment protocol

Before implanting the INS (Implantable NeurStimulator), a screening test is performed to assess the clinical efficacy of sacral nerve stimulation. There are two screening test protocols.

The first, known as Percutaneous Nerve Evaluation (PNE), uses a non anchored test lead placed into the S3 foramen and connected to an external battery, also known as an external pulse generator (EPG). The test period extends between 4 and 14 days after which the test lead is removed. The procedure is usually done in an outpatient setting. The overall response rate for PNE is around 55% [17, 18]. Lead migration is considered the main factor leading to false negative results [19, 20].

The definitive lead electrode has self-anchoring tines that reduce the risk of migration, and is called the tined lead. The second protocol for screening uses this tined lead for testing. The lead is placed into the S3 foramen usually under general anaesthesia, although local anaesthesia is possible in an outpatient setting. Correct positioning is guided with fluoroscopy and the lead is subcutaneously connected to a temporary extension lead that exits

the skin and is connected to an EPG. This procedure, which is known as the first stage tined-lead test (FSTLP), enables test periods up to three to four weeks. If the patient has a good response during the test, the present lead is connected to an INS, which would be the second stage. This procedure is performed under local or general anaesthesia. Because of the decreased risk of migration and the longer test duration, this test has a higher response rate. According to a study by Kessler et al, prolonged screening with the tined lead has a response rate of 67% compared to 43% during PNE testing [21]. The costs for the test protocol with the tined leads are much higher compared to the PNE test. Currently the use of either one of the two screenings option is arbitrary.

Both batteries, the INS and EPG, can have a variety of settings. The electrical waveform that the battery produces is a square wave pulse. The pulse-rate can be set between 2.1 and 130 Hz and the pulse-width between 60 and 450 μ s. Furthermore, the amplitude can be changed from 0.05 to 10.55 V. Most centres that treat patients with SNM commonly use pulse rates between 10 and 16 Hz and pulse-width of 120 μ s [17, 22, 23]. These settings are mostly empirical. Data on the effect of the different parameters is still lacking and therefore the potential effect of pulse changes was one of the topics of our research for this thesis.

Effectiveness for I-OAB

There is convincing evidence for the success of SNM therapy among patients with I-OAB who are refractory to conservative treatments. Three randomised controlled trials (two on patients with urgency incontinence and one on patients with urgency frequency) and many articles on long-term observational studies have been published [17, 18, 23-28]. In all reported studies, clinical success is defined as a > 50% improvement in one of the relevant urinary voiding parameters. Good clinical response is reported between 64 and 88% of all patients. All parameters reported showed significant improvement compared to the placebo group: a 23-46% decrease in the number of voids per day, 44-77% increase in the average voided volume, 56-90% decrease in incontinence episodes per day, 64-100% decrease in pads and 39% increase in maximum cystometric capacity (Table 1).

A five year follow-up study on 121 patients with refractory I-OAB showed persistence of the clinical success in the long term: 84% of the patients with urgency incontinence and 71% of the patients with urgency/frequency which had a successful outcome one year after implantation continued to have a successful outcome after five years [26]. A study on the tined lead

procedure in 21 patients with I-OAB showed around 90% clinical success after an average of 15.5 months[28].

Satisfaction and quality of life scores after SNM have also been studied. Cappellano et al. showed a significant improvement in the quality of life score in patients with urgency incontinence who underwent SNM, with a mean score between 34 and 76 [29]. At 18 months follow-up patients were asked whether they would undergo this treatment again. Ninety percent responded yes and 100% would recommend it to a relative or friend. Foster et al. asked 49 patients with urgency incontinence on their satisfaction with SNM treatment. The majority of the patients, 84% and 80% respectively, were “satisfied” and would “do it all over again” [30]. Little is known about the daily experience or daily use of SNM.

Table 1. Short-term results of treatment with sacral neuromodulation or with placebo among patients with overactive bladder.

	FU period months	Overall improvement	# of voids reduction per day	Increase in voided vol	IE improvement per day	Proportion of group with 100% continence	Improvement in # pads/ day	Improvement MCC
<i>RCT's</i>								
Weil et al.	6				90%	56%	92%	39%
Schmidt et al.	6				73%	47%	82%	
Hassouna et al.	12	88%	46%	77%				
<i>Observational studies</i>								
Kerrebroeck et al.	49		23%	79%	56%		64%	
Voskuilen et al.	64.2	64%						
Sutherland et al.	22	69%	35%		88%	50%	100%	
Voskuilen et al.	15.5	80%	38%	44%	65%			
Hijaz et al.	16	75%						

*significant compared to placebo, FU: follow-up, IE: incontinence episodes, MCC: maximum cystometric capacity

Effectiveness for retention

The evidence of SNM for non-obstructive urinary retention is based on one randomised controlled trial and several cohort studies on both the short and long-term follow-up [22, 26, 28]. Good clinical response, defined as more than 50% improvement in bladder diary variables, such as catheter volume per catheterisation, number of catheters per day, total catheter volume per day, maximum catheter volume per day and number of voids per day, is reported between 55% and 90%.

In the randomised controlled trial all parameters reported showed significant improvement compared to the placebo group: an average of 86% decrease in the catheter volume per catheterization per day, 64% decrease in number of catheterisations per day, 82% decrease in total catheter volume per day, 85% decrease in maximum catheter volume per day and 224% increase in number of voids per day [22].

SNM is an effective treatment for non-obstructive urinary retention on the long-term. A study with a 5 year follow-up showed persistence of the clinical success: 78% of the patients with non-obstructive urinary retention which had a successful outcome one year after implantation continued to have a successful outcome after five years [26]. Another study on the tined lead procedure showed, in 9 patients with non-obstructive urinary retention, 90% clinical success after an average of 15.5 months [28].

SNM has a positive impact on the satisfaction and quality of life scores. In a quality of life study among patients with non-obstructive urinary retention treated with SNM, significant improvement on the physical, social and psychological levels was shown [31].

Table 2. Most frequent adverse events associated with sacral neuromodulation therapy

	Pain at implant site	Lead migration	Other pain	Bowel function disturbance	Infection
Weil et al.	42%	21%	18% (leg)	5%	
Schmidt et al.	33%	13%		5%	4%
Hassouna et al.				4%	
Kerrebroeck et al.	19%	5%	7.9% (lead site)	7%	8%
Voskuilen et al.	28%	7%	43% (pain or discomfort)		4%
Sutherland et al.	15%			5%	10%
Voskuilen et al.	7%	3%	3% (leg stimulation)		
Hijaz et al.	3%	1%			5%

Adverse Events

Adverse events are usually related to the implant procedure, the presence of the implant or undesirable sensations or effects due to the electrical stimulation. The most common adverse event reported is pain at the implantation site. The occurrence in most studies varies between 3 to 42% (Table 2) [18, 23-28, 32]. Other adverse events reported are lead migration (1 to 21%), bowel dysfunction (4 to 7%) and infection (4 to 10%). Technical improvements throughout the years have significantly decreased the incidence of adverse events. Two important improvements were the introduction of tined leads (leads with hooks) and the gluteal, instead of

abdominal, placement of the INS. Ever since, both the incidence of adverse events and the reoperation rate per implanted patient has decreased (Figure 2) [27].

Figure 2. Average number of adverse events and surgical revision per implanted patient [25]

The majority of adverse events do not require surgical intervention. Decreased efficacy because of electrode migration and undesirable stimulation can generally be solved by reprogramming of the INS. A retrospective analysis among 83 implanted patients with a reduced response or complications, such as pain at the INS-site, showed that 18% of the cases could be conservatively helped [25]. Furthermore, the incidence of adverse events is lower with the new tined leads in comparison with non-tined leads (respectively 28% and 73%) [25]. A study among 235 patients confirmed that tined leads migrate less often, with an incidence of 2.1% [33]. The available data indicate that the further development and optimisation of sacral neuromodulation limits the risk of adverse events.

Aim and outline of this thesis

The aim of this thesis is to further improve or optimise SNM treatment in Urology. The first part of this thesis deals with the long-term efficacy, satisfaction and experience with SNM. In the second part SNM will be compared with a different treatment option in a cost-effectiveness study. The third part of this thesis discusses the optimal way of selecting and treating patients by comparing two screening methods and by changing the battery parameters.

Chapter 1 presents a general introduction to the thesis and discusses the aim and outline.

Chapter 2 describes a single centre study that assessed the long-term efficacy and adverse events of SNM with TLP.

In **Chapter 3** a study is described which evaluates the long-term satisfaction of patients on SNM therapy and their daily experiences with the treatment.

Chapter 4 is an overview of SNM and BTX treatment in the second-line management of adults with I-OAB, based on the available clinical evidence concerning the efficacy and safety.

Chapter 5 provides a cost-effectiveness study comparing either starting treatment with SNM or BTX in patients with refractory I-OAB from a societal perspective.

In **Chapter 6** a study is described in which the response rate of the two types of screening options to determine eligibility for SNM therapy, FSTLP and PNE test, are compared. **Chapter 7** presents the results of a pilot study in which the impact of pulse rate changes (5.2Hz–10Hz–21Hz–40Hz) is evaluated among patients with suboptimal response to SNM therapy on clinical outcome, the sensory responses and SNM-related pain symptoms.

Chapter 8 presents the general discussion and future perspectives on sacral neuromodulation therapy

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Chapter 2

PNE versus 1st stage tined lead
procedure: a direct comparison to select
the most sensitive test method to identify
patients suitable for sacral
neuromodulation therapy

Randall K. Leong, Stefan G.G. De Wachter, Fred H.M.
Nieman, Rob A. de Bie and Philip E.V. van Kerrebroeck.

Neurourology and Urodynamics. 2011;30(7):1249-52

Abstract

Aims: To compare the patient's response rate to the Percutaneous Nerve Evaluation test (PNE) and the 1st stage tined-lead placement test (FSTLP) for sacral neuromodulation therapy (SNM).

Methods: Single centre study on patients with refractory idiopathic overactive bladder syndrome (OAB) or non-obstructive urinary retention, screened with both PNE and FSTLP. Patients were followed prospectively and their response rate based on bladder diary after PNE was compared to that after FSTLP. More than 50% improvement in at least two relevant urinary symptoms was considered a positive response. A Wilcoxon paired test was done to compare the rates of the two screening options and logistic regression to determine possible associations. A follow-up was conducted to determine the long-term failure rate.

Results: One hundred patients were included (82 female, 69 OAB). The mean age was 55 years (SD 13). The positive response rate on PNE was 47%. FSTLP showed a 69% positive response rate, which was negatively related to age. The 22% gain in positive response was statistically significant ($p < 0.001$) and positively associated with female gender and younger age. All 69 patients with a positive response to FSTLP received SNM treatment. Failure rate after an average of 2 years was 2.9%.

Conclusions: This study suggests that FSTLP may be a more sensitive screening method than PNE to identify patients eligible for SNM therapy, warranting randomized trials.

Introduction

Sacral Neuromodulation (SNM) is a well established therapy for patients with idiopathic overactive bladder syndrome (OAB) or non-obstructive urinary retention (retention). The long-term success rate varies between 56 and 71% depending on the underlying bladder dysfunction [1, 2]. In order to achieve optimal results, accurate screening tests are crucial. Patients considered eligible for SNM therapy are selected based on their response to a test period of SNM with an external neurostimulator. Currently two different methods are used to screen patients for their response to SNM: the Percutaneous Nerve Evaluation test (PNE) which uses a standard electrical wire electrode, and the first stage tined-lead placement test (FSTLP) which uses a special electrode with small anchors to reduce the risk of lead migration [3]. Patients who show more than 50% reduction in urinary symptoms during this test period are considered good candidates for definitive SNM therapy.

Currently only one study evaluated the difference in response rate to PNE and FSTLP [4]. In 30 urgency incontinent patients, they showed that 6 out of 13 patients in the PNE group showed a successful response compared to 15 out of 17 patients in the FSTLP group. Therefore more patients received the definitive implant after FSTLP than after PNE [4].

The primary goal of this study is to compare the response rate of FSTLP with PNE test to determine eligibility for SNM therapy among patients with either idiopathic OAB or non-obstructive urinary retention. The secondary goal was to evaluate whether age, gender, type of bladder complaint (OAB or retention) and lead position have an effect on the results. Finally the long-term SNM failure rate of patients selected through FSTLP was evaluated to determine the validity of the screening tests.

Materials and Methods

This single-centre prospective observational study included patients with idiopathic OAB or non-obstructive retention, refractory to conservative therapy, and was conducted in accordance to the ethical committee guidelines of the local university hospital.

All patients were first screened with the PNE (30576SC, Medtronic, Minneapolis, Inc.) and afterwards with the FSTLP (3889-28, Medtronic Inc.). All procedures were performed under local anaesthesia. The PNE procedure was performed according to the method described by Jonas and coworkers [5]. Electrode position was determined based on the clinical motor and sensory response towards stimulation. Following the PNE procedure an X-ray was taken to determine the position of the lead. At the end of the testing period patients were asked if they still felt the electrical sensation in

the correct area. If not, the electrode position was evaluated by X-ray and in case of dislocation the PNE procedure was repeated.

The FSTLP was performed according to Spinelli et al [6]. During the FSTLP fluoroscopy was used to determine proper electrode position in the third sacral foramen. The response to the PNE and FSTLP was assessed based on the bladder diary data before (baseline) and during the two screening tests. PNE was tested for three consecutive days because of the increasing risk of lead migration after this period. For the baseline and PNE evaluation, patients were asked to complete the diary for at least three days and for FSTLP for at least one week. However for FSTLP only the data of the first three days were used to match the test duration of PNE.

Parameters used for patients with OAB were the frequency of voids per day, the average voided volume per void and the maximum voided volume. For the OAB patients with urinary incontinence, the average frequency of leakages per day, the severity of leakage and the average number of pads used per day were additionally noted. For patients with non-obstructive retention the average voided volume per void was noted, together with the post void residual urine, determined by catheterization. A positive response was defined as at least 50% improvement in two or more relevant parameters.

Failure rate was determined by reviewing patient's chart in order to establish the validity of FSTLP among patients who received a definite SNM implant. Since this study was one of the first to analyze FSTLP test results for sacral neuromodulation therapy it was difficult to perform a power analysis not knowing the strength of the associations of the predictors used in analysis in advance. Therefore a tentative number of 100 patients was used to gauge the sensibility of the tests. Test results were cross-tabulated in a 2-by-2 table using Kappa (κ) as a measure of agreement and the Wilcoxon test to test differences. Three dichotomous outcome measures were first analyzed by univariate statistics only: the results of the PNE test, the results of the FSTLP test and the results of the difference or potential gain in positive result between both tests. Next, a logistic regression analysis was done for each of the outcome measures using backward elimination -2 log-likelihood chi-squares ($-2LL\chi^2_L$) as the searching technique in modeling. Predictors used in the analyses were patient's gender, age, type of complaint (OAB or retention) and position of lead (based on X-ray: left or right foramen, Sacral foramen position 2, 3, 4 or 5, and depth lead (superficial, correct or too deeply placed). First-order interaction effects between predictors were tested by the forward selection technique. If age had a statistically significant effect, optimal dichotomous categorizing was used to determine cut-off points within age. A p-value of less than 0.05 was

considered to be statistically significant. All data-analysis was done with SPSS-pc version 16.0.

Results

Between July 2002 to December 2008, in total 100 patients were tested with both the PNE and the FSTLP test; 82 were female and 18 male. The mean age was 55 years (SD 13). Sixty-nine were diagnosed with OAB and 31 with non-obstructive urinary retention.

Significantly more patients responded positively to the FSTLP test compared to the PNE test (Wilcoxon test $p < 0.001$) (table 1). The number of patients respectively was 69 for FSTLP and 47 for PNE test. Furthermore, all patients that responded positively to PNE, did also respond positively to FSTLP. The agreement between the positive responses of both tests was $\kappa = 0.57$ (95%CI 0.43-0.71, $p < 0.001$). All 69 patients who had a positive response to the FSTLP test received a definite SNM implant. At a mean follow-up of 26 months (SD 18), therapy failed in only 2 patients (2.9%). Both were female OAB patients who had a positive response to both PNE and FSTLP. One failure was because of lack of efficacy and one because of pain at battery site requiring removal of the implanted device.

For the PNE test neither age, gender nor type of complaints were univariately related to a positive outcome of the test (table 1). X-rays taken post PNE procedure showed that 61 had the lead placed in a correct depth while 13 had it placed too superficial and 26 too deep. A total of 46 patients had their lead placed in the S3 foramen, while 3 had it in S2, 36 on S4, 8 on S5 and 7 lateral of the sacral bone. Multivariate analysis also showed no significant relationship between a positive outcome and localisation and depth of the electrode.

For FSTLP, a successful response was negatively related to the patient's age (univariate OR=0.96, 95%CI: 0.93-1.00, $p = 0.036$), however not to the type of complaint. The optimal cut off point for age was 65 years (OR=0.33, 95%CI: 0.13-0.87, change in $-2LL\chi^2 = 5.07$, $p = 0.024$) (Table 1), that is, patients older than 65 years of age had a significantly lower probability to respond positively to FSTLP. In the multivariate analysis corrected for age, neither gender or type of complaint was related to a positive FSTLP response.

Analysis of the group of 22 patients who responded successfully to FSTLP after failing the PNE test showed that relatively more patients were younger than 45 years of age (OR=0.29, 95%CI: 0.10-0.87 ($-2LL\chi^2 = 4.70$, $p = 0.030$) and relatively more patients were female: only 1 (6%) of the 18 males versus 21 (26%) of the 82 females (OR=6.59, 95%CI: 0.80-54.43, $-2LL\chi^2_L = 4.79$, $p = 0.029$) (Table 3).

Table 1. Univariate results for positive response with PNE and FSTLP

Predictors	Category	PNE						FSTLP					
		N	% pos.	χ^2_L	p-value	OR	95% C.I. OR	N	% pos.	χ^2_L	p-value	OR	95% C.I. OR
	All	100	47					100	69				
Gender	Male	18	56	0.64	0.42	-		18	61	0.62	0.43	-	
	Female	82	45			0.66	0.24-1.84	82	71			1.54	0.53-4.44
Age				0.22	0.64	0.99	0.96-1.02			4.39	0.036	0.96	0.93-1.00
	≤ 65 years	76	50	1.16	0.28	-		76	75	5.07	0.024	-	
	> 65 years	24	38			0.60	0.23-1.54	24	50			0.33	0.13-0.87
Type of complaint	Retention	31	45	0.06	0.81	-		31	61	1.22	0.27	-	
	OAB	69	48			1.11	0.48-2.61	69	73			1.66	0.68-4.07
Lead depth position	Superficial	13	54	3.81	0.15	1.06	0.32-3.51						
	Correct	61	53			-							
	Too deep	26	31			0.40	0.15-1.07						
Lead sacral position	S2	3	33	2.42	0.66	0.50	0.04-5.91						
	S3	46	50			-							
	S4	36	39			0.64	0.26-1.54						
	S5	8	63			1.67	0.36-7.80						
	none	7	57			1.33	0.27-6.64						

(-) = reference category; 0=negative, 1=positive response on test.

Table 2. Univariate results for gain in positive response between FSTLP and PNE

Predictors	Category	N	% pos.	χ^2_L	p-value	OR	95% C.I. OR
	All	100	22				
Gender	Male	18	6	4.35	0.037	-	
	Female	82	26			5.85	0.73-46.70
Age				3.03	0.082	0.97	0.93-1.01
	≤ 45 years	20	40	4.27	0.039	-	
	> 45 years	80	18			0.32	0.11-0.92
Type of complaint	Retention	31	16	0.94	0.33	-	
	OAB	69	25			1.70	0.56-5.12

(-) = reference category

Table 3. Final logistic regression model results for gain in positive response on FSTLP after PNE

Final logistic regression model						
<i>Predictors</i>	<i>Category</i>	<i>B</i>	<i>S.E.</i>	<i>p-value</i>	<i>OR</i>	<i>95% C.I. OR</i>
Gender	Male				-	
	Female	1.89	1.08	0.080	6.59	0.80-54.43
Age	</= 45 years				-	
	45 years	-1.24	0.57	0.028	0.29	0.10-0.87
Constant		-2.00	1.09	0.065	0.14	
Significance test in -2LLχ^2						
<i>Predictors</i>	<i>Log likelihood</i>	<i>Change in -2LL</i>	<i>df</i>	<i>Sig. of the change</i>		
Gender	-50.56	4.79	1	0.029		
Age	-50.52	4.70	1	0.030		

0= negative or positive result on both tests , 1=a positive response on FSTLP after a negative one on PNE, (-) = reference category

Discussion

The PNE test was initially the only method to screen patients for their eligibility for sacral neuromodulation. The success rate for this method is reported to lie around 48-60% [6, 7], which corresponds with the findings of this study. The lead used during this test is a standard electrical wire electrode that has the potential to migrate if stresses occur. This may lead to false negative responses during the PNE, as shown by Janknegt et al. [8]. Eight out of 10 patients that failed PNE after having an initial good effect during the test (probably due to migration) were successfully treated with SNM therapy with the definitive electrode (which at that time was an electrical wire with four electrodes, sutured subcutaneously to minimize lead migration). In our study, none of the patients reported having a change in the sensitivity to the stimulation, implying that no lead migration had occurred. However, since no confirmatory fluoroscopy had been performed, hypothetically minor dislocations might have occurred without a change in sensation of the stimulation.

In 1997, the two-stage implantation technique was introduced, with the use of definite lead for testing. When the test was successful, a pulse generator was implanted [8]. Everaert et al. showed that the failure rate for patients with an implanted SNM device was lower for a two-staged procedure than for a one-stage procedure [9]. In 2002, a new lead was introduced with tines or anchors to minimize the risk of migration and soon after the two stage

tined lead placement followed [6, 10]. Positive response rates to FSTLP ranges from 67 to 88% [3, 4, 11], comparable to the 69% found in this study.

The difference in response rate between PNE and FSTLP could partly be attributed to lead migration during the PNE test, although no change in sensory response was noted in this study. However the lead location or position during the placement may also account for it. In our study, during the PNE procedure, anatomical landmarks and motor/sensory responses of the bellow and great toe were used to guide electrode placement, fluoroscopy was not used to check electrode position. A control X-ray after placement showed an incorrect location of position of the PNE electrode in some patients, although the sensory and motor responses were noted. Analysis showed that neither the depth nor the foramen used were statistically related to a positive response to PNE nor to FSTLP after failing PNE.

For patients with urgency incontinence, the positive response-rate with sacral neuromodulation has been associated with patient's age, with older patients having a lower chance to achieve complete continence by sacral neuromodulation [12]. Our study also shows that age is negatively related to a successful outcome of the FSTLP test. Furthermore, among patients who failed PNE test, higher age results in a lower probability to respond successfully to FSTLP. It is still a matter of speculation why older patients are less likely to respond to sacral neuromodulation. Age related changes in the bladder and/or neural system may reduce the efficacy of the currently used forms of neuromodulation.

In this study female gender was related to a higher probability for success with FSTLP after failing PNE. Currently, no data are available to suggest gender as a predictive factor for positive response to SNM, and from our current setup no clear explanation can be found. Factors as comorbidity, previous history of stress incontinence surgery or complaint duration have been linked to the outcome on neuromodulation, [12-14] however these were not addressed in our study.

The purpose of this study was to compare patient's response to PNE and FSTLP test in a study design where all patients received both tests and therefore were their own control group. A limitation of this design is that it is not a randomized control study. Although no power analysis was conducted, a number of 100 patients were estimated to sufficiently provide a reliable comparison. The data from this repeated measure study suggest a superior effect of FSTLP compared to PNE.

At the moment, there is no consensus concerning the optimal SNM screening methods. Therefore, the decision to choose PNE, FSTLP or even both as screening depends on the surgeon's experience. Clearly different aspects may influence the choice. PNE placement is faster, the test period is shorter, and the procedure is cheaper than FSTLP. On the other hand, FSTLP appears to be more effective, has a lower migration rate and it has the advantage of ensuring the place where the lead is implanted is effective before the battery is implanted. Performing both screening tests in the same patient also has some advantages. By performing PNE first, patients who experience pelvic floor side effects or worsening of their complaint can be identified and excluded. In addition, there is an option to exclude all patients who are mentally or even physically unable to cope with the SNM implant. Another advantage of doing both techniques is that the amount of stress during the TLP might be reduced when the patient already had experienced PNE. This may also be beneficial in patients with a reduced coping capability. Although our study suggests FSTLP as the most sensitive screening method, it is clear that individual tailoring of screening methods may be necessary in certain patients, for example in those with coexisting psychological problems.

Conclusions

In this study more patients had a positive response to FSTLP than PNE (69% vs. 47%). The difference or gain was statistically significant ($p < 0.001$) and was negatively affected by male gender and higher age. Logistic regression of the PNE found no predictors for positive response. However the same analysis for the FSTLP showed a negative effect of age. All patients who had a positive response to FSTLP received the SNM treatment. The failure rate of these patients after an average of 2 years was 2.9%. In conclusion, this study suggests that FSTLP may be a more sensitive screening method than PNE to identify patients eligible for SNM therapy, warranting randomized trials.

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Chapter 3

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

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Journal of Urology 2011;185(5):1781-5

Abstract

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

Materials and methods: This pilot study we evaluated the effect of 4 different 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 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 $\pm$ 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, a individualized approach to optimize treatment efficacy by changing the pulse rate appears to be useful.

Introduction

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 μ seconds, and amplitude can be changed from 0.05 to 10.55V.

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 suggest that the pulse rate should not exceed 50 Hz since this might 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 with chronic non-obstructive 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 a pulse width 210 μ seconds. 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 μ seconds) 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 with 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 of 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 tests was used to compare baseline (control) and 10 Hz outcomes to assess the validity of diary results. Repeated measures ANOVA was done to test the 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 analyses SPSS® PC, version 16.0 were used.

Results

Clinical outcome

Of the 50 patients 40 were female (80%). Mean $\pm$ SD age was 55.5 ± 12 years. A total of 41 patients (82%) had urinary incontinence and 9 (18%) had urinary retention. Mean followup after implantation was $6.2 \pm$ SD 4.8 years. Comparison of the baseline 10 Hz voiding diary with 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 with at least one setting, and 2 of the 9 (22%) patients with 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 the voiding diary data, controlled for age and type of complaint, 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. No statistically significant difference was noted in the other voiding diary parameters (see table).

Multivariate analysis of questionnaire parameters also revealed a significant difference in the number of voids daily ($p = 0.021$) in younger patients only. At rates other than 40 Hz this effect was not noted. No statistically significant difference was found for the other visual analogue scale parameters (see table). Optimal dichotomous categorizing of age resulted in a cutoff of 44 years.

Sensory response

During pulse rates reprogramming patients were repeatedly asked to locate the sensation site. Answers were categorized as the: 1) anal area, 2) perineal or genital area, 3) buttock area or 4) another area. Of the 50 patients 38 (76%) reported a change in the sensation site for at least 1 of the 4 pulse rates. Patients reported different sensation sites at different pulse rates, but we noted no significant relation between any 1 rate and the sensation site. Furthermore, no relation was found between the sensation site and clinical effect.

A, effect of each pulse rate setting on clinical outcome on voiding diary in 50 patients. Improvement was defined as greater than 20% improvement. B, of 28 patients those with no stimulation related pain at baseline who had onset of pain during study. C, of 22 patients those with perceived stimulation related pain at baseline who had decreased pain during study.

Pain symptoms

During the study we documented perceived pain symptoms related to stimulation at different pulse rates. At baseline 28 patients reported no pain or discomfort related to electrical stimulation. Of these patients 12 (43%) reported de novo pain during the study at 1 pulse rate setting but only 5 (18%) reported that the pain was bothersome in daily life. Part B of the figure shows the number of patients with onset of pain symptoms at each pulse rate. Statistical analysis revealed no significant relation between any of the 4 pulse rates and pain symptoms.

Of the 50 patients 27 reported stimulation related pain at baseline, including 4 in whom the pain was bothersome in daily life. Of the 22 patients 18 (82%) reported a decrease in pain symptoms for at least 1 pulse rate setting during the study. Part C of the figure shows the number of patients with decreased pain symptoms at each pulse rate. No significant relation was found for any of the 4 settings and decreased pain symptoms. There was no relation between the disappearance of pain at a certain pulse rate and clinical efficacy.

The Effect of Pulse Rates Changes on Clinical Outcome in Sacral Neuromodulation

Diary and visual analogue scale questionnaire results in 50 patients

	Mean ± SD Baseline	Mean ± SD 5.2 Hz	Mean ± SD 10 Hz	Mean ± SD 21 Hz	Mean ± SD 40 Hz	p Value	
						Base vs 10 Hz (paired sample t test)	Univariate (repeated measures ANOVA) [□]
Diary							
Overall:							
Max voided vol (ml)	418 ± 149	426 ± 154	428 ± 149	410 ± 134	411 ± 136	0.603	0.323
No. voids/day [‡]	8.3 ± 3.2	8.2 ± 2.8	8.3 ± 2.8	8.0 ± 2.8	8.0 ± 2.6	0.734	0.610
Voided vol/void (ml)	225 ± 83	225 ± 77	230 ± 78	224 ± 81	228 ± 82	0.715	0.566
OAB wet (41 pts):							
Incomplete episodes/day	4.4 ± 2.4	3.6 ± 2.8	3.5 ± 3.0	3.7 ± 2.9	3.9 ± 2.9	0.080	0.862
Pads/day	2.5 ± 1.9	2.3 ± 2.2	2.1 ± 1.6	2.1 ± 1.6	1.8 ± 1.5	0.188	0.525
Severe leakage	1.5 ± 0.5	1.3 ± 0.5	1.4 ± 0.6	1.2 ± 0.6	1.4 ± 0.5	0.058	0.641
Retention (9 pts):							
Max vol/catheterization (ml)	233 ± 157	149 ± 145	140 ± 128	171 ± 94	161 ± 164	0.734	0.724
No. catheterizations/day	6.5 ± 2.9	4.4 ± 4.1	5.0 ± 3.5	5.6 ± 3.5	4.1 ± 3.5	0.278	0.407
Catheterized vol/catheterization (ml)	126 ± 104	88 ± 97	88 ± 85	113 ± 75	90 ± 105	0.315	0.606
Questionnaire							
General urinary voiding	57 ± 25	57 ± 23	59 ± 25	57 ± 24	59 ± 26	0.716	0.882
No. voids [‡]	54 ± 24	57 ± 25	51 ± 28	56 ± 25	58 ± 28	0.329	0.331
Urinary flow	52 ± 32	51 ± 29	47 ± 29	48 ± 32	52 ± 29	0.543	0.463
Urinary urge sensation	55 ± 31	56 ± 28	55 ± 30	53 ± 30	56 ± 30	0.808	0.781
Empty bladder sensation	51 ± 33	58 ± 32	55 ± 33	57 ± 34	57 ± 34	0.255	0.686
Bladder control	49 ± 30	57 ± 28	56 ± 30	55 ± 28	59 ± 28	0.192	0.824
Dry	55 ± 32	62 ± 31	59 ± 30	61 ± 28	61 ± 27	0.369	0.798

[□] Four-way analysis of 5.2 vs 10 Hz vs 21 Hz vs 40 Hz. [†] Multivariate risk factor was age or complaint type and final model included difference in number of voids at 40 Hz vs remainder by age 44 or less and greater than 44 years (diary and questionnaire best fit repeated ANOVA/ANCOVA p = 0.004 and 0.012, respectively).

Discussion

SNM is a well accepted treatment option in cases of OAB or nonobstructive urinary retention that are refractory to conservative treatment. At most clinics where SNM is applied it is customary to set the pulse rate of the implantable neurostimulator between 10 and 16 Hz [5-7]. However, these settings are based on early SNM experiments, in which optimal stimulation parameters were determined by the effect on urethral closure pressure [8]. Today it is generally assumed that the SNM mechanism of action involves the modulation of spinal cord reflexes and brain networks by peripheral afferents rather than direct stimulation of the motor response of the detrusor or urethral sphincter [11].

In electrophysiological experiments on rat dorsal root ganglion neurons the pulse rate by natural physiological stimuli was approximately 5 Hz in C, 15 Hz in A δ and 100Hz in A β fibres [12, 13]. Thus pulse rate alterations could have different effects on different fiber types and SNM treatment efficacy may be optimized by evaluating the clinical effect of different pulse rates.

In a study by Tai et al of pudendal nerve stimulation 3 and 20Hz pulse rates in chronic spinal cord injured rats different effects were observed on bladder capacity and voiding efficiency [14].

To date few clinical studies have been done to evaluate the effect of different pulse rates in patient who receive SNM. In 2003 Malaguti et al used somatosensory evoked potentials of the pudendal nerve to evaluate the suprasacral action of SNM [15]. Measurements were made at 21 and 40 Hz. They found a higher decrease in pudendal somatosensory evoked potentials latency when the pulse rate was set to 40 Hz, indicating that a 40 Hz setting more effectively facilitates afferent transmission to the central nervous system.

In patients with faecal incontinence Dudding et al noted that a 31 Hz pulse rate resulted in a significant increase in rectal compliance compared to that at 14 Hz [16]. Although these findings indicate that pulse rate alterations can influence nerve transmission or rectal compliance, to our knowledge the effect of pulse rate alterations on the clinical outcome has never been evaluated in a large group of patients.

In our study population no specific pulse rate appeared to be superior in terms of the clinical effect. Younger age has already been implicated as a positive predictive factor for clinical success [17-20]. In our study the 40 Hz setting resulted in a significantly lower number of voids daily in younger patients. However, in our opinion, the clinical relevance of this finding seems limited.

Although no significant difference was found among the pulse rates, our results clearly show that pulse rate alterations can improve the clinical

response in individuals since 76% experienced improved voiding symptoms for at least 1 pulse rate setting. Also, 20% of patients with OAB became completely dry and 22% with retention had no more need for catheterization. This means that changing the pulse rate can be useful to improve treatment efficacy in patients who experience suboptimal SNM effect.

Generally sensation sites are used as a guide for proper stimulation during screening or reprogramming visits in patient receiving SNM. It has been assumed that the optimal sensory response is located in the anal or genital area since this is the most commonly observed response during stimulation of the S3 nerve root [21]. However, there is not much evidence in the literature for this assumption, and no studies have clearly evaluated the relation between the sensation site and clinical effect. In our series most patients noticed a change in sensation site for at least 1 pulse rate setting. In some patients the sensation site changed from a desired area, such as the anus, to an undesired area such as the buttock. We found no significant relation between pulse rate and sensation site or between sensation site and clinical effect. Hence, these data question the role of sensation site as predictive factor for optimal stimulation.

To our knowledge the effect of pulse rate settings on stimulation related pain symptoms has never been evaluated, although it is believed that higher stimulation frequencies may result in painful stimulation. A pulse rate higher than 50Hz is not recommended due to the possibility of nerve injury and, thus, it is advised to set the pulse rate at 10 to 16 Hz [10, 22]. We evaluated the effect on pain symptoms of 4 pulse rates and none was significantly related to the onset of stimulation related pain. Although pain could be decreased by changing the pulse rate in individuals with pain symptoms at baseline, no relation was found between a specific pulse rate and a decrease in pain.

These findings imply that all 4 pulse rates can be effectively used during reprogramming of the neurostimulator and there does not seem to be a preference for 1 particular setting. However, since the number of patients in this pilot study was relatively small, power may have been too low to detect a significant difference between the pulse rates. Furthermore, we only evaluated the effect of each pulse rate during 1 week. Thus, the effect of chronic stimulation cannot be predicted. It would be interesting to evaluate the effect of different pulse rates in a group of patients directly after implantation. Also, we studied patients who were treated with SNM for many years, which may have influenced our results. Unfortunately we did

not evaluate the effect of turning the stimulator off in these patients before the start of the trial. Finally, we did not include a control group and, thus, the role of a possible placebo effect cannot be evaluated.

Conclusion

In this pilot study none of the 4 pulse rates appears to have had a significantly different effect on clinical outcome or stimulation related pain. Nevertheless, an individualized approach to optimize treatment efficacy by changing the pulse appears to be useful.

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Chapter 4

Long-term Results of Sacral Neuromodulation with the Tined Lead Procedure

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Journal of Urology 2010; 184 (5):1997-2000

Abstract

Purpose: We present long-term followup data on the outcome of sacral neuromodulation using the tined lead procedure.

Materials and Methods: We conducted a single center study including all patients who received an implantable neurostimulator between 2002 and 2005 using the tined lead technique. Treatment efficacy was evaluated by comparing the data of a 3-day voiding diary filled out in May 2009 to the data before the onset of sacral neuromodulation treatment (baseline). Clinical success was defined as more than 50% improvement in at least 1 of the relevant voiding diary parameters.

Results: A total of 64 patients underwent implantation with an implantable neurostimulator using the tined lead procedure. Mean followup was 53 months (range 35 to 77). Five patients died of causes unrelated to sacral neuromodulation and they were not included in analysis. The implantable neurostimulator was removed from 7 patients and 3 stopped using the neurostimulator. Voiding diary analysis showed that 38 of 59 patients (64%) were successfully treated. There were 21 patients (33%) who underwent a surgical revision due to an adverse event and 1 (1.6%) who underwent lead revision because of suspected lead migration.

Conclusions: Sacral neuromodulation with the tined lead procedure is a safe and effective treatment for patients with overactive bladder symptoms or urinary retention.

Introduction

Sacral neuromodulation (SNM) is an accepted treatment option for patients with idiopathic overactive bladder syndrome (OAB) or chronic non-obstructive urinary retention that is refractory to conservative treatment [1-3]. Since Food and Drug Administration approval in 1997, an increasing number of patients have been treated with SNM. Initially the permanent lead was implanted using an open surgical technique with an incision made in the midline over the sacrum and the lead placed under direct vision into the sacral foramen. The lead was then secured with a suture to the sacral periosteum. The long-term success rate for this initial procedure is reported to be 60-70% [4-6].

In 2002 a new technique was introduced that enabled percutaneous placement of a self-anchoring, tined silicone lead [7, 8]. This lead can be easily placed in the third sacral foramen under radiological guidance. Potential advantages of the tined lead procedure (TLP) include a shorter operation time, reduced risk of infection, less pain and shorter postoperative recovery time. In addition, the lead can be inserted with the patient under local anesthesia, enabling evaluation of the sensory responses to acute stimulation.

Short-term studies showed a decrease in the numbers of adverse events and the occurrence of lead migration with the TLP [9, 10]. However, the efficacy and number of adverse events in the long-term are currently unevaluated.

The primary objective of this study was to assess the long-term efficacy and adverse events of SNM with the tined lead procedure. A Secondary objective was to correlate the degree of improvement during test stimulation with long-term outcome.

Methods

This single center observational study included all patients who were screened for SNM therapy between 2002 and 2005. The study was approved by the ethical committee and all participants signed an informed consent. Patients included those with idiopathic OAB symptoms, with (OAB wet) or without (OAB dry) incontinence, and those with chronic nonobstructive urinary retention. All cases were refractory to conservative treatments or could not tolerate the side effects. All patients in the retention group performed clean intermittent catheterization and had more than 100 ml residual volume. No patients had signs of anatomical obstruction.

Patients received an implantable neurostimulator (INS) after showing a successful response to PNE or first stage tined lead screening tests. Success was defined as more than 50% improvement in at least one of the relevant voiding diary parameters compared to baseline. For OAB wet cases these

parameters included a reduction in daily episodes of incontinence or pad use, and for OAB dry cases a reduction in the number of daily voids or an increase in voided volume per void. For patients with non-obstructive urinary retention parameters were a reduction in the number of daily catheterizations or increase in voided volume.

Between 2002 and 2005 all patients were initially screened with a PNE test unless they were at high risk for lead migration (for instance, those who were obese or underweight). Patients who showed a negative response to PNE were additionally screened with the TLP. The tined lead placement was performed as previously described [7, 8]. The lead (InterStim® Model 3889) was placed in the left or right S3 foramen with fluoroscopy guidance. All procedures were performed under local anesthesia in an outpatient setting. After implantation, patients visited the outpatient clinic after 6 weeks, 6 months and yearly thereafter. In cases of decreased efficacy the impedances and battery life span were checked. Parameter settings were adjusted to restore efficacy. In case of permanent loss of efficacy electrode position and cable integrity were checked using fluoroscopy. Adverse events and reoperations were reported for all implanted cases.

In May 2009 all patients who were still using the INS were asked to keep a voiding diary to record the effect of SNM on urinary symptoms. SNM therapy was considered successful if 50% or more improvement was noted compared to baseline in any of the primary voiding diary variables. The variables at baseline and followup were compared using the Wilcoxon signed rank test. Treatment in those who had the system explanted or discontinued SNM therapy was considered unsuccessful and the patients were assumed to return to baseline symptoms.

Overview of all patients screened for SNM treatment. Note that 16 patients were immediately screened with TLP without prior PNE test due to increased risk of lead migration. Total of 64 patients showed positive response to screening and received INS.

Results

Screening and followup

Between 2002 and 2005, 92 patients were screened for SNM, of whom 64 (70%) responded successfully and received an INS using the tined lead procedure. Of the 64 patients, 53 were female and 11 were male with a mean age of 49 years (range 22 to 75, SD 12). (see figure 1 and table 1). During follow-up 5 patients died of causes unrelated to neuromodulation. These patients were not included in the evaluation of treatment efficacy since no objective data could be obtained. Of the remaining 59 patients 45 had overactive bladder syndrome (40 OAB wet and 5 OAB dry) and 14 had non-obstructive urinary retention.

By May 2009 of 59 patients 49 were still using their INS. There were 7 patients who had the INS explanted, including 1 due to psychiatric reasons, 1 due to repeated need for magnetic resonance imaging evaluation, 3 due to loss of efficacy (1 after a vaginal wall correction and 2 after minor trauma) and 2 patients because of persistent stimulation related pain. Three patients turned their INS off permanently, including 2 due to loss of efficacy and 1 after trauma requiring a suprapubic catheter due to reduced mobility. These patients preferred not to undergo INS removal.

Table 1. Overview of long-term results

	OAB Wet	OAB Dry	Retention	Totals (%)
No. died	3	1	1	5 (8)
No. explant/stimulator off	6	0	4	10 (16)
No. less than 50% improvement in voiding diary	9	1	1	11 (17)
No. greater than 50% improvement in voiding diary	25	4	9	38 (59)
Totals (%)	43 (67)	6 (9)	15 (24)	64 (100)

Voiding diary analysis

The voiding diary was filled out by 49 patients. Patients who had the device explanted or turned the INS off were assumed to return to baseline symptoms. Mean follow-up was 51 months (range 35 to 74, SD 11). The changes in voiding diary parameters for each subgroup are illustrated in table 2.

A sub-analysis was performed for patients with 50 to 90% and more than 90% improvement in voiding diary data during test stimulation. The long-term success rate for each group was 52% and 80% respectively. A borderline significant association was found between patients with greater than 90% improvement during test stimulation and long-term success (Fisher's exact test $p = 0.05$, OR 3.6, 95% CI 1.1-11.7).

Safety and complications

Adverse events and reoperations were evaluated for all 64 patients. No serious or life-threatening adverse events occurred. In 3 patients a haematoma was seen perioperatively which was treated with antibiotics. A wound infection developed in 1 patient which required INS removal. Postoperatively 23 reoperations were performed in 21 patients (33% reoperation rate). In 7 patients the INS was removed, in another 7 the INS was repositioned for pain at the INS site and in 5 a lead revision was required (1 due to lead migration, 3 due to decreased efficacy and 1 due to pain). In 4 patients the INS had to be replaced because of battery depletion. Mean followup before battery replacement was 62.3 months (range 49 to 75).

There were 17 patients (27%) who reported pain during follow-up. Pain at the INS site was reported most commonly, followed by pain caused by

bothersome stimulation. Of these patients 9 were treated by changing the stimulation parameters. The remaining 8 patients required surgical intervention, because reprogramming the INS was insufficient.

Readjustment of stimulation parameters was evaluated for each patient since implantation. The mean number of reprogramming sessions was 2.8 per patient (0.7 per year), and the most common reasons were loss of efficacy and painful stimulation. There were 11 patients (17%) who not require any readjustment of the parameters, 41 patients (66%) required up to 5 reprogramming visits and 12 (17%) required more than 5 reprogramming visits. Of these 12 patients, none was successfully treated with mere adjustment of the stimulation parameters.

Table 2. Results of voiding diary analysis

	Mean Baseline (SD)	Mean Test Stimulation (SD)	Mean Followup (SD)
OAB wet:			
Voided vol (ml)/void	151 (70)	228 (68) [□]	183 (72) [†]
Voids/day	11.2 (6.1)	7.7 (3.3) [†]	9.2 (3.6)
Leakage/day	7.7 (5.0)	2.1 (2.1) [□]	4.0 (3.8) [□]
Pads/day	4.6 (3.0)	0.7 (0.8) [□]	2.3 (2.8) [□]
OAB dry:			
Voided vol (ml)/void	131 (17)	231 (28) [†]	195 (35) [†]
Voids/day	16.5 (2.3)	7.0 (1.4) [†]	9.1 (3.2) [†]
Leakage/day	0.0 (0.0)	0 (0.0)	0.0 (0.0)
Retention:			
Voided vol (ml)/void	96 (101)	267 (109) [□]	203 (126) [□]
Voids/day	4.2 (3.5)	6.8 (2.3) [†]	5.9 (2.8) [†]
Catheters/day	4.7 (2.0)	4.5 (2.1)	1.9 (2.8) [□]

[□] p < 0.01, [†] p < 0.05

Discussion

With the introduction of the TLP, sacral neuromodulation has become a minimally invasive treatment for patients with overactive bladder syndrome or urinary retention. Although some advantages of this new technique have been demonstrated in short-term trials, the efficacy of treatment and the sufficiency of lead fixation in the long-term are unclear.

In our study, the success rate was 64% (38 of 59 implanted cases), which is comparable to that of previous long-term studies evaluating the nontined lead [4-6]. This suggests that the minimally invasive nature of the TLP does not decrease treatment efficacy. However, it does permit adequate placement of the lead to be performed with the patient under local anesthesia using guidance with fluoroscopy, and clinical sensory and motor responses.

Patients who showed a large improvement during screening (greater than 90% improvement in voiding diary parameters) tended to do better in the long term than patients who showed between 50 and 90% improvement ($p=0.05$). This finding suggests that the clinical response during the test phase has some predictive value for treatment efficacy in the long term and reinforces the importance of good patient selection.

The number of adverse events appears to decrease with the TLP compared to the non tined lead, since in the current study electrode migration was seen in only 1 patient (1.6%). Long-term studies conducted before the introduction of the tined lead showed electrode migration rates between 6.7% and 27% [4-6, 11]. The low rate of electrode migration in our study could be a result of better electrode fixation with the new tined lead technique, and similar results were previously shown in short-term studies with the TLP [10, 12, 13].

The number of patients requiring surgery due to an adverse event was 33%, which is only slightly lower than reported revision rates using the nontined lead, which range from 38% to 40% [4-6]. Comparison among various studies may be difficult due to differences in patient selection and surgical procedures. Furthermore, replacement of the INS due to battery depletion was included in the number of adverse events in our study. A long-term study conducted in our centre using the nontined lead procedure showed a revision rate of 48% [11]. Therefore, the new tined lead technique seems to result in a lower revision rate, mostly due to a decrease in the number of infections and lead migrations.

In 1999 the location of INS placement was changed from the lower abdomen to the buttock, which facilitated the surgical procedure and was thought to reduce device related pain[14]. In our study each INS was placed in the buttock but still the operation rate for repositioning the INS due to pain (11%) was similar to the rate reported in a worldwide long-term study using the initial technique (12%) [4]. Therefore, it is questionable whether buttock placement actually decreases device related pain.

Since to our knowledge no true algorithm exists for the adjustment of the stimulation parameters, the number of reprogramming visits in our study

varied per patient. Most patients (82%) required 1 or more reprogramming sessions. In all patients who had more than 5 reprogramming visits parameter adjustment failed to resolve the adverse event. Therefore, we believe performing more than 5 reprogramming visits for the same adverse event seems ineffective.

Conclusion

Long-term sacral neuromodulation with the tined lead is a safe and effective treatment for patients with overactive bladder symptoms or urinary retention. Using the tined lead appears to reduce the occurrence of lead migration but does not increase the long-term success rate compared to previous reports using the nontined lead. Patients who show more than 90% improvement during test stimulation appear to have a higher chance of long-term success than patients with 50 to 90% improvement.

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Chapter 5

Satisfaction and patient experience with Sacral Neuromodulation Therapy: a systematic single-centre survey

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Journal of Urology 2011;185(2):588-92

Abstract

Purpose: We systematically assessed a long-term satisfaction and patient experience with sacral nerve modulation therapy.

Materials and Methods: All patients who received sacral neuromodulation therapy between 1990 and 2007 at our centre and who are still had the implant were included in the survey. All received a postal questionnaire regarding their satisfaction and their experiences with the system, such as side effects, complications, burden, impact on sexuality and defecation changes.

Results: Of the 275 questionnaires sent 207 were returned for a 75% response rate. The population was 83% female. Overall treatment was done for overactive bladder syndrome, nonobstructive urinary retention, combined overactive bladder and retention, and pelvic pain in 55%, 24%, 20% and 1% of patients, respectively. Overall satisfaction with sacral neuromodulation was high at 90%. No correlations were found between the satisfaction rate, and pretreatment age, gender, complaint type, sexual dysfunction or therapy duration. However, 56% of patients reported side effects, such as pain at the internal nerve stimulator site and due to stimulation. However, 89% of these patients did not seek further therapy. Of patients with additional defecation problems 47% experienced relief of complaints.

Conclusions: This study shows a high satisfaction rate in patients with SNM. There was no relation between patient age, complaint type, therapy duration or side effects and the satisfaction rate. The number of side effects was limited but further analyses in prospective cohorts should identify patients who are likely to have side effects or stop SNM treatment.

Introduction

For almost 2 decades sacral neuromodulation (SNM) therapy has been used as a safe, effective treatment option in patients with lower urinary tract dysfunction. Clinical studies show its positive effect for refractory urge incontinence, nonobstructive urinary retention and urgency-frequency syndrome [1-4]. In addition to urological disorders, SNM is also being done for fecal incontinence and chronic constipation [5, 6].

Currently, most studies of SNM have focused on clinical efficacy or technique improvement. The outcome parameters mainly used are clinically oriented such as greater than 50% improvement in 1 or 2 relevant urinary symptoms and the presence of adverse events. Impact on quality of life has been described but to a lesser extent and as mostly evaluated by non-Overactive Bladder syndrome (OAB) or retention specific questionnaires [2, 4, 7]. Since functional bladder disorders have a negative impact on quality of life, evaluating patient satisfaction is also important because it may provide an overall view of how the patients experience treatment on a daily basis. Our main goal was to systematically evaluate long-term satisfaction in patients on SNM and evaluate their daily experiences with the treatment.

Materials and Methods

A postal questionnaire was sent to all patients at our center who had been treated with SNM for at least 1 year. Implantation was done from 1990 to 2007. They were asked to reply within 14 days and a reminder was sent after 1 month to nonrespondents. The study was approved by the local medical ethics committee. Due to the intimate nature of some questions on sexual function patients were given the choice to respond anonymously.

The primary outcome of this sample survey was patient satisfaction. Patients were asked how satisfied they were with treatment, including very satisfied, moderately satisfied and not satisfied. The factors and variables used for univariate analysis of satisfaction with SNM were age, gender, primary urological condition, concurrent urological, gastrointestinal and sexual complaints, duration of complaints before SNM and intervening medical events (operations). We also analyzed perception of problems with SNM (the burden of extra visits to the hospital and decreased efficacy), use of the switch off mode, change in amplitude and attitude toward scheduled yearly followup.

When univariate interval type of data appeared to be normally distributed, the mean $\pm$ SD is shown. When not, the score range is provided. Univariate categorical data are presented as the rate and percent. To test the relationship between the main outcome (satisfaction with SNM) and dichotomous nominal data we used the Mann-Whitney test. To test the relationship between main outcome and polytomous nominal data we used the Kruskal-Wallis test and to

test it with ordinal data we used the Jonckheere-Terpstra test. The degree and sign of association between the main outcome and ordinal type of data were calculated and tested by Spearman's rank correlation coefficient (ρ). Multivariate analysis using satisfaction with SNM as an outcome variable was done with multiple (dummy) regression analysis using list wise deletion of missing cases, ie all cases with valid, nonmissing scores on each outcome variable and all predictors used in the model. Statistically significant results from forward selection and backward elimination techniques were combined in cross-section fashion to find and test the best fitting regression model. Results of the final model are shown including unstandardized and standardized coefficients, p values, etc. For this final model residual analysis was done to test the assumption of normality of distribution of the Student test residuals and inspect residual plots for digression from normality. For all data analysis SPSS® PC, version 16.0 was used with $p < 0.05$ considered as statistically significant.

Results

We reviewed the records of all patients implanted between 1990 and 2007, excluding those who died during followup. The 13 patients in whom the device was removed were not included in the survey since most questionnaire items addressed experience with current stimulator use. A total of 275 patients at our clinic were sent a postal questionnaire, of whom 207 (75%) replied, including 27 (13%) anonymously. Of the patients 5% could not be contacted since they had moved to a different address and 20% did not respond to the survey even after the reminder. Of the 180 patients who responded nonanonymously to the questionnaire 83% were female and 17% were male. In that group mean age at implantation was 48.6 ± 10.8 years (range 16 to 73) and mean age at followup was 56 ± 11 years. The median post-implantation period was 77 months (range 12 to 214). Table 1 lists urological indications for SNM and the prevalence of self-reported comorbidity.

Questionnaire results

Most patients reported satisfaction with SNM and 80 (40%) reported having some concern for future life with the treatment. The most common reasons were decreased treatment efficacy, battery replacement procedure, medical need for MRI, problems with reimbursement, pregnancy and long-term systemic effects on the body. A total of 45 patients (22%) perceived some limitation due to the implant. The most common reasons were a regular feeling of pain, trouble with metal detectors in stores or when traveling, and not being able to undergo MRI.

The reported long-term rate of SNM perceived effectiveness for urological complaints was high but the perceived effect on other pelvic floor disorders

varied. Overall 40 patients (20%) noticed fecal pattern improvement and 25 (12%) experienced worsening of the fecal pattern. Of the 76 patients who had 1 or more additional fecal problems before SNM 36 (47%) experienced symptom relief. Similarly most patients noticed no difference in sexual function. Only a small group reported improved libido (10 patients or 5%) and orgasm (8 or 4%) while 14 (7%) and 16 (8%) reported worse libido and orgasm.

At the start of treatment all patients received a patient programmer and instructions how to use it but only a few reportedly used the programmer. Of the patients 39 (9%) turned the INS on or off on a regular basis. The most common reasons were undergoing operation or computerized tomography, or passing through metal detectors at airport customs. When patients were asked whether they experienced improvement by altering the amplitude, 13 (58%) replied that they did so. Other, less common reasons for using the programmer were sleeping, driving a car, sexual intercourse and sun bed use.

Of all patients 23 (11%) and 35 (17%) reported having visited a physician due to temporary loss of efficacy and pain at the INS site, respectively. The most commonly reported reasons for temporary loss of efficacy were life stress and cold weather. Pain at the INS site occurred mostly when sitting on a hard chair, bending, walking or doing sports and lying on a hard bed, or when the INS implant site was touched or accidentally bumped.

Of the patients 29% reported difficulty when passing through detectors at stores or airports. Of all patients who traveled by airplane 29 (23%) were separately searched and some were even strip searched at the airport. Furthermore, the ID card provided by the manufacturer, which states that the patient has an INS implant, was not considered authentic by the authorities in 32 patients (25%).

Analysis Results

Univariate

Satisfaction with SNM was not univariately associated with patient age ($p = 0.147$, $p = 0.052$), gender ($p = 0.033$, $p = 0.667$) or the urological indication for SNM treatment (F ratio 0.523, $p = 0.419$, Kruskal-Wallis chi-square 2.830, 3 df, $p = 0.419$). The relationship between satisfaction and self-reported comorbidity was tested by categorizing patients into 3 groups by the number of comorbidities, including none in 70 (34%), 1 in 90 (44%) and more than 1 in 45 (22%). The response was missing in 2 patients (1.0%). Univariate analysis revealed an almost significant relation between comorbidity and satisfaction with SNM (Kruskal-Wallis chi-square 5.995, 2 df, $p = 0.050$).

Table 1. Demographic characteristics in 207 study patients

	No. Pts (%)
Gender:	
M	31 (17)
F	149 (83)
Missing data due to anonymous response	27 (13)
Urological indication for SNM:	
OAB	116 (57.4)
Retention	57 (28.2)
OAB + retention	26 (12.9)
Pain	3 (1.5)
Missing data	5 (2.4)
Other pelvic complaints before SNM:	
Urinary stress incontinence	55 (26.8)
Chronic constipation	40 (19.5)
Fecal incontinence	27 (13.2)
Irregular fecal pattern	29 (14.1)
Unspecified sexual dysfunction	33 (16.1)
Abdominal pain	58 (28.3)
Missing data	2 (1.0)

Multiple dummy regression

Table 2 lists the results. Multiple regression analysis of satisfaction with SNM revealed that patients with no comorbidity were significantly more satisfied than patients with more than 1 comorbidity ($\beta = 0.274$, $p = 0.003$). Satisfaction was positively related to the perceived effect at followup and decreased INS function was negatively related to satisfaction ($\beta = -0.365$, $p < 0.001$). The way that patients evaluated yearly hospital outpatient visits was also related to the satisfaction rate. Patients who did not like the regular followup tended to have lower satisfaction with treatment ($\beta = 0.251$, $p = 0.001$). Finally, patients who mentioned improvement in complaints when they altered battery amplitude were significantly more satisfied than those without improvement and those who never altered the amplitude ($\beta = -0.189$, $p = 0.012$). This effect was significantly higher in men ($\beta = 0.531$, $p = 0.014$).

All first order interactions between the 4 main effects were tested and were not statistically significant except the described interaction between changing INS parameters and gender. Upon inspection of residual standardized plots in

the final model we decided that multiple (dummy) regression analysis could be used for data analysis.

Discussion

Sacral neuromodulation is a well established treatment for idiopathic OAB or nonobstructive urinary retention refractory to conservative treatment [1, 2, 4, 8]. Long-term efficacy and adverse events have been described previously [3, 9]. We focused on patient satisfaction and daily experience with SNM.

Patients with OAB or urinary retention often have other concomitant lower urinary tract or gastrointestinal dysfunctions [8, 10]. For example, fecal incontinence was reported in up to 26% of patients undergoing a urodynamic test [10]. Of our patients, 66% reported other concomitant dysfunction, such as stress urinary incontinence, fecal incontinence or constipation. Although neuromodulation therapy was done for lower urinary tract dysfunction, 22 of the 46 patients (48%) with concomitant fecal problems also had symptom relief of their gastrointestinal problems after SNM treatment. This is comparable to the rate in studies specifically evaluating the effect of SNM in patients with bladder and bowel problems [11-13].

The patient satisfaction rate was high at 90% and significantly related to the perceived clinical effect. However, we did not include patients in whom the device was removed and, thus, the satisfaction rate may have been overestimated. However, when considering the 13 explanted cases as failures, the satisfaction rate in our study would still be 85%.

We found no significant relationship with patient demographics, treatment duration or the complaint type for which SNM was indicated. Patient satisfaction was also shown in other ways. Of the patients 90% stated that they would undergo treatment again and 91% would recommend it to a friend or family in similar need. These results are also consistent with previous findings. Foster et al noted a similar satisfaction rate in 52 patients who underwent SNM [14]. At an average of 27 months 84% of patients was satisfied and 80% stated that they would undergo the same treatment again, if needed. In a quality of life study in 113 patients with SNM Capellano et al found that after 18 months 90% would elect this treatment again and 100% would recommend it to a relative or friend [7].

Satisfaction was significantly lower in patients with more than 1 pelvic floor comorbidity. This may be explained by a higher rate of a moderate SNM effect due to a more complex pelvic floor disorder. As mentioned, satisfaction was significantly related to the perceived effect of SNM.

Table 2. Dummy regression analysis using satisfaction with neurostimulator as dependent outcome variable

	Unstandardized Coefficients				
Predictors [□]	B (95% CI)	SE	Standardized Coefficient β	t	p Value
Constant	1.900 (1.315–2.486)	0.296		6.425	<0.001
Gender (F—1 vs M—0)	–0.681 (–1.073––0.290)	0.198	–0.398	–3.447	0.001
Retention vs OAB	0.157 (–0.051–0.364)	0.105	0.119	1.497	0.137
OAB + retention vs OAB	0.245 (–0.017–0.507)	0.132	0.140	1.851	0.067
No. comorbidities:					
1 vs 0	–0.069 (–0.281–0.144)	0.107	–0.056	–0.641	0.523
2 or Greater vs 0	0.385 (0.136–0.634)	0.126	0.274	3.066	0.003
Adjustability (yes vs no)	–0.790 (–1.267––0.314)	0.241	–0.645	–3.283	0.001
Yrly followup visit	0.280 (0.115–0.444)	0.083	0.251	3.366	0.001
Function evaluation (still working vs not)	–0.553 (–0.777––0.329)	0.113	–0.365	–4.895	<0.001
Gender interaction adjustability	0.647 (0.134–1.161)	0.259	0.531	2.495	0.014

[□] Highly satisfied—1 and not satisfied—3 with 0.396 variance explained by the model and list wise deletion of 128 missing patients.

The patient attitude toward yearly followup was related to the degree of satisfaction. Although the reason could not be deduced from this study, it may have been partly due to differences in travel distance. Patients who mentioned using the patient programmer and noticed improvement were significantly more satisfied than those who did not notice improvement or never used the

programmer. This may explained by a feeling of control over OAB or retention symptoms in these patients.

Most patients were satisfied but 40% overall reported having some limitation or concern with SNM. Some concerns appeared realistic, such as exclusion from MRI after an INS was implanted, while others seemed less relevant, such as possible changes in future reimbursement. Also, 56% of patients reported having discomfort at the INS site and a significant portion of the examined patient population had experienced a problem with metal detectors. However, most patients with discomfort did not see a physician for this problem and problems with metal detectors were usually limited. These results show the importance of informed consent and providing good information before and after treatment.

We describe several issues that are usually overlooked in SNM treatment in a large patient group with long-term followup. To our knowledge this is the first study focused on patient perceptions of limitations and concerns, and on the daily experience of patients on SNM therapy. Although some issues may seem trivial at first, each health care worker who deals with neuromodulation therapy will recognize these issues as being an important part of followup visits in most patients.

The response rate of this survey was high at 75%. Thus, in our opinion this study provides a representative view of patient satisfaction and experience with SNM. However, there may have been selection bias, and the subjective and retrospective nature of most questions could have resulted in recall bias. Nevertheless, we believe that this study provides new, valuable information on the patient experience with SNM treatment and suggests further research questions.

Conclusion

Patients undergoing sacral neuromodulation therapy at our clinic showed a 90% satisfaction rate. Satisfaction was significantly and positively related to the patient perceived effect, number of pelvic floor comorbidities, view of yearly outpatient evaluations up and experience with the patient programmer. No direct relationship was found with patient age, gender, therapy duration or type of complaint for which SNM was offered. Of patients with additional fecal problems before SNM 48% experienced relief of the problem. Despite the high satisfaction rate regularly perceived pain and discomfort at the INS site was reported by 56% and 40% of patients, respectively. Nine of the 10 patients who reported regular pain at the INS site also reported not requiring further treatment for it. Patient perceived limitations and concerns about SNM therapy were mostly related to MRI, reimbursement and pregnancy. Overall this study shows that sacral neuromodulation is a safe, satisfactory treatment.

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Chapter 6

Current information on Sacral
Neuromodulation and Botuline Toxin
treatment for refractory idiopathic
overactive bladder syndrome: a review

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Urologia Internationalis 2010;84(3):245-53

Abstract

The overactive bladder syndrome (OAB) negatively affects the daily life of many people. Conservative treatments, such as antimuscarinics, do not always lead to sufficient improvement of the complaints and/or are often associated with considerable side effects resulting in treatment failure. In the case of failure or intolerable side effects, sacral neuromodulation (SNM) and botulinum toxin are minimally invasive and reversible alternatives. Currently, of these alternatives only SNM with InterStimTM Therapy has FDA approval for use in OAB patients. This review attempts to provide an update on the current position of SNM and botulinum toxin in the second-line management of adults with idiopathic OAB, based on the available clinical evidence concerning the efficacy and safety.

Introduction

Idiopathic overactive bladder syndrome (I-OAB) is characterized by a combination of bladder filling symptoms: urgency with or without urgency urinary incontinence, usually accompanied by frequency and nocturia [1]. Large-scale surveys in Europe and in the US estimated an OAB prevalence of approximately 16-17%, of which a third (predominantly women) also have complaints of urgency urinary incontinence [2, 3]. Frequency and urgency can be as distressing as urgency incontinence, and OAB syndrome as a whole has a strong negative impact on the quality of life [2, 4].

In 2009 the International Consultation on Incontinence (ICI) published an algorithm intended to serve as a guide for the treatment of patients with I-OAB (figure 1) [1]. Behavioural and lifestyle interventions are recommended firstly, followed by bladder and pelvic floor muscle training, or pharmacological treatment with antimuscarinics. However many patients have insufficient improvement with these treatments [4]. When conservative treatments fail after 8-12 weeks, alternative therapies should be considered [1]. These alternatives used to be invasive and irreversible surgical procedures, such as bladder augmentation or urinary diversion. Currently new and minimally invasive techniques are available such as sacral neuromodulation (SNM; recommended by ICI – level of evidence A), posterior tibial nerve stimulation (not recommended by ICI – insufficient scientific data) and intradetrusor injection of botulinum toxin (BTX) (BTX; ICI – off label treatment – level of evidence C) [1].

Because both SNM and BTX injections are increasingly being applied in clinical practice, an overview is given on the available scientific and clinical evidence on safety and efficacy. The position of SNM and BTX as second-line treatment options for adults with I-OAB is discussed.

Botulinum toxin

Introduction

BTX is a protein that is produced by the anaerobic Gram-positive bacteria *Clostridium botulinum*. Local injection of BTX leads to temporary chemical denervation and loss or reduction of nerve cell activity at the tissue. Use of BTX as a muscle relaxant is indicated for various neurological disorders, such as torticollis spasmodica or other spastic diseases of the musculoskeletal system, serious primary caudal hyperhydrosis, and for aesthetic reasons.

Among urologist there is a growing popularity of products containing BTX mostly type A in particular Botox® (Allergan, USA) and Dysport® (high-value biotech, France).

Working mechanism

The effect of BTX in I-OAB patients is based on a temporary inhibition of the neuromuscular nerve signals, which leads to relaxation of the smooth muscles in the bladder. Previously, the main effect was considered as temporary blockage of presynaptic vesicle release which decreases acetylcholine to the neuromuscular junction. Recent research shows expanded effects such as inhibited release of other transmitters (neuropeptide substance P, APT) and downregulation of the axonal expression of purinergic p2x3-and capsaicin-TPRV1-receptors of the nerve endings in the (sub)urothelium, contributing to the afferent desensitization [5]. Besides an effect on the afferent bladder signals, it is very likely that efferent nerves are also being affected. BTX decreases detrusor pressure during both the filling and the voiding phase, and may increase the post-void residual volume [5].

Figure 1: Algorithm derived from ‘evidence-based’ recommendations of the ICI from 2008

Treatment protocol

There is no standard protocol for the application of BTX. In most published trials, 100-300 U Botox or 500 U Dysport are injected at 10-30 different sites

of the bladder wall (table 1) [6-11]. Injections can be performed under local or general anaesthesia. The possibility of using no anaesthesia at all is also being tested [12]. In terms of injection technique, a comparative study showed a significantly better effect after 9 months when BTX was injected into the detrusor muscle compared to injection into the bladder suburothelium. Both detrusor or suburothelium injection in the bladder body were better compared to suburothelium injection into bladder base [13]. However injection into the bladder base reduced the urgency episodes significantly, while the other sites did not. In most trials, the trigone is not injected to eliminate risk of iatrogenic vesicoureteral reflux. However, recent studies argue against this postulation [13-15].

Dose-response studies show that low dosages (100 instead of 150- 300 U) injected into the detrusor or suburothelium, lead to a significant reduction of the side effects, but also to a reduction in the duration of the therapeutic effect and the quality of life scores [16, 17].

Table 1. Technique overview

First author	Patients				
RCT	Placebo	BTX	Dose, U	Injections	Injection site
Sahai [6]	18	16	200	20	bladder wall
Flynn [20]	7	15	200/300	8-10	detrusor
Brubaker [19]	15	28	200	15-20	detrusor
Observational					
Kalsi [8]	x	38	200	20-30	detrusor
Khan [21]	x	81	200	20	detrusor
Schmid [22]	x	220	100	30	suburothelium

Effectiveness

Currently four randomized controlled trials (RCT) have been published. The first one used BTX type B and showed significant improvements; however, the effect was of short-term (6 weeks) [18]. The other three trials used BTX type A [6, 19, 20]. Several nonrandomized, prospective open-label studies have investigated the value of BTX treatment in I-OAB patients. Unfortunately, in most studies, the patient numbers are limited (10 to 30 patients), reducing the reliability of the results. Only three studies cover relatively large groups of patients [8, 21, 22].

Comparison of all of these studies is difficult due to the differences in the methodology and parameters used. All the RCT trials and the open-label studies show promising results (table 2). Generally, around 80% of the patients treated with BTX experience improvement. The number of voids per day decreases on an average with 12-53%, urgency episodes per day

with 28-70%, and incontinence episodes per day with 35-87%. The maximum cystometric capacity increased by an average by 45%. The Impact Questionnaire-Short Form score decreased by a mean of 54-57%, and the Urological Distress Inventory score decreased with a mean of 38-64%. Almost all parameters used in the RCT trials showed significant improvements compared with placebo.

Long-term follow-up trials show an average recurrence rate of 27-66%, with a mean duration of clinical improvements of 6-14 months and a mean interinjection interval of 14- 23 months (table 3). While some patients have a temporary effect, some patients seem to be 'cured' after one or two treatments. Khan et al. showed a cure rate of 10% and Schmid et al of 38% after the first injection while another 33% showed a 'permanent' good effect when combining the treatment with anticholinergics [21-22].

A study on the satisfaction of patients who underwent BTX showed that among 38 patients with neurogenic or I-OAB, 93% of the patients would undergo the procedure again [23]. Overall, patients were satisfied giving the treatment an average score of 6.9 in a satisfaction scale between 0 and 10. Furthermore, 90% of the patients reported clear improvement in their voiding situation, and 6.7% had adverse events.

Table 2. Effect of BTX

First author	Follow-up	General improvement	Voids/day	Urgency/day	IE/day	100% continence	Pads/day	24-hour pad weight	MCC	IIQ-7 score	UDI-6 score
Sahai [6]	12 weeks		-40	-70	-70	50			45	-57	-53
Flynn [20]	6 weeks		-12		-57		-50	-45	x	-67	-38
Brubaker [19]	12 months	79			-87						-39
Kalsi [8]	16 weeks	79	-18.20	-28.10	-35				46		
Khan [21]	4 weeks									-54	-64
Schmid [22]	9 months	86	-53			85	-90		63		

Figures indicate percentages, unless otherwise indicated. IE = Incontinence episodes; MCC = maximum cystometric capacity;

IIQ-7 = Impact Questionnaire-Short Form; UDI = Urogenital Distress Inventory-Short Form; x = no significant difference vs. placebo

Table 3. Reinjections

First author	Follow-up	Recurrence rate, %	Duration of clinical improvements	Interinjection interval	"Cure", %
Sahai [6]	9 months		6 months		
Flynn [20]	-	-	-	-	-
Brubaker [19]	13 months	66	307 days		
Kalsi [8]	27 months		13.86 months	1.9 years	16.7 (> 27 months)
Khan [21]	2,8 years	57		14 months	10 (> 14 months)
Schmid [22]	7 years	26.8	9 months	13.5 months	38

Safety

BTX is generally well tolerated. No major complications were noted in any RCTs or large open-label studies (table 4). The most common adverse events were high post-void residual (19-43% depending on criteria used) requiring clean intermittent self-catheterization (4%-43% depending on the criteria used) and urinary tract infection (10-43%) [6, 22, 24]. However, this incidence seems to be dose dependent. A dose-effect study among 313 I-OAB patients who received either placebo, 50, 100, 150, 200, or 300 U BTX showed an incidence of post void residual (>200cc) of 0%, 12.5%, 14.5%, 20.0%, 28.8%, 27.3% respectively [17].

Aside from local side effects of BTX, muscular weakness as a result of unintentional dissemination of the toxin outside the target area may also occur. Between 2003 and 2007, four adverse events were reported in a Danish registry after BTX treatment for urological interventions [25]. Although the real incidence cannot be deduced from these data, it is estimated around 10/10,000 interventions. All adverse events involved muscle weakness, two were throughout the whole body, one in the arms and one in the thoracic muscles necessitating artificial respiration. The latter occurred in a patient with neurogenic bladder dysfunction. In general, serious side effects can occur such as problems with speech, swallowing (dysphagia) or breathing. Mortality after BTX treatment has been reported before, although rarely and only in patients with known neurological disease. Because of this, manufacturers of products containing BTX, after consultation with European regulators, issued a warning about the safety in France, Denmark, Spain, Germany and the UK [25-29].

The safety of repeated injections is rarely or not described. Although the impact of repeated injections on the bladder compliance is unknown, no change in compliance has been demonstrated after up to three injections

[30]. Although BTX in its present form has a small antigenic potential and some immune resistance has been reported on I-OAB and BTX, an immune response can occur after repeated injection, and ultimately even tachyphylaxis [10, 31]. Schulte-Baukloh et al reported the presence of BTX-antigen among 8 out of 25 patients after two injections [31]. Further analysis showed a possible correlation between the presence of BTX-antigen and the reduction in treatment effect. To minimize the risk of immune resistance and response as much as possible, it is advisable to wait at least 3 months between injections, and to choose the lowest dose that will achieve the desired clinical effects [32].

Table 4. Most common adverse events associated with BTX therapy

First author	UTI, %	AUR, %	Mean PVR, ml	De novo PVR, %	CIC, %
Sahai [6]	20.50	0	44 => 51	37,5 (>150 ml)	37.5
Flynn [20]	13	ND	25 => 107	26,6 (>200 ml)	6.7
Brubaker [19]	44	ND	ND	43 (>200 ml)	32
Kalsi [8]	-	-	-	-	-
Khan [21]	15	ND	ND	43 (>100 ml)	43
Schmid [22]	10	4 (>400ml)	21 => 85	19 (>150 ml)	4

UTI = Urinary tract infection; AUR = acute urinary retention; PVR = post-void residual urine; CIC = clean intermittent catheterization.

Sacral neuromodulation

Introduction

SNM comprises the stimulation of the sacral nerves that innervate the bladder, urethral sphincter and pelvic floor muscles. Stimulation electrodes are placed at the level of the third sacral nerve (S3) and connected to a electrical stimulator that is implanted. The implantable nerve stimulator (INS) that is being used for SNM therapy uses the Interstimtm-technology (Medtronic, Minneapolis, Minn., USA).

The indications for SNM therapy are I-OAB, nonobstructive urinary retention, faecal incontinence and chronic constipation.

Working mechanism

The precise mechanism of action of SNM is still not entirely clear. It is assumed that SNM affects the 'neuroaxis' at various levels and restores the balance between excitatory and inhibitory regulation at various locations within the peripheral and central nervous system [33]. Furthermore, SNM may also activate the afferent bladder somatosensors which run to the micturation centre in the brain stem, and/or activate the hypogastric sympathetic nerves [34].

Treatment protocol

Before implanting the INS, a screening test is performed to assess the clinical effect of sacral nerve stimulation. There are two test protocols. The percutaneous nerve evaluation (PNE) test uses a non-anchored test lead placed into the S3 foramen and connected to an external stimulator. The test period extends between 4 and 14 days, after which the test lead is removed. The procedure is usually done in an outpatient setting. The overall response rate for PNE is around 55% [35, 36]. Lead migration is considered the main factor leading to false negative results [37, 38].

The definitive lead electrode has self-anchoring tines that reduce the risk of migration. These leads can also be used for testing. The lead is usually placed into the S3 foramen under general anaesthesia (although some centres also use local anaesthesia in an outpatient setting), correct positioning is guided with fluoroscopy, the lead is subcutaneously tunnelled and connected subcutaneously to a temporary extension lead that exits the skin and is connected to an external pulse generator. This procedure enables test periods of up to 3-4 weeks. If the patient has a good response during the test, the present lead is connected to an internal nerve stimulator. This procedure is done under local or general anaesthesia. Because of the decreased risk of migration and the longer test duration, this test has a higher response rate. According to a study of Kessler et al. prolonged screening with the tined lead has a response rate of 67% compared to 43% during PNE testing [39]. The costs for test protocol with the tined leads are much higher compared to the PNE test. Currently the use of either one of the two screenings option is arbitrary.

Effectiveness

There is convincing evidence for the success of SNM with the Interstim technique for refractory I-OAB. Three RCTs (two on patients with urgency incontinence and one on patients with urgency frequency) [35, 36, 40] and many articles on long-term observational studies have been published [41-45]. Good clinical response is reported between 64 and 88% of all patients. All parameters reported, showed significant improvement compared to the placebo group: a 23-46% decrease in the number of voids per day, 44-77% increase in the average voided volume, 56-90% decrease in incontinence episodes per day, 64-100% decrease in pads and 39% increase in maximum cystometric capacity (table 5).

A 5-year follow-up study on 121 patients with refractory I-OAB showed persistence of the clinical success in the long-term: 84% of the patients with urgency incontinence and 71% of the patients with urgency/frequency who had a successful outcome 1 year after implantation continued to have a

successfully outcome after five years [43]. A study on the tined lead procedure in 21 patients with I-OAB showed clinical success after an average of 15.5 months around 90% [45]. In all reported studies, clinical success is defined as a > 50% improvement in one of the relevant urinary voiding parameters.

Satisfaction and quality of life scores after SNM have also been studied. Cappellano et al. showed a significant improvement in the quality of life score in patients with urgency incontinence who underwent SNM from a mean score of 34 to 76 [46]. At 18 months follow-up they were asked whether they would undergo this treatment again. 90% responded yes and 100% would recommend it to a relative or friend. Foster et al. asked 49 patients with urgency incontinence on their satisfaction with SNM treatment. The majority of the patients were satisfied (84%) and would “do it all over again” (80%) [47].

Table 5. Short-term results of treatment with sacral neuromodulation or with placebo among patients with overactive bladder.

First author	Follow-up, months	General improvement, %	Voids/day, %	Voided vol., %	IE/day, %	Proportion of group with 100% continence, %	Pads/day, %	MCC, %
Weil [36]	6				-90	56	-92	39
Schmidt [35]	6				-73	47	-82	
Hassouna [40]	12	88	-46	77				
van Kerrebroeck [43]	49		-23	79	-56		-64	
van Voskuilen [44]	64,2	64						
Sutherland [42]	22	69	-35		-88	50	-100	
Voskuilen [45]	15,5	80	-38	44	-65			
Hijaz [41]	16	75						

Safety

Adverse events are usually related to the implant procedure, the presence of the implant or of undesirable stimulation. The most common adverse event reported is pain at the implant site. The occurrence in most studies varies

between 3 and 42% (table 6) [22, 36, 40-45]. Other adverse events reported are lead migration (1-21%), bowel dysfunction (4-7%) and infection (4-10%). Technical improvements throughout the years have decreased the incidence of adverse events significantly. Two important improvements were the introduction of tined leads (leads with hooks) and the gluteal placement of the INS instead of abdominal. Ever since, both the incidence of adverse events and the reoperation rate per implanted patient have decreased (Fig. 2) [44].

The majority of adverse events do not require surgical intervention. Decreased efficacy because of to electrode migration and undesirable stimulation can easily be solved by reprogramming of the INS. A retrospective analysis among 83 implanted patients with a reduced response or complications, such as pain at the INS site, showed that 18% of the cases could be helped conservatively [42]. Furthermore, the incidence of adverse events is lower with the new tined leads in comparison with non-tined leads (28% and 73%, respectively) [42]. A study among 235 patients confirmed that tined leads migrated less often, which occurred among 5 patients (2.1%) [48]. The available data indicate that the further development and optimization of SNM limits the risk of adverse events.

Table 6. Most frequent adverse events associated with SNM therapy

First author	Pain at implant site, %	Lead migration, %	Other pain, %	Bowel function disturbance, %	Infection, %
Weil [36]	42	21	18 (leg)	5	
Schmidt [35]	33	13		5	4
Hassouna [40]				4	
van Kerrebroeck [43]	19	5	7.9 (lead site)	7	8
van Voskuilen [44]	28	7	43 (pain or discomfort)		4
Sutherland [42]	15			5	10
Voskuilen [45]	7	3	3 (leg stimulation)		
Hijaz [41]	3	1			5

Other considerations, SNM versus BTX

Both SNM and BTX have similar effectiveness rates and both have relatively small, treatable and nonpermanent side effects. When having to choose between SNM and BTX, urologists may rely on other data such as long term safety and effect data and cost-effectiveness data.

Recently, three cost-effectiveness studies have been published on SNM versus BTX, all three in the form of abstract. Arlandis and colleagues compared SNM with BTX from a public health point of view in Spain, Leong's group compared SNM with BTX from a hospital point of view in the Netherlands, and Leng's group compared SNM with BTX from a public health point of view in North America. Both Arlandis' group and Leong's group concluded that SNM is cost-effective compared with BTX, whereas Leng and co-workers concluded that BTX treatment dominated SNM (more effect at less cost), even after repeated sensitivity analysis. More data on these abstracts is required to explain these contradictory results.

Another way of choosing between SNM and BTX is a patient-specific approach. Patients with comorbidities in the pelvic region may be better off with SNM. Some studies have shown that other urinary voiding disorders such as urinary retention are present in 1 out of 3 I-OAB patients, and that 26% of women with lower urinary tract disorders also have faecal incontinence [49, 50]. SNM is also approved for the treatment of urinary retention, faecal incontinence and chronic constipation [51, 52]. Recent studies have shown that patients can experience relief for both OAB and other pelvic floor disorders at the same time when treated with SNM [53, 54]. On the other hand patients who need regular MRI scans may be better off with BTX treatment, because so far SNM is not MRI proof.

Figure 2. Average number of adverse events and surgical revision per implanted patient.[44]

Conclusion

OAB has a significant impact on the quality of life in both men and women. If conservative treatments are not effective, then there are various second-line treatment options available. SNM and BTX therapy are the most commonly used. Both of these treatments have similar effectiveness rates

and both have relatively small, treatable and nonpermanent side effects. Cost-effectiveness analyses have shown contradictory results. BTX treatment has not yet been officially approved for urological disorders due to lack of long-term effect and safety data and lack of consensus regarding the proper dosage and the injection method. However, all BTX studies on patients with I-OAB are promising and point to the direction of approval. Until then, SNM is the only minimal invasive option approved for I-OAB patients who are refractory to conservative treatment.

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Chapter 7

Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder

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British Journal of Urology International 2011;108(4):558-64

Summary

Objectives: To assess and compare the costs and effects value of either starting with sacral neuromodulation (SNM) or botulinum toxin A (BTX) treatment in patients with refractory idiopathic overactive bladder from a societal perspective.

Materials and Methods: An economic model comparing SNM with BTX was developed. A clinical relevant effect (i.e. success) was defined as 50% or greater reduction in incontinence episodes or urgency frequency symptoms. Information on the clinical effectiveness of the two treatments and on the course of the disease with the two treatments were based primarily on published literature and, when required, on expert opinion. Both treatments were assumed to be performed under general anesthesia and, for SNM treatment, first-stage timed lead test was used. All costs were based on national data from the year 2008. Analyses from the societal perspective were conducted for a 5-year duration. Costs were discounted at 4% and effects at 1.5%. In addition, different modelling scenarios were used to determine if any changes in the results obtained.

Results: Starting with SNM resulted in a higher quality adjusted life year (QALY) gain (difference of 0.23) and a higher cost (difference of €6,428) compared to starting with BTX. The corresponding incremental cost-effectiveness ratio was €27 991/QALY. The probability of this ratio being cost effective (e.g. under €40 000/QALY) is 88%. SNM starts to be cost-effective after four years. SNM was not cost-effective in some other scenarios, such as when BTX was conducted under local anaesthesia or when percutaneous nerve evaluation or bilateral testing was used for SNM.

Conclusions: Starting with SNM, treatment is cost-effective after 5 years compared to BTX. However, in some scenarios, such as the use of local anaesthesia for BTX treatment and SNM percutaneous nerve evaluation or bilateral test, SNM was not cost-effective.

Introduction

Overactive bladder syndrome (OAB) is a combination of urinary symptoms and is defined as urgency with or without urge incontinence, usually with frequency and nocturia [1]. Estimated prevalence is between 12-17% of which one-third of cases experience urgency urinary incontinence [2-5]. This syndrome significantly impacts the patient's health-related quality of life (HRQL) and the costs for OAB management are estimated between €250 million and €4.2 billion in selected European countries [6-9].

Treatment of patients with OAB is complex and international guidelines suggest lifestyle interventions, pelvic floor muscle training, bladder retraining and medication (anti-muscarinics) as first line treatment options [1]. When these therapies fail or are intolerable for patients, other more invasive options are available. Sacral neuromodulation (SNM) and Botulinum toxin A (BTX) are two minimal invasive treatment options that have shown positive results in clinical trials and should be considered before more invasive surgery, such as bladder augmentation [10-13].

Besides clinical effectiveness, cost-effectiveness should also be considered when making a choice between SNM and BTX. Cost-effectiveness analysis compares the combination of health outcomes and resource costs for different health technologies. It applies clinical outcomes and data on resources from clinical trials or when these resources are unknown or insufficiently documented through modelling techniques [14]. Previously, it has been shown that BTX is cost-effective compared to conservative treatment [15]. SNM has not been compared to conservative treatment, although, in a cost-consequence study, Aboseif et al. showed that drug, diagnostic and outpatient visit costs were significantly reduced after SNM treatment [16].

The present study aimed to assess and compare the costs and effects value of either starting treatment with SNM or BTX in patients with refractory idiopathic OAB from a societal perspective.

Material and Methods

Decision Model

The cost-effectiveness analysis from a societal perspective in the Netherlands was performed using a probabilistic Markov analytic model. The study population consisted of patients with refractory idiopathic OAB who failed conservative treatment and the analysis was conducted over 5 years. The model compares two different treatment pathways: one that starts with BTX and the other with SNM including its test procedures. If a patient failed a therapy then the next successive treatment option according to treatment

transition rates specified in the model figure was given (Fig 1). In this case it was assumed that 75% of the failures would receive the alternative treatment (either SNM or BTX) and 25% would receive no further treatment. If a patient failed both treatment options then no further treatment was offered. Success would be followed by repeat with the same therapy when necessary.

The decision model was constructed and analyzed with Microsoft Office Excel software (Microsoft Corp., Redmond, WA, USA).

Figure 1. Model figure

Parameter estimates:

Parameter estimates are based on the literature data if available (Table 1). The screening test used for SNM treatment was the first-stage timed lead test. The success rate was estimated at 75% and the 1-year success rate at 90% [17, 18]. The yearly drop-out rate for SNM was 4.3%, which was based on data of two previous long-term SNM studies [12, 18]. Time interval for SNM retreatment in the form of battery replacement as a result of depletion was estimated at a mean (range) of 7 (5-10) years preceded by a period of 3 months with loss of effect (average time between start complaint, outpatient clinic and actual battery replacement). The adverse event rates for each patient undergoing SNM treatment included 16% for surgical revision as a result of pain or loss of effect and 7.5% for removal of system as a result of pain, infection or loss of effect [18].

The success rate for BTX treatment was estimated at 79% [19]. Because data on the yearly drop-out rate for BTX is lacking, an assumption was made that BTX drop-out rate is equal to SNM drop-out rate. The adverse event rates for each patient undergoing BTX was estimated at 38% for urinary retention requiring intermittent self catheterization and 41% for urinary tract infection requiring antibiotic treatments [10, 19, 20]. In addition, expert opinion was obtained through a survey that was sent to 13 urologists in the Netherlands who perform BTX and SNM to estimate effect and treatment duration. On the basis of this survey, it was assumed that treatment effect lasted for 9 months, patients were fully symptomatic for 3 months and retreatment was performed every 12 months.

Cost inputs

The cost analysis considered direct costs to the society in the Netherlands in 2008 in Euros. Costs were accounted for healthcare resource consumption during pretreatment, treatment, symptomatic periods, follow-up treatment, treatment of adverse events, and treatment after failure. On the basis of common practice in the Netherlands, both SNM test and definitive implantation procedure were performed in an operating room or at an ambulatory surgical center, with procedures each lasting 45 minutes, followed by inpatient stay for the definitive implantation. On the basis of common practice in the Netherlands, the BTX procedure included the use of 200 U of Botox® (Allergan, Irvin, CA, USA) and was performed at an operating room or at an ambulatory surgical center, which took 30 min, followed by inpatient stay. SNM adverse events costs included costs for the use of antibiotics, removal and replacement of lead or implantable pulse generator device and inpatient stay. BTX adverse events costs included catheter use, urine culture and antibiotics. Unit costs for treatment and concomitant medications, investigations, surgical procedures and disease management were obtained from published sources [21]. These costs were then multiplied by rates of resource use consumption, aiming to derive direct costs for the initiation and each outcome of treatment (table 2). A discount rate of 4% per annum was applied to account for the present value of the future stream of costs [22].

Table 1. Input parameters per patient

Variable	Value	Range
Basecase scenario		
Utility value improvement	0.95	0.90-1.0
Utility value no improvement	0.73	0.48-0.98
Success rate SNM test	75%	65 - 80
SNM Battery replacement	1/7 years	5 – 12
SNM Loss of effect period	3months/7years	0 - 5
SNM Surgical revision	16%	15-33
SNM Removal of system	7.5%	4-8
Initial success BTX	79%	76 – 95
BTX Retreatment rate	1/12months	7 – 14
BTX loss of effect period before retreatment	3months/years	0.5 – 4
Urinary retention requiring CIC	38%	19.3-43
Urinary tract infection	41%	6.5-44
Yearly drop-out rate SNM or BTX	4.3%	SD=0.0043
Pads use 'improvement'	1/day	
Pads use 'no improvement'	7/day	
SNM pre-procedure costs (€)	278	21 – 347
1 st stage tined lead procedure (incl. material) costs (€)	3445	2339 – 3744
2 nd stage tined lead procedure (incl. Interstim 1) costs (€)	9150	7862 – 9498
SNM surgical revision costs (€)	2590	1483 – 2889
SNM surgical removal/replacement costs when infected (€)	11,448	8874 - 12,144
BTX pre-procedure costs (€)	290	22 - 362
BTX procedure (incl. 200 U BTX) costs (€)	1564	117 – 1839
Urinary Retention costs (€)	449	34 - 561
UTI costs (€)	100	8 – 125
Out-patient follow-up costs (€)	70	5 - 88
Pads costs (€)	0.45	0.23 - 1.83
Other scenarios		
PNE test procedure (incl. material) (€)	439	182 – 523
2 nd stage tined lead procedure with Interstim 2 (€)	11,346	8772 - 12,042
Bilateral 1 st stage tined lead procedure (incl. material) (€)	6491	4647 - 6989
Local anesthesia 2 nd stage tined lead procedure (€)	8699	7828 – 8934
Local anesthesia BTX procedure (including BTX) (€)	839	492 - 933

BTX, botulinum toxin A; CIC, clean intermittent catheterization; PNE, peripheral nerve evaluation; SNM, sacral neuromodulation.

Outcomes

Treatment outcomes included success (> 50% improvement in number of leakages, pad use, and number of voids or volume per void) or failure (< 50% improvement). The utility values were 0.73 for incontinence episodes or no treatment improvement and 0.95 for no incontinence or treatment improvement [23]. Quality adjusted life years (QALYs) were discounted at an annual rate of 1.5% per year [22]. The incremental costs were compared with the incremental effectiveness (e.g. QALYs) to obtain incremental cost-

effectiveness ratios (ICERs) for SNM versus BTX. An ICER of less than €40 000/QALY was considered cost-effective, which is a well accepted threshold to define cost-effectiveness [24].

Different scenarios/ one-way sensitivity analysis

To study the impact of treatment period, the duration of the study was shortened to 1, 2, 3, 4 and lengthened to 10 years, assuming the effects and costs would stay the same. On the basis of the most common situation in the Netherlands, the base case scenario for both SNM and BTX in the present included the use of operation room or ambulatory surgical centre followed by inpatient stay and the use of the tined lead procedure (TLP) as SNM test and Interstim 1 as the SNM battery model. However, different hospitals use different type of devices for SNM therapy and have different protocols regarding use of operation room or inpatient stay. Therefore, several options were evaluated: use of peripheral nerve evaluation (PNE) (response rate 55%); use of bilateral PNE; use of bilateral TLP; use of battery model Interstim 2; SNM procedure placed under local anaesthesia in operation room without inpatient stay; BTX procedure performed under local anaesthesia outside the operation room without inpatient stay; and both procedures under local anaesthesia [13, 25].

Because proper utility value for urinary incontinence is lacking different values (e.g. 0.80, 0.85, 0.90, 0.94) were used to determine its impact on the results. The yearly drop-out rate for BTX is still unknown. Therefore different drop-out rates, e.g. 2% and 6%, were used to determine any impact on the results obtained.

Uncertainty of the input parameters was addressed in a second-order Monte Carlo simulation with 1000 random draws and one-way sensitivity analyses to assess the robustness of the model [26]. For all analyses, the probability of cost-effectiveness was determined by drawing cost-effectiveness acceptability curves.

Results

The results of the CE analysis are given in Table 2. The base case of the cost-effectiveness analysis over a 5-year period showed 4.95 QALYs for SNM compared to 4.72 for BTX. Additional effectiveness for SNM was 0.23 (range 0.11-0.35) QALYs per patient. The 5-year costs were €25 780 for SNM and €19 353 for BTX, resulting in additional costs of €6,428 (95% CI, €3131-11 142) per patient for SNM. The corresponding ICER was €27 991/QALY. The cost-effectiveness acceptability curve shows that the probability of this ratio to be cost-effective (e.g. at a maximum of €40.000/QALY) is 88% (Fig. 2).

Varying durations of between 1 and 10 years showed that, after 1 year, SNM is inferior to BTX. However, the ICER drops from €84,660/QALY in year 2 to €14,493/QALY in year 10 (Fig. 2 and Table 2). Starting treatment with SNM becomes cost-effective (ICER > €40,000) after 4 years.

Sensitivity analyses showed that over a 5-year time horizon the ICER remained below the €40,000 threshold for cost-effectiveness when SNM was performed under local anaesthesia whereas BTX was not, when the drop-out rate was changed to 2% or 6% and when the utility for incontinence or no improvement was changed to 0.80 (Fig. 3-6 and Table 2). SNM was not cost-effective (ICER > €40,000) in all other scenarios, such as when BTX was conducted under local anaesthesia or when PNE or bilateral testing was used for SNM (Fig. 3-6 and Table 2).

Table 2. Results base case and sensitivity analyses

	SNM therapy		BTX therapy		Incremental		iCER €/QALY
	Cost €	QALY	Cost €	QALY	Cost €	QALY	
1 year	20,105	1.66	9,359	1.66	10,745	-0.01	SNM dominated
2 year	21,444	2.51	11,524	2.39	9,920	0.12	84,660
3 year	22,840	3.34	14,173	3.18	8,666	0.16	54,291
4 year	24,288	4.15	16,793	3.96	7,495	0.20	38,327
5 year (Base case scenario)	25,780	4.95	19,353	4.72	6,428	0.23	27,991
6 year	27,307	5.73	21,851	5.47	5,456	0.26	20,827
7 year	32,192	6.49	24,289	6.20	7,903	0.29	27,010
8 year	33,763	7.24	26,848	6.92	6,916	0.32	21,502
9 year	35,347	7.98	29,194	7.63	6,153	0.35	17,623
10 year	36,878	8.69	31,485	8.32	5,393	0.37	14,493
PNE test	22,264	4.72	19,189	4.72	3,075	0.00	3,219,121
Bilateral PNE test	22,775	4.72	19,223	4.72	3,552	0.00	3,717,822
Interstim 2	31,111	4.95	19,406	4.72	11,706	0.23	50,974
Bilateral 1 st stage (Interstim 1)	30,366	4.95	19,599	4.72	10,767	0.23	46,888
Bilateral 1 st stage (Interstim 2)	35,696	4.95	19,652	4.72	16,045	0.23	69,870
Local anesthesia (SNM only)	24,748	4.95	19,304	4.72	5,444	0.23	23,707
Local anesthesia (BTX only)	25,376	4.95	13,978	4.72	11,398	0.23	49,634
Local anesthesia (SNM and BTX)	24,343	4.95	13,929	4.72	10,414	0.23	45,350
Drop out rate 2%	25,765	4.95	19,196	4.79	6,569	0.17	39,265
Drop out rate 6%	25,791	4.95	19,463	4.68	6,328	0.27	23,121
Utility 'no improvement' 0.80	25,780	5.03	19,353	4.87	6,428	0.17	38,572
Utility 'no improvement' 0.85	25,780	5.09	19,353	4.97	6,428	0.12	52,837
Utility 'no improvement' 0.90	25,780	5.15	19,353	5.08	6,428	0.08	83,847
Utility 'no improvement' 0.94	25,780	5.20	19,353	5.16	6,428	0.04	158,058

BTX, botulinum toxin A; CIC, clean intermittent catheterization; PNE, peripheral nerve evaluation; SNM, sacral neuromodulation.

Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder.

Figure 2. Acceptability curves of different follow-up years

Figure 3. Acceptability curves of different devices.

Figure 4. Acceptability curves of different procedure protocols.

Figure 5. Acceptability curves of different drop out rates BTX.

Figure 6. Acceptability curves of different utility values.

Discussion

According to our analysis, a similar number of patients are successfully treated after 5 years, independent of starting treatment with either SNM or BTX. However because of the repeated loss of effect and thus loss of QALY between BTX reinjections, the overall QALYs gained after 5 years were lower for BTX than for SNM. With respect to costs, BTX treatment is cheaper, despite the need to repeat the treatment on a yearly basis. The ICER was €27 991, which is below the threshold used in most industrialized countries, implying that starting with SNM treatment is cost-effective compared to BTX.

The first publication on cost-effectiveness comparing SNM with BTX treatment concluded that BTX is more cost effective than SNM over a 2-year period [23]. Considering the retreatment rate for Botox and the stable long-term efficacy of SNM, we consider that a 2-year period is too short to make an adequate comparison [12]. Therefore a 5-year duration was used in the present study and the results obtained show that SNM becomes cost effective (ICER < €40.000) from the third treatment year onward.

Studies comparing SNM and BTX in terms of long-term effectiveness and complication rate, as well as their effect on the HRQL, are lacking. In prospective studies, patients with SNM have been followed for 5 years and with BTX for 1 year. In retrospective studies, SNM patients have been followed for more than 11 years and BTX patients for seven years [27, 28]. Therefore, we had to make some essential assumptions. Our model

extrapolates the effect rate, the utility values and the yearly drop-out rate between 1 and 10 years by keeping them constant, which may not be an accurate representation of the real treatment benefit. Sensitivity analysis shows that starting treatment with SNM is cost-effective irrespective of the BTX drop-out rate.

The utility value for OAB is hard to determine and is dependent on the type of HRQL questionnaire used. This is because most non-disease-specific HRQL questionnaires focus on physical problems, whereas OAB gives mostly a psychological problem. A study evaluating the utility value among patients with OAB by using the Kings Health Questionnaire found an average utility value of 0.941, with a small range of 0.887 to 0.996 [29]. Another study that used EQ-5D found an average utility value of 0.85 for patients with OAB [7]. The utility value assigned in the present study for incontinence/no improvement was based on a study by Siddiqui et al., which in turn was based on a study on women with stress incontinence using the Health Utility Index 3 questionnaire [23]. We realize that this is not a true representation for OAB patients; however, to our knowledge no other relevant utility values are published. One-way sensitivity analysis using different utility values showed that employing a utility value of 0.85 or higher for OAB results in an unfavourable situation for starting treatment with SNM compared to starting treatment with BTX (e.g. ICER > €40.000).

The present study gives an indication of the long-term financial burden from a societal point of view. However, the costs for surgery and for the devices may vary significantly between countries and even between hospitals within one country. Furthermore, there are inevitable differences from hospital to hospital in the management of idiopathic OAB with BTX and SNM. Sensitivity analysis shows that, in settings where all SNM patients are being tested with either PNE, bilateral PNE, bilateral TLP or when using Interstim 2 instead of 1, starting with SNM treatment is not cost-effective. The main reason that the use of PNE test is not cost-effective is a result of its lower response rate, which in turn results into lower QALY value [13, 25]. Starting with SNM treatment is also not cost-effective under the scenario where the BTX procedure is performed under local anaesthesia, whereas SNM is not, or when both treatments are performed under local anaesthesia.

Further (comparative) studies on the effectiveness and complication in the long-term, and their effect on the HRQL for both SNM and BTX, have to be conducted aiming to further assess the cost-effectiveness.

Conclusion

In conclusion, starting with SNM compared to starting with BTX for patients with idiopathic OAB is cost-effective over a period of 5 years. However, in some scenarios, such as the use of local anaesthesia for BTX treatment and SNM PNE or bilateral test, SNM was not cost-effective. Further sensitivity analysis shows that more information is necessary to determine whether the cost-effectiveness conclusion is still valid. Comparison studies of these two treatments options with respect to long-term effectiveness, complication rates and their effect on the HRQL are needed.

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A black and white photograph of a rocky coastline. The image shows a steep, rocky cliff face on the right side, with waves crashing against its base. The water is turbulent, with white foam from the waves visible. The sky is a uniform light gray, suggesting an overcast day. The overall tone is dramatic and naturalistic.

Chapter 8

General Discussion and Future Perspectives

Since the late 1980's when Tanagho et al. developed sacral neuromodulation therapy, continuing research has evolved this treatment into a minimally invasive, safe and effective treatment option for patients with chronic lower urinary tract dysfunction, including urgency incontinence, urgency-frequency, and non-obstructive urinary retention [1-4]. Currently an increasing number of patients are being treated with this therapy worldwide, including patients with faecal incontinence and constipation [5-8].

This thesis has mainly focused on finding ways to improve SNM therapy among patients with urological indications.

Battery improvement

Patients presenting with pain at the implantation site and not being able to undergo an MRI scan are important issues for SNM therapy. In the satisfaction study half of the patients reported experiencing pain at the battery implant site. This corresponds with other publications [9, 10]. Not being able to undergo an MRI-scan is one of the most common concerns patients have with SNM therapy, and is often neglected by physicians. According to the guidelines of the manufacturer, the system is not MRI proof. Little is known about the consequences of undergoing an MRI-scan, so it is discouraged by the manufacturer. The basis for this policy is the potential hazards such as dislocation of the IPG and leads, heating of the leads and damage to the IPG. However, two recent studies reported reassuring results on patients with Interstim therapy that underwent 0.6 and 1.5 Tesla MRI of brain, cervical spine and even the pelvis [11, 12]. In total 17 patients were described and all but one showed no side effects or failures after MRI. Only the first patient in the Chermansky et al. study had an IPG failure. In this patient the magnetic switch on the IPG was not switched off [11]. This issue may be resolved as the manufacturer is designing an MRI-compatible device.

In 2006, Medtronic developed a smaller battery model, the Interstim II, which is just a little bigger than a 2 euro coin. Another improvement of this model is that there is no connection piece needed to connect the lead to the IPG, which could flip the IPG. This could reduce the incidence of pain at the IPG site, but there is not yet scientific data to confirm this. A disadvantage of the current IPG is that it is not rechargeable, so replacement is on average needed every 7 to 8 years for the Interstim I and 5-6 years for the Interstim II. Rechargeable devices could resolve this burden in the future.

Setting improvement

Documentation about stimulation parameters (pulse width, amplitude and frequency) and their effect on the clinical outcome among urology patients is limited. The settings of the battery that is currently used are based on early animal models [13, 14]. In this thesis we have shown that changing the pulse rate (5Hz, 10Hz, 20Hz or 40Hz) could improve clinical outcome in some patients. Although no predefined setting could be demonstrated to work for all patients, no association was found with the type of complaint of the patient (OAB or urinary retention). It is currently unknown if this is inherent to the treatment or due to differences in patient characteristics or even lead position. In addition, pulse width could also play a role.

Dudding and colleagues performed a similar study on patients with faecal incontinence [15]. Of 12 patients, 6 showed a subjective improvement after increasing the pulse-rate from 14 to 31Hz and 2 after lowering the pulse-width from 210 μ s to 120 μ s. Lower frequency (7.5Hz) or higher pulse-width (450 μ s) did not result in clinical improvement.

A recent study among healthy cats showed that the optimal pulse-rate for achieving maximum inhibition of isovolumetric bladder contraction was 7.5 and 10 Hz for stimulation at the dorsal penile nerve, the pudendal nerve and S1 sacral nerve, however only with relatively high intensity. Only stimulation of the dorsal nerve of the penis could also achieve similar results with 5 Hz and lower intensity [16]. A potential explanation for this is the more specific nerve stimulation due to convergence of afferent nerve fibres, when moving proximally from dorsal nerve of the penis to the pudendal nerve to the S1.

Other stimulation sites

With sacral neuromodulation, nerve fibres are stimulated that run in the vicinity of the third sacral foramen. It is still unknown which nerve fibres need to be stimulated for SNM to work and therefore the exact working mechanism of SNM is still a matter of speculation and theories. Recent studies with functional MRI and PET scans showed that sacral neuromodulation results in cortical changes in the brain presumably by stimulating the afferent nerve cells rather than the efferent nerve cells [17, 18]. Current opinion on the mechanism of action is that SNM reorganises the spinal reflexes and regulates cortical activity [19]. Other approaches to stimulate these spinal reflexes and cortical activity are being tested. Pudendal nerve stimulation stimulates fibres that enter the sacral roots S2 – S3 – S4 [20-22]. Clinical results are encouraging and some researchers consider this as the rescue stimulation for SNM failures [20, 23]. Percutaneous Tibial Nerve Stimulation is another minimally invasive treatment that is currently under investigation. This treatment shows similar

short term results as SNM, however long-term studies are still lacking [24, 25]. Another approach that can possibly be used in the future is the “laterograde” approach for stimulation at the level of the lumbar spine [26]. More studies on the PTNS and the lumbar spine approach would have to be conducted.

Cost-effectiveness

At the moment SNM and Botulinum toxin injection are two treatment options for patients with urgency incontinence or urgency-frequency who are refractory to conservative treatment. While both have similar short-term results, the initial and long-term costs are very different. This has led to studies comparing these two treatment options. Siddiqui et al. found that after 2 years Botulinum toxin treatment was more cost-effective than SNM [27]. This result was probably biased by a follow-up that was too short. In the cost-effectiveness study of this thesis, where we compared SNM to Botulinum toxin treatment, SNM became cost-effective after 4 years and continued to be cost-effective until the maximum follow-up period of 10 years. A similar study by Arlandis confirms this result [28]. However, it should be noted that in our study this was only in the base case scenario (which includes both treatments being performed under general anaesthesia and the use of first stage tined lead test for SNM treatment) or when SNM was performed under local anaesthesia while Botulinum toxin treatment was performed under general anaesthesia. For all other scenarios cost-effectiveness was not shown.

Even though SNM is cost-effective compared to Botulinum toxin therapy, further improvement of SNM is still needed. The costs would be less, for instance, if there are less adverse events and if the effectiveness could be increased due to patient selection optimisation. Up to now, predictive factor studies for treatment outcome with sacral neuromodulation have not found an absolute predictive factor [29-31]. Trial stimulation is considered the only reliable way of choosing the right patients. Therefore trial stimulation is offered to every patient eligible for sacral neuromodulation before proceeding to the permanent battery implant.

Psychiatric history has been thought to be a negative predictive factor [30, 32]. However, recent studies show that psychiatric history is not so much a predictive factor for the effectiveness of the treatment but rather for the complication rate. Patients with a psychiatric history have a higher chance of developing a complication [10, 33].

Findings at the start of the treatment, such as the improvement rate or the amplitude and impedance of battery implant, might predict successful treatment outcome on the long run.

The long-term result study in this thesis shows that patients who had more than 90% improvement during the trial stimulation appear to have a greater chance of long-term success than those with 50-90% improvement. Ghazwani et al reported an association of high stimulation parameters (amplitude and impedance) at the time of implantation with loss of efficacy at the long-term follow-up [34].

Both urinary and faecal problems

SNM is a treatment option for patients with urinary (urgency, urge-incontinence and urinary bladder retention) and faecal (faecal incontinence and constipation) problems. While most patients have either a urinary problem or a faecal problem, some have both. Between 22-36% of patients with mainly urinary problems have additional faecal problems [35, 36]. In the satisfaction study among patients with urinary problems, one third had additional faecal problems, and almost half of them (47%) perceived improvement of their faecal problems. This corresponds with a recent study by Caremel et al., which found that of the patients with both urinary and faecal incontinence, and who were successfully treated with SNM for a predominant type of incontinence, 48.7% had an improvement in the other type of incontinence [37].

SNM is possibly a good treatment option for patients with both urinary and faecal problems however, a long-term prospective study among this population group is lacking.

Conclusion

To conclude, even though sacral neuromodulation is an effective, minimally invasive and safe therapy for chronic lower urinary tract dysfunction, further studies are needed to improve patient comfort (new battery), efficacy (optimal stimulation parameters, possible new location of stimulation) and cost-effectiveness (predictive factors study, less adverse events).

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A black and white photograph of a rocky coastline. The image shows a steep, rocky cliff face on the right side, with waves crashing against its base. The water is white with foam from the breaking waves. The sky is a uniform light gray. The overall scene is dramatic and captures the power of the ocean.

Chapter 9

Summary

Sacral neuromodulation (SNM) is an accepted treatment option for patients with idiopathic overactive bladder syndrome (I-OAB) or non-obstructive urinary retention and who are refractory to conservative treatment. Since FDA approval in 1997, an increasing number of patients have been treated with SNM. **Chapter 1** provides an overview of the evidence behind SNM, based on the available clinical evidence concerning the efficacy and safety. Clinical studies have demonstrated its positive effect for the treatment of I-OAB and non-obstructive urinary retention. The long-term success rate varies between 56 and 71% depending on the underlying bladder dysfunction.

Patients considered eligible for SNM therapy are selected based on their response to a test period of SNM with an external neurostimulator. Currently two different methods are used to screen patients for their response to SNM: the Percutaneous Nerve Evaluation test (PNE) which uses a standard electrical wire electrode, and the first stage tined-lead placement test (FSTLP) which uses a special electrode with small anchors to reduce the risk of lead migration. In **Chapter 2** a study is described in which the response rate of the FSTLP test to determine eligibility for SNM therapy was compared with PNE. In this single centre study patients with refractory I-OAB or non-obstructive urinary retention, were screened with both PNE and FSTLP. Patients were followed prospectively and their response rate based on a bladder diary after PNE was compared to that after FSTLP. More than 50% improvement in at least two relevant urinary symptoms was considered a positive response. One hundred patients were included (82 female, 69 I-OAB). The mean age was 55 years (SD 13). The positive response rate on PNE was 47%. FSTLP showed a 69% positive response rate, which was negatively related to age. The 22% gain in positive response was statistically significant ($p < 0.001$) and positively associated with female gender and younger age. Logistic regression analyses of the PNE results found no predictors for positive response. However, the same analysis for the FSTLP showed a negative effect of age. All 69 patients with a positive response to FSTLP received SNM treatment. Failure rate after an average of 2 years was 2.9%. This study suggests that FSTLP may be a more sensitive screening method than PNE to identify patients eligible for SNM therapy, warranting randomised trials.

The implantable neurostimulator of SNM therapy can have a variety of settings. The waveform that the stimulator produces is a square wave pulse. The pulse-rate can be set between 2.1 and 130 Hz and the pulse-width between 60 and 450 μ s. Furthermore, the amplitude can be changed from 0.05 to 10.55 V. **Chapter 3** describes a pilot study that evaluates the impact of pulse rate changes (5.2Hz–10Hz–21Hz–40Hz) in patients with suboptimal

response to SNM therapy on clinical outcome, the sensory responses and SNM-related pain symptoms. Fifty patients were included of which 40 (80%) were female. Mean age was 55.5 years (SD 12.3). Forty-one patients (82%) had I-OAB and 9 (18%) had chronic non-obstructive urinary retention. In this study no significant difference was found regarding clinical outcome (voiding diary and questionnaire) or the occurrence of SNM-related pain between the different pulse rates. On a group level, none of the four pulse rates in this study appears to have a significantly different effect on clinical outcome or SNM-related pain. However, a tailor-made approach for optimising treatment efficacy by changing the pulse rate appears to be useful. On individual basis, patients appear to benefit from changing the pulse rate for both treatment efficacy or stimulation related pain.

In 2002, a new technique was introduced, which enabled percutaneous placement of a self-anchoring tined silicone lead also known as the tined lead procedure (TLP). This lead can be easily placed in the third sacral foramen under radiologic guidance. Short-term studies showed a decrease in the number of adverse events and the occurrence of lead migration with TLP. **Chapter 4** describes a single centre study that assessed the long-term efficacy and adverse events of SNM with TLP. In this study 64 patients who received an implantable neurostimulator between 2002 and 2005 using the TLP technique were included. Mean follow-up was 53 months (range 35 to 77). Five patients died of causes unrelated to SNM and they were not included in the analysis. The implantable neurostimulator was removed in 7 patients. Furthermore, 3 patients stopped using the neurostimulator. Voiding diary analysis showed that 38 of 59 patients (64%) were successfully treated. There were 21 patients (33%) who underwent a surgical revision due to an adverse event and 1 (1.6%) who underwent lead revision because of suspected lead migration. This study shows that in the long-term SNM therapy with the TLP technique is a safe and effective treatment for patients with I-OAB or non-obstructive urinary retention. Furthermore, TLP appears to reduce the occurrence of lead migration but does not increase the long-term success rate compared to data based on non-TLP technique. Patients who show more than 90% improvement during test stimulation appear to have a greater chance of long-term success than those with 50%-90% improvement.

Most studies on SNM focus on clinical efficacy or on technique improvement. Impact on quality of life has been described, however, to a lesser extent and mostly evaluated with non-OAB or non-obstructive urinary retention-specific questionnaires. Because functional bladder disorders have a negative impact on the quality of life, evaluating patient satisfaction is also important as it may give an overall view on how the patients experience

their treatment on a daily basis. In **Chapter 5** a study is described that evaluates the long-term satisfaction of patients with SNM therapy and their daily experiences with the treatment. All patients who received SNM therapy between 1990 and 2007 at our centre and who still have the implant received a postal questionnaire regarding their satisfaction and their experiences with the system. In total 275 questionnaires were sent, with a response rate of 75% (207). The population consisted of 83% females. Out of the total group 55% were being treated for I-OAB, 24% for non-obstructive urinary retention, 20% for a combination of I-OAB and retention and 1% for pelvic pain. Overall satisfaction with SNM was high (83%). Satisfaction was significantly and positively related to the patients' perceived effect, number of pelvic floor co-morbidities, their view on yearly outpatient check-up and experience with the use of the patient programmer. No direct relationship was found with the patient's age, sex, therapy duration, or type of complaint for which SNM treatment was offered. Forty-eight percent of the patients who had additional faecal problems before SNM treatment, experienced relief of their faecal problems. Despite the high satisfaction rate, regularly perceived pain or discomfort at the implant site was reported by 56% and 40% of the patients, respectively. In total 10 patients report having regular pain at the implantation site. However 9 out of 10 also reported not requiring further treatment for it. Patients' perceived limitations and concerns of SNM therapy were mostly related to MRI use, reimbursement and pregnancy.

SNM and Botulinum toxin A (BTX) are two minimally invasive treatment options for patients with I-OAB. **Chapter 6** is an overview of SNM and BTX treatment in the second-line management of adults with I-OAB, based on the available clinical evidence concerning the efficacy and safety. This review shows that both of these treatments have similar effectiveness rates and have relatively small, treatable and non-permanent side effects. BTX treatment has not yet been officially approved for urological disorders due to lack of long-term effect and safety data and lack of consensus regarding the proper dosage and the injection method. However, all BTX studies on patients with I-OAB are promising and point in the direction of approval. Until then, SNM is the only minimally invasive option approved for I-OAB patients who are refractory to conservative treatment.

Besides clinical effectiveness, cost-effectiveness should also be considered when making a choice between SNM and BTX. **Chapter 7** provides a cost-effectiveness study comparing either starting treatment with SNM or BTX in patients with refractory I-OAB from a societal perspective. For this study information on the clinical effectiveness of the two treatments and on the course of the disease with the two treatments were based primarily on

published literature and, when required, on expert opinion. All costs were based on Dutch data from the year 2008. This study shows that starting with SNM resulted in a higher Quality Adjusted Life Years (QALY) gain (0.23 difference after 5 years) and a higher cost (€6,428 difference) compared to starting with BTX, assuming both treatments were performed under general anaesthesia and for SNM treatment with FSTLP. The corresponding incremental cost-effectiveness ratio was €27,991/QALY. The probability of this ratio to be cost effective (e.g. under €40,000/QALY) is 88%. SNM starts to be cost-effective after four years. However, SNM was not cost-effective in some scenarios such as when BTX treatment was performed under local anaesthesia or when PNE or bilateral testing was used for SNM. Furthermore, sensitivity analysis shows that more information is necessary to determine whether the cost-effectiveness conclusion still holds. Especially, comparison studies of these two treatments options on long-term effectiveness, complication rate and their effect on the QOL are needed.

A black and white photograph of a rocky coastline. The image shows a steep, rocky cliff face on the right side, with waves crashing against its base. The water is white with foam from the breaking waves. The sky is a uniform light gray. The overall scene is dramatic and captures the power of the ocean.

Chapter 10

Nederlandse Samenvatting

Sacrale neuromodulatie (SNM) is een geaccepteerde behandeloptie voor patiënten met een idiopathisch overactieve blaassyndroom (I-OAB) of een niet-obstructieve urineretentie, die refractair zijn ondanks conservatieve behandeling. Sinds de FDA goedkeuring gaf in 1997, wordt een toenemend aantal patiënten behandeld met SNM. Hoofdstuk 1 geeft een overzicht van de wetenschappelijke onderbouwing van SNM, gebaseerd op de beschikbare klinische data betreffende de effectiviteit en veiligheid tot 2009. Klinisch onderzoek toonde een positief effect aan voor patiënten met I-OAB en niet-obstructieve urineretentie. Het succespercentage op de lange termijn varieert tussen 56 en 71%, afhankelijk van het onderliggend blaaslijden.

Patiënten die in aanmerking komen voor SNM, worden geselecteerd op basis van hun reactie op SNM via een externe neurostimulator, gedurende de testperiode. Momenteel worden er twee methodes gebruikt om patiënten te selecteren voor het wel of niet positief reageren op SNM: de Percutaneous Nerve Evaluation test (PNE, percutane zenuwstimulatie) die een standaardelektrode gebruikt, en een First Stage Tined-Lead Placement test (FSTLP) waarbij een speciale elektrode met kleine ankers gebruikt wordt, die de kans op onbedoelde verplaatsing van de elektrode vermindert, de zogenoemde elektrodemigratie. In **hoofdstuk 2** wordt een studie beschreven waarin de reactie op FSTLP wordt vergeleken met PNE, om te bepalen welke van deze twee tests de respons op SNM het beste kon voorspellen. In deze single-centre studie werden patiënten met refractair I-OAB of niet-obstructieve urineretentie gescreend door middel van beide methodes. Patiënten werden prospectief gevolgd en het effect op PNE, gebaseerd op plasdagboeken, werd vergeleken met dat van FSTLP. Meer dan 50% verbetering van tenminste twee relevante symptomen werd beschouwd als een positieve reactie. Honderd patiënten werden geïnccludeerd (82 vrouwen, 69 I-OAB). De gemiddelde leeftijd was 55 jaar (SD 13). Het percentage met een positieve reactie op PNE was 47%. Bij FSTLP was dit 69%. De toename van de positieve reactie van 22% was statistisch significant ($p < 0.001$) en positief geassocieerd met vrouwelijk geslacht en jongere leeftijd. Bij logistische regressieanalyse op PNE werden geen voorspellende waarden voor een positieve reactie gevonden. Dezelfde analyse liet zien dat hogere leeftijd een negatief effect had op het succespercentage van FSTLP. Alle 69 patiënten met een positieve reactie op FSTLP ontvingen SNMtherapie. Na een gemiddelde periode van 2 jaar hadden 2,9% van de patiënten geen reactie meer op SNM. Deze studie suggereert dat FSTLP een sensitievere screeningsmethode is voor de identificatie van patiënten die in aanmerking komen voor SNM therapie dan PNE. Verder gerandomiseerd onderzoek is echter noodzakelijk.

Er zijn verschillende instellingen mogelijk bij de implanteerbare neurostimulator. De door de stimulator geproduceerde impuls is een blokgolf. De pulsfrequentie kan variëren tussen 2.1 en 130 Hz en de pulsbreedte varieert tussen 60 en 450 μ s. Verder kan de amplitude ingesteld worden tussen 0,05 en 10,55V. **Hoofdstuk 3** beschrijft een pilotstudie bij patiënten met suboptimale reactie op SNM therapie, waarin de gevolgen van frequentieverandering (5.2Hz–10Hz–21Hz–40Hz) worden onderzocht op het klinisch effect, de sensorische reactie en SNM gerelateerde pijnklachten. Vijftig patiënten werden geïnccludeerd waarvan 40 (80%) vrouwen. De gemiddelde leeftijd was 55,5 jaar (SD 12.3). Eenenvieftig patiënten (82%) hadden I-OAB en 9 (18%) hadden last van chronische niet-obstructieve urineretentie. In dit onderzoek werden geen significante verschillen gevonden met betrekking tot de klinische effectiviteit (plasdagboek en vragenlijst) of tot de ontwikkeling van SNM gerelateerde pijn tussen de verschillende frequenties. Op groepsniveau toonde geen van de vier frequenties significant verschil met betrekking tot klinische reactie of SNM gerelateerde pijn. Desalniettemin zou, door de verandering van de frequentie, een individueel aangepaste benadering voor het optimaliseren van de effectiviteit overwogen kunnen worden. Op individueel niveau lijken patiënten namelijk wel voordelen te hebben met betrekking tot de effectiviteit en SNM gerelateerde pijn door de frequentie te veranderen.

In 2002 werd een nieuwe techniek geïntroduceerd, die de percutane plaatsing van een elektrode met zelfverankerende siliconenhaken, genaamd tined lead procedure (TLP), mogelijk maakte. Deze elektrode kan onder radiologische begeleiding gemakkelijk in het derde sacrale foramen worden geplaatst. Kortetermijnstudies met TLP lieten een vermindering zien van het aantal elektrodemigraties en ongewenste complicaties. **Hoofdstuk 4** beschrijft een single-centre studie die de lange termijneffecten en complicaties van SNM met TLP onderzoekt. Vierenzestig patiënten die tussen 2002-2005 een implanteerbare neurostimulator door middel van TLP techniek ontvingen, werden geïnccludeerd. De gemiddelde follow-up was 53 maanden (range 35-77). Vijf patiënten overleden aan niet-SNM gerelateerde oorzaken, zij werden niet in de analyse geïnccludeerd. Bij 7 patiënten werden de implanteerbare neurostimulatoren verwijderd en 3 patiënten stopten de behandeling op eigen initiatief. Plasdagboekanalyse liet bij 38 van de 59 patiënten (64%) een succesvolle behandeling zien. 21 patiënten (33%) ondergingen chirurgische revisie wegens complicaties en bij één patiënt (1.6%) wegens verdenking op elektrodemigratie. Dit onderzoek laat zien dat op de lange termijn SNM therapie met de TLP techniek voor patiënten met I-OAB of niet-obstructieve urineretentie veilig en effectief is. Verder lijkt TLP het aantal elektrodemigraties te reduceren. Vergeleken echter met studies

die geen TLP techniek gebruikten, is er op de lange termijn geen verschil in de effectiviteit van SNM te constateren. Daarnaast hadden patiënten die gedurende de testperiode een verbetering van hun klachten van meer dan 90% in het plasdagboek vertoonden, een grotere kans op lange termijn succes vergeleken met patiënten die 50 tot 90% verbetering lieten zien

De meeste studies over SNM bespreken de klinische effectiviteit of stellen technische verbeteringen voor. De invloed op de kwaliteit van leven wordt eveneens beschreven maar in mindere mate en vaak met niet-specifieke vragenlijsten voor OAB of niet-obstructieve urineretentie. Omdat functionele blaasaandoeningen een negatieve invloed hebben op de levenskwaliteit, is het evalueren van de patiënttevredenheid belangrijk. Het geeft inzicht in de dagelijks ervaringen van de patiënt gedurende de therapie. In **hoofdstuk 5** worden zowel de lange termijn tevredenheid van patiënten gedurende SNM therapie als hun dagelijkse ervaringen beschreven. Alle patiënten die binnen onze afdeling tussen 1990 en 2007 SNM therapie ondergingen en nog steeds een implantaat hebben, ontvingen een vragenlijst per post betreffende hun tevredenheid en ervaringen met SNM. In totaal werden 275 vragenlijsten verstuurd. De respons was hoog, aangezien 207 (75%) van de patiënten de vragenlijst retourneerden. 83% van de respondenten waren vrouwen, 55% werden behandeld voor I-OAB, 24% voor niet-obstructieve urineretentie, 20% voor een combinatie van I-OAB en retentie en 1% voor bekkenpijn. De algemene tevredenheid met SNM was hoog (83%). Tevredenheid was significant en positief gecorreleerd met het effect dat de patiënt had ervaren, het aantal bekkenbodemp Problemen of aandoeningen van de bekkenbodem, hun instelling ten opzichte van de policonrolebezoeken, en hun ervaring met het gebruik van de afstandsbediening. Er werd geen directe relatie gevonden met de leeftijd of het geslacht van de patiënt, met het aantal jaren van behandeling, of met het type klachten waarvoor SNM geïndiceerd werd. Van de patiënten die bijkomende fecale problemen hadden vóór SNM, had 48% ook verbetering van deze klachten ervaren. Ondanks hoge tevredenheidspercentages gaven 56% van de patiënten regelmatig pijn en 40% ongemak aan op de plaats van het implantaat. Negen van de tien patiënten die regelmatig pijn hadden, gaven aan geen behoefte aan pijnbehandeling te hebben. De meest voorkomende reden voor bezorgdheid en beperkingen door SNM waren gerelateerd aan MRI-gebruik, vergoeding en zwangerschap.

SNM en Botulinum toxine A (BTX) therapie zijn twee minimaal invasieve behandelingsopties voor patiënten met I-OAB. **Hoofdstuk 6** geeft een overzicht van de tweede lijnsbehandeling voor volwassenen met I-OAB, waarvoor gegevens werden gebruikt die evidence based zijn met betrekking

tot effectiviteit en veiligheid. Dit overzicht laat zien dat beide behandelingsmethoden een gelijkwaardige effectiviteit hebben en gepaard gaan met relatief milde bijwerkingen die goed behandelbaar en niet blijvend zijn. BTX therapie is tot nu toe nog niet officieel erkend omdat de lange termijn effecten en de veiligheid niet voldoende onderzocht zijn. Bovendien heerst er geen consensus over de juiste dosering en toedieningmethode. Toch zijn alle studies omtrent BTX bij patiënten met I-OAB veelbelovend en vormen een goede basis voor officiële registratie. Zolang er nog geen officiële registratie is voor BTX therapie, blijft behandeling met SNM de enige erkende minimaal invasieve behandelingsmethode zijn voor patiënten met I-OAB patiënten, die therapieresistent zijn voor conservatieve behandelingen.

Naast het klinisch effect speelt ook de kosteneffectiviteit een rol bij de beslissing tussen SNM en BTX. **Hoofdstuk 7** laat een kosteneffectiviteitsstudie zien waarin het starten met SNM- of BTX therapie bij patiënten met refractair I-OAB wordt vergeleken vanuit een maatschappelijk perspectief. Voor dit onderzoek werd de informatie over de klinische effectiviteit van de twee behandelmethoden en over het ziekteverloop primair gebaseerd op gepubliceerde literatuur en tevens, voor zover noodzakelijk, op meningen van experts. Alle kosten zijn gebaseerd op gegevens uit Nederland voor het jaar 2008. Deze studie laat zien dat het starten met SNM resulteert in hogere Quality Adjusted Life Years (QALY) winst (0,23 verschil na 5 jaar) en hogere kosten (€ 6.428,- verschil na 5 jaar) vergeleken met het starten met BTX, ervan uitgaande dat bij beide behandelingen algehele narcose werd toegepast en dat bij SNM de FSTLP techniek werd gebruikt. Het corresponderende incrementele kosteneffectiviteitsratio bedroeg € 27.991/QALY. De kans dat deze ratio kosteneffectief is (oftewel lager dan € 40.000/QALY) is 88%. SNM begint kosteneffectief te worden na vier jaar. SNM was niet kosteneffectief onder bepaalde omstandigheden zoals bij toediening van BTX onder lokale anesthesie, bij gebruik van PNE of bij de bilaterale test voor SNM. Verdere sensitiviteitsanalyse maakt duidelijk dat meer informatie nodig zal zijn om een definitieve uitspraak te doen over de betrouwbaarheid van de conclusies betreffende de kosteneffectiviteit in deze studie. Met name vergelijkende studies van deze twee behandelvormen met betrekking tot lange termijn effecten, complicatiepercentages en hun effecten op kwaliteit van leven zijn noodzakelijk.

Dankwoord

Bij het schrijven van dit dankwoord komen er veel herinneringen naar boven. Er zijn veel mensen die bij hebben gedragen aan het tot stand komen van dit proefschrift, direct of indirect. Een aantal van hen wil ik hierbij expliciet bedanken:

Prof. van Kerrebroeck, ik dank u dat u mij de kans hebt gegeven voor dit promotietraject en de steun die u daarbij gaf. Ik heb mij daardoor verder kunnen ontwikkelen als arts en wetenschapper

Dr. de Wachter, beste Stefan. Toen je in Maastricht kwam werken, werden we tijdelijk kamergenoten. Ik herinner me nog goed de verwarring en grappige momenten die ontstonden tijdens onze gesprekken. Laten we zeggen: ik heb snel een aantal Vlaamse uitdrukkingen moeten leren. Ik dank je voor je begeleiding en ondersteuning, zelfs nadat je in Antwerpen bent gaan werken.

Prof. de Bie, beste Rob. Het was steeds een genoegen om met je af te spreken. Je gaf me praktische ondersteuning en je gaf me altijd het gevoel dat het goed kwam. Uiteindelijk heb je gelijk gekregen. Ik dank je hiervoor.

Terugdenkend aan mijn tijd als onderzoeker kijk ik met veel plezier terug aan de goede tijden die ik had met mijn collegaonderzoekers. Dennis, we hebben kort samen gewerkt, ik wil je bedanken voor het wegwijs maken in het wereldje van de Sacrale Neuromodulatie in Maastricht. Het team van 'caviaonderzoekers': Rhea, Sajjad, Simone en Bart bedankt voor de gezelligheid zowel tijdens als na werktijd.

Tom, mede-onderzoeker, paranimf en vriend. Toen ik vertrok, heb ik het je al gezegd: ik kan je niet genoeg bedanken voor de leuke tijd die we hadden, zowel in onze werkkamer (of moet ik zeggen: hokje) en daarbuiten. Ik mis het squashen, lekker eten (met of zonder satésaus) en films kijken.

Micha, we hebben elkaar op de gang van onze afdelingen ontmoet en het leidde tot een bijzondere vriendschap. Je hebt mij steeds kunnen enthousiasmeren en motiveren tijdens de afgelopen jaren om deze promotie tot een goed einde te brengen. Ik ben je 'super' dankbaar en ik ben blij dat je mijn paranimf wilt zijn.

Dr. Weil, beste Ernest. Je hebt me niet alleen de procedure van SNM geleerd, je hebt me ook geholpen bij ook het verfijnen van mijn chirurgische vaardigheden. Je kon hierbij streng zijn en daar ben ik je uiteindelijk heel erg dankbaar voor.

Dr. Nieman, beste Fred. Ik dank je voor je snelle steun bij statistische problemen. Het was leerzaam en leuk om met je te werken.

Dr. Joore, beste Manuela. Ik dank je voor het meewerken aan het kosten-effectiviteitsartikel.

Ik wil de staf en medewerkers van de afdeling urologie bedanken voor de steun en samenwerking. In het bijzonder de secretaresses, Anja en Nancy, ik kon altijd met alle vragen en verzoeken bij jullie terecht. Jullie bijdrage aan dit proefschrift is groter geweest dan jullie misschien denken. Ik dank jullie wel.

Bilbo ik dank je voor je hulp met de vormgeving van de cover en de uitnodigingen, ik ben heel blij met het resultaat!

Cathelijn, met jouw vriendschap en bovengemiddelde linguïstische vaardigheden heb je mij vaak goed geholpen, bedankt hiervoor. Trouwens, dankzij jouw eeuwige correcties weet ik nu dat je altijd 'het' moet gebruiken voor een woord dat eindigt met 'tje'. Blijf vooral doorgaan met corrigeren.

Papi, mami, Vivian i Sue-Ann, danki pa boso sosten aunke mi sa cu e no tawata facil pa compronde lokual mi trabow como promovendus tawata insinua.

Aan de rest van mijn vrienden en (schoon)familie, ik dank jullie voor jullie interesse en steun.

Lieve Hanna, mijn vrouw en moeder van mijn zoon Damian, je bent een anker in mijn leven. Dankzij jouw steun, geduld en begrip tijdens mijn promotiejaren heb ik dit proefschrift met succes kunnen afronden. Ik hou van je en ik ben je eeuwig dankbaar.

A black and white photograph of a rugged coastline. In the foreground, a large, dark, craggy rock formation dominates the lower half of the frame. To its left, the ocean is turbulent, with white, frothy waves crashing violently against the base of the rocks, creating a stark contrast with the dark water and rock. The background shows a steep, rocky cliff rising from the water's edge, its surface textured with various rock formations and sparse vegetation. The sky is a pale, uniform grey, suggesting an overcast day. The overall mood is one of raw, natural power.

List of publications

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PNE versus 1st stage timed lead procedure: a direct comparison to select the most sensitive test method to identify patients suitable for sacral neuromodulation therapy.

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Psychological and psychiatric factors as predictors for success in sacral neuromodulation treatment.

T. Marcelissen, **R. Leong**, F. Nieman, J. van Lankveld, P. van Kerrebroeck, S. de Wachter. *British Journal of Urology International* 2011 Dec;108(11):1834-8.

A black and white photograph of a rocky coastline. The image shows a steep, rocky cliff face on the right side, with waves crashing against its base. The water is turbulent, with white foam from the waves visible. The sky is a uniform light gray, suggesting an overcast day. The overall mood is dramatic and powerful.

Curriculum Vitae

Randall Leong werd op 25 juli 1981 geboren op Aruba. De middelbare schoolopleiding (HAVO en VWO) volgde hij aan het Collegio Arubano in Oranjestad van 1993 tot 2000. Met als doel arts te worden vertrok hij in 2000 naar Canada om te studeren aan de McMaster University in Hamilton, Ontario. Daar behaalde hij in 2001 zijn propedeuse in 'Natural Science' en besloot om naar Nederland te gaan voor zijn verdere opleiding. In 2001 begon hij zijn studie geneeskunde aan de Universiteit Maastricht waarbij hij het honoursprogramma 'Onderzoekstraject Geneeskunde' met succes doorliep en haalde zijn artsdiploma in 2007. Het laatste jaar van zijn opleiding was een combinatiestage van onderzoek en klinisch werk op de afdeling urologie in het Atrium MC in Heerlen bij dr. K.P.J. Delaere. Na zijn afronding van zijn basisopleiding geneeskunde begon hij als arts-onderzoeker te werken aan deze promotie op de afdeling Urologie in het Maastricht UMC onder leiding van Prof. dr. Ph.E.V. van Kerrebroeck. Na 2,5 jaar onderzoek doen begon hij met werken in de kliniek, 6 maanden als ANIOS urologie in het Maastricht UMC en 6 maanden als ANIOS interne geneeskunde in het Atrium MC in Heerlen. In januari 2011 start hij met zijn opleiding tot uroloog in het St. Antonius ziekenhuis te Nieuwegein op de afdeling chirurgie bij dr. P.M.N.Y.H. Go. Vanaf 2013 zal hij de opleiding vervolgen met twee jaar op de afdeling urologie in het St. Antonius ziekenhuis bij dr. P.L.M. Vijverberg en twee jaar op de afdeling urologie in het UMC Utrecht bij prof. dr. J.L.H.R. Bosch.

Randall Leong was born on the 25th of July in Aruba. He attended secondary school (HAVO and VWO) at Collegio Arubano, Oranjestad from 1993 until 2000. With the ambition to become a doctor he moved to Canada to study at the McMaster University, Hamilton, Ontario. In 2001, after finishing the first year of a Bachelor's degree in 'Natural Science' he decided to move to The Netherlands to continue his education there. He then started medical school at the Maastricht University and in 2007 obtained his medical degree with completion of the Honours Programme in 'Research Track in Medicine'. In the final year he did a combined rotation consisting of research and clinical work in Urology at Atrium Medical Centre in Heerlen with Dr. K.P.J. Delaere MD. Following medical school he started working as a medical researcher on his dissertation in the Department of Urology at the

Maastricht University Medical Centre under the leadership of Professor E.V. van Kerrebroeck MD, PhD, Professor of Urology. In 2010, after 2.5 years working as a researcher, he worked as resident-not-in-training in Urology at the Maastricht University Medical Centre for 6 months followed by 6 months as resident-not-in-training in Internal Medicine at Atrium Medical Centre in Heerlen. In 2011 Randall started his 2 year residency in the surgery department of St Antonius Hospital Nieuwegein (under Dr. P.M.N.Y.H. Go, MD). In 2013 he will begin his 4 year residency in urology, beginning with 2 years at St Antonius Hospital in the Department of Urology (under Dr. P.L.M. Vijverberg, MD) followed by 2 years in the Department of Urology at UMC Utrecht (under Prof. J.L.H.R. Bosch MD, PhD).