Patients with medication-refractory OAB symptoms should be further treated with neuromodulation

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Overactive bladder (OAB) is a condition defined by the International Continence Society (ICS) as urgency with or without urgency incontinence, usually with increased daytime frequency and nocturia.[1] Patients with OAB have significantly reduced quality of life.[2] Population-based surveys done in Canada have shown high prevalence (14%) in both sexes.[3] In a survey of over 19 000 adults in Canada and Europe, the overall prevalence of OAB was 12.8% in women and 10.8% in men.[4] The similar study in United States showed that overall, 16.5% of the U.S. population aged ≥18 years (about 33 million people) have symptoms of OAB.[5] The initial treatment of the OAB includes anticholinergic medications. Compliance and satisfactory results, however, are low after 1 year and range from 18% to 65%.[6,7] Patients with medication refractory OAB have the option of sacral neuromodulation (SNM), intravesical injection of Botulinum Toxin type A (BTX A) or surgery, such as bladder augmentation or diversion.

I strongly belief the most appropriate option for these patients is SNM. It is the most innovative treatment modality developed in recent years for the management of OAB and other voiding dysfunctions; it has also been approved by Health Canada for this indication since 1999. The ideal treatment should be effective, safe and financially sound. There is no question that SNM is effective. Brazzelli and colleagues systematic review found that 80% (4 randomized controlled trials) and 67% (30 case series) of patients became dry or achieved a >50% improvement in symptoms after implantation.[8] Our own data showed 84.8% success rate with a median follow-up of 50 months (Fig. 1).[10] Furthermore, in a recent study, overall satisfaction was reported as high as 90%.[9] There are very little initial complications with the device. The infection rate is under 5%; in our series of 96 implants, no infection was reported at all. There is a possibility of seroma formation which was described occasionally. In our experience, the reoperation rate due to malfunction of the device or lack of improvement was initially high at 40%. The main reason for revisions (50%) was poor response. The second most common indication (17%) for revision was local pain from the device. The median time for revision was 24 months. Review of the literature of 855 patients, showed 33% revision rate. Most of the studies, including ours, consist of sacral nerve stimulation non-tined lead data, which have higher complication rates associated with the open fasciotomy procedure and lead migration.[10] With the advances in the equipment and surgical technique, this rate was reduced to 26% with a combined revision rate of 32% in our experience. The biggest improvement was in the introduction of the tined-lead which can be implanted through percutaneus, minimal invasive technique. Some patients also complained of unpleasant sensations or pain. This, however, was usually resolved with reprogramming. Patients are followed on a regular basis the third and sixth month mark, and then yearly. The battery life was on average 113 months.

Patients with refractory OAB symptoms, other than SNM, have very few options left. Ileocystoplasty or diversion can be a very extensive surgery associated with complications and severe consequences; also, it has an overall low satisfaction rate. Other treatments available for these pateints include BTX A, which is still considered investigational in Canada. It is not approved in Canada for OAB and its use is off-label. The satisfaction rate, although in the 60% to 70% range, not long-lasting. One of the limiting factors with BTX A is urinary retention, which ranges from 0 to 44%[11,12] or high post-void residual requiring intermittent catheterizations in 5% to 43% of patients.[13] Urinary tract infections are in the range of 13% to 44%. On average, OAB patients require repeat bladder BTX A injections every 6 to 9 months.

There are no Canadian studies on the cost-effectiveness of SNM and BTX A. Recently, European researchers concluded that SNM treatment is cost-effective after 5 years

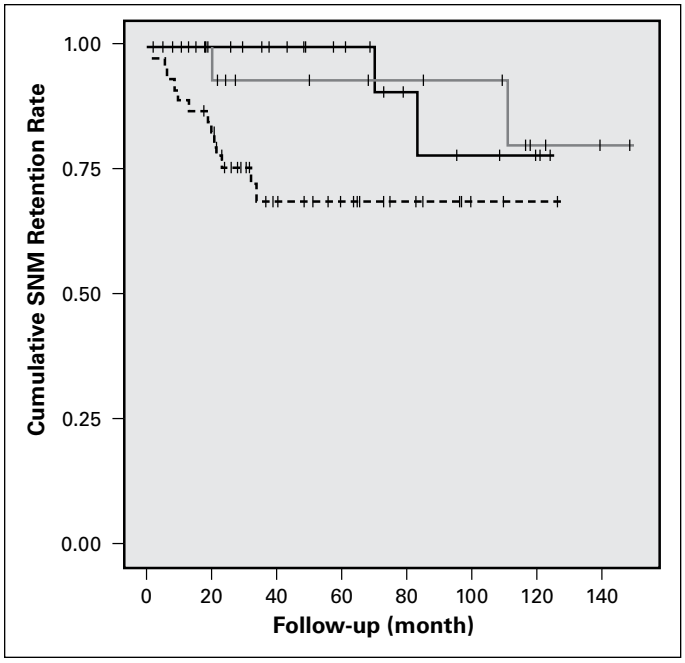

Fig. 1. Kaplan-Meier graph of sacral neuromodulation retention (SNM) rate. The black curve indicates urge urinary incontinence. Dotted curve indicates bladder pain syndrome. Grey curve indicates IUR. Adapted from Al-zahrani et al.10.[10]

compared to BTX A in most cases.[14] However, when local anesthesia is used for BTX A treatment and if a peripheral nerve evaluation is not a stage procedure or bilateral test, SNM was not cost-effective. These are, however, European data which are difficult to extrapolate to the Canadian health care environment. There are some reports from United States which suggest the use of SNM instead of medication for patients with OAB symptoms.[15] This suggestion must also be placed within the Canadian health care context.

In conclusion, SNM remains the obvious alternative for patients with refractory OAB symptoms.

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Concerns regarding sacral neuromodulation as a treatment option for medical-refractory overactive bladder

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Sacral neuromodulation (SNM) with Interstim therapy (Medtronic, Minneapolis, MN) has become one of the accepted treatment options for patients with medication-refractory overactive bladder (OAB) with or without incontinence.[1] While this modality has shown some interesting results, many unanswered questions remain. With the current data available, we do not recommend SNM for OAB patients for the following reasons.

Heterogeneous patient population and vague indications for SNM

Implanted SNM has been proposed as a treatment option for patients suffering from severe urgency-frequency and urinary urge incontinence (UUI). Three large, randomized controlled trials (RCTs) have corroborated its use.[2-4] However, Brazelli and colleagues explained that there was a discrepancy in the clinical characteristics of the patients' treatment history prior to the implantation.[5] Most patients received pharmacological and/or surgical operations, while other patients received only conservative non-surgical therapy. Moreover, there were inconsistencies with the severity and duration of symptoms. Evidence based on heterogeneous patient populations and discrepancies in clinical predictors of success makes it difficult to conclude which patients would truly benefit from this procedure.

Patient selection and surgeon/hospital variability

The indications for SNM are not absolute and the rate at which the procedure is performed depends on the preference of the surgeon and the wishes of the patient. Significant variability exists with the use of this treatment modality. By reviewing administrative billing data, Cameron and colleagues reported the success rates of SNM in the United States, including Medicare beneficiaries (n = 1490) and privately insured individuals (n = 1060).[6] The authors concluded that success rates in the community were significantly lower to those in published case series and RCTs. The overall mean success rate was 39.9% and 49.1% in the Medicare sample and the privately insured, respectively. This was significantly lower than the 88% reported and the 52% to 77% rates of success for the Brazzelli and Siddiqui studies, respectively.[5,7] Selection criteria and experience of the surgeon clearly affects success. Furthermore, RCTs and single institution case series have been limited to experts with better patient selection and availability of state of the art technology. Van Voskuilen and colleagues reported a surgical re-intervention rate of 48% in 149 patients with SNM at a mean follow-up of 64.2 months and correlated the high reoperation rate to a considerable learning curve in patient selection and surgical technique.[8] Most studies did not include information on the level of expertise of the clinicians performing the procedure. Moreover, the backup facilities of the hospital or the clinic where the procedures were performed were never described. Therefore, SNM cannot be recommended to large heterogeneous populations and should only be considered after counselling patients realistically about their chances of success and potential complications.

Criteria for success and lack of long-term follow-up

Clinical success has been defined as an improvement of 50% or more in symptoms during testing. This definition seems somewhat arbitrary and problematic. Some patients may just attain the threshold of being classified as responders to SNM (i.e., >50% response), while other patients may have a substantially greater response. Bosch addressed this limitation. He stated that a report of success using a binary endpoint for testing and after implantation based on a more

than 50% threshold grossly overestimates the benefits of this treatment.[9] The clinical heterogeneity in endpoints have rarely been discussed or addressed. A 50% improvement, while receiving pharmacological therapy, would hardly be considered a success by most patients, especially if they are suffering from OAB or UUI.[10] Results using a more stringent definition for SNM success would be valuable.

An important consideration was that not all patients who were satisfied with the SNM testing underwent implantable pulse generator (IPG) insertion. About 7% to 10% of patients, who expressed improvement in symptoms when tested, did not undergo IPG implantation.[11,12] Moreover, 20% of successful peripheral nerve evaluation (PNE) will not experience the same efficacy after their permanent lead placement supporting the use of a tined lead.[9]

Few studies had long-term follow-up data in outcome and complications. This is an important consideration given that follow-up has been found to be the best predictor of revision and explantation.[13] In case series with follow-up longer than 3 years, total failure rates ranged from 29% to 40%.[5] In a 14 year experience from a Canadian centre, the explantation rate was 20.8%, and 39% of patients in this study needed revision of their SNM implant,[14] comparable to other worldwide clinical studies.[12] Loss of efficacy of the SNM implant was the most common reason for explantation. It was interesting to note that revision occurred late after implantation, with a median time to revision of 26.5 months.[14] This evidence strengthens the argument that long-term data must be generated to justify SNM use in the community outside the context of clinical trials.

Adverse events

A discussion of the therapeutic advantages of SNM cannot be addressed without first interpreting its potential complications. Pain at the stimulation site (15.3%), new pain (9%), pain at the lead site (5.4%), suspected lead migration (8.4%), infection (6%), transient electric shock (5.5%) and changes in bowel function (3%) have all been reported complications of a permanent implantation after a PNE testing.[3] Leong and colleagues, in a single centre sample survey, reported that 56% of patients reported having discomfort at the site of implantation, while a significant proportion of patients experienced problems with metal detectors.[15] These complication rates must be reported to patients during informed consent.

Cost-benefit analysis

Sacral neuromodulation is costly and this must be considered. Implanted hardware alone costs €8400 per implant. Significant additional costs of pre-implantation procedures and surgical revision have also been reported.[16] The pulse generator has an expected battery life of up to 7 years at which point it will need replacement at a cost of €5300. Bosch and colleagues conducted a prospective study in patients with refractory UUI and included a health technology assessment that showed that a break-even point for cumulative cost of SNM per patient versus the costs of continued conservative management was only reached at 18.2 years.[17] Since the cure rates are mostly unknown, the true cost-benefit ratio of this expensive type of treatment remains unknown.[10]

Conclusion

Although the precise mode of action remains unknown, SNM has been recommended for patients, suffering from urgency-frequency symptoms and UUI, who have failed conservative measures. Although results have shown its potential benefits, uncertainty exists as to the best techniques and the best stimulation settings. Furthermore, the biological effects have been demonstrated in very heterogeneous patient groups with soft definitions of success and unclear cure rates.

For patients with OAB with or without incontinence who have failed anticholinergic therapy, botulinum toxin A (BTX A) injections has recently been shown to offer an effective alternative to neuromodulation in a double-blind placebo controlled trial.[18] Therefore the risks and benefits of SNM could be considered as being a last resort before surgical urinary diversion, invasive catherization or long-term use of containment devices, such as incontinence pads. However, the authors believe that the indications for the use SNM will become more restricted and its use will be replaced by more minimally invasive and cost-effective modalities including intravesical BTX A.

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