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Review

Intravesical therapy options for neurogenic detrusor overactivity

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Study design: Review article.
Setting: Neuro-Urology, Spinal Cord Injury Center, Balgrist University Hospital, Zurich, Switzerland.
Objectives: This review considers intravesical treatment options of neurogenic detrusor overactivity and discusses the underlying mechanism of action, clinical safety and efficacy, and the future trends.
Methods: The available literature was reviewed using medline services.
Results: Oral anticholinergic drugs are widely used to treat detrusor overactivity, but they are ineffective in some patients or cause systemic side effects such as blurred vision or dry mouth. As an alternative, topical therapy strategies have been suggested to achieve a profound inhibition of the overactive detrusor and to avoid high systemic drug levels. Currently available intravesical treatment options either act on the afferent arc of the reflex such as local anaesthetics or vanilloids or on the efferent cholinergic transmission to the detrusor muscle such as intravesical oxybutynin or botulinum toxin. Although an established and effective therapy, intravesical oxybutynin is not widely used. Evidence for clinical significance of intravesical atropine and local anaesthetic is missing. Intravesical capsaicin has been shown to improve clinical and urodynamic parameters, but cause pain in some patients. The intravesical instillation of resiniferatoxin and the injection of botulinum-A toxin into the detrusor muscle are promising new options; however, randomised placebo-controlled studies to prove their safety and efficacy are still missing.
Conclusion: Intravesical treatment strategies in patients with neurogenic detrusor overactivity may provide alternatives to established therapies such as oral anticholinergics. The selectivity of the intravesical treatment and the reduction or even the absence of side effects are major advantages of this topical approach.
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Introduction

Urinary incontinence due to detrusor overactivity remains an enormous problem for people with neurological disorders. According to the standardisation of terminology of lower urinary tract function published by the International Continence Society, detrusor overactivity is a urodynamic observation characterised by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. According to the cause this observation may be qualified to neurogenic detrusor overactivity when there is a relevant neurologic condition.[1]

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A considerable number of disturbances of the lower urinary tract are caused by neurological disorders such as spinal cord injury, multiple sclerosis, meningomyelocele and other diseases affecting brain structures or spinal pathways involved in the control of bladder and urethra. Many patients suffer from urinary incontinence and the urodynamic examination usually reveals a neurogenic detrusor overactivity. This pathology is based on a spinal reflex arc involving small unmyelinated type C fibres that become relevant after disconnection of the bladder from higher centres.[2] Treatment options either act on the afferent arc of the reflex such as local anaesthetics or vanilloids or on the efferent cholinergic transmission to the detrusor muscle such as oral anticholinergic drugs (Figure 1). These agents are widely used to treat detrusor overactivity. However,

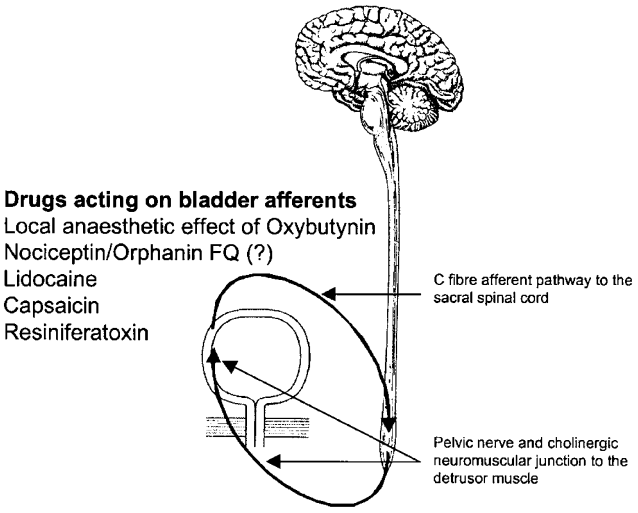

Figure 1 Targets for intravesical therapy options to treat neurogenic detrusor overactivity – blocking afferent C fibres or efferent cholinergic transmission

they are ineffective in some patients or cause systemic side effects. Anticholinergic side effects such as blurred vision or dry mouth limit the applicable dose.

As an alternative, topical therapy strategies have been suggested to achieve a profound inhibition of the overactive detrusor and to avoid high systemic drug levels. This review considers the available literature concerning the intravesical treatment options of neurogenic detrusor overactivity and discusses the underlying mechanism of action, clinical safety and efficacy, and the future trends.

Intravesical local anaesthetics

In clinical practice, intravesical local anaesthetics have been used for diagnostic and therapeutic purpose. Intravesical administration of lidocaine produces effective mucosal anaesthesia and was found to increase bladder capacity.[3,4] In children with meningomyelocele intravesical lidocaine could improve bladder capacity and compliance and decrease the number of uninhibited detrusor contractions.[5] Also, intravesical bupivacaine was found to have an effect in patients with spinal cord injury.[6] However, the effect of both drugs is only of short duration and long-term observations are not available. There is some evidence that intravesical lidocaine could be used to differentiate between neurogenic and idiopathic detrusor overactivity[7] and within the group of neurological disturbed patients to distinguished between detrusor overactivity caused by spinal cord or brain lesions.[8] Some results suggest that the instillation of lidocaine could predict which patients might respond to intravesical vanilloids.[8] However, in another study the procedure was not reliable to predict the clinical response to oral oxybutynin.[5]

Intravesical vanilloids

Capsaicin and resiniferatoxin are vanilloids that act on bladder afferents transmitting sensory information from urothelium and bladder muscle layers to the spinal cord and brain. When applied into the bladder, vanilloids activate nociceptive type C fibres that convey noxious signals and induce painful sensations. Both substances bind a nonselective cation channel known as vanilloid receptors type 1. These receptors have been demonstrated in rat by immunohistochemistry in urothelium, basal lamina and smooth muscle layers.[9] Also, in the human bladder this receptor has been identified recently and vanilloid receptors type 1 immunoreactive fibers were found to be scattered throughout the suburothelium and traverse muscle layers.[10] Binding of vanilloids to the vanilloid receptors type 1 initially induces excitement and later desensitisation of the C fibres. Pathological sensitisation or recruitment of these fibres, for example, following spinal cord injury are involved in inducing bladder overactivity. Vanilloids block these afferent fibres and interrupt the pathological reflex activity.

Intravesical capsaicin

The first study in 1991 by Fowler *et al*[11] demonstrated in patients with neurogenic bladder due to multiple sclerosis that intravesical instillation of 100 ml of 1–2 mmol/l capsaicin in 30% ethanol in saline was effective in reducing neurogenic detrusor overactivity. Since this first report at least 12 studies were published but only two were randomised placebo-controlled trials.[12,13] Both studies tested the effects of 30 mg capsaicin in 30% ethanol versus ethanol alone and found that intravesical capsaicin significantly improved clinical and urodynamic parameters in patients with neurogenic detrusor overactivity. In contrast, another placebo-controlled crossover study could not find 1 mmol capsaicin superior to saline.[14] In a meta-analysis, the results of 115 patients treated in seven centres were analysed.[15] In this population, 97 (84.3%) were found to have at least partial remission of symptoms. In addition, the urodynamic parameters improved, the mean increase of the maximum cystometric bladder capacity varied from 53 to 151 ml and the mean decrease of detrusor pressure from 17 to 30 cm H_2O. The pre-instillation of lidocaine reduced pain and did not influence mechanism of action of capsaicin.[16] The duration of effect of a single instillation of capsaicin may exceed 6 month[15,17] and repeated instillations resulted in the same benefit and duration of the effect.[18,19]

Intravesical resiniferatoxin

Resiniferatoxin, an ultrapotent capsaicin analogue, acts also on the vanilloid receptor and induces, as in capsaicin, a desensitisation on the afferent bladder innervation.[20] Compared to capsaicin, the major advantage is that resiniferatoxin acts without the initial excitatory effect on the nerve fibres which may be responsible for pain observed after capsaicin instillation. The initial study by Cruz *et al*[21] demonstrated, in patients with neurogenic detrusor overactivity, that intravesical instillation of resiniferatoxin (50–100 nmol/l) could improve clinical as well as urodynamic parameters for a period of up to 3 month. Being more potent, resiniferatoxin seems to be also more efficient than capsaicin.[22,23] Patients who failed to respond to capsaicin were successfully treated with resiniferatoxin.[23] Silva *et al*[24] reported that the effect of a single instillation of 50–100 nM resiniferatoxin lasted up to 12 months in seven out of 13 patients.

Two randomised studies are currently available, one comparing resiniferatoxin to placebo in patients with hypersensitive disorder or bladder pain and the other comparing resiniferatoxin to capsaicin in patients with neurogenic detrusor overactivity. Resiniferatoxin (10 nM) was found to be superior than placebo in non-neurogenic patients.[25] Secondly, a recent prospective randomised study comparing the two vanilloids (2 mM capsaicin versus 100 nM resiniferatoxin) demonstrated that the intravesical administration of resiniferatoxin is superior to that of capsaicin for both clinical benefit and improvement of urodynamic parameters.[22] Randomised and placebo-controlled trials of intravesical resiniferatoxin in neurogenic patients are still not available.

Intravesical nociceptin/orphanin FQ

Nociceptin/orphanin FQ is a neuropeptide that influence physiological processes by activating a specific G protein-coupled receptor called opioid receptor-like OP4.[26,27] In rats, this peptide has been reported to inhibit the voiding reflex.[28] A study in humans investigated the effect of nociceptin/orphanin FQ in healthy subjects and patients with neurogenic detrusor overactivity.[29] After intravesical instillation of 1 μM nociceptin/orphanin FQ, a significant increase in mean bladder cystometric capacity and volume threshold for the appearance of neurogenic detrusor overactivity in patients compared to healthy subjects group was observed. However, the clinical and urodynamic effect lasted for 2 weeks only. In this study, it was also hypothetised that nociceptin/orphanin FQ acts on the afferent limb of the micturition reflex in spinal cord injured patients and activates inhibitory opoid receptor-like OP_4 expressed on afferent type C fibres of the bladder.[29] Recently, a randomised, placebo-controlled and double-blind study on 14 patients with neurogenic detrusor overactivity has been published and the results indicated that 1 μM nociceptin/orphanin FQ provides an acute inhibitory effect on the micturition reflex in this patient population.[30] The bladder capacity and the threshold for the appearance of detrusor overactivity increased significantly from 139 to 240 ml and from 84 to 201 ml, respectively. Since this was an acute experiment, the duration of the effect as well as the ideal dose remain still unknown.

Intravesical atropine

When applied intravesically the unselective antimuscarinic agent atropine acts on the efferent arc of bladder innervation and blocks the cholinergic transmission to the detrusor muscle. The intravesical administration of the drug has been studied in patients with neurogenic detrusor overactivity due to spinal cord injury and multiple sclerosis. In spinal cord injury, atropine could reduce the maximum detrusor pressure during an uninhibited contraction and increase the reflex volume as well as the volume when the first leak occurred.[31] A significant increase in bladder capacity was demonstrated in a placebo-controlled crossover study in patients with multiple sclerosis.[32] The systemic antimuscarinic activity was studied recently and intravesical instillation of atropine was not found to have any systemic antimuscarinic side effects.[33] The duration of the effect has not been exactly determined, but it was suspected to last less than 6 h.

Intravesical oxybutynin

Oxybutynin chloride is a tertiary amine with antimuscarinic, spasmolytic, and local anaesthetic properties. The intravesical instillation of oxybutynin had been suggested in the late eighties instead of oral administration of the drug to avoid high plasma levels and systemic side effects.[34] When comparing the oral to the intravesical administration, the instillation provides a profound reduction of occurrence and severity of side effects.[34–36] However, after intravesical instillation there is a substantial absorption of the drug. Pharmacokinetic studies indicated that the effects on the detrusor muscle are systemic due to its absorption on the blood.[36,37] Recent findings revealed that serum levels after intravesical instillation are as high as after oral intake,[38] suggesting another mechanism for less side effects after instillation. Different ratios between the drug and its metabolites as well as a reduced first pass mechanism after instillation have been discussed.[39]

Target structures of the intravesical oxybutynin are the bladder afferents by a local anaesthetic effect on type C fibres[40] and the efferent cholinergic transmission by an anticholinergic effect. Several reports have been published over the years that established safety and efficacy of intravesical oxybutynin in adults[34–36,41] and children[42–45] with neurogenic detrusor overactivity. A dual therapy strategy combining oral and intravesical oxybutynin (15 mg three times daily) was found to be more effective than oral treatment alone.[46] However, there is only one randomised and placebo-controlled study in a

small population reporting a clinical benefit in patients with neurogenic and idiopathic detrusor overactivity.[38]

Although an effective treatment, current problems limiting the clinical use are the necessity of catheterisation and the high costs of special preparations due to lack of commercially available solutions in many countries.

Botulinum-A toxin injection into the detrusor muscle

Botulinum neurotoxin type A, synthesised in *Clostridium botulinum*, is the disease agent for botulism and the most potent natural poison. From the structural point of view the toxin is a 150 kDa amino acid di-chain molecule consisting of a light (50 kDa) and a heavy chain (100 kDa) that are linked by a disulphide bond.[47] The toxicity of the botulinum toxin is a result of a multistep mechanism.[48] The neurotoxin binds to the presynaptic nerve endings of cholinergic neurons and enters the neuron by receptor-mediated endocytosis. There the catalytic domain specifically cleaves the SNAP-25 protein essential for normal synaptic vesical fusion. This cleavage results in the inhibition of neuronal acetylcholine secretion, ultimately leading to a temporary chemodenervation and the loss or reduction of neuronal activity at the target organs.[47,49] In general, this chemodenervation is fully reversible. Regeneration process relies on the formation of functional neuronal sprouts that reconnect presynaptic nerve endings with their target organs (muscles or glands).[50] After the blocked presynaptic nerve ending re-established the connections to the target organ, the sprouts have been shown to disappear.[50]

The underlying hypothesis for the use of the neurotoxin for bladder disorders was based on the study of Dickson and Shevky[51] suggesting that parasympathetic action may be blocked by botulinum-A toxin.[51] Disorders of the parasympathetic autonomic nervous system such as achalasia and hyperhidrosis have been successfully treated with botulinum-A toxin injections.[52–54] A marked loss of contraction in a rat bladder after acute botulinum poisoning with decrease in acetylcholine release at motor nerve stimulation was observed by Carpenter.[55]

The effect of injecting botulinum-A toxin into the human detrusor muscle in patients with neurogenic detrusor overactivity was first reported in 2000 in a nonrandomised prospective study.[56,57] The patients with spinal cord injury selected for a preliminary study had severe neurogenic detrusor overactivity and suffered from incontinence resistant to anticholinergic drugs.[56] They emptied their bladder by intermittent self-catheterisation. Patients with low bladder compliance due to organic detrusor muscle changes or fibrosis were excluded. In total, 200–400 U of botulinum-A toxin (Botox®) were injected into the detrusor muscle sparing the trigone. A total of 19 patients were regularly observed over a period of 9 months by clinical and urodynamic checks. A 6 weeks follow-up after injections showed a significant increase in the reflex volume and in the maximum cystometric bladder capacity. There was also a significant decrease in the maximum detrusor voiding pressure. At the 36 weeks follow-up, ongoing improvement occurred. The amount of anticholinergics could be reduced or even completely abolished. Continence was restored in all but two patients and the patients' satisfaction was high. The recent experience increased to approximately 200 patients with the same results and profile.[58]

In 2002, the efficacy of botulinum-A toxin in children with neurogenic detrusor overactivity due to meningomyelocele was described.[59] The 17 children were using clean intermittent catheterisation and anticholinergic drugs. Included were children aged 1–16 years with either neurogenic detrusor overactivity or high intravesical pressure exceeding 40 cm H_2O resistant to anticholinergic medication or presenting with unacceptable side effects. In all, 85–300 U of botulinum-A toxin (Botox®) were injected into the detrusor muscle and urodynamic checks were performed 2–4 weeks after injection. The mean reflex volume, mean maximum bladder capacity and mean detrusor compliance increased, and the mean maximal detrusor pressure decreased. All results were significant and continence could be restored until at least the 4 weeks follow-up. In a recent study from the same group, the follow-up has been extended to 6 months, suggesting that in children also the botulinum-A toxin injection into the detrusor muscle is effective for a period of about 6 months, and then reinjection is necessary.[60] The results of these nonrandomised prospective studies are promising, especially considering the fact that in both studies the patients included were difficult cases for conservative treatment. In summary, at present botulinum-A toxin injections into the detrusor muscle seem to be indicated in spinal cord injured patients with incontinence due to neurogenic detrusor overactivity. This treatment option seems to establish its indication in cases where anticholinergic medication fails or is intolerable and appears to be a valuable alternative to surgery. However, randomised and placebo-controlled studies are absolute necessary to prove the effect on an evidence-based foundation, to determine the exact duration of the effect and to optimise the injection technique concerning toxin dilution and number of injection sites.

Conclusion

Intravesical treatment strategies in patients with neurogenic detrusor overactivity may provide alternatives to established therapies such as oral anticholinergics. The selectivity of the intravesical treatment and the reduction or even the absence of side effects are major advantages of this topical approach. The intravesical instillation of resiniferatoxin and the injection of botulinum-A toxin into the detrusor muscle are promising new options; however, randomised placebo-controlled studies to prove their safety and efficacy are still missing.

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