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Review

The management of overactive bladder refractory to medical therapy

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ABSTRACT

Overactive bladder (OAB) is a clinical syndrome describing the symptom complex of urgency, with or without urgency incontinence and is usually associated with frequency and nocturia. Whilst many women may be initially managed using a clinical diagnosis alone a number will fail primary therapy and will require further investigation. Those women with refractory symptoms following initial conservative and medical therapy may benefit from alternative treatment modalities including intravesical Botulinum toxin, neuromodulation or reconstructive surgery.

This review, the second of two covering the treatment of intractable OAB symptoms in women, will focus on management following the failure of medical therapy. It will principally focus on the role of Botulinum toxin, neuromodulation and reconstructive surgery.

Contents

1. Introduction

Overactive bladder (OAB) is the term used to describe the symptom complex of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1].

The aim of this review is to provide an overview of the management of women complaining of lower urinary tract symptoms suggestive of OAB who have failed to improve using the primary approach of conservative measures with, or without medical therapy.

Whilst the majority of patients with OAB will gain benefit from medical therapy there are a number of patients who will complain of persistent or refractory symptoms. In general these patients should be referred to secondary or tertiary care for further investigation and management including urodynamic investigations. Once alternative pathology has been excluded they may benefit from more invasive therapy such as intravesical Botulinum toxin, neuromodulation or perhaps ultimately reconstructive surgery.

2. Botulinum toxin

Intravesical Botulinum toxin, a neurotoxin derived from the anaerobic bacterium *Clostridium botulinum*, may be an alternative

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for those women with intractable OAB. Botulinum toxin is postulated to work via several separate mechanisms but its exact action is not completely understood. It is thought to inhibit release of acetylcholine (ACh), adenosine triphosphate (ATP) and substance P from the urothelium which have been implicated in mediating the intrinsic and spinal reflexes that lead to OAB. Botulinum toxin is also known to inhibit release of ACh from parasympathetic nerve endings, which leads to detrusor paralysis and consequently may reduce many of the symptoms of OAB. There is also an additional action on C-fibre afferents that is thought to be the mechanism behind the reduction in the sensation of urgency [2]. Botulinum toxin is injected into multiple sites in the detrusor muscle via cystoscopy (flexible or rigid) either under local or general anaesthesia.

Although Botulinum toxin type A (BoNTA) is the most common subtype used, botulinum toxin type B is also effective in symptom reduction, but seems to be effective for a shorter period of time. A number of proprietary BoNTA preparations are commercially available. They are produced by very different isolation, extraction, purification, and formulation processes. Although all BoNTA products have the same serotype, their dose, efficacy, duration of effect and safety profile, are sufficiently different for them to be considered totally different compounds and not generically equivalent [3]. Current evidence supports the short-term efficacy of 200 units of onabotulinum toxin A in idiopathic detrusor overactivity (DO) [4] and 300 units in neurogenic DO [5]. However, there is a significant dose-related risk of voiding difficulties [6], ranging between 8.9% (50 units) and 25.5% (300 units). A dose of 100 units may be the dose that appropriately balances symptom benefits with the post-void residual urine volume related safety profile for patients with idiopathic DO.

The effect of botulinum toxin may last for between three and 12 months, but robust evidence on long-term outcome is lacking [7]. Whilst there are few studies regarding the efficacy and complications associated with repeat injections, the current data would suggest that repeat procedures are safe and remain effective [8].

3. Neuromodulation

Neuromodulation may also be used in women with refractory symptoms and may be peripheral, central or cutaneous.

3.1. Peripheral neuromodulation: percutaneous posterior tibial nerve stimulation (PTNS)

Percutaneous posterior tibial nerve stimulation (PTNS) may be useful in those women with refractory OAB symptoms. The postulated mechanism of action for PTNS is through stimulation of the S3 sacral nerve plexus, using a retrograde pathway through direct stimulation of the posterior tibial nerve, accessed just above the ankle. PTNS involves insertion of a 34-gauge needle approximately 3–4 cm cephalad to the medial malleolus of the left or right ankle. A surface electrode is applied near the arch of the foot and the needle and electrode are connected to a low voltage electrical stimulator. The stimulation current is titrated to elicit curling of the big toe or fanning of all toes. It is usually offered as a course of 12 weekly, 30-min outpatient sessions. However, shorter courses with 12 stimulations performed at a rate of four per week have been reported in the literature [9].

PTNS has been shown to be a safe and effective treatment option, with objective outcome comparable to that of pharmacotherapy [10]. A recent systematic review and meta-analysis [11] reported a pooled subjective success rate of 61.4% (95% CI 57.5–71.8) and an objective success rate of 60.6% (95% CI 49.2–74.7). A significant drawback of PTNS in treating a chronic condition such as OAB is the need for repeated stimulations, as symptoms deteriorate by 6–12 weeks [12]. There are limited long-term data in the literature with few studies looking at ongoing treatment over 12 months. A recent study has shown that with an average of 1.3 treatments per month, PTNS therapy is a safe, durable, and valuable long-term treatment option to sustain clinically significant OAB symptom control [13].

3.2. Central neuromodulation: sacral nerve stimulation

For those with refractory OAB, sacral nerve stimulation (SNS) has emerged as an important potential therapeutic option. It was introduced in 1997 and worldwide over 50,000 patients have already received it to treat a variety of lower urinary tract symptoms. SNS uses a surgically implanted lead and generator to stimulate the S3 sacral nerve root. The stimulation of afferent nerve fibres modulates reflex pathways involved in the filling and evacuation phase of micturition through spinal circuits mediating somato-visceral interactions within the sacral spinal cord. SNS is thought to activate or 'reset' the somatic afferent inputs that play a central role in the modulation of sensory processing and micturition reflex pathways in the spinal cord [14].

SNS incorporates a temporary test stimulation that allows patients and physicians to assess SNS over a trial period. The original technique involved a preliminary test, known as percutaneous nerve evaluation (PNE) [15]. A test needle is inserted under local anaesthetic into the third sacral foramen to establish the integrity of the sacral nerves. A home evaluation phase of 4–14 days follows the initial outpatient hospital testing. Migration of the temporary lead and failure of this technique to identify responders to permanent SNS led to the development of a two-stage implant technique [16]. With this technique a permanent 'tined lead' is implanted under local anaesthesia and connected to an external stimulator and left in place for 3–4 weeks (stage 1). If the patient's symptoms improve by at least 50% then the patient is a candidate to undergo the stage 2 or permanent step in which the permanent implantable pulse generator (IPG) is implanted in the soft tissue of the patient's buttock.

SNS has been shown to be an effective treatment for OAB in more than 40 studies. Most of these studies define success as greater than 50% improvement in clinical symptoms. Whilst the reported success rates for subjects who actually received the implantation varied between 60% and 100%, an intention to treat analysis in a recent systematic review revealed success rates between 21% and 48% for one stage implantation with PNE and 75–80% for two-stage implantation [17].

However, a longitudinal study of 60 women with long-term follow-up reported gradual decrease of the success rate from 87% at 1 month to 62% at 5 years [18]. Other limitations of the SNS are the high cost and high reoperation rate. A recent study reported an explantation rate of 21% and a surgical revision rate of 39% [19]. Reasons for reoperation are no response, infection, loss of stimulation, painful stimulation, and radiation of stimulation to the leg. The reoperation rate appears to be decreased with the introduction of the tined lead technique [20].

3.3. Cutaneous neuromodulation: patient managed neuromodulation system

More recently a cutaneous patient-managed sacral neuromodulation system (PMNS) (Verv, Ethicon, Somerville, NJ, USA) has been developed which may offer a less invasive approach. The PMNS transmits a transdermal amplitude-modulated signal wirelessly, through a disposable adhesive patch applied once per week in a precise location of the sacral region. Short-term (4 weeks) PMNS treatment appears to be safe and effective in the management of refractory OAB [21], but more data are required before its introduction into everyday clinical practice. Unfortunately at present there