Neurogenic Detrusor Overactivity: An Update on Management Options

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ABSTRACT

Neurogenic detrusor overactivity (NDO) affects a variety of patients with storage and voiding dysfunction including those with multiple sclerosis, spinal cord injuries, Parkinson's disease, cerebral palsy, and myelomeningocele, and includes symptoms of urinary frequency, urgency, and incontinence. Primary treatment goals are 1) preventing renal injury, and 2) improving quality of life. First-line therapies include behavioral and anticholinergic agents, with onabotulinum toxin-A as the only FDA-approved second-line therapy, and non-FDA approved second-line therapies including neuromodulation, and intravesical vanilloids. Surgical intervention is reserved for those at risk for upper-tract deterioration and with persistent incontinence. In select individuals an indwelling catheter may be necessary.

KEYWORDS: incontinence, detrusor overactivity, neurogenic lower urinary tract dysfunction

INTRODUCTION

Patients with neurogenic detrusor overactivity (NDO) are a heterogeneous group with storage and voiding dysfunction. Symptoms of NDO include urinary frequency, urgency and incontinence. Neurologic conditions associated with NDO include multiple sclerosis (MS), spinal cord injury (SCI), Parkinson's disease, cerebral palsy and myelomeningocele. Neurogenic bladder dysfunction is present in 80.8% of individuals with MS, 90% with myelodysplasia, virtually all SCI patients with persistent neurologic deficits and 70% of ambulatory SCI patients.[1] NDO affects more than quality of life, increasing risk for urinary tract infection and upper urinary tract damage. The goals of treatment are (1) prevention of upper urinary tract damage and (2) improvement of symptoms to improve quality of life and promote independent living and rehabilitation.

Behavioral therapy is part of the management of NDO, but may be limited by the patient's underlying neurologic condition as well as social factors. The primary therapies for the management of NDO are anticholinergic therapies for patients with detrusor overactivity (DO) and poor compliance, and clean intermittent catheterization (CIC) for those with poor bladder emptying. Although not FDA approved, neuromodulation (electrical stimulation) has been used in patients who have failed anticholinergics. Intra-detrusor injection of onabotulinum toxin-A is approved by the FDA for the management of NDO in patients refractory or intolerant of anticholinergics. In select individuals, a chronic indwelling catheter may be indicated. Surgical intervention may be indicated for protection of the upper urinary tract in high-risk patients or to achieve continence.

Anticholinergic Therapy

Anticholinergic agents inhibit the binding of acetylcholine to muscarinic receptors in the bladder detrusor muscle, decreasing involuntary detrusor contractions, increasing bladder capacity, and improving bladder compliance (ability of the bladder to accommodate urine at low pressure). Oxybutynin is the only agent currently FDA approved for the treatment of NDO in children; however studies have demonstrated efficacy with other anticholinergic agents in children and adults with NDO.[2-5] Dose flexibility and extended–release delivery systems allow for dose titration and decreased incidence of side effects, particularly dry mouth. Angioedema of the face, lips and mouth has recently been reported with anticholinergics, and they are contraindicated in patients with narrow angle glaucoma. Anticholinergics may be poorly tolerated in the elderly because of memory, behavioral and cognitive side effects. Although anticholinergics are the mainstay in the treatment of NDO, there are few published randomized controlled trials.[6]

Intravesical therapies – the vanilloids, capsaicin, and resiniferatoxin – have been evaluated in the treatment of NDO. These agents increase bladder capacity and decrease urge incontinence by blocking C fiber afferent pathways. A systematic review of the efficacy and tolerability of the vanilliods in neurogenic bladder dysfunction demonstrated that capsaicin-treated patients had a reduction in incontinence episodes per day and a decrease in the number of pads used per day compared to placebo, but 50% of the capsaicin group reported pelvic pain and burning and flushing, compared to 25% with the placebo group.[7] Currently, their use is investigational.

Onabotulinum toxin-A

In 2011, Onabotulinum Toxin-A (OnaBoNT-A) intra-detrusor injection was approved by the FDA for the treatment of urinary incontinence due to NDO in adults who have an

inadequate response to or are intolerant of an anticholinergic. When injected into the detrusor, the OnaBoNT-A toxin is taken up by the presynaptic cholinergic nerve terminal via endocytosis, binds to the SNARE protein complex, and prevents the binding and subsequent release of acetylcholine from the presynaptic nerve terminal.[8] This prevents stimulation of muscarinic receptors in the bladder detrusor muscle. The recommended dose of OnaBonT-A is 200 units, administered as 20-30 separate intradetrusor injections of 1ml each throughout the bladder, sparing the trigone. Treatments are repeated roughly every 10-12 months. The onset of effect is usually within 2 weeks of injection. The maximum dose injected anywhere throughout the body is 360 units over 3 months. A multicenter, randomized, double-blind, placebo-controlled study in patients with MS (154) and SCI (121) with a mean of 33.5 incontinence episodes per week at baseline treated with 200 Units of OnaBoNT-A demonstrated a significant reduction in the number of weekly episodes of incontinence episodes at 6 weeks compared to placebo (-21.8 vs. -13.2, P 0.01). A significantly greater proportion of patients treated with OnaBoNT-A compared to placebo were fully continent at 6 weeks (38% vs. 7.6%). Patients undergoing intradetrusor injection of OnaBoNT must be willing to perform clean intermittent catheterization given the risk of post-procedural retention that may persist as long as the clinical response.[9] Costs of 200 U of Botox may exceed $1000 in many locations in the United States, not including cystoscopic or consultation costs.[10]

Neuromodulation

Neuromodulation, although not FDA approved for the treatment of NDO has been used in patients with NDO. Sacral nerve stimulation, posterior tibial nerve stimulation and anogenital stimulation have been evaluated.

Sacral nerve stimulation (Interstim, Medtronic, Minneapolis, MN) is approved for the treatment of urinary retention and the symptoms of OAB, but the safety and efficacy of SNS in patients with NDO has not been established. A recent review of the literature found a 92% overall success rate (defined as > 50% improvement in bladder diary variables) with permanent implantation in patients with NDO related to MS, SCI, pelvic surgery, and disc disease, over a mean follow-up of 26 months.[11] Chaabane et al noted that 66.1% of patients with neurogenic bladder dysfunction had more than 50% improvement on urodynamic evaluation and bladder diary.[12] A limitation of the use of SNS is the potential need for future MRIs as individuals who have had a permanent implant placed cannot undergo MRI.

Posterior tibial nerve stimulation is a less invasive alternative form of neuromodulation. The mechanism of action is unclear. It is thought to inhibit bladder activity by depolarizing somatic sacral and lumbar afferent fibers. Preliminary studies of PTNS in patients with NDO are limited but promising.

Catheterization

Chronic intermittent catheterization (CIC) is the recommended method for managing emptying problems in patients with neurogenic bladders.[13] CIC reduces morbidity and mortality, and improves body image and self-esteem. Vandyananthan et al evaluated quality of life in patients with SCI before and during CIC plus oxybutynin. Patients on the CIC plus oxybutynin achieved socially acceptable continence with improved quality of life and enhanced sexuality. To be able to perform CIC, education and support, manual dexterity, and access to the urethra or catheterizable channel is needed. In select patients an indwelling catheter, urethral, or suprapubic tube may be preferred. Patients with impaired use of their upper extremities, obesity, and spasticity may have difficulties performing CIC and may benefit from a suprapubic tube. Suprapubic tubes tend to be better tolerated over the long term, allow for sexual function, and avoid the risk of urethral erosion. Complications related to indwelling catheters include infections, urethral erosion with urethral catheters, stones, and the potential increased risk of bladder cancer.

Surgical Intervention

Surgical intervention is indicated in patients with NDO when conservative therapies fail to protect the upper urinary tracts or don't achieve satisfactory continence. Such procedures are invasive, complex, and often irreversible, and include augmentation cystoplasty (bladder augmentation), urinary diversion, continent urinary diversion, and ileovesicostomy. The choice of procedure varies depending on the individual's bladder and sphincteric function, and ability to perform CIC. Utilization of bowel in urinary tract reconstruction may result in electrolyte abnormalities related to the absorptive properties of the bowel and therefore requires monitoring and treatment. Metabolic acidosis is the most common and may require treatment with alkalinizing agents.

Augmentation cystoplasty (AC) increases bladder capacity and decreases bladder pressure by augmenting the bladder with a "patch" of detubularized intestine, typically ileum or colon. A catheterizable abdominal stoma can be created for individuals who are unable to access the native urethra or in whom the bladder neck is surgically obstructed to promote continence. A meta-analysis by Campbell et al found complete continence rates ranging from 69%-100% at medium (1+ year) follow-up, and subjective improvement of symptoms in 78%-100% of patients.[14] Complications of augmentation cystoplasty include persistent leakage, bladder perforation, bladder stones, vitamin B12 deficiency, mucus production causing catheter obstruction, and increased risk of bladder cancer. Urinary diversion utilizes a short segment of intestine to which the ureters are anastomosed, typically terminal ileum, to serve as a conduit for urine which is brought to the abdominal wall as a stoma with a collecting device placed over it. Complications include ureteroenteric strictures, stomal stenosis, parastomal hernia, and bowel

obstruction from adhesions, renal calculi and infections.

Urinary diversions can also be made continent via creation of a "pouch" of intestine that stores urine and is emptied by catheterizing an abdominal stoma. Indications are the same as for urinary diversion. Patients with a continent diversion report a significantly higher quality of life versus incontinent diversion patients. Risks related to continent urinary diversion include ureteroenteric stricture, stomal stenosis, conduit and renal calculi, infections, and bowel obstruction. Cutaneous ileovesicostomy is one such procedure whereby a short segment of ileum is anastomosed to the bladder and brought to the lower abdominal wall with a stoma.

CONCLUSION

NDO occurs in individuals with a variety of neurologic conditions. First-line therapies include behavioral therapy, anticholinergic agents and CIC. Onabotulinum toxin A is FDA approved for the management of NDO in patients with an unsatisfactory response or tolerance of anticholinergics. Neuromodulation, sacral nerve stimulation and posterior tibial nerve stimulation are not FDA approved for the treatment of NDO but may have some benefit. Surgical intervention is indicated when other therapies fail to protect the upper urinary tract or provide continence.

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