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Professional Paper

SACRAL NEUROMODULATION IN TREATING OVERACTIVE BLADDER PATIENTS – FIRST-TIME APPLICATION IN CROATIA

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SUMMARY – Sacral neuromodulation (SNM) is a safe, efficacious, and minimally invasive advanced therapy that involves electrical stimulation to sacral nerve root to modulate neural pathway. Indications for SNM include symptoms of overactive bladder (OAB), urinary incontinence, urinary retention, urgency and frequency and, regarding bowel dysfunction, fecal incontinence . In Europe and Canada, indication is also established for chronic constipation. The mechanism of action is still not fully elucidated and complete understanding is yet to be determined. It is proposed that SNM modulates neural circuits in both central and peripheral pathways, thus having an impact on the brain, as well as on the bladder-targeting neuronal activity. Another possible significant effect on irregular bladder activity is through inhibition of the bladder afferent pathways by stimulation of the pudendal nerve. Over the past two decades, with more than 300 000 treated patients, SNM has confirmed its efficacy to relieve refractory OAB symptoms, as well as urinary retention or fecal incontinence. First SNM applications in Croatia were uneventful and we are glad to offer our patients this novel therapy in the future.

Key words: *Sacral neuromodulation; Overactive bladder; Croatia*

Introduction

Sacral neuromodulation (SNM) is a safe, efficacious, and minimally invasive advanced therapy that involves electrical stimulation to sacral nerve root to modulate neural pathway with good long-term outcomes[1,2]. The first medical approval was obtained from the Food and Drug Administration in 1997, although it was introduced as a revolutionary concept 15 years before by Tanagho and Schmidt[3]. It is used to treat bladder, as well as bowel dysfunction. Indications for SNM include symptoms of overactive bladder (OAB), urinary incontinence, urinary retention, urgency and frequency and, regarding bowel dysfunction, fecal incontinence. It is offered to patients refractory to behavioral and pharmacological therapy that are mostly prescribed as the first choice[4]. In Europe and Canada, indication is also established for chronic constipation[5].

Most of the urologic patients that are treated with SNM have symptoms of OAB, which is defined by the International Continence Society (ICS) as a syndrome of urinary urgency, often with urinary frequency and nocturia, in the absence of local pathologic factors[6]. OAB is a daily and all-day problem for affected patients, which has an impact on all aspects of life, and its prevalence increases with age[7]. It reduces work productivity and affects mental health of individuals who

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avoid prolonged absence from a familiar environment, most often their own home. Such patients are more likely to have episodes of depression, they withdraw from social events, and reduce social contacts. They often spend time and energy planning every outing according to the available toilets. Affected patients have a higher rate of erectile dysfunction and, in general, decreased sexual desire. The costs increase not only for the patient, especially if incontinence is present, but also for the health care system as a whole[8,9]. Milsom *et al*. published a population-based prevalence study and concluded that the overall prevalence of OAB symptoms in individuals aged ≥40 years was 16.6%, with frequency (85%) as the most commonly reported symptom, followed by urgency (54%) and urge incontinence (36%)[10].

Even in patients with mild symptoms of OAB, if progressing during watchful waiting, conservative therapy is advised, usually starting with behavioral therapy followed by pharmacotherapy. In patients with refractory OAB symptoms, instillation of onabotulinum toxin A or SNM is considered. In Croatia, intravesical onabotulinum toxin A therapy has been available for OAB patients for a few years, while SNM is now available for the first time.

Mechanism of Action

The mechanism of action is still not fully elucidated and complete understanding is yet to be determined, especially having in mind effective results in patients with otherwise mutually contrary clinical dysfunctions such as urinary incontinence and urinary retention. SNM involves an implantable electrode in the area of the sacral nerve plexus, usually through S3 foramen, which continuously stimulates the nerve root. Concerning patients with OAB, results from most of the studies indicate that SNM inhibits detrusor muscle without influencing urethral resistance or contractility of detrusor muscle during the voiding phase[11]. It is proposed that SNM modulates neural circuits in both central and peripheral pathways[12], thus having an impact on the brain, as well as on the bladder-targeting neuronal activity. In OAB patients with neurogenic underlying condition, afferent C fibers can be involved in neurologic and inflammatory activation of voiding reflexes, in response to bladder distension. By blocking C fiber activity, SNM inhibits neurogenic detrusor overactivity and irregular voiding responses, thus contributing to reduction of OAB symptoms[13]. Another possible significant effect on irregular bladder activity is through inhibition of the bladder afferent pathways by stimulation of the pudendal nerve[14]. Results of other studies focused on the central nervous system suggest that certain patterns of increased brain activity in women with OAB, especially in responders to therapy, could be associated with better outcome[15].

In patients with non-obstructive urinary retention, it is presumed that inhibition of the vesicourethral guarding reflex by lowering sphincter tonus and blocking inhibition of urethral afferents is responsible for clinically better voiding results[16,17].

Indications

Although anticholinergics and beta-3 agonists have been proven to be effective and safe in patients with OAB, they may be inadequate in some cases and SNM is then considered. SNM represents an alternative to onabotulinum toxin A therapy in patients with refractory OAB, as it has shown good success rates and an acceptable safety profile.

The European Association of Urology guidelines recommend offering SNM to patients who have urgency urinary incontinence refractory to medical therapy and are willing to undergo surgical treatment. According to the American Urological Association guidelines, clinicians may offer SNM as third-line treatment in a carefully selected patient population characterized by severe refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo a surgical procedure[18]. Best results in terms of OAB symptom reduction are observed and expected in OAB patients with urinary incontinence (OAB-wet). Patients should be carefully chosen and properly evaluated prior to SNM procedure. Also, of great importance is to harmonize patient expectations with pre-SNM severity of symptoms. Substantial efficacy has not been demonstrated in patients with mixed urinary incontinence or solitary stress urinary incontinence. Younger patients and those with less severe cognitive deficits are prone to greater benefit of therapy[4].

As for patients with non-obstructive urinary retention, idiopathic urinary retention is one of the most challenging problems in neurological practice. Treatment in the form of clean intermittent catheterization (CIC), onabotulinum toxin A injection of the urethral sphincter and alpha blockers has been advised. However, some patients are not able to perform CIC, not

eligible for or not satisfied with the treatment proposed. In these patients, SNM should be considered as an option[19]. In a prospective, randomized study by Jonas *et al.*[20], the efficacy of SNM was investigated in patients with idiopathic urinary retention with 18-month follow-up. Results showed that patients implanted with the InterStim system had statistically and clinically significant reductions in the catheter volume *per* catheterization, 69% of treated patients eliminated catheterization at 6 months, and an additional 14% had a 50% or greater reduction in catheter volume *per* catheterization. The authors conclude that successful results were achieved in 83% of the implant group with retention compared to 9% of the control group at 6 months, which demonstrated effectiveness in patients with urinary retention refractory to other forms of treatment.

Our first three patients were selected according to the indications proposed. First patient was a 35-year-old male with symptoms of OAB-dry and no known neurological pathology. He had previously been treated with pharmacotherapy and onabotulinum toxin A. Second patient was a 50-year-old female with symptoms of OAB-wet after brain tumor operation and no significant improvement on pharmacotherapy. Third patient was a 52-year-old female with underactive bladder and consequently complete urinary retention after surgical procedure in the pelvis. In all patients, urodynamic study was performed prior to SNM procedure.

Technique

Initially, SNM procedure was a one-stage process, but in 2003 it was changed to create a two-step algorithm for permanent implantation. In our center, patient is preoperatively evaluated by the anesthesiologist and admitted to the hospital. In the first phase, placement of the test electrode is performed to evaluate the efficacy of SNM. It is recommended to give one dose of intravenous prophylactic antibiotics before implantation of a tined lead and implantable pulse generator (IPG). We performed evaluation procedure under general anesthesia, without muscle relaxants. The patient is placed prone and fluoroscopy is positioned appropriately. General landmarks of the sacrum are then identified and sketched. Under fluoroscopy control, a foramen needle is inserted into the S3 foramen at an angle of 60 degrees and optimal lead placement is ensured by placing the needle in such a way that it tracks the S3 nerve root. Correct lead placement is essential step in the procedure for better efficacy and successful outcome, i.e., lower amplitudes required to achieve beneficial results[21,22]. It is usually the most difficult and time-consuming step of the procedure. The neuromuscular activity should include great toe dorsiflexion and visualization of levator ani muscle contractions called bellows reflex. An appropriate motor and/or sensory response at a stimulus amplitude of less than 2 mA at all four electrodes is recommended by the ICS[23]. Aperture of the foramen needle is used to insert a directional guide, which facilitates passage of the introducer. Through the introducer sheath, the tined lead is carefully advanced to the position of the sacral nerve root. Pushing of the electrode is done under fluoroscopy to ensure appropriate entry direction and movement into the pelvis. The lead stylet and introducer sheath are then removed so that the leads could anchor their position. Once the electrode is positioned, test stimulation is applied to each of the four contacts at the external top of the electrode. After the electrode test, the lead is tunneled through an incision over the iliac crest and connected to a percutaneous extension cable. Usually, the connection site is manually spread to form a pocket. Then, the percutaneous extension cable is tunneled subcutaneously to the contralateral side and through the skin incision extracted and plugged into the external neurostimulator.

If the patients experienced ≥50% symptom improvement after lead implantation during stage 1, they are progressed to implantation of the IPG in stage 2[24]. Incision is made in the former connection site. Lead is disconnected and inserted directly into the IPG at the neurostimulator head and the percutaneous extension cable is removed. Skin is sutured and the procedure is finished.

Contraindications and Complications

Most commonly, adverse events include pain at the neurostimulator site (11.8%) and lead migration (7.9%)[25], which could lead to revision and/or surgical relocation of the device. In another study, the most common adverse events were pain at the stimulator site (15.3%), new pain (9.0%), suspected lead migration (8.4%), infection (6.1%), and transient electric shock (5.5%)[26]. The authors report that significant predictors of adverse events were history of trauma, change in body mass index class, enrolment in a pain clinic, duration of follow-up, and history of adverse events[26].

Contraindications to placing the device would include failure to respond to the test device in the 1st phase, patient inability to operate the device, and patient planning to undergo diathermy or magnetic resonance imaging study in the future.

Conclusion

Sacral neuromodulation is an effective method for voiding dysfunction or urinary retention in a refractory population, with studies demonstrating it to be an effective treatment with potentially long-term benefits. Over the past two decades, with more than 300 000 treated patients, SNM has confirmed its efficacy to relieve refractory OAB symptoms, as well as urinary retention or fecal incontinence. First SNM applications in Croatia were uneventful and we are glad to offer our patients this novel therapy in the future.

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Sažetak

SAKRALNA NEUROMODULACIJA U LIJEČENJU BOLESNIKA S PREKOMJERNO AKTIVNIM MOKRAĆNIM MJEHUROM – PRVA PRIMJENA U HRVATSKOJ

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Sakralna neuromodulacija (SNM) je sigurna, učinkovita i minimalno invazivna napredna terapija koja uključuje električnu stimulaciju korijena sakralnog živca s ciljem podešavanja aktivnosti neuralnih putova. Indikacije za SNM uključuju simptome prekomjerno aktivnog mokraćnog mjehura (PAMM), inkontinenciju mokraće, zadržavanje mokraće, urgenciju i učestalost, kao i fekalnu inkontinenciju. U Europi i Kanadi dodatno je postavljena indikacija za kroničnu opstipaciju. Mehanizam djelovanja još uvijek nije u cijelosti razjašnjen te potpuno razumijevanje tek treba utvrditi. Smatra se da SNM modulira neuronske krugove središnjih i perifernih živčanih putova čime utječe na aktivnost u mozgu, kao i na neuronsku aktivnost usmjerenu na mjehur. Drugi mogući značajan učinak na poremećenu aktivnost mokraćnog mjehura je inhibicijom aferentnih putova mjehura stimulativnim djelovanjem na pudendni živac. Tijekom posljednja dva desetljeća s više od 300.000 liječenih bolesnika SNM se sve češće rabi za ublažavanje refraktornih simptoma PAMM-a, kao i za liječenje zadržavanja mokraće te fekalne inkontinencije. Prvi postupci postavljanja SNM-a u Hrvatskoj protekli su bez komplikacija i zadovoljstvo nam je bolesnicima ponuditi ovu novu terapiju i u budućnosti.

Ključne riječi: *Sakralna neuromodulacija; Prekomjerno aktivni mokraćni mjehur; Hrvatska*