APPLICATION OF SACRAL AND PUDENDAL NERVE STIMULATION IN CHILDREN

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19/04/2012

Loret Nele

Prof. Hoebeke
Preface

I chose this subject for my dissertation, because the technique of neuromodulation intrigued me. Given the fact that the exact working mechanism of neuromodulation is not yet discovered, I had the ambition to go more deeply into that subject.

This paper focusses on the use of sacral and pudendal neuromodulation in children. Only five small studies have previously investigated the effect of sacral neuromodulation in a pediatric population, so the evidence is still very limited. This survey aims to bring more information about the effect of neuromodulation in different pediatric urologic indications.

I would like to thank everyone who made it possible to achieve this dissertation. Firstly I would like to thank my co-promotor, Dr. Groen, and my promotor, Prof. Hoebeke, for the help, but also for trusting me and allowing me a lot of latitude in this experimental thesis. Secondly I would like to render thanks to my parents, my sisters Griet and Lotte, and Matthias, for being a great support and for their constructive criticism.

I hope this paper will contribute to the development of larger prospective studies to investigate sacral and pudendal neuromodulation in children.
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Abstract

PURPOSE: Sacral neuromodulation (SNM) with an implantable pulse generator (IPG) has been applied in adults since the FDA approval in 1997. It is not yet approved for pediatric use, so little is known about the effectiveness of SNM in children and even less is known about the results of pudendal neuromodulation in a pediatric population. Only 5 surveys have evaluated SNM in children with neurogenic bladder or dysfunctional elimination syndrome (DES). The results of our series of InterStim therapy in children with severe LUT dysfunction (including two not previously described indications: bladder overactivity and Fowler’s syndrome), in whom neither intensive medical treatment nor behavioral therapies have succeeded, are described. The objective of the study was to detect patient characteristics favorable for a good outcome.

MATERIALS AND METHODS: A retrospective analysis of 18 patients (9 to 17 years old) with neurogenic bladder dysfunction, Fowler’s syndrome, DES and/or bladder overactivity (44% had proven overactivity) was performed. The mean follow-up time was 28.8 (+/- 43.83) months after implantation. Seven patients received pudendal nerve stimulation (5 of them had sacral stimulation first) and a total of 16 patients underwent sacral nerve stimulation. Statistical analysis was done using Wilcoxon matched-pairs signed-ranks test and Mann-Whitney U test.

RESULTS: Of the 7 patients with Fowler’s syndrome 4 had improvement of their symptoms (less incontinence episodes and smaller volumes of incontinence) and in 3 the SNM therapy failed. In all patients with neurogenic bladder due to spina bifida (n=3) the lead was explanted because of unsatisfactory results. Two other patients with neurogenic bladder due to anal atresia and Guillain-Barré syndrome had less urgency and 80% less weekly enuresis episodes. The patient with anal atresia also had 50% less incontinence episodes. Of the 4 patients with bladder overactivity 1 had her lead explanted due to failure, 2 were completely continent and 1 had less enuresis episodes. One patient with dysfunctional elimination syndrome had 70% less urinary tract infections and resolution of urinary incontinence, where as another patient with dysfunctional elimination syndrome had a complete resolution of her perineal pain and dysuria. Reported complications were pacemaker infection (n=2), dislocation of the pacemaker/loss of effect (n=6) and pain at the implantation site (n=2). Two patients required reintervention because of battery depletion. In 4 of the 7 patients (57%) who received pudendal nerve stimulation the therapy was successful.
CONCLUSIONS: Given the fact that these children are extremely refractory to conventional therapy, a success rate of 73% (11 of the 15 children with a definitive IPG) was considered as satisfactory. This success rate could be increased by more selective use of neuromodulation for specific indications. Fowler’s syndrome, bladder overactivity and DES seem to be good indications whereas the result in severe neurogenic bladder due to spina bifida is less successful. If S3 implantation is impossible or unsuccessful, pudendal nerve stimulation proves to be a feasible alternative. However, larger prospective trials are recommended.
**Dutch summary**

**INLEIDING: Sacrale of pudendus neurostimulatie met een implanteerbare neurostimulator wordt regelmatig toegepast bij volwassenen met therapierezistente aandrang, aandrangincontinentie, urinaire retentie en hoge mictiefrequentie, sinds het goedgekeurd werd door de FDA in 1997. Voor pediatrisch gebruik is er echter nog geen goedkeuring. Er is bijgevolg weinig gekend over de effecten van sacrale neurostimulatie bij kinderen, en nog minder over de resultaten van pudendusstimulatie in deze groep. Slechts 5 studies hebben tot dusver onderzoek gedaan naar het gebruik van sacrale neurostimulatie bij kinderen met neurogene blaas en dysfunctioneel eliminatiesyndroom. Dit onderzoek werd uitgevoerd om de bevindingen van sacrale en pudendus neuromodulatie bij kinderen verder te documenteren, ook voor twee indicaties die nog niet eerder onderzocht werden: overactieve blaas en Fowler syndroom. Bovendien werd getracht om patiëntkenmerken te ontdekken die een goede uitkomst voorspellen.**

**METHODE:** Er werd een retrospectieve analyse van 18 patiënten (9 tot 17 jaar oud) met neurogene blaas, Fowler syndroom, dysfunctioneel eliminatiesyndroom of overactieve blaas (44% had blaasoveractiviteit bij urodynamisch onderzoek) verricht. De gemiddelde follow-up tijd bedroeg 28,8 (+/- 43,83) maanden na implantatie. Zeven patiënten kregen een pudendusstimulatie (vijf hiervan hadden eerst een sacrale neurostimulator) en zestien kinderen ondergingen een sacrale neurostimulatie. De Wilcoxon matched-pairs signed-ranks test en de Mann-Whitney U test werden gebruikt voor de statistische analyse van de resultaten.

**RESULTATEN:** Vier van de zeven patiënten met Fowler syndroom ondervonden een verbetering van hun symptomen (minder incontinentie episodes en kleinere volumes urineverlies) en bij de overige drie faalde de neurostimulatie behandeling. Bij alle patiënten met neurogene blaas als gevolg van spina bifida (n=3) werd de elektrode verwijderd omwille van onbevredigende resultaten. Twee andere patiënten met neurogene blaas, als gevolg van anale atresie en het syndroom van Guillain-Barré, hadden minder aandrang en 80% minder enuresis episodes. De patiënt met anale atresie had bovendien 50% minder incontinentie episodes. Van de vier kinderen met overactieve blaas waren er twee volledig continent, één had minder enuresis episodes en bij de vierde werd de elektrode verwijderd wegens het falen van de therapie. Eén patiënt met dysfunctioneel eliminatiesyndroom had 70% minder urineweginfecties en was volledig continent, terwijl een ander kind met dysfunctioneel eliminatie syndroom geen perineale pijn en dysurie meer had. De complicaties waren infectie van de pacemaker (n=2), verplaatsing van de pacemaker/verlies van effect (n=6) en pijn ter hoogte van de implantatie plaats (n=2). Twee patiënten hadden een revisie nodig omwille van een lege batterij. Bij vier (57%) van de zeven kinderen met pudendusstimulatie was de behandeling succesvol.
CONCLUSIE: Aangezien deze kinderen extreem resistent zijn voor conventionele behandelingen, werd een succespercentage van 73% (11 van de 15 kinderen met een definitieve IPG) als tevredenstellend beschouwd. Dit percentage kan verhoogd worden door neuromodulatie selectiever toe te passen, voor specifieke indicaties. Fowler syndroom, overactieve blaas en dysfunctioneel eliminatie syndroom lijken goede indicaties. De resultaten bij neurogene blaas als gevolg van spina bifida blijken evenwel tegen te vallen. Pudendusstimulatie is een adequaat alternatief, indien S3 implantatie onmogelijk of onsuccesvol is. Toch zijn grotere, prospectieve studies aangewezen om meer evidentie omtrent de indicaties aan te brengen.
1. Introduction

1.1 Anatomy, neuroanatomy and neurophysiology

The human bladder has a dual function: storage of urine at a low intravesical pressure and emptying of urine. To fulfil these tasks the anatomy and innervation of the bladder has to be intact.

The bladder consists (from the outside, to the lumen) of the serosa, smooth muscle (the detrusor muscle) and extracellular matrix (ECM), the lamina propria and the urothelium. It is divided in two parts, with a different innervation: the bladder base, which encloses the bladder neck and the trigone, and the body, which is the supratrigonal portion. The bladder sphincter (internal and external) is important to ensure the storage function. The external urethral sphincter (EUS) is a circular striated muscle which lies around the smooth muscle layer of the urethra. The internal bladder sphincter is not yet defined properly: males have an internal sphincter which consists of smooth muscle around the bladder neck, whereas in females no circular smooth muscle sphincter can be distinguished. The male bladder neck contains a lot of α₁-adrenergic receptors, whereas the female bladder neck has poor adrenergic innervation.

The dual function of the bladder can only be realized thanks to the complex coordination of the peripheral autonomous, peripheral somatic and central nervous systems (CNS) (figure 1).

![Innervation of the lower urinary tract (in a female)](image)

*Figure 1: Innervation of the lower urinary tract (in a female)*
1.1.1 Peripheral nervous system

**Efferent pathways (figure 2).** The parasympathetic efferent nerve fibres (pelvic nerve) arise from segments S2-S4 and synapse in ganglia close to and in the bladder wall. They mediate detrusor contraction by transmitting acetylcholine (ACh) to the muscarinic receptors (mainly M3 receptors). Some postsynaptic parasympathetic neurons transmit nitric oxide (NO) to the internal urethral sphincter, which causes a relaxation of this smooth muscle sphincter during micturition.

The sympathetic efferent nerves leave the spinal cord at L2 through T1, go through the sympathetic trunk, the inferior mesenteric ganglion (where the preganglionic nerves synapse with the postganglionic nerves), the hypogastric nerves and the pelvic plexus to end at the bladder and urethral sphincter. They modulate relaxation of the trigone (by transmitting norepinephrine (NE) to β2- and β3- adrenergic receptors) and contraction of the bladder outlet and urethra (by transmitting NE to α1- adrenergic receptors).

The somatic efferent nerves originate from the ventral horn in segments S2-S4 (Onuf’s nucleus) and travel through the pudendal nerve to the EUS and other striated pelvic floor muscles, where they release ACh onto the nicotinic receptors in the striated muscles. In this way they mediate contraction of the EUS. (1, 2)

![Diagram of efferent pathways](image)

**Figure 2: Efferent pathways to the lower urinary tract (2)**

**Afferent pathways (figure 3).** Afferent nerves are lying in the detrusor muscle (especially the trigone and bladder neck) and the suburothelium. They travel within the pelvic and pudendal nerves to the sacral dorsal root ganglia S2-S4 and within the hypogastric nerves to the thoracolumbar dorsal root ganglia T10-L2. These dorsal root ganglia contain the nerve cell bodies of the first-order neurons. From there, axons enter the spinal cord through the dorsal root (visceral afferent fibres from pelvic and pudendal nerves ascend in the spinal cord within Lissauer’s tract) and synapse with the second-order neurons in the spinal cord.
cord, who in turn carry afferent information to the brain stem centres that control micturition and storage. There are two types of pelvic nerve afferents: myelinated Aδ axons, who sense bladder fullness and unmyelinated C axons, who respond to stretch and nociception to overdistention and chemical irritation (for example when there is a bladder infection). The neurotransmitters are glutamate in the Aδ fibres and glutamate, substance P and calcitonin gene-related peptide in the C fibres.(1, 2) C-fibre afferents can also facilitate micturition reflexes (protection system to evacuate noxious irritants or infectious organisms).(5)

![Afferent pathways of the lower urinary tract](image)

**Figure 3: Afferent pathways of the lower urinary tract (2)**

### 1.1.2 Central nervous system

Two areas in the pons are important for normal micturition and storage of urine: the pontine micturition centre (PMC), located in the dorsal pontine tegmentum, and the pontine storage centre (PSC), which is situated ventrolateral of the PMC. They receive input from higher brain centres (including periaqueductal gray, cingulated cortex, thalamus, hypothalamus, prefrontal cortex and other areas) and from afferent nerves of the lower urinary tract. The cerebral cortex is essential for the inhibition of the micturition reflex and spontaneous detrusor reflex contractions. The main function of the pontine areas is to coordinate detrusor contraction and urethral sphincter relaxation.

Another important function of the central nervous system is to control the timing of micturition, in such way that voiding is only initiated at the appropriate moment (on the toilet). Finally the central nervous system has to intensify weak smooth muscle contractions to build up a sufficient rise of intravesical pressure to evacuate the urine.(1, 2, 5) In order to achieve these functions the bladder receives mainly voluntary rather than autonomic innervation (unlike most other visceral organs such as the heart and the gastrointestinal tract).(5)
Both spinal afferent signals from somatic pathways (from the perineal muscle/skin) and pelvic visceral organs, and input from the brain centers can initiate efferent stimuli to the lower urinary tract.(5)

1.1.3 Storage reflexes
During the storage phase, Aδ fibres are activated by bladder filling. This results in a spinal reflex pathway (guarding reflex) with stimulation of the sympathetic efferent fibres leading to contraction of the bladder base and proximal urethra and augmentation of the somatic pudendal efferent activity leading to contraction of the EUS. The guarding reflex prevents incontinence in case of coughing or other situations which raise intravesical pressure. During the storage phase, the sympathetic activity also inhibits parasympathetic transmission in bladder ganglia, resulting in detrusor relaxation. The guarding reflexes are suppressed by the brain during voiding.(1, 2, 5)

1.1.4 Voiding reflexes
The micturition phase is initiated by the cerebral cortex, which mediates relaxation of the EUS. Subsequently bladder-bladder reflexes cause parasympathetic stimulation and consequently detrusor contraction (through ACh release) and bladder-urethral reflexes cause relaxation of the internal urethral sphincter (through NO release). Relaxation of the bladder base and proximal urethra is also mediated through sympathetic inhibition. This leads to flow of urine into the proximal urethra, which activates sensory afferent nerves that carry information to the PAG and subsequently to the PMC. This input and the amplification of this bladder afferent activity through positive feedback loops is fundamental to maintain the voiding reflex until the bladder is empty (spinobulbospinal reflex).(1, 2, 5)
Nevertheless, this positive feedback system can result in bladder overactivity and involuntary voiding, if central inhibition is lost or in case of sensitization of bladder afferent pathways. To compensate for this, extra systems for inhibition of the micturition reflex, located in the spinal cord, can be activated by somatic and visceral afferent nerve stimulations. It is thought that these inhibitory neural modulation mechanisms are triggered by sacral neuromodulation therapy in OAB. (5)
1.2 Pathogenesis of urinary incontinence in children

1.2.1 Definitions (ICCS terminology)

**Urinary incontinence** means uncontrollable leakage of urine which can be **continuous** (constant urine leakage, almost exclusively associated with congenital malformations) or **intermittent** (urine leakage in discrete amounts during the day and/or night in children of five years and older).

**Enuresis** means intermittent incontinence while sleeping. In case of **monosymptomatic enuresis**, the child has enuresis without any other lower urinary tract (LUT) symptoms. On the other hand, children with **nonmonosymptomatic enuresis** do have other LUT symptoms.

**Decreased daytime voiding frequency** means three or less voidings daily, where as a daily voiding frequency of eight times of more designates an **increased daytime voiding frequency** (2, 6)

**Voided volume** is de voided volume at micturition, which is documented by a bladder diary. The **maximum voided volume** is the largest voided volume, also documented in a bladder diary. The **expected bladder capacity for age** (EBC) is the age related expected maximum voided volume (= 30 + age in years x 30ml). This formula can be used until the age of twelve. At this age the EBC has to be approximately 300ml (2).

An amount of 20ml urine or more left in the bladder immediately after voiding (on repetitive measurements) is considered to be **residual urine** (6).

1.2.2 Daytime LUT conditions

Urinary incontinence may be caused by disturbances of the filling phase, the voiding phase or both.

To avoid confusion, 4 parameters should be documented in patients with LUT conditions: incontinence, voiding frequency, voided volume and fluid intake. The following recognized syndromes are applicable from the age of five years. (6)

1) **OAB and urge incontinence**

This condition is characterized by urgency, sometimes accompanied with urgency incontinence and/or increased voiding frequency. These children generally have detrusor overactivity on cystometric evaluation (2, 6).

2) **Voiding postponement**

These children with daytime incontinence are habituated to postpone micturition, using typical holding maneuvers (2, 6).
3) **Underactive bladder**
This condition is characterized by a low voiding frequency and the need to raise intra-abdominal pressure to start, continue or complete micturition. This is referred to as ‘straining’. (2, 6)

4) **Dysfunctional voiding**
This refers to children who repeatedly contract the urethral sphincter during micturition, producing a staccato pattern on uroflowmetry. It can also be demonstrated by urodynamic evaluation. (2, 6)

5) **Obstruction**
These children have a mechanical or functional, static or phasic obstruction to urine flow during micturition, a raised detrusor pressure and a decreased urine flow rate. (2, 6)

6) **Stress incontinence**
In this condition, raised intra-abdominal pressure or exercise causes small amounts of urine leakage.

7) **Vaginal reflux**
Vaginal entrapment of urine provokes incontinence within 10 minutes after normal micturition. (2, 6)

8) **Giggle incontinence**
In these children, mostly girls, an ostensible complete voiding occurs during or promptly after laughing. When they are not laughing, the bladder function is normal. (2, 6)

9) **Extraordinary daytime urinary frequency**
The daytime voiding frequency is once or more in an hour and the mean voided volume is below 50% of EBC. The nocturnal bladder function is normal. This condition is applicable from the age of three years. (2, 6)

**1.2.3 Fowler’s syndrome in children**
This syndrome is characterized by the association of isolated painless urinary retention, polycystic ovaries and a typical external urethral sphincter electromyography (EMG) pattern in young women (and sometimes in children). Two types of abnormal EMG patterns are discerned: complex repetitive discharges (CRD) and decelerating bursts. In case of complex repetitive discharges, transmission of the nerve impulse goes from muscle cell to muscle cell through ephaptic spreading.

Two theories have been suggested about the origin of the condition. Firstly hormonally induced instability of the cell membranes of the muscle cells of the EUS would cause chaotic routes of action potentials, inhibiting EUS relaxation. Secondly a channelopathy is also postulated as possible cause.

Urinary retention is probably caused by inhibition of detrusor contraction, as a consequence of increased guarding reflexes following continuous EUS contraction. In most women, the retention was triggered by a gynecologic intervention under general anesthesia.
The only successful therapy in Fowler’s syndrome is sacral neuromodulation. The success rate of SNM therapy is even higher (approximately 70%) than in women with urinary retention without the typical decelerating bursts or CRDs on EMG (approximately 45%). (7-9)

Other causes of urinary retention in women are, among other things, neurological diseases, antimuscarinic side effects of medication, pregnancy, fecal impaction and uterine fibroids. (8)

1.2.4 Neurogenic bladder sphincter dysfunction (NBSD) in children

Neurogenic bladder sphincter dysfunction (NBSD) refers to a lower urinary tract dysfunction caused by a condition of central and/or peripheral nervous system involved in the control of the lower urinary tract system. It can origin from different pathologies such as spinal cord diseases/lesions, neural tube defects (mainly spina bifida), brain tumors, head trauma and sequelae of transverse myelitis. In NSBD absence of control of micturition, high bladder filling pressures and dyssynergia between sphincter and detrusor are typical. Urodynamic evaluation can distinguish four major subtypes of NSBD: 1) sphincter overactivity with detrusor underactivity, 2) sphincter overactivity with detrusor overactivity, 3) sphincter underactivity with detrusor underactivity and 4) sphincter underactivity with detrusor overactivity. Despite the different etiologies of neurogenic bladder, the therapy is largely the same and depends on the subtype of NSBD (anticholinergics with our without CIC). Early therapy is important to prevent secondary damage to lower and upper urinary tract. (10-12)

1.2.5 Dysfunctional elimination syndrome in children

Dysfunctional elimination syndrome (DES) refers to the combination of bowel and lower urinary tract dysfunction in the absence of anatomical or neurological abnormalities, accompanied by symptoms of detrusor overactivity, constipation and low voiding frequency. (2, 6, 13, 14). The urinary disorders can be underactive bladder, nocturnal enuresis, OAB (urge syndrome), voiding postponement and dysfunctional voiding. There is also a high prevalence of urinary tract infection (UTI) and vesicoureteral reflux (VUR) in children with DES (15), although Shaikh et al. report no association between UTI and VUR before the age of two years and DES in school-aged children (16). Most common symptoms are urinary incontinence, nocturnal enuresis, urgency, frequency, urinary retention, constipation and encopresis. DES can be treated with standard urotherapy, biofeedback, pelvic floor exercises, pharmacological therapy and neuromodulation. (15-19)
1.2.6 Neural mechanisms in LUT dysfunction

1.2.6.1 Bladder overactivity and urge incontinence
When central inhibition is lost, primitive involuntary micturition reflexes become active. This can cause bladder overactivity and urinary incontinence. Neurological diseases as well as inflammation, infection and anatomic abnormalities can result in sensitization of C-fibres to bladder distension. In this way, C-fibres can generate new involuntary micturition reflexes (figure 4). Another cause of involuntary reflex mechanisms becoming active is the reactivation of neonatal reflex patterns.(5)

![Figure 4: Pathogenesis of involuntary reflex mechanisms in bladder overactivity(5)](image)

1.2.6.2 Bladder sphincter dyssynergia and urinary retention
In normal situation, communication between brain centers and lower spinal centers (such as Onuf’s nucleus) allows bladder sphincter coordination and efficient micturition. Consequently major spinal cord lesions result in bladder sphincter dyssynergia, but even subtle neurologic damage (such as in patients with idiopathic urinary retention) can result in dyssynergia. In neurological diseases, this inability of the brain to switch off guarding reflexes can also result in urinary retention.(5)

1.3 Prevalence
Daytime wetting with or without nigh-time wetting occurs in 8% of the ten to fourteen year old Belgian school children, fecal soiling in 3% and monosymptomatic nocturnal enuresis (MNE) in 1% of this population.(20) Another study reports a prevalence of 4.2% of daytime wetting in a Turkish population of five to fifteen year old children, decreasing with increasing age and without a significant difference between sexes.(21) In a population based survey in Brazil (children aged five to eighteen years) the prevalence of lower urinary tract symptoms was 87% and 27% in enuretic and nonenuretic children respectively. Urgency, holding maneuvers and daytime incontinence were the most frequent daytime
Generally the prevalence rates of urinary incontinence in children range from 1 to 20 percent, depending on the used definitions and study designs. (2, 23)

It is remarkable that only a small number of children with daytime wetting sought medical help (varying from 16 to 51.7%) (21, 23)

Factors associated with daytime incontinence include smoking during pregnancy, delayed initiation and punishment of the child in toilet training, urgency, voiding frequency, soiling, UTI history, lower performance at school, poor social adaptation and positive familial history of wetting. (21)

1.4 Evaluation of children with incontinence
At first, a comprehensive history, a voiding diary (in which fluid intake, number of voids, voided volume and urine loss are documented during three days) and a clinical examination should be accomplished. The history should include obstetric problems, age of continence by day and at night and other developmental details, voiding habits, congenital and neurological abnormalities, day- and nighttime urologic symptoms, infections, bowel function, relevant surgery, menstrual and sexual functions in pubertal children and familial history. Clinical examination is necessary to exclude anatomical and neurological abnormalities (e.g. occult spina bifida, sacral agenesis or sacral anomalies) and to assess psychomotor development.

This can be supplemented with urinalysis and uroflow studies (sometimes in combination with pelvic floor electromyography). In case of proved LUT dysfunction, a pre-void and post-void ultrasound should also be performed.

Every child with an abnormal clinical examination, uroflow or ultrasound has to be referred to a specialized center. An invasive urodynamic evaluation should be preserved for children in whom ultrasound or uroflow patterns indicate obstruction, reflux, increased storage pressures or bladder neck dysfunction and for children with neurological or anatomical abnormalities or failure of empirical therapy.

Magnetic resonance imaging of the spinal cord may be indicated if neurological abnormalities are present. Cystoscopy is only occasionally required. (24, 25)
1.5 Therapy of urinary incontinence

1.5.1 Objectives and principles
The treatment intends to obtain a normal micturition pattern, a normal bladder and pelvic floor function and to cure LUT symptoms.(25) The cornerstone of the treatment remains urotherapy and the combination of different therapeutic options is more effective. It is important to always treat fecal incontinence first.(26) Table 1 shows the evidence levels of different pharmacological and non-pharmacological therapies for urinary incontinence in children.

<table>
<thead>
<tr>
<th>Overactive bladder/discoordinated micturition</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-pharmacological interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Behavioral alarm treatment</td>
<td>3</td>
</tr>
<tr>
<td>Urotherapy</td>
<td>3</td>
</tr>
<tr>
<td>Biofeedback</td>
<td>3</td>
</tr>
<tr>
<td>Self-catheterization</td>
<td>4</td>
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<tr>
<td>Neuromodulation</td>
<td>4</td>
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<tr>
<td><strong>Pharmacotherapy</strong></td>
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<tr>
<td>Propiverine</td>
<td>1</td>
</tr>
<tr>
<td>Oxybutinin</td>
<td>3</td>
</tr>
<tr>
<td>Trospium chloride</td>
<td>3</td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>3</td>
</tr>
</tbody>
</table>

*Table 1: Evidence levels of pharmacological and non-pharmacological interventions in urinary incontinence in children* (26)

1.5.2 Nonpharmacological treatment

1.5.2.1 Standard urotherapy
Standard urotherapy (nonsurgical, nonpharmacological treatment) comprises information and demystification, instructions with regard to voiding habits, advice about drinking behavior and nutrition, documentation by using bladder diaries and support and stimulation through regular follow-up.(6, 26)

1.5.2.2 Specific urotherapy
Examples of specific urotherapeutic interventions are pelvic floor training, biofeedback, electrical stimulation (see 1.6 Neuromodulation), behavioral modification and self-catheterization.(6) In biofeedback, the physiological activity is recorded and showed to the child in the form of a visual or acoustic signal. It can be used in case of discoordinated micturition. The main limitation of biofeedback is the need for cooperation of the child which makes it difficult to use in children with learning or behavioral problems.(23, 26)
1.5.2.3  **Surgery**
Bladder augmentation is an invasive treatment option that increases the storage function of the bladder and decreases the intravesical pressure. It is a salvage procedure in children with elevated detrusor pressure who are resistant to pharmacological treatment, urotherapy, botulinum toxin and neuromodulation. Because this therapy is irreversible and because of the risk of need for lifelong clean intermittent catheterization (CIC), it is rarely performed in children.(5, 23)

1.5.3  **Pharmacological treatment**

1.5.3.1  **Antimuscarinic therapy**
In children with a small functional bladder capacity or OAB, antimuscarinic therapy can be started, if urotherapy alone is not enough. Antimuscarinic agents increase bladder capacity and bladder compliance and decrease detrusor overactivity. At present, only oxybutynin IR (immediate-release) and oxybutynin ER (extended-release) are approved by the FDA (Food and Drug Administration) for pediatric use. The most common side effects include dry mouth and constipation. Other reported side effects are abnormal vision, dizziness, facial flushing, heat stroke, tachycardia, headache, psychological/personality changes and lack of concentration. Because of these side effects 10% of the children stops the treatment. Other antimuscarinic agents, which are not approved for use in children, are tolterodine, trospium, propiverine and solifenacine.(2, 23, 25, 26)

1.5.3.2  **Alpha blockers**
Blockage of alpha receptors leads to relaxation of the proximal urethra and the bladder outlet. Accordingly children with dysfunctional voiding can be treated with alpha blockers (doxazosin, tamsulosin and terazosin), although the efficacy is varying and the pediatric use of these agents is not FDA approved. The most common side effects in children are headache, nausea and somnolence. (2, 23, 25)

1.5.3.3  **Botulinum toxin A**
This is a neurotoxin that suppresses acetylcholine release at the neuromuscular junction, and thus causes detrusor muscle relaxation. Cystoscopically directed intravesical injections of botulinum toxin are used in children with mainly neurogenic but also non-neurogenic detrusor overactivity. They can improve urgency, urgency incontinence, bladder capacity, bladder compliance and the incidence of urinary tract infections. The main disadvantages are the need for general anesthesia and the temporary effect (the nerve terminals recover after approximately six to nine months). Furthermore it has not yet been approved by the Food and Drug Administration for pediatric use. External urethral injections to treat dysfunctional voiding are less commonly used and only a few surveys have investigated this. (2, 23, 25)
1.6 Neuromodulation

1.6.1 What is neuromodulation?

Neuromodulation is a reversible and minimal invasive technique that has been used in Europe since the European conformity approval in 1994 (CE mark). It is approved by the FDA for the treatment of refractory frequency, urgency, urge incontinence and urinary retention in adults, but it is not approved for pediatric use.\(^{(23, 27, 28)}\)

The exact mechanism of neuromodulation remains still unknown. Electrical current, applied through electrodes, activates neural structures and influences neural plasticity and afferent and efferent activity of the lower urinary tract. Neurostimulation can lead to neuromodulation. The first leads to immediate effects, whereas the latter results in more long-lasting control of lower urinary tract dysfunction through electrical modulation of a nerve.\(^{(5, 29)}\) Different hypotheses have been postulated about the working mechanism of neurostimulation. One theory states that by artificially stimulating afferent sacral nerves, inhibitory stimuli are induced in efferent sacral nerves to the bladder. This could restitute the balance and coordination of spinal and/or spinobulbous reflex arcs. Another hypothesis argues that dominant activity of afferent C-fibres in neurogenic bladder dysfunction is suppressed by the neuromodulation technique.\(^{(2, 5, 23, 30)}\) One more theory states that electrical stimulation may reset neural thresholds necessary to create action potentials.\(^{(31)}\) Furthermore, S3 stimulation changes bladder sensation to electrical stimulation applied by electrodes. Finally, effects on spinal cord, brain stem (periaqueductal grey) and cortical areas are possible. Actually Braun et al demonstrated EEG activity in sensory cortex areas during S3 neurostimulation.\(^{(32-34)}\)

Beside the effect on neural structures, neurostimulation also causes chemical changes. There is an increase of beta-adrenergic neurotransmitters (stimulating bladder relaxation), a decrease of cholinergic activity and changes in other neurotransmitters. Furthermore, neurostimulation causes raised endorphins and encephalins in the cerebrospinal fluid, which in turn can suppress detrusor overactivity.\(^{(35)}\)

Both somatic and visceral afferents can influence bladder and urethral reflexes: the input can come from anal canal, vagina, sphincter muscles, cutaneous innervation from the perineum and so on. As a consequence different types of electrical nerve stimulation are used: parasacral or suprapubic transcutaneous electrical neural stimulation (TENS) with surface electrodes, percutaneous posterior tibial electrical neural stimulation (PTNS)(= Stoller afferent nerve stimulation, SANS), endoanal electrical neural stimulation (ENS), anogenital ENS with for example vaginal plug electrodes and dorsal penile nerve electrodes, intravesical ENS and sacral or pudendal implanted devices.\(^{(5, 36)}\)
How can electrical neural stimulation promote voiding?

Stimulation of S3 somatic afferents by SNM therapy can promote voiding and reduce urinary retention and dysfunctional voiding by suppressing guarding reflexes and spastic behavior of the striated muscles of the pelvic floor and EUS (figure 5).

Before the maturation of brain control, the pudendal nerve can induce micturition through activation of efferent circuits to the bladder and inhibition of efferent circuits to the urethra. It is thought that the same pudendal activity is triggered by SNM therapy in patients with urinary retention. This inhibition of sphincter reflexes also enhances micturition because sphincter contraction causes afferent signals that can suppress bladder contraction.(5, 33)

![Diagram](image)

Figure 5: When the brain can’t switch off the guarding reflex (such as in neurologic conditions) SNS can suppress the guarding reflex, leading to micturition (5)

How can electrical neural stimulation suppress bladder overactivity?

Bladder overactivity can be reduced by SNM in different ways. The most important mechanism is the inhibition of sacral interneuronal transmission on the ascending part of the micturition reflex, resulting in less transfer of bladder signals to the pontine micturition center (figure 6). The descending efferent pathways from the brain to the bladder are not suppressed. As a consequence the involuntary detrusor contractions are suppressed, without inhibiting voluntary voiding. Another mechanism to inhibit bladder overactivity consists of sacral nerve stimulation (SNS) directly suppressing bladder preganglionic neurons of the efferent part of the micturition reflex.(5) De Groat et al. have indeed documented the existence of inhibitory pathways from somatic and visceral afferents to the sacral preganglionic efferent neurons. (37-40)
In this way, detrusor contractions can be inhibited by stimulation of the afferent anorectal branches of the pelvic nerves, afferent sensory fibres in the pudendal nerve and muscle afferents from the lower limbs.(33)

![Diagram of neural pathways](image)

**Figure 6:** Inhibition of detrusor contractions by suppressing interneuronal transmission on the ascending part of the micturition reflex, through pudendal afferent nerve stimulation(5)

**How can electrical neural stimulation reduce pelvic pain?**

An additional effect of sacral neuromodulation is the decrease of pelvic pain, which can be explained through the gate theory: pain from a visceral origin can be reduced when somatic afferent stimuli from the same dermatome enter the spinal cord. For example afferent signals from the bladder can be interrupted by posterior tibial nerve stimulation.(5)

### 1.6.2 Technique

The implantable device system consists of a lead with a quadripolar electrode which is mostly placed in sacral foramen S3 (or in Alcock’s canal in pudendal nerve stimulation), an extension cable and a neurostimulator which is placed subcutaneously (figure 7).(5)

![Image of implantable pulse generator](image)

**Figure 7:** definitive IPG in subcutaneous tissue of gluteal region (41)
Usually the implantation consists of two stages. In the first stage, a definitive lead is placed adjacent to the dorsal S3 root (figure 8). The lead is connected to an external neurostimulator device through a subcutaneous tunnel (figure 9). The effect of the neurostimulation is evaluated during a testing period of one to four weeks. If the urinary symptoms improve more than 50%, the patient is qualified for the second stage. In the second stage, the extension is dislodged and the permanent implantable pulse generator (IPG) is placed into the soft tissue of the gluteal region. The brand name of the neurostimulator device is InterStim® (Medtronic).

Some surgeons prefer to do a one-stage procedure. In this case, the patient undergoes a sacral neuromodulation (SNM) test, in which temporary leads are used. This is called percutaneous nerve evaluation (PNE). If the symptom improvement exceeds 50%, the definitive lead and the IPG are inserted during one intervention. (23, 27, 42, 43)

After permanent IPG implantation the stimulator settings can be fine-tuned and the system can be turned off and on noninvasively through an electronic programming device. (5)

![Figure 8: Site of stimulation of sacral root by the tined lead (41)](image1)

![Figure 9: Testing phase with tined lead and external neurostimulator device (41)](image2)
1.6.3 Pudendal nerve stimulation
In case of a pudendal implanted device, the compound pudendal nerve is stimulated. This nerve consists mainly of afferent fibres from S1, S2 and S3 sacral roots but also of efferent fibres to striated pelvic floor muscles. (29) Figure 10 shows the anatomical path of the pudendal nerve: it runs through the intrapiriform foramen (number 2), then turns around the ischial spine (number 3) and finally passes through the lesser sciatic foramen to end in the ischiorectal fossa. At this place it runs through Alcock’s canal, and this is the site where the nerve is stimulated by the tined lead. (44) In a single-blinded randomized trial of Peters et al. adult patients (with voiding dysfunction) with simultaneous implantation of both sacral and pudendal nerve quadripolar tined lead reported a greater reduction of symptoms with the pudendal lead than with the sacral lead. (45) Spinelli et al. also observed a statistically significant improvement with pudendal nerve stimulation in patients with refractory neurogenic bladder. (46) In most cases pudendal nerve stimulation is chosen after failure of sacral nerve stimulation. Peters et al. report a positive effect of pudendal nerve stimulation in 93.2% of the patients in whom sacral neurostimulation had failed. (47)

Figure 10: Anatomical course and stimulation site of the pudendal nerve (44): 1 = pudendal nerve, 2 = intrapiriform foramen, 3 = ischial spine

1.6.4 Evidence of neuromodulation in a pediatric population
Only five former studies have been published about the use of sacral neuromodulation in children, all of them consisting of small numbers of patients. Guys et al. evaluated the effect of sacral neuromodulation in 42 children with neurogenic bladder (mainly due to spina bifida) through a prospective randomized controlled study. There was some improvement, but this was not significantly different from the control group, which received conventional treatment. (48) Humphreys et al. followed 23 children with dysfunctional elimination syndrome (DES) in a multicenter trial. They reported a complete or partial improvement of urinary incontinence in 84% of the patients. There was also amelioration of nocturnal
enuresis, bladder pain, urgency, frequency and constipation. Some patients were able to decrease catheterization frequency and the medication needed postoperatively also decreased. (30) McGee et al. found that the use of incision-less first stage and second stage without fluoroscopy resulted in less radiation exposure. This technique implies the use of a subcutaneous bolus of methylene blue to mark the site of the lead connector. In this way, fluoroscopy is no longer needed in the second stage to place the IPG. (18) Haddad et al. performed a multicenter, open label, randomized crossover study including 33 children with urinary and/or fecal incontinence due to neurogenic bladder or anatomical malformation. Sacral neuromodulation was more effective than conservative treatment for both types of incontinence (p= 0,001). (11) In a prospective single center survey Roth et al. evaluated SNM as treatment for 20 patients with refractory DES. Urinary incontinence, frequency, urgency, constipation and nocturnal enuresis improved in the majority of the children.(49) The foregoing shows that most of the surveys report positive effects of SNM in a selected pediatric population, however they hardly obtain significant results due to the small number of patients included in the studies.

1.6.5 Side effects of neuromodulation in a pediatric population
Reported complications are seroma formation, skin sensitivity over the device site, device failure, lead migration, faulty connection, wound infection and the need for lead revision/replacement. The overall complication rate varies from 18% to 22%. (11, 30, 48, 49) The revision rate in adults is clearly lower (between 5% and 16%). (50, 51) However Van Kerrebroeck et al report an increase of the complication rate in adults over time (from 19,9% at one year to 42,1 at 5 years of follow-up).(28) Children need to undergo general anesthesia for these revisions, where as adults can have these some of these reinterventions under local anesthesia.(52)
A specific complication in a pediatric population, especially in pubertal children, is loss of efficacy because of somatic growth. This growth can cause lead migration, fracture and stretching. However the quadripolar electrode allows some growth. Other concerns about using SNM in children are the long term effect on bladder development and the life span of the battery (8 years according to van Kerrebroeck et al). (11, 28, 52)

1.6.6 Recurrence rates
Only two studies reported information about the recurrence of symptoms after device deactivation. Roth et al. found that the symptoms returned in three (60%) of the five patients who deactivated the device. Haddad et al. reported a sustained response after device deactivation in 5 patients. This could be explained by training of deficient neural pathways or by accelerating nerve maturation through SNM therapy.(11, 49)
1.6.7 Patient satisfaction and quality of life with neuromodulation

Beside the clinical effect of SNM, it is also important to assess the impact on the quality of life (Qol) and the satisfaction in patients with SNM. This is not documented for children, but there are a few studies that have investigated this in adults. Cappellano et al. and Das et al. both reported significant improvement in health-related Qol and depression in patients implanted with the stimulation device, until at least 12 months of follow-up. This improvement strongly correlated with the decrease in frequency of urinary incontinence episodes. Especially the patient’s perceived ability to carry out daily activities and work showed the greatest amelioration.(53, 54) Eighty to ninety percent of the patients would undergo the treatment again.(55, 56) Limitations and concerns experienced by patients were mostly about MRI, pregnancy, reimbursement, problems with metal detectors (for example at airports) and regular pain at the implantation site. Patients with more than one pelvic floor disorder reported a significantly lower satisfaction. The reason is that a more complex pelvic floor disorder results in a higher chance of moderate SNM effect, and this correlates with the patient satisfaction.(56)

Obviously these results can’t be generalized for children but one can assume that the quality of life would also improve in children with a good clinical response of the SNM treatment. Consequently surveys that focus on the Qol aspect in children are necessary to investigate this topic.

1.6.8 Cost-effectiveness

In this time of growing costs of health care and limited budgets, it is essential to consider the cost-effectiveness of a new therapy. The price of a two-stage procedure in Belgium is 12000 euro, when performed as an outpatient procedure. Differences for other countries may be important, as even the price of the device is different in other countries.

There are no surveys about cost-effectiveness of sacral neuromodulation in a pediatric population, but there are limited data about the cost-effectiveness in an adult population. Siddiqui et al. found that sacral nerve stimulation in adults with refractory urge incontinence was more expensive, but also more effective than botulinum toxin A during a period of two years. The incremental cost-effectiveness ratio (ICER) of SNM during a 2-year period was $116 427 per quality adjusted life-year (QALY) (2008 U.S. dollars). This corresponds to approximately 85 000 euro per QALY. Given the societal willingness to pay threshold of 30 000 euro per QALY in Belgium, SNM is not cost-effective.(57)

Leong et al. reported that SNM for idiopathic overactive bladder becomes cost-effective only after four years (using a societal willingness to pay threshold of 40 000 euro per QALY) and remains cost-effective during five years when SNM is performed under local anesthesia. Using a threshold of 30 000 euro per QALY, SNM would start to be cost-effective after five years. When PNE or bilateral testing is used, SNM is not cost-effective (ICER> 40 000 euro/QALY). (58) The principal cause for PNE not to be cost-effective is that it results in a lower response rate, which causes less QALY’s. (59, 60) Aboseif et al.
showed that voiding-related health care costs decreased after InterStim therapy because of less outpatient visits for urinary symptoms, less diagnostic and therapeutic procedures and less drug costs. However they did not take into account the cost of SNM placement/revision. (55)

To obtain more accurate economic analyses, more information about the impact of incontinence on Qol, about the long-term complications and about the indirect costs of incontinence (loss of productivity) are needed. (57, 58)

In addition, none of the surveys was conducted in Belgium (but in New Zealand, U.S. and the Netherlands) and the costs of therapies and surgery may be different in other countries. Finally, the results of cost-effectiveness in adults can't be extrapolated without any problem to children: one can expect that the costs will be higher in children because of a higher complication rate and need for revisions due to somatic growth.

1.7 Objectives of the study
SNM has proven to be effective in adults with refractory frequency, urgency, urge incontinence and urinary retention, but very little is known about SNM in children. A few studies hitherto have reported a positive effect of SNM in a pediatric population, however they hardly obtain a significant result because of the small number of patients. The evidence about SNM in children is obviously very limited. In addition, it would be interesting to specify the indications that benefit from SNM.

This retrospective study aims to evaluate the clinical outcome of InterStim therapy for different indications in a pediatric patient population and to identify the lower urinary tract conditions in which SNM is most effective.

My task consisted of retrieving information from the electronic patient files about the diagnosis, therapy, urologic symptoms, complications and patient satisfaction of the children who underwent InterStim therapy in the University Hospital in Gent. After sorting this data in a database, I performed statistical analysis of the results.
2 Methods

Between March, 1996 and May, 2010, 3 boys (mean age 15 years) and 15 girls (mean age 14 years) younger than 18 (9 to 17 years) with persistent urinary tract dysfunction underwent sacral and/or pudendal nerve stimulation with the InterStim system. They were all included in this retrospective study. The mean follow-up time was 28.8 (+/- 43.83) months after implantation with a median of 11 months (range 1 to 180).

Seven girls had Fowler’s syndrome (one of them also had bladder overactivity). Three girls and 1 boy had bladder overactivity. Two girls and 1 boy had neurogenic bladder due to spina bifida, 1 boy suffered from neurogenic bladder due to Guillain-Barré syndrome and 1 girl had neurogenic bladder due to anal atresia (table 2). The preoperative symptoms are represented in table 3.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAB</td>
<td>4</td>
</tr>
<tr>
<td>Dysfunctional elimination syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Fowler’s syndrome</td>
<td>7</td>
</tr>
<tr>
<td>Neurogenic bladder sphincter dysfunction (NBSD)</td>
<td></td>
</tr>
<tr>
<td>Spina bifida (meningomyelocele)</td>
<td>3</td>
</tr>
<tr>
<td>Anal atresia</td>
<td>1</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

*Table 2: Overview of indications*

<table>
<thead>
<tr>
<th>% Male (No.)</th>
<th>% Female (No.)</th>
<th>Overall % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>urinary incontinence</td>
<td>33 (1)</td>
<td>73 (11)</td>
</tr>
<tr>
<td>nocturnal enuresis</td>
<td>67 (2)</td>
<td>40 (6)</td>
</tr>
<tr>
<td>encopresis</td>
<td>0 (0)</td>
<td>20 (3)</td>
</tr>
<tr>
<td>CIC</td>
<td>33 (1)</td>
<td>27 (4)</td>
</tr>
<tr>
<td>UTI</td>
<td>33 (1)</td>
<td>80 (12)</td>
</tr>
<tr>
<td>urgency</td>
<td>67 (2)</td>
<td>53 (8)</td>
</tr>
<tr>
<td>pain</td>
<td>0 (0)</td>
<td>33 (5)</td>
</tr>
</tbody>
</table>

*Table 3: Overview of preoperative symptoms*

The selection of patients for InterStim therapy was done on a case by case basis. All of them received urodynamic evaluation preoperatively. In total, 44% had urodynamically proved detrusor overactivity (table 4 and 5). If Fowler’s syndrome was suspected a qualitative needle EMG was performed to confirm the diagnosis.
<table>
<thead>
<tr>
<th>Urodynamic variable</th>
<th>Mean (+/- SD) (number of patients of whom data were available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cystometric bladder capacity</td>
<td>321.9 ml (+/- 151.08) (14 pts)</td>
</tr>
<tr>
<td>maximum post-voiding residual</td>
<td>104.4 ml (+/-140.87) (17 pts)</td>
</tr>
<tr>
<td>maximum flow rate</td>
<td>17.8 ml/s (+/-12.82) (14 pts)</td>
</tr>
<tr>
<td>pressure at peak flow</td>
<td>36.8 cm H2O (+/-21.62) (10 pts)</td>
</tr>
</tbody>
</table>

*Table 4: Overview of preoperative urodynamic parameters*

<table>
<thead>
<tr>
<th>Urodynamic variable</th>
<th>% Male (No.)</th>
<th>% Female (No.)</th>
<th>Overall % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urodynamically proved detrusor overactivity</td>
<td>67 (2)</td>
<td>40 (6)</td>
<td>44 (8)</td>
</tr>
</tbody>
</table>

*Table 5: Distribution of detrusor overactivity*

All children were extremely refractory to conventional therapy, containing intensive medical treatment and behavioral therapies. All non-neurogenic patients (n=13) received urotherapy/medical therapy first, followed by 2 weeks in hospital training by a pediatric urotherapist, with screening and support offered by a child psychologist. Only in some of the 24% patients with persisting symptoms after this therapy, SNM was considered.

The urotherapy consisted of correcting voiding and drinking patterns and was ambulatory or in the form of a ‘voiding school’. It embraced different treatment modalities (sometimes in combination): cognitive bladder training, capacity increasing exercises, daytime alarm, biofeedback training, percutaneous nerve stimulation (SANS)(62) and transcutaneous nerve stimulation (TENS)(63). Six patients were treated with antibiotic prophylaxis because of recurrent urinary tract infection. In patients with low bladder capacity or urgency, anticholinergic drugs were added when OAB was suspected. Ten patients were treated with off label treatments: Duloxetine and Solifenacin. Six patients had undergone intravesical injections of botulinum toxin A (one of them 5 times). Despite all these therapies, none of them was cured.

Thirteen patients underwent a two-stage procedure with a test phase by using a definitive tined lead with an external test-pulse generator.(64) During a period of approximately 1 to 2 weeks, the result of the test was evaluated by means of a voiding diary. If the testing phase was successful, the extension was dislodged and the implantable pulse generator (IPG) inserted (n =10).(27, 65) In five patients a test phase was performed by placing a temporary PNE wire percutaneously in the S3 foramen. Three patients with a successful test phase, were implanted with the IPG and the definitive lead at the same time (one-stage procedure).(27, 43) Two patients still had a two-stage procedure after successful PNE (figure 11).

Criteria for placement of an IPG were one of the criteria mentioned in table 6, in addition to patient satisfaction. The implantation rate was 83% (15/18). The devices (InterStim I/II) were placed by an experienced functional urologist according to the technique of Spinelli (46, 64, 66) and the IPG was implanted in the buttock position.(67)
Sixteen patients received sacral nerve stimulation from the start. In one patient bilateral PNE could not obtain an S3 stimulation. Because of that, a pudendal 2-stage implant was chosen from the start. For another patient the same was done because of a sacral lipoma. Five patients who initially had a sacral neurostimulator, received a pudendal neurostimulator following a revision (two of them because of dislocation and the other three due to unsuccessful S3 neuromodulation) (figure 12).
Figure 12: Distribution of sacral versus pudendal stimulators

Daytime incontinence was evaluated in reduction in number of episodes and quantity of urine loss measured as grams/day in a 24 hour pad test. Voided volumes were documented in voiding diaries. Post void residual volume was measured by ultrasound or in CIC patients by post-void CIC volumes. Other information was retrieved from consultation reports, uroflowmetry examination reports and surgery records from the electronic patient files. These evaluations were done after approval of the local ethical committee (registration number B670201110913) and after obtaining informed consent from the patients or their parents. Criteria of success are defined in table 7.

<table>
<thead>
<tr>
<th>Criteria of success</th>
<th>Full response</th>
<th>Partial response</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt;90% objective improvement for at least one of the implantation criteria AND 100% patient satisfaction</td>
<td>50-90% Objective improvement for at least one of the implantation criteria AND Patient satisfaction</td>
<td>&lt;50% Objective improvement OR No patient satisfaction</td>
</tr>
</tbody>
</table>

*Table 7: Criteria of success*
Statistical analysis is performed with SPSS®, version 19.0 software. Wilcoxon matched-pairs signed-rank test is used to compare the number of incontinence episodes weekly before and after treatment, the amount of urine loss (gram) before and after treatment, catheterization frequency before and after treatment and bladder capacity (ml) before and after treatment: these scale variables consist of two paired samples (non-parametric). Mann-Whitney U test is performed to compare the test interval in patients with and without infection (non-parametric, unpaired samples). The used significance level is $\alpha = 0.05$ and p-values are 2-tailed in all tests. The Shapiro-Wilk test is used as normality test, because it is most suited for small samples: $p<0.05$ for all variables used in the tests except for the CIC frequency, the bladder capacity and the test interval, however QQ-plot and histogram clearly show a non-Gaussian distribution in these variables (null-hypothesis is erroneously rejected because of insufficient power of the Shapiro-Wilk test). Results are represented as means and standard deviation.
3 Results

In 3 patients (2 with Fowler’s syndrome and 1 with neurogenic bladder due to spina bifida) the testing phase (with definitive leads) was unsuccessful, and consequently the IPG was not implanted. All other children met the criteria for IPG implantation (table 6). A summary of the symptoms and the post-voiding residual during trial period is given in tables 8 and 9.

<table>
<thead>
<tr>
<th></th>
<th>% Male (No.)</th>
<th>% Female (No.)</th>
<th>Overall % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>3</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>urinary incontinence</td>
<td>33 (1)</td>
<td>27 (4)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>nocturnal enuresis</td>
<td>67 (2)</td>
<td>27 (4)</td>
<td>33 (6)</td>
</tr>
<tr>
<td>encopresis</td>
<td>0 (0)</td>
<td>7 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>CIC</td>
<td>33 (1)</td>
<td>20 (3)</td>
<td>22 (4)</td>
</tr>
</tbody>
</table>

*Table 8: Overview of symptoms during trial period*

<table>
<thead>
<tr>
<th>Urodynamic variable</th>
<th>Mean (+/- SD) (number of patients of whom data were available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>maximum post-voiding residual</td>
<td>53.5 ml (+/-44.84) (7 pts)</td>
</tr>
</tbody>
</table>

*Table 9: Overview of post-voiding residual during trial period*

Analysis of the different subgroups (OAB, Fowler’s syndrome, neurogenic bladder and DES) is performed to detect indications with a high chance of resulting in a good outcome.
3.1 Bladder overactivity

In the OAB group 3/4 had urinary incontinence before SNM treatment (graph 1) with an average of 4.3 (+/- 1.53) daily incontinence episodes and 142 (+/- 51.6) g/day, which decreased to a mean of 2.4 (+/- 1.25) incontinence-episodes/day and 4.8 (+/- 2.84) g/day with the test stimulator. After InterStim therapy urinary incontinence resolved in 2/3 (full response) and was unchanged in 1.

Preoperatively 3/4 suffered from nocturnal enuresis with a mean of 6.3 (+/- 1.16) enuresis events weekly and 124 (+/- 161.2) g/night. After SNM treatment, nocturnal enuresis resolved in 1/3 (full response) and improved in 2/3.

Before SNM treatment, 4 children complained of urgency (with or without incontinence) which resolved in 2, improved in 1 and remained unchanged in 1 after InterStim therapy.

Three-fourths of the OAB group developed urinary tract infections (UTIs) at least twice yearly before implantation, and none of them had recurrence in a period of approximately 12 months after InterStim therapy.

Mean daily voiding frequency was 6.8 (+/- 2.22) before SNM treatment, 4.8 (+/- 2.36) during the trial period and unknown after placement of the permanent device.

All in all 1 patient with OAB had her lead explanted due to failure (25%), 2 were completely continent during the day (one of them also had less enuresis) (full response in 50%) and 1 had less enuresis (partial response in 25%).

Graph 1: Number of patients with LUT symptoms preoperatively, during trial period with external test stimulator and after IPG implantation, among patients with bladder overactivity
### 3.2 Fowler’s syndrome

![Graph 2: Number of patients with LUT symptoms, CIC and encopresis preoperatively, during trial period with external pulse generator and after IPG implantation, among patients with Fowler’s syndrome](image)

Of the 7 children with Fowler’s syndrome 5 suffered from urinary incontinence before the InterStim therapy (graph 2), with an average of 4,5 (+/- 3,83) daily incontinence episodes and 314 (+/- 160,5) g/day. In the testing phase 4/5 became completely continent and 1/5 had a decrease from 5 to 3 incontinence episodes a day consisting of very small volumes of urine loss (with an average of 8 gram/day). After InterStim placement in four patients (one didn’t achieve the implantation criteria), 2/4 were completely continent, 1 had improvement of incontinence and 1 had a failure of InterStim therapy.

Before InterStim therapy, nocturnal enuresis was a complaint in 3/7 with a mean of 7,0 (+/-0,00) wet nights weekly and 247 (+/-4,2) g/night. After the IPG implantation enuresis improved in 1 patient and remained unchanged in 2.

One girl with Fowler’s syndrome had encopresis before the InterStim therapy, which completely resolved after IPG implantation.

Preoperatively, 3/7 had urinary retention and therefore required treatment with clean intermittent catheterization (CIC) with a mean of 5,7 (+/-2,08) times daily. After permanent device placement 1/3 no longer needed CIC and 2/3 had a decrease in frequency to an average of 3,5 (+/-0,71) times daily.

Before SNM therapy, 5/7 patients had 3 or more urinary tract infections yearly. During a follow-up period of approximately 12 months after InterStim placement 4/5 had no UTIs anymore and 1/5 had 1 UTI.
A total of 3/7 patients complained of urgency incontinence preoperatively, which improved in 3/3 after InterStim therapy.

All in all 4 (57%) of the 7 patients with Fowler’s syndrome had improvement of their symptoms: 2 (29%) had a partial response and 2 (29%) had a full response. InterStim therapy failed in 3 (43%) children: two of them didn’t meet the implantation criteria and the other had her lead and IPG removed after 40 months.

3.3 Neurogenic bladder

![Graph 3: Number of patients with LUT symptoms, CIC and encopresis preoperatively and after IPG implantation, among patients with neurogenic bladder](image)

Of the 5 patients with neurogenic bladder 3 had urinary incontinence before SNM treatment (graph 3). During the trial period, urinary incontinence resolved in 2/3. Postoperatively, urinary incontinence improved in 1/3 with a decrease from 2 to 1 incontinence episodes daily, and remained unchanged in 2/3. Preoperatively, 2/5 suffered from nocturnal enuresis, with an average of 5,5 (+/-2,12) weekly enuresis events, which decreased to an average of 0,8 (+/-0,35) enuresis events weekly after the InterStim therapy. Two children in the neurogenic bladder group had encopresis before SNM treatment which resolved in 1 but persisted in the other child after IPG implantation.

Before InterStim placement, 2/4 required treatment with CIC, with a mean daily catheterization frequency of 4,5 (+/-0,71) which decreased from 5 to 3 times daily in 1/2 and was no longer needed in 1/2 after SNM treatment.

In 3/5 patients with at least one UTI yearly before SNM, the number of UTIs remained unchanged in 1/3, decreased in 1/3 and is unknown in 1/3.
Eventually the lead was explanted in all patients with neurogenic bladder due to spina bifida (n=3) because of unsatisfactory results (failure in 60%) (one of them never had a definitive IPG after unsuccessful trial period). The patient with neurogenic bladder due to anal atresia had less urgency, 86% less enuresis episodes and was completely continent during the day at 1 year follow-up. After a period of three years, she became incontinent again (with 50% less incontinence episodes, compared to the baseline situation) (partial response). The patient with Guillain-Barré syndrome had less urgency symptoms and 75% less enuresis episodes weekly (partial response).

### 3.4 Dysfunctional elimination syndrome

In one patient with DES the number of UTI’s decreased from 3 yearly before to approximately once yearly after InterStim therapy, and the urinary incontinence (with an average of 3 incontinence-episodes/day and 4.7 g/day preoperatively) resolved after SNM treatment (full response). The other patient with DES had important improvement of perineal/pelvic pain and dysuria and a decrease of post-voiding residual from 360cc to 30cc after IPG implantation (full response).

Mean daily voiding frequency was 7.8 (+/-1.02) before SNM treatment, 6.2 (+/-0.21) during the trial period and unknown after placement of the permanent device.

### 3.5 Adverse events

Eight patients were reoperated for complications, excluding explantation of the IPG. The indications were pacemaker infection (n=2) and dislocation of the pacemaker/loss of effect (n=6). Pain at the implantation site was another reported complication (n=2) (table 10). Two patients required reintervention because of battery depletion, which cannot be considered a complication but rather a sign of success (long term use of the battery).

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. Pts (% of all patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pacemaker infection</td>
<td>2 (11)</td>
</tr>
<tr>
<td>dislocation of the pacemaker/loss of effect</td>
<td>6 (33)</td>
</tr>
<tr>
<td>pain at the implantation site</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

Table 10: Adverse events
3.6 Overall postoperative results

3.6.1 Urinary incontinence

Table 11 and graph 4 show the results of the InterStim therapy. Globally the number of patients with urinary incontinence decreased with 42% (from 12 to 7), and of the remaining 7 with incontinence 2 had an important decrease of daily incontinence episodes (table 12) and of volumes of urine loss (the other 5 had their lead explanted due to failure). The number of incontinence episodes improved statistically significant from 23.2 (+/- 12.44) weekly to 1.3 (+/-2.63) among the 12 patients with incontinence preoperatively (p=0.027; Wilcoxon matched-pairs signed-rank test). The quantity of incontinence decreased from 183 (+/- 156.3) grams to 2 (+/-2.9) grams, among the 12 patients with incontinence before SNM treatment (p=0.317; Wilcoxon matched-pairs signed-rank test). The most remarkable decline in proportion of patients with incontinence is found in the group with bladder overactivity, followed by the group with Fowler’s syndrome (graph 5) (DES was not taken into account because the group consists only of 2 patients).

<table>
<thead>
<tr>
<th>% Male (No.)</th>
<th>% Female (No.)</th>
<th>Overall % (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>urinary incontinence</td>
<td>0 (0)</td>
<td>47 (7)</td>
</tr>
<tr>
<td>nocturnal enuresis</td>
<td>67 (2)</td>
<td>33 (5)</td>
</tr>
<tr>
<td>encopresis</td>
<td>0 (0)</td>
<td>7 (1)</td>
</tr>
<tr>
<td>CIC</td>
<td>33 (1)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>urgency</td>
<td>33 (1)</td>
<td>40 (6)</td>
</tr>
</tbody>
</table>

Table 11: overview of postoperative symptoms
3.6.2 Nocturnal enuresis, encopresis and CIC

The rate of patients with nocturnal enuresis decreased with 12% (from 8 to 7) (graph 4), and of the remaining 7 with enuresis 5 had an important decrease of weekly enuresis events (table12). The quantity of patients with encopresis decreased with 67% (from 3 to 1), the number of patients who required CIC with 40% (from 5 to 3) and the number with urgency with 30% (from 10 to 7 patients) (graph 4 and table 11). The average frequency of catheterization decreased significantly from 5.2 (+/- 1.64) times daily before treatment to 2.0 (+/- 1.87) times daily after treatment (p=0.038; Wilcoxon matched-pairs signed-ranks test).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Preoperative</th>
<th>Trial period</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler’s syndrome</td>
<td>Mean (number of patients of whom data were available)</td>
<td>4.0 (10)</td>
<td>0.9 (11)</td>
</tr>
<tr>
<td>Neurogenic bladder</td>
<td>Mean (number of patients of whom data were available)</td>
<td>6.4 (8)</td>
<td>2.3 (7)</td>
</tr>
<tr>
<td>Bladder overactivity</td>
<td>Mean (number of patients of whom data were available)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysfunctional elimination syndrome</td>
<td>Mean (number of patients of whom data were available)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Table 12: Mean number of daily incontinence episodes and weekly enuresis events*
3.6.3 Bladder capacity
The mean bladder capacity of 305,3 ml (+/- 148,86) before treatment increased to a mean of 355,0 ml (+/- 197,41) after neuromodulation (graph 6). This improvement was not significant (p= 1,00; Wilcoxon matched-pairs signed-ranks test). Maybe this could become significant with a larger patient group.

![Graph 6: Mean bladder capacity (ml) before and after treatment](image)

3.6.4 Efficacy of pudendal nerve stimulation
In 4 of the 7 patients (57%) who received pudendal nerve stimulation the therapy was successful: 3 (43%) had a full response and 1 (14%) had a partial response.

3.6.5 Overall success rates
An initial full response was achieved in 50% (9/18) and a partial response in 28% (5/18) of the patients (short term follow-up). At the end of the study, our series of InterStim resulted in a full response rate of 40% (6/15), a partial response rate of 33% (5/15) and an explantation rate of 27% (4/15) because of failure (long term follow-up), among the 15 patients with a definitive IPG.
4 Discussion

Globally the number of patients with urinary incontinence decreased with 42%. The number of weekly incontinence episodes improved statistically significant with 94% (from 23,2 to 1,3) and the mean frequency of catheterization decreased significantly with 62% (from 5,2 to 2,0 times daily).

Bladder overactivity (50% full and 25% partial response), Fowler’s syndrome (29% partial and 29% full response) and DES (full response in 2/2) seem to be indications favorable for a good outcome whereas neurogenic bladder due to spina bifida is a less successful indication. This is in contrast with the positive results in neurogenic bladder in children, described by Guys et al. (not significant) and Haddad et al. (significant).(11, 48) However Scheepens and Keppene found that urinary incontinence with a neurological etiology (in adults) is an unfavorable characteristic, particularly in case of severe neural lesions and long existing symptoms.(68, 69) Probably SNM could still be an option for children with NBSD with a preserved neural pathway on one side, and if SNM is done shortly after diagnosis.(11, 63)

The success rate in Fowler’s syndrome in our series is 57%, which is lower than the 72% in adult women with Fowler’s syndrome reported by De Ridder et al.(7)

The result in DES is a confirmation of the series of Humphreys et al., reporting 16% resolution and 68% improvement of urinary incontinence.(30) The series of Roth et al. show higher success rates in DES, with a complete resolution of incontinence in 75%.(49)

Our long-term success rate of 73% is similar to the results in adults: in a prospective, worldwide study van Kerrebroeck et al. demonstrate a successful outcome, meaning at least 50% improvement of the primary voiding diary variables, in 68% of the patients with urge incontinence and in 71% with urinary retention.(28)

Unfortunately the rate of complications which required surgery in our study is high (44%) in comparison with the reported complication rates of 18% to 22% in other trials in children (11, 30, 48, 49). The main causes for revision were lead dislocation, loss of effect and infection. The high dislocation rate of 33% (6/18) may be explained by three reasons:

1. The older age of our patients (mean 14,4 +/- 2,50) compared to the other surveys (mean age between 10,1 and 12,2) may be a cause of more pubertal growth and thus more dislocations (11, 18, 30, 48, 49).

2. Some of the other studies have investigated children with neurogenic bladder (11, 48) who tend to be less active and to have more medical problems that can interfere with growth (52).

3. Children generally have a higher degree of physical activity compared to adult patients.

In spite of this, trials to adapt the tined lead for pediatric use are recommended.
The infection rate was 11% (2/18) (similar to the 12% reported by Haddad et al (11)), which can be explained in one patient by an extended test period in a two-stage procedure. The mean test interval was 9.5 (+/-6.36) days in the group with pacemaker infection, compared to 23.3 (+/-13.09) days in the group without infection. The test interval was not significantly longer in patients with an infection (p=0.2; Mann-Whitney U test), however efforts should be made to keep the interval as short as possible to prevent infection of the implant. Despite these complications SNM is safe in children (30, 49), but it is essential to inform patients and their parents about the possible need for revision, before signing the informed consent.(52)

A remarkable phenomenon is that symptoms (incontinence, urgency and nocturnal enuresis) were more improved during testing phase than after permanent device placement, which was also found by Humphreys et al.(30) So it is important to tell patients in trial period that symptoms will not necessarily be better after IPG implantation.

A specific difficulty in children is the change of bladder function over time (because of growth and development). This means that changes in bladder parameters are not always due to therapy, but may be the result of maturation. In addition one LUT condition can develop into another. Another problem is the absence of consensus about normal reference values for several urodynamic parameters for young children of different ages and the absence of validated tools to evaluate the outcome.(30, 35)

Limitations of this study are the retrospective design (and thus quite a lot missing data), the absence of a control arm, the small number of patients and the heterogeneous patient group. In addition the unblinded design (data were obtained from patient files completed by doctors, nurses and other caregivers) may have induced some bias. Consequently larger, controlled (with standard therapy as control arm), randomized surveys are recommended. Therefore a prospective study is actually planned in our center based on the encouraging results of the retrospective study.

In the future, there is still need for more research about clinical patient predictors favorable for a good outcome, making a testing phase unnecessary, and about the exact working mechanism of neuromodulation. Daneshegari and Stroller suggest the development of suitable animal models to better understand the mechanisms. Bosch proposes functional brain imaging to evaluate the effects of neuromodulation on the central nervous system. In addition, development of standardized tools to measure the effect of SNM, perhaps through urinary biomarkers, is required. Moreover additional information about the difference between pudendal and sacral nerve stimulation and pediatric indications for pudendal nerve stimulation is desirable.(70) Finally, the costs of SNM therapy in children should be investigated.
5 Conclusion

Overall, our series of InterStim therapy resulted in a long-term success rate of 73% (11/15): a full response in 40% (6/15) and a partial response in 33% (5/15). Given the fact that these children are extremely refractory to conventional behavioral and pharmacological therapy, a success rate of 73% is considered as satisfactory. This success rate could be increased by more selective use of neuromodulation for specific indications. In this survey a positive experience is observed for Fowler’s syndrome, bladder overactivity and DES. However it is hard to draw conclusions from this small study. If sacral responses are unsatisfactory during PNE or in case of failure of sacral neuromodulation, pudendal nerve stimulation proves to be a feasible alternative.

We can conclude that SNM therapy can be a valid option in children with LUT dysfunction refractory to conventional treatment (20% to 40% of the children), before considering more invasive and irreversible surgery. (11, 63) The results are comparable to those in adults, but the complication rate is a lot higher in children. Reduction of the complications and need for reintervention in children might be feasible by adapting the device specifically for children.
6 List of abbreviations

Ach = acetylcholine
CE = “European Conformity”
CIC = clean intermittent catheterization
CNS = central nervous system
CRD = complex repetitive discharges
DES = dysfunctional elimination syndrome
EBC = expected bladder capacity for age
ECM = extracellular matrix
ENS = electrical neural stimulation
EUS = external urethral sphincter
FDA = Food and Drug Administration
ICCS = International Children’s Continence Society
ICER = incremental cost-effectiveness ratio
IPG = implantable pulse generator
LUT = lower urinary tract
MNE = monosymptomatic nocturnal enuresis
NBSD = neurogenic bladder sphincter dysfunction
NE = norepinephrine
NO = nitric oxide
OAB = overactive bladder
PAG = periaqueductal gray
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMC</td>
<td>pontine micturition centre</td>
</tr>
<tr>
<td>PNE</td>
<td>percutaneous nerve evaluation</td>
</tr>
<tr>
<td>PSC</td>
<td>pontine storage centre</td>
</tr>
<tr>
<td>PTNS</td>
<td>posterior tibial electrical neural stimulation</td>
</tr>
<tr>
<td>QALY</td>
<td>quality adjusted life-year</td>
</tr>
<tr>
<td>Qol</td>
<td>quality of life</td>
</tr>
<tr>
<td>SANS</td>
<td>Stoller afferent nerve stimulation</td>
</tr>
<tr>
<td>SNM</td>
<td>sacral neuromodulation</td>
</tr>
<tr>
<td>SNS</td>
<td>sacral nerve stimulation</td>
</tr>
<tr>
<td>TENS</td>
<td>transcutaneous electrical neural stimulation</td>
</tr>
<tr>
<td>VUR</td>
<td>vesicoureteral reflux</td>
</tr>
</tbody>
</table>
7 References


Appendix: Poster made for the presentation of our abstract on the 23rd Annual ESPU Congress, May 9th - 12th 2012 in Zurich

8 Appendix

Introduction

Sacral neuromodulation (SNM) with an implantable pulse generator (IPG) has been applied in adults for more than a decade. Little is known about the effectiveness of sacral neuromodulation in children and even less is known about the results of pudendal nerve stimulation in the pediatric population. The results of our series of InterStim therapy in children with therapy resistant lower urinary tract dysfunction are described.

Materials and methods

- 18 patients (9 to 17 years old)
- Mean follow-up time was 28.8 months after implantation
- 7 underwent pudendal nerve stimulation and 16 underwent sacral nerve stimulation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fowler’s syndrome</td>
<td>7</td>
</tr>
<tr>
<td>Neurogenic bladder dysfunction</td>
<td></td>
</tr>
<tr>
<td>Spina bifida</td>
<td>3</td>
</tr>
<tr>
<td>Anal atresia</td>
<td>1</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Dysfunctional elimination syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Bladder overactivity</td>
<td>4</td>
</tr>
</tbody>
</table>

Results

1) Proportion of patients with incontinence, baseline and postop

2) The mean frequency of catheterization decreased from 5.2 (+/- 1.64) times daily before treatment to 2.0 (+/- 1.87) times daily after treatment (p=0.038; Wilcoxon test).

3) The number of incontinence episodes improved from 23.2 (+/- 12.44) weekly to 1.3 (+/- 2.63) among the 12 patients with incontinence preoperatively (p=0.027; Wilcoxon test)

4) Reported complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>number of patients with that complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacemaker infection</td>
<td>2</td>
</tr>
<tr>
<td>Dislocation of the pacemaker/loss of effect</td>
<td>6</td>
</tr>
<tr>
<td>Pain at the implantation site</td>
<td>2</td>
</tr>
</tbody>
</table>

5) In 4 of the 7 patients (57%) who received pudendal nerve stimulation the therapy was successful.

Conclusions

- Fowler syndrome, bladder overactivity and DES are good indications
- Severe neurogenic bladder due to spina bifida seems to be a less successful indication
- Pudendal nerve stimulation is a feasible alternative if S3 implantation is impossible or unsuccessful

- **Succes rate of 73% (11/15)**
Our abstract has been presented on two international congresses:

Oral Presentation: Application of sacral and pudendal nerve stimulation in children with a voiding disorder: a retrospective analysis
Nele Loret\(^1\), Luitzen A. Groen\(^1\), Erik Van Laecke\(^1\), Johan Vande Walle\(^2\), Piet B.Hoebek\(^1\) and Karel Everaert\(^1\), (1)Urology & Pediatric Urology, University Hospital Ghent, Ghent, Belgium, (2)Pediatric Nephrology, University Hospital Ghent, Ghent, Belgium

2. 23\(^{rd}\) Annual ESPU Congress - Zurich, Switzerland - 9-12-may-2012.
Poster Presentation: Results of sacral and pudendal nerve stimulation in children with neurogenic or non-neurogenic lower urinary tract dysfunctions
Luitzen Albert GROEN\(^1\), Nele LORET\(^1\), Erik VAN LAECKE\(^1\), Karel EVERAERT\(^2\) and Piet HOEBEKE\(^1\)
1) University Hospital Ghent, Paediatric Urology, Ghent, BELGIUM - 2) University Hospital Ghent, Urology, Ghent, Belgium