Sacral Nerve Modulation for Urinary Disorders: Overactive Bladder

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11.1 Introduction

Overactive bladder (OAB) syndrome is a combination of complex urinary symptoms and is defined as urinary urgency with or without urgency urinary incontinence, usually accompanied by frequency and nocturia, in the absence of urinary tract infection or other obvious pathologies [1].

OAB syndrome affects more than 400 million people worldwide [2]. The estimated prevalence is between 12 and 17 %, and one-third of patients experience urgency urinary incontinence [3, 4]. The prevalence increases with age, affecting 30–40 % of the population >75 years of age [2]. Frequency is the most commonly reported symptom (85 %), while 54 % complained of urgency and 36 % of urgency urinary incontinence [4]. Also this syndrome has an important impact on the patient's quality of life.

OAB symptoms are due to involuntary contractions of the detrusor muscle during the filling phase of the micturition cycle. These involuntary contractions are termed detrusor overactivity and are mediated by acetylcholine-induced stimulation of bladder muscarinic receptors [5]. It has been estimated that 64 % of patients with OAB have urodynamically proven detrusor overactivity and that 83 % of patients with detrusor overactivity have symptoms of OAB [6].

11.2 General Principles of Treatment

The treatment of patients with OAB is complex, and international guidelines suggest lifestyle interventions, pelvic floor reeducation, bladder retraining, and antimuscarinic drugs as first-line treatment options.

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11.2.1 Medical Treatment

While a conservative approach is justified initially, drug therapy is the main treatment in the management of women with OAB syndrome. The most recent systematic review [7], including six different drugs, supports the efficacy of antimuscarinic therapies in patients with OAB syndrome. They have been proven to be more effective than placebo, confirming a grade A of level of recommendation for OAB in women. Nevertheless, all types of antimuscarinic agents cause side effects, with dry mouth (30 %) and constipation (8 %) as the most frequent. Consequently, the compliance with immediate release preparations has been reported to be low, with only 18 % of patients continuing therapy at 6 months [8]. This has not improved despite the introduction of long-acting slow-release drugs. A recent retrospective study has shown persistence rates with the antimuscarinic therapy at 12 months ranging from 14 to 35 %, with little difference among different preparations [9]. The high discontinuation rate of antimuscarinic treatment may be due to intolerable side effects and insufficient improvement of symptoms. However, it is well known that younger patients were more likely to stop using antimuscarinic agents.

An important role has been proposed for the beta 3-adrenergic receptor in promoting urine storage in the bladder by inducing detrusor relaxation [10]. Mirabegron is a beta 3-adrenergic receptor agonist that has been developed for the treatment of OAB and represents a new class of drug therapy with proven efficacy and good tolerability [11]. Further long-term studies are needed to demonstrate the true efficacy and safety of the drug.

When conservative therapies fail, alternative treatments should be considered.

11.2.2 Minimally Invasive Techniques

New and minimally invasive techniques are available such as percutaneous tibial nerve stimulation (PTNS), intradetrusor injection of botulinum toxin (BTX), and sacral neuromodulation (SNM).

PTNS involves stimulation of afferent fibers of the posterior tibial nerve (L4–S3) accessed just above the ankle. In a recent meta-analysis on the effectiveness of PTNS, the subjective success rate was 61.4 % (95 % CI 57.5–71.8), and objective success rate was 60.6 % (95 % CI 49.2–74.7) [12], but the maintenance treatment was necessary to successfully treat the patients with OAB [13].

BTX is a neurotoxin derived from *Clostridium botulinum*, and its effect is to inhibit the release of acetylcholine, adenosine triphosphate, and substance P from the urothelium. The BTX injected into multiple sites in the detrusor muscle via cystoscopy should lead to bladder paralysis and consequently may reduce the symptoms of OAB, but its exact action is not completely understood [14]. A recent study on botulinum toxin type A (200 units) injected in the detrusor muscle showed that 31 % of patients with OAB were continent after 6 months, but urinary tract infection (31 %) and self-catheterization (16 %) were common [15]. Furthermore the effect

of BTX may last between 3 and 12 months, but robust evidence on long-term outcome is lacking [16].

11.3 Sacral Neuromodulation

SNM has been approved by the Food and Drug Administration (FDA) in 1997, and more than 150,000 patients have already received this treatment worldwide [17]. SNM is currently recommended by expert panels for the treatment of intractable OAB syndrome [18].

SNM therapy involves the use of mild electrical pulses to stimulate the sacral nerves. During the test phase of peripheral nerve evaluation (PNE), a temporary lead is placed, with patient under local anesthesia, next to the sacral nerve, usually S3, that gives intraoperatively the better motor response on the patient's pelvic floor. A positive motor response with or without a sensory response has been shown to be a better predictor than a sensory response alone of a positive test stimulation [19]. The subchronic phase is usually considered successful when there is at least 50 % improvement of symptoms. Patients with a successful treatment receive a permanent implant, which consists of a definitive electrode connected to an implantable pulse generator.

Migration of the temporary lead and failure of this technique to identify responders to permanent SNM led to the development of a two-stage implant technique [20]. With this technique a permanent tined lead is implanted under local anesthesia and connected to an external "screener" and left in place for 4–8 weeks. If the symptoms of patient improve by at least 50 %, the permanent implantable pulse generator is implanted in the soft tissue of the patient (usually in the buttock). The reoperation rate appears to be decreased with the introduction of tined lead technique [21].

11.3.1 Efficacy

The results of seven randomized trials have been reported in the literature [22–28], and they are consistently in favor of the implant. When complete continence was studied, almost 50 % of the implanted patients were continent at 6 months as opposed to 1.6 % in patients in the delay group, while a total of 87 % showed an improvement more than 50 % in the number of leakage episodes as opposed to 3 % in the delay group [29] (Table 11.1).

Weil et al. [28], Schmidt et al. [26], and Hassouna et al. [25] showed that the daily number of leakage episodes and of pads used was significantly lower 6 months after implantation in the stimulation group compared with baseline. Weil et al. [28] also observed that mean bladder capacity assessed by cystometry increased at 6 months compared with baseline in the stimulation group.

Although evidence from case series studies can be less reliable than evidence from randomized trials, because of the risk of confounding, it is notable that these results are similar to those of the randomized trials. In more than 40 case series

Table 11.1 Success rates at 6 months in the randomized trials

	Stimulation group (%)		No treatment group (%)	
References	Cured	Improved	Cured	Improved
Weil [28]	9/16 (56)	Not reported (29)	1/22 (5)	0/22 (0)
Schmidt [26]	16/34 (47)	10/34 (29)	0/42 (0)	2/42 (5)
Hassouna [25]	–	22/25 (88)	–	8/25 (32)

studies, about 39 % of patients with urgency urinary incontinence were cured following implantation, and 67 % of patients achieved 50 % or greater improvement in incontinence symptoms [29]. In addition, in the case series studies, the benefits of neuromodulation were reported to persist at follow-up periods 3–5 years after implantation.

Results of persistence of the clinical success in the long term appear to be conflicting. A randomized study [30] suggested some reduction of efficacy with time: a similar proportion (46 %) of patients with urgency urinary incontinence remained dry at 3 years and 6 months after SNM, but only 59 %, as opposed to 87 %, showed greater than 50 % improvement in the number of leakage episodes. Further, a multicenter 5-year prospective trial showed reduction of the number of leakage episodes and pads used in patients with urgency urinary incontinence and decrease in frequency and urgency and increase in mean voided volume per micturition episode in OAB dry patients [31].

By contrast, a 5-year follow-up study [24] on 121 patients with refractory OAB showed persistence of the clinical success in the long term: 84 % of the patients with urgency urinary incontinence and 71 % of the patients with urgency/frequency who had a successful outcome 1 year after implantation continued to have a successfully outcome after 5 years.

The use of SNM may also be recommended for particular populations such as the elderly. Despite age over 55 years and the presence of three or more chronic comorbidities were considered as negative predictive factors for successful outcome with SNM in urinary urge incontinence [32]; in our study [33] on 18 patients over 65 years affected by intractable OAB, 15 women obtained an overall success rate of 83 %. Among all women who underwent implantation of SNM, there was also a statistically significant improvement in the health-related quality of life. No major long-term complications occurred; minor ones happened in two patients (13.3 %) who complained of pain at the pulse generator site; in both cases the event resolved after 3 months using anti-inflammatory treatment. SNM can be considered a viable alternative for treating OAB syndrome in well-selected elderly women.

11.3.2 Quality of Life

Satisfaction and quality of life after SNM have also been studied. Quality of life improvements have been reported in patients with detrusor overactivity, and a strong

correlation was identified between the number of incontinence episodes and quality of life index.

Cappellano et al. [34] showed a significant improvement in the quality of life score in patients with urgency urinary incontinence who underwent SNM: at 18 months of follow-up, 90 % of subjects gave a positive response to treatment and 100 % of patients recommended it to a relative or friend. In addition, Foster et al. [35] showed that the majority of patients (84 %) were satisfied with SNM treatment.

11.3.3 Adverse Events

Adverse events associated with SNM implant have been extensively discussed in the literature. A recent study reported an explantation rate of 21 % and a surgical revision rate of 39 % [36]. The most common complications [25, 28, 31] are pain at the implant site (3–42 %), lead migration (1–21 %), wound problems (5–8 %), bowel dysfunction (4–7 %), infection (4–10 %), and pulse generator problems (5 %). The majority of adverse events do not require surgical intervention, but conservative treatment. The introduction of the tined lead and the two-staged procedure have positively affected the adverse event and reoperation rates. Lower incidences of pain (2.5 %), lead migration (0.6 %), and infection (2.5 %) were reported in a follow-up study [37]. Surgical revision was required in 16 % of patients including those with reduced efficacy (10 %) [37]. The learning curve and patient selection may have an additional beneficial effect on the reoperation rates [31].

11.3.4 SNM Versus Botulin Toxin

Studies comparing the effectiveness of the SNM versus BTX have produced conflicting results [15, 31]. A decision analysis model was constructed using values for efficacy and complications from the literature and the personal series. Markov state transition modeling was used with health states and transitions between states designed to fully account for the complex interplay of therapeutic efficacy and multiple possible complications. Overall outcomes and complications for the two operations (SNM vs. BTX injection) were yearly compared (Fig. 11.1), and the probability of success of the SNM was higher than the BTX injection (59 % vs. 48 %, $p < 0.05$, respectively).

11.3.5 Cost-Effectiveness

Few studies have examined the cost-effectiveness of SNM. Siddiqui et al. [38] suggested that SNM treatment strategy was more expensive ($ 15743 vs. $ 4392) but also more effective (1.73 vs. 1.63 quality-adjusted life years – QALYs) than BTX injections in the first 2 years of therapy. However Leong et al. [39] showed that SNM treatment was cost-effective after 5 years compared to BTX injection.

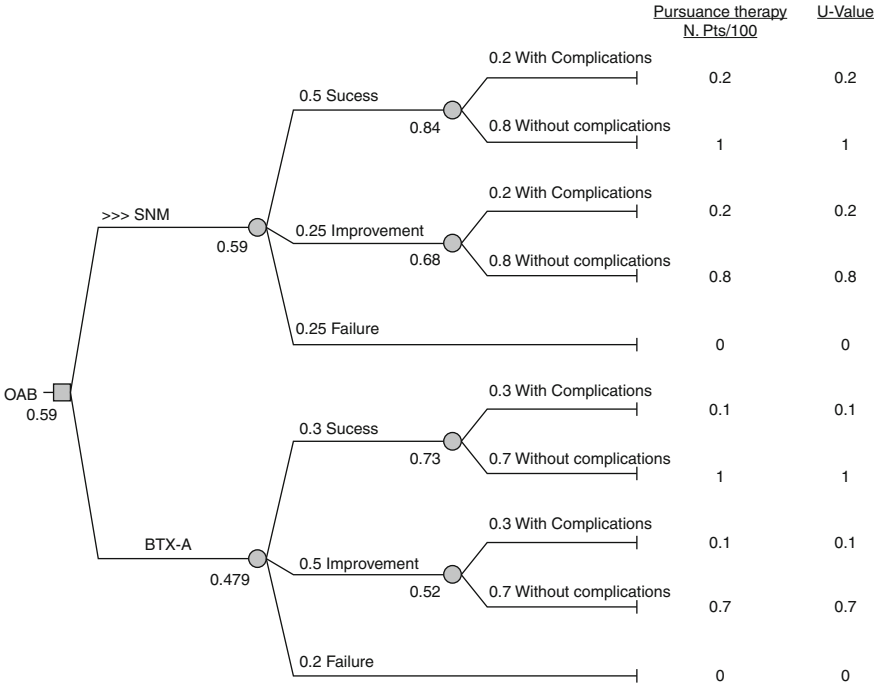

Fig. 11.1 Decision-makers on the clinical benefits between SNM and BTX

11.4 Conclusions

In conclusion, current evidence supports the short- and long-term efficacy of SNM in treating intractable OAB syndrome, and, in addition, there is a low incidence of adverse events, many of which do not require reoperation. Currently SNM stands as the single licensed second-line treatment for OAB, but more research is needed to improve the selection of patients and the identification of more prognostic factors and to clarify the reduction in effectiveness over time.

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