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Tzu Chi Medical Journal

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Review Article

Neurotoxin Versus Neuromodulation for the Treatment of Refractory Overactive Bladder Syndrome

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Article info:

Article history:
Received: December 17, 2007
Revised: January 2, 2008
Accepted: February 2, 2008

Keywords:
Detrusor overactivity
Neuromodulation
Neurotoxin
Overactive bladder

Abstract

Overactive bladder (OAB) is common and is estimated to affect 16.5% of the adult population. In patients refractory to pharmacotherapy, new treatment modalities, such as neuromodulation and botulinum toxin (BoNT), have had encouraging results. Neuromodulation has promising efficacious results in treating refractory OAB, urinary retention and bowel dysfunction, but the reoperation rate is relatively high, and the full mechanism of action of sacral nerve modulation is incompletely understood. BoNT is another potential alternative to surgical intervention for patients with refractory OAB, neurogenic detrusor overactivity and interstitial cystitis. BoNT-A injection in patients with idiopathic detrusor overactivity have reported increases in cystometric capacity, improved subjective symptoms and urodynamic parameters, and improved quality of life. BoNT injection offers an efficacious, minimally invasive alternative to sacral nerve modulation for the treatment of refractory OAB. [*Tzu Chi Med J* 2008;20(2):109–111]

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1. Introduction

The overactive bladder (OAB) syndrome is characterized by urgency with or without urge urinary incontinence (UUI), and is usually associated with frequency and nocturia. OAB is common and is estimated to affect 16.5% of the adult population [1]. First-line therapy for OAB is conservative in nature, and can include behavioral techniques (bladder training), physical therapies (electrical stimulation), and pharmacotherapy (antimuscarinic and anticholinergic drugs). In patients refractory to pharmacotherapy, new treatment modalities, such as neuromodulation and botulinum toxin, have had encouraging results as alternatives to surgical intervention (augmentation and urinary diversion).

2. Sacral nerve modulation

Sacral nerve modulation (SNM) has been under investigation since the early 1980s. The use of SNM is based on the premise that electrical stimulation of the pudendal nerves can modulate neural reflexes that influence bladder and pelvic floor behavior. The current approved indications for SNM include refractory

OAB (US and Europe), urinary retention, and bowel dysfunction (Europe). For patients with OAB, the device is tested using an external stimulator for a trial period of days to weeks. The external stimulator is considered to be successful when the main incontinence symptoms improve by at least 50%; if this device is successful, a permanent stimulator is implanted, which can later be removed if necessary.

3. Clinical results with SNM

A systematic review, which included data from patients with 1827 implants, reported a >50% improvement in UUI in 80% and 67% of patients who were included in randomized controlled trials and case series, respectively [2]. Incontinence episodes, leakage severity, voiding frequency, and pad use were significantly lower after implantation, and benefits were reported to persist for up to 3–5 years. Adverse effects, primarily pain at the lead or implant site, new pain such as leg pain and infection, were documented in 27 studies, with an overall reoperation rate of 33%. Despite the promising efficacious results with this technique, the reoperation rate is relatively high, and the full mechanism of action of SNM is incompletely understood.

4. Botulinum neurotoxin

Botulinum neurotoxin (BoNT) is another potential alternative to surgical intervention for patients with refractory OAB. BoNT is believed to bind at peripheral cholinergic terminals, inhibiting the exocytosis of synaptic vesicles containing acetylcholine at the neuromuscular junction, which results in regional decreased contractility at the site of injection. A dual mechanism of action of BoNT has been proposed: in addition to binding to cholinergic terminals, BoNT might also affect afferent nervous transmission, thereby decreasing urgency [3]. Apostolidis et al [4] proposed that the primary afferent effect of BoNT involves the inhibition of acetylcholine, ATP, and substance P, and a reduction in the axonal expression of the capsaicin and purinergic (P2X) receptors. These investigators further speculate that this action might be followed by central desensitization through a decrease in uptake of substance P and neurotrophic factors. Seven BoNT serotypes have been isolated, two of which—BoNT-A and BoNT-B—have been investigated in treating bladder dysfunction. Although BoNT has not been approved by the FDA for urologic use in the US, it has been approved for other indications for >25 years, and BoNT is currently being investigated for urologic indications in phase III trials worldwide. Currently, BoNT is available as three major commercial preparations: BOTOX® (BoNT-A; Allergan, Irvine, CA, USA), Dysport® (BoNT-A; Ipsen, Slough, UK) and Myobloc® (BoNT-B; Solstice Neurosciences, San Diego, CA, USA). Each of these preparations has different dosages, safety profiles, and efficacy profiles, and they cannot be used interchangeably.

5. Clinical results with BoNT

In a double-blind, placebo-controlled trial of bladder injection of 200 or 300 units of BoNT-A, for the treatment of neurogenic detrusor overactivity (DO), Schurch et al [5] reported a significant reduction in UUI episodes, an increase in cystometric capacity, improved quality of life, and no systemic side effects at 24 weeks. Double-blind, placebo-controlled [6] and open-label [7] trials of BoNT-A injection in patients with idiopathic DO have reported increases in cystometric capacity, improved subjective symptoms and urodynamic parameters, and improved quality of life. Although the long-term effects of neurotoxin instillation in the bladder are unknown, to date, no systemic effects from BoNT bladder injection have been reported. Localized side effects in these trials have included urinary tract infection (22%) [5] and increased post-void residual volume requiring clean intermittent catheterization (38%) [6]. In a double-blind, placebo-controlled trial of BoNT-B injections in patients with refractory DO, Ghei et al [8] reported symptomatic and quality-of-life improvement with a 6-week duration of action, and they concluded that the benefits of BoNT-B might not be long-lasting enough to justify its use over BoNT-A.

BoNT-A chemical denervation is reversible, and therefore the main disadvantage of BoNT-A injection is the need to undergo repeated injections. The efficacy of repeat BoNT-A injections is, however, maintained: in our series, every patient who responded well to the initial BoNT-A injection had similar clinical improvement after subsequent (up to six) injections [9]. Although the durability of SNM is longer than that of BoNT-A (3–5 years for SNM [2] versus 6–9 months for BoNT-A injection [9]), the revision rate for SNM is >30%, and two surgical procedures are required for initial device implantation. BoNT injection under local anesthesia is an attractive alternative to SNM because it is less time-consuming and requires no adjustments/programming. While the risk of urinary retention is a concern in patients receiving BoNT, it has been observed in <10% of our closely followed-up patients [9].

In our practice, we inject between 10 and 30 locations (100–300 units of BoNT-A diluted in 10–30 mL sterile saline), targeting the bladder base and trigone areas [9]. The dosage and number of injections should be tailored to the individual needs of each patient. Many patients with neurogenic DO are already performing

clean intermittent catheterization at the time of evaluation, and our goal in these patients is to completely paralyze the bladder, to maximize symptomatic relief and to reduce detrusor pressure. In patients with OAB or interstitial cystitis, our goal is to provide symptomatic relief, while avoiding negative side effects such as straining to void and urinary retention. Our modified injection technique to target sensory nerve pathways and to limit toxin dosage and distribution in patients with idiopathic DO has previously been described (10).

While BoNT injection appears to be expensive, Kalsi et al (11) reported in their cost analysis that BoNT therapy for neurogenic or idiopathic DO costs UK£826 per patient, with a cost-effectiveness ratio of UK£617 per patient-year with ≥25% clinical improvement. Direct costs (excluding physician and hospital charges) in Pittsburgh are US$1280 per BoNT injection compared with US$18,125 for SNM implantation. Further cost comparison with alternative therapies is warranted.

6. Conclusion

BoNT injection offers an efficacious, minimally invasive alternative to SNM for the treatment of refractory OAB. Currently available data do not show superiority for one treatment plan, and therapy options in these patients should be tailored to specific patient and physician preference.

Competing interests

M.B. Chancellor has declared an association with Allergan.

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