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Past, Present, and Future of Chemodenervation With Botulinum Toxin in the Treatment of OAB

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Abstract

Purpose—We systematically reviewed both pre-clinical and clinical studies on bladder chemodenervation with onabotulinumtoxin A to highlight current limitations and future drug delivery approaches.

Materials and Methods—We identified peer-reviewed basic and clinical research studies of onabotulinumtoxin A (onaBoNT-A) in the treatment of neurogenic bladder and refractory idiopathic overactive bladder (OAB) published between March 2000 and March 2016. Paired investigators independently screened 125 English language articles to identify controlled studies on onaBoNT-A administration in MEDLINE® database and abstracts presented at annual American Urological Association meetings. The review yielded an evidence base of over 50 articles relevant to the approach of injection free onaBoNT-A chemodenervation.

Results—The efficacy and safety of intradetrusor injection of onaBoNT-A for the treatment of OAB is sensitive to both injection volume and depth, and this issue has motivated researchers to study injection-free modes of drug delivery into the bladder. Urothelial denudation with protamine sulfate or dimethyl sulfoxide (DMSO), liposome encapsulated onaBoNT-A, and other physical approaches are all being studied to increase toxin permeability and avoid intradetrusor injections. Liposome encapsulated onaBoNT-A enhances toxin activity while reducing its toxin degradation. The safety and efficacy of liposome encapsulated onaBoNT-A was tested in a multi-center, placebo controlled study. Although this treatment successfully reduced urinary frequency and urgency, it did not significantly reduce urgency urinary incontinence episodes.

Conclusions—Intradetrusor injection of onaBoNT-A is safe and effective as reported in several large multicenter randomized controlled trials. Injection of the toxin into the bladder wall impairs both afferent and efferent nerves, but drug delivery approaches that avoid injections impair only bladder afferent nerves. Further studies are needed to develop better drug delivery platforms that

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overcome the drawbacks of intradetrusor injection, increase patient acceptance, and reduce the treatment costs.

Keywords

Chemodenervation; botulinum toxin; liposomes; hydrogel and cationic peptide

Introduction

Overactive bladder (OAB) is defined by the International Continence Society (ICS) as urinary urgency, with or without urgency urinary incontinence, usually accompanied with urinary frequency and nocturia. The etiology of OAB is thought to be multifactorial, and the factors involved are either myogenic, neurogenic, and/or integrative (trigger mediated). Although currently available antimuscarinics are the standard of care for overactive bladder (OAB), their long-term compliance is limited by minimal efficacy and poor tolerability from dry mouth and constipation. Antimuscarinics are also associated with drug tolerance and dysuria, both of which compromise patient adherence to these drugs. Newer treatments such as oral mirabegron, neuromodulation, and chemodenervation have been embraced by many OAB patients.

Bladder chemodenervation with neurotoxins seeks to target the neurogenic factors that contribute to the pathophysiology of OAB by blocking the release of neurotransmitters from bladder afferent and efferent nerves. Chemodenervation via the intradetrusor injection of onabotulinumtoxin A (onaBoNT-A) is a FDA approved treatment for both neurogenic detrusor overactivity (NDO) and refractory OAB. Bladder onaBoNT-A has been found safe and effective in several large multicenter, randomized controlled trials. This review is focused on the promise of improving drug delivery with the development of injection-free approaches for bladder chemodenervation (see Table 1).

Neuronal control of micturition

The micturition process involves two phases: urine storage and voiding. The neuronal control of micturition relies heavily on intact afferent transmission from the bladder to the brain followed by efferent transmission from the brain back to the bladder and urethral sphincter¹. Parasympathetic nerves release acetylcholine during the voiding phase. Norepinephrine released by sympathetic nerves innervating the bladder induces relaxation via β -adrenoceptors. Antimuscarinics suppress detrusor smooth muscle activity and inhibit DO; however, urinary urgency and frequency, which are both alleviated by antimuscarinics, are bladder storage symptoms. Because parasympathetic activity is usually absent during bladder storage, antimuscarinics work to improve these symptoms by acting on afferents found within the urothelium².

Pathological & Therapeutic Denervation of Bladder

Neuronal control of micturition makes it highly susceptible to the injuries affecting neuronal pathways³. Therefore, the dysfunctional voiding that results from neurologic injury justifies denervation using either surgical or pharmacological approaches. Surgical denervation

involves transection of the nerve roots innervating the bladder. In contrast, pharmacological denervation or chemodenervation utilizes neurotoxins to disrupt both efferent and afferent neurotransmission by inhibiting neurotransmitter release. Rhizotomy involves transection of the sacral nerve roots to the external urethral sphincter, thereby preventing detrusor dysnergia; however, rhizotomy results in loss of reflexive erectile function, vaginal lubrication, and pelvic floor muscle strength⁴. Therefore, chemodenervation, which doesn't affect these functions, is more widely used.

Bladder chemodenervation impairs neurotransmitter release from both afferent and efferent nerves. The neurotransmitters involved in the neural control of micturition include acetylcholine, norepinephrine, dopamine, serotonin, excitatory and inhibitory amino acids, adenosine triphosphate, nitric oxide and neuropeptides⁵. Peripherally acting drugs, such as resiniferatoxin (RTX) and onaBoNT-A are of clinical value. Intravesical capsaicin and RTX are vanilloids that selectively block afferent nerves, which are rarely used clinically due to difficulty in delivery, inconsistent efficacy, and acute pain⁶. OnaBoNT-A injected into the bladder wall blocks both afferent and efferent nerves⁷⁻⁹, and recent studies suggest that restricting the action to only afferent nerves may improve the safety profile of onabotulinumtoxin¹⁰.

OnaBoNT-A received Food and Drug Administration (FDA) approval for the treatment of NDO in 2011 and refractory OAB in 2013. There have been 7 immunologically distinct antigenic subtypes of botulinum toxin identified: A, B, C1, D, E, F, and G. Although types A and B are in clinical use, most studies have been performed with type A. Different pharmacological formulations of botulinum toxin are available, and they may have different diffusion characteristics due to protein complex size, product format, and pharmacological properties. Potency units of botulinum toxin are not interchangeable between different preparations.

Mechanism of Action

OnaBoNT-A is composed of two subunits, a 50 kDa light chain and a 100kDa heavy chain. The light chain is the catalytic moiety of the toxin. Following injection, the heavy chain of onaBoNT-A binds with high affinity receptors called synaptic vesicle proteins type 2 (SV2) expressed on neurons¹¹. Recently, the transcript for SV2 was demonstrated in human urothelium cells. OnaBoNT-A inhibits the exocytosis of neurotransmitters from nerve terminals. The translocation of the onaBoNT-A light chain A into the neuron is dependent on the integration of the heavy chain into the membrane bilayer¹².

OnaBoNT-A prevents the exocytosis of acetylcholine into the synapse by proteolytic cleavage of synaptosomal-associated protein of 25 kDa (SNAP-25), an integral part of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex. The cleavage of SNAP-25 by onaBoNT-A blocks the neuroexocytosis of neurotransmitters¹³ and neurotrophins¹⁴, both of which are essential for micturition¹⁵. Therefore, cleavage of SNAP-25 is studied as a surrogate of onaBoNT-A treatment efficacy. The inhibitory effect of onaBoNT-A on nerve evoked release of acetylcholine is only demonstrated following its injection into the bladder wall¹³ and is not observed following topical application onto the

bladder¹⁶. Reduction of detrusor contractility by onaBoNT-A is critically dependent on its reaching the neuronal sites responsible for exocytosis of acetylcholine. Recent studies demonstrate that apart from neuronal release, onaBoNT-A can also block non-neuronal release of acetylcholine from urothelium¹⁷, and this is relevant to the understanding the action of onaBoNT-A instilled within the bladder. A recent study using guinea pig bladder found that number of SNAP-25 positive neuronal fibers were directly proportional to the injection volume at constant dose of the toxin¹⁸.

Clinical Efficacy of Intradetrusor Injection

Nitti et al reported on the long-term efficacy of intradetrusor onaBoNT-A in idiopathic OAB patients over 3.5 years¹⁹. Patients treated with onaBoNT-A saw reductions from baseline in urgency urinary incontinence (UI) by 3.1 to 3.8 episodes per day across 6 treatments²⁰. The incidence of urinary tract infection (UTI) was the most common adverse event (AE) and risk of de novo urinary retention requiring clean intermittent catheterization after the first treatment was 4%, which was higher than in the placebo arms. The median duration of effect was 7.6 months, and durable quality of life improvements were seen over the 3.5 years.. Treated neurogenic OAB patients showed significant improvement in bladder storage symptoms with similar increase in the maximum cystometric capacity (MCC) of 157 and 157.2cc at 6 week followup following 200IU and 300IU of onaBoNT-A²¹. Study found a lack of dose dependent increase in efficacy and UTI was noted in 27.6 and 30.8% of patients treated with 200IU and 300IU of onaBoNT-A, respectively²⁰. The frequency of adverse outcomes increases with higher and repeated doses of onaBoNT-A¹⁵. A recent retrospective study of onaBoNT-A treatment in non-neurogenic, refractory OAB patients found that rate of urinary retention was 35%²². Mean age of the 160 patients studied was 64 years, and 24% of the patients were men. These authors found that urinary retention was associated with increased preoperative PVR. Urinary retention is associated with the need to initiate clean intermittent catheterization and bacteriuria.

Injection technique

There remains no consensus on the ideal template for injecting onaBoNT-A into the bladder. A randomized trial of 45 patients evaluated the effectiveness of onaBoNT-A injections into the suburothelium, bladder body, and bladder base²³. The authors found that bladder body injections were the most effective, followed by suburothelial and bladder base injections. A subsequent meta-analysis of OAB patients found no significant differences in efficacy between trigonal sparing and nontrigonal sparing injection techniques with short-term cure rates of 52.9% and 56.9%, respectively²⁴. The incidence of post-operative urinary retention for trigonal and extratrigonal injection was 4.2% and 3.7%, respectively. and incidence of UTI in respective groups was 7.5 vs 21.0 %.

Studies on guinea pig bladders found that the potency of intradetrusor onaBoNT-A injections are sensitive to injection volume and depth¹⁸. Furthermore, the different onaBoNT-A formulations may not diffuse into the bladder wall the same way because of variability in protein size, product format, and pharmacological properties. Dosing of botulinum toxin as measured in units is not interchangeable between the different

preparations. Furthermore, high-quality studies are needed to determine optimal dosing and long-term application of Botox. Off-label uses of onaBoNT-A within urology include detrusor external sphincter dyssynergia (DESD) and interstitial cystitis/bladder pain syndrome (IC/BPS).

Tissue Spread of Injected Toxin—The extent of tissue spread may impact the risk of adverse events including urinary retention and recurrent UTIs. Concerns with the present injection technique include leakage of toxin outside the bladder, hematuria, pain, and uneven toxin distribution. Magnetic resonance imaging represents a powerful non-invasive tool to track the spread of paramagnetic substances; however, onaBoNT-A is not paramagnetic and its spread cannot be directly detected by MRI. Several studies have reported mixing onaBoNT-A with gadolinium based contrast agents of different polarity, osmolarity, and chemical structure^{25, 26}.

Mehnert et al injected a mixture of onaBoNT-A 300U diluted in 27 mL of 0.9% saline and 3 mL of Magnevist (a linear charged gadolinium chelate) into 6 neurogenic bladder patients²⁶. This mixture was injected into 30 sites in 3 patients and into 10 sites in 3 patients. Pelvic MRI was performed immediately after the injections. The authors found that 82.4% of the total injected volume was found within the detrusor, regardless of the number of injection sites. The remaining 17.6% was found in the lateral extraperitoneal fat tissues adjacent to the bladder dome.

Alsinnawi et al injected onaBoNT-A with a macrocyclic uncharged gadolinium chelate²⁵. OnaBoNT-A dosed at either 100U or 200U was reconstituted with 19 mL of 0.9% saline and 1 mL of Gadovist into either idiopathic overactive bladders or neurogenic bladders, respectively. Twenty patients received 20 injections of intradetrusor onaBoNT-A, including two injections into the trigone. The depth of each injection was 2 mm. MRI performed 3 hours after injection found the injected contrast within the bladder wall of 18 patients, and extravescical extravasation was noted in 80% of the patients.

Existing evidence regarding the risk of tissue spread of onaBoNT-A outside of the bladder remains insufficient, and further studies are necessary. MRI studies make an erroneous assumption about the similarity in the migration of contrast agent and toxin outside the bladder. Nevertheless, studying injected contrast agents of different polarity and structure does shed light into the migration of onaBoNT-A injected into the bladder.

Injection-free chemodenervation

There has been increased interest in developing an injection-free approach of delivering onaBoNT-A to the bladder. Instillation of onaBoNT-A reconstituted with saline into the bladder lumen was ineffective in animal studies^{27, 28}. Intraluminal onaBoNT-A instillation without injection failed because of toxin degradation by urine proteases, toxin dilution by urine at the time of instillation, and poor uptake of onaBoNT-A (a large macromolecule) across the urothelium (see Fig. 1).

The molecular weight of onaBoNT-A is 150 kDa, and this large size is the major impediment in its uptake into the bladder wall. Urothelial denudation by protamine sulfate and organic solvents has been assessed to increase onaBoNT-A uptake into the bladder wall.

Dimethyl sulfoxide (DMSO)—DMSO is an organic solvent that has been used to facilitate delivery of several anticancer drugs into animal bladders²⁹. A study of the effects of DMSO on pig bladders demonstrated histological changes within the urothelium that increased the permeability of instilled agents³⁰. Another study utilized female rats that received 10U of intravesical onaBoNT-A in either saline or 25% DMSO for a 2 hour period²⁸. Subsequently, the rats were infused with 0.25% acetic acid for 1 hour at either 1 or 4 weeks after onaBoNT-A instillation. The group instilled with onaBoNT-A in DMSO showed protection against acetic acid induced bladder irritation. Furthermore, increases in both SNAP-25 cleavage and transcript levels of CGRP were seen 1 week in the rats that received onaBoNT-A in DMSO.

DMSO and onaBoNT-A—Regulatory approval of DMSO and onaBoNT-A allows ease of clinical testing of this combination. Petrou et al studied 25 women with idiopathic DO refractory to antimuscarinics that were given onaBoNT-A mixed with DMSO³⁰. OnaBoNT-A 300U mixed with 50 mL of 50% DMSO was given to 22 patients and 2/3 of that dose was given to 3 patients. Efficacy and toxicity was assessed at baseline, 1 month, and 3 months after treatment with 24-hour pad weights, voiding diaries, and PVRs. In addition, patients completed the Incontinence Impact Questionnaire-short form (IIQ-7) and the Urogenital Distress Inventory (UDI-6) questionnaire. The median number of UI episodes decreased from 4 at baseline to 2 at 1 month ($p=.004$) and then increased back to 4 at 3 months. Also, significant reduction in symptom scores from baseline was noted. The IIQ-7 improved from 13 to 7 at 1 month ($p=.007$), and the UDI-6 improved from 10 to 5 at 1 month ($p=.003$). No serious AEs or urinary retention were noted.

Protamine & Protein Transduction Domains

Protamine is an arginine-rich polycationic peptide with a molecular weight of 5.1 kDa. Protamine is used as an antidote to heparin overdoses and as a complexing agent for long-acting insulin. Protamine internalizes into cells through heparin sulfate mediated endocytosis³¹. Several studies have noted that protamine instillation at concentrations of 10–30 mg/mL denudes the urothelium³². This effect on the urothelium was used to enhance the uptake of onaBoNT-A into the bladders of spinal cord-injured rats²⁷. The efficacy of onaBoNT-A was only detectable in rats pre-treated with protamine sulfate, suggesting that onaBoNT-A cannot cross the intact urothelium.

Protein Transduction Domains—Protamine belongs to a family of cationic peptides that cross membranes through protein transduction. Small sections of these proteins (10–16 residues long) are responsible for Protein Transduction Domains (PTDs)³³. PTDs facilitate the transport of fused materials across cellular membranes through an energy-dependent endocytosis, macropinocytosis, and direct membrane translocation³¹. In contrast to the sequential addition of protamine and onaBoNT-A into the bladder²⁷, PTDs can be linked

covalently to onaBoNT-A to facilitate its entry into any cell type independent of receptors and transporters.

PTDs are recognized as promising vehicles for the delivery of macromolecules. PTDs are categorized into two types, polycationic and amphipathic. TAT peptide is a PTD derived from human immunodeficiency virus (HIV), and TAT that has opened the door for macromolecule delivery across the urothelium. In 1991, Mann and Frankel demonstrated that the basic domain of TAT encompassing amino acids 38–58 retained the transducing ability. This 11-amino-acid peptide fragment of the TAT protein basic domain of TAT has been used in the cellular uptake of proteins, oligonucleotides, and nanoparticles. TAT binding to cellular membranes is mediated through charge-interaction between the basic region of TAT and charged polysaccharides.

We previously reported on the successful uptake of peptide nucleic acids conjugated with the TAT peptide into rat bladders³⁴. As such, successful intravesical delivery of onaBoNT-A into the bladder wall was thought possible can be easily envisioned following conjugation with TAT peptide. Recently, successful transdermal delivery of onaBoNT-A conjugated to PTDs has been reported³⁵. This approach, developed by Revance Therapeutics in Newark CA USA as a gel application, reduced skin wrinkles in 45 patients by 44.5%. As discussed later, topical gel administration into the bladder is another injection free approach for chemodenervation³⁶.

Liposomes

Liposomes (lipid vesicles) have been extensively studied as a drug delivery platform for anticancer drugs, and several such products have received FDA approval. Liposomes have been previously studied as toxin carriers to enhance efficacy at lower doses. Liposomes rely on vesicle endocytosis for intravesical drug delivery. In contrast to DMSO or 10% ethanol, liposomes do not compromise bladder permeability. Empty liposomes composed of endogenous lipids have been reported to have therapeutic effect in interstitial cystitis³⁷. Ultrastructural and confocal microscopy on cultured urothelial cells showed that bladder uptake of fluorescent liposomes is endocytosis³⁸ and energy dependent³⁹. The cellular uptake of electron dense gold encapsulated liposomes was found to be temperature dependent, indicating a role for energy dependent endocytosis in the uptake of liposomes^{38,40}. Our group has previously reported on the use of liposomes for the intravesical delivery of capsaicin⁴⁰ and onabotulinumtoxin A⁴¹.

Reversible complexation of Liposomes and Botulinum toxin—The lipid bilayer of liposomes was used as a cell membrane model for understanding the translocation of the light chain of onaBoNT-A^{12, 42}. The secondary structure of onaBoNT-A after its interaction with liposomes was analyzed using circular dichroism and Fourier-transform infrared spectroscopy at different pH values. Both heavy and light chains of onaBoNT-A induce a partially reversible aggregation of liposomes at a pH of 4 to integrate into the lipid bilayer¹². The pH dependent aggregation and endocytosis of onaBoNT-A within liposomes is possible because the pH of the endocytic vesicles is 4. Denaturation studies of the heavy chain of onaBoNT-A indicate major structural reorganization upon its interaction with cell

membranes at low pH. This aggregation of onaBoNT-A with liposomes is reversible, allowing the toxin to be available for enzymatic action at a pH of 7 within the cytosol.

Enzymatic activity of liposome bound toxin—Caccin et al studied the enzymatic activity of onaBoNT-A complexed with liposomes⁴² in the cleavage of a SNARE protein called vesicle associated membrane protein (VAMP)⁴². Binding of the toxin to lipid membranes enhanced the actions of onaBoNT-A, and tetanus.

Proteolytic degradation of onaBoNT-A—Since direct instillation of onaBoNT-A into the bladder exposes it to urine proteases, it is likely that the reduced potency of instilled onaBoNT-A compared to intradetrusor injection is due to proteolytic degradation of the toxin. Therefore, it is relevant to examine the protection afforded by complexing the toxin to liposomes. A recent study evaluated the degradation of onaBoNT-A bound to liposomes⁴³. OnaBoNT-A with or without liposomes was exposed to pepsin and then put through gel electrophoresis to assess toxin cleavage. Peptide bands were then excised, digested with trypsin, and extracted for mass spectrometry. Electrophoresis and mass spectrometry analysis confirmed that liposomes protected the toxin from pepsin cleavage with the formation of oligomeric membrane-associated intermediates. Fluorescence experiments suggested that amino acid residues within the heavy chain of the toxin move to a hydrophobic environment upon association with liposomes. The reduced proteolytic degradation of onaBoNT-A complexed with liposomes seen in vitro resulted in further testing.

Testing onaBoNT-A complexed with liposomes in animal models—The instillation of onaBoNT-A complexed with liposomes into rat bladders significantly reduced bladder overactivity caused by acetic acid⁴¹. One week after instillation, the group treated with onaBoNT-A complexed with liposomes showed increased voided volumes compared to controls. The duration of the onaBoNT-A effect was similar to the duration reported with DMSO⁴³.

Clinical experience of onaBoNT-A complexed with liposomes—A multi-center placebo controlled study to assess the safety and efficacy of onaBoNT-A complexed with liposomes was performed in men and women with OAB^{44, 45}. This treatment successfully reduced urinary frequency and urgency; however, the treatment did not reduce UUI episodes. Furthermore, onaBoNT-A complexed with liposomes did not result in urinary retention. Risk of UTI was similar between placebo and treatment arms. It can be inferred that instillation of onaBoNT-A complexed with liposomes successfully impairs afferent neurotransmission but not the efferent neurotransmission.

Thermosensitive Hydrogel

Several investigators have studied intravesical thermosensitive hydrogels to increase the residence time of drugs within the bladder^{36, 46}. The hydrogel is formed by an aqueous solution of a polymer which exhibits temperature dependent non-newtonian fluid behavior. The unique rheological property of the hydrogel allows the instillation to be liquid at room temperature of 25°C, and then it becomes semi-solid at body temperature³⁶.

In our earlier study, we modified the biodegradable triblock polymer Poly(ethylene glycol)-Poly[lactic acid-co-glycolic acid]-Poly(ethylene glycol) for bladder instillation³⁶. The understood mechanism of temperature sensitive gelation at 37°C is due to micelle packing with an increase in micelle volume fraction; however, lower micelle volume fraction at 25°C makes it a free flowing liquid. In our study, we showed that intravesical thermosensitive hydrogel extended the residence time of a fluorescent probe within the bladder³⁶.

Thermosensitive hydrogel & onoBoNT-A—A recent clinical study from Urogen (previously Theracoat) reported that thermosensitive hydrogel can improve the intravesical delivery of onaBoNT-A in 15 patients with IC/BPS⁴⁷. That study reported that hydrogels within the bladder allowed a gradual release of 200U of onaBoNT-A for up to 6–8 hours, well beyond the typical 2 hours for saline instillation. Validated Interstitial Cystitis Symptom Problem Index (ICSPI) and visual analog score (VAS) was collected at baseline and at 12 weeks. One severe AE was reported - benign submandibular lymphadenopathy that was pre-existing. Three cases of mild constipation following instillation were noted as possibly drug-related AEs. Non-related AEs included flu and worsening depression symptoms⁴⁷. Urogen is currently pursuing clinical testing of their hydrogel and onoBoNT-A product in Europe. One potential safety concern of hydrogels placed within the bladder is possible urinary retention from obstruction to urine flow.

Physical Approaches

Iontophoresis—The increasing use of onaBoNT-A as a treatment for DO in children has motivated the search for injection-free administration. Electromotive force (EMF) is a physical approach to increase the bladder permeability similar to the chemical means seen with protamine and DMSO. EMF involves placement of one electrode inside the bladder and one outside on the abdomen to create a potential difference for driving the diffusion of instilled drugs into the bladder. A total of 15 children (mean age of 7.8 years) with NDO from myelomeningocele were studied with this approach⁴⁸. OnaBoNT-A 10U/kg was inserted into the bladder through a catheter with a pulsed current generator that delivered 10mA for 15 minutes. Urodynamic parameters measured included maximal bladder capacity and maximal detrusor pressure. Also, vesicoureteral reflux (VUR) grading was evaluated before treatment and at 1, 4, and 9 months after treatment. The combination of intravesical onaBoNT-A and iontophoresis improved VUR grade and bladder capacity. AEs included skin erythema and dysuria in 6 subjects.

Low energy shock wave (LESW)—This method involves delivery of shock waves to the target organ, thereby increasing cell permeability. Use of LESW for intravesical drug delivery is predicated on reports of an increase in tissue permeability following shock wave application with increased drug delivery to the cells. Kodama et al. suggested that shock waves could cause shear forces generated by movement of liquid relative to cells, thereby increasing the permeability of the plasma membrane⁴⁹. Shock waves can deliver molecules of up to 2,000,000 molecular weight inside the cell. We recently reported that onaBoNT-A delivered into IC/BPS rat bladders using LESW reduced inflammation, reduced SNAP 23 and 25, and increased voided volumes⁵⁰.

Conclusions

OnoBoNT-A is a large macromolecule, and the urothelium impedes its easy delivery into the bladder wall. Success in animal models was seen with intravesical onaBoNT-A administration following urothelial denudation by protamine sulfate. In addition, DMSO has been used to facilitate onaBoNT-A penetration into the bladder, thereby demonstrating clinical efficacy. Biochemical studies have shown that onaBoNT-A complexed with liposomes prevents proteolytic degradation of the toxin to enhance its efficacy. Liposomes have been extensively researched as a platform for delivering neurotoxins including onaBoNT-A. Liposomes complexed with onaBoNT-A show promise in clinical studies on OAB patients, reducing urinary frequency and urgency and resulting in no urinary retention. Novel approaches to the injection free delivery of onaBoNT-A have so far not demonstrated efficacy comparable to intradetrusor injection; however, continued research with a variety of approaches shows great promise.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

onaBoNT-A	onabotulinumtoxin A
RTX	resiniferatoxin
PTD	Protein Transduction Domains
VAMP	vesicle associated membrane protein
SNARE	(Soluble NSF Attachment Protein) Receptor
ICSPI	Interstitial Cystitis Symptom Problem Index (ICSPI)
VAS	visual analog score
EMF	Electromotive force
LESW	low energy shock wave
PVR	post-void residual
IC/PBS	Interstitial cystitis/painful bladder syndrome

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Fig. 1.

Schematic illustration of different approaches attempted for intravesical delivery of botulinum toxin. Intradetrusor injection of native toxin can chemodenervate both efferent and afferent arm of micturition reflex of OAB. Liposomes based intravesical delivery of botulinum toxin can only chemodenervate afferent arm of micturition reflex. Botulinum toxin has been conjugated with cationic peptide and complexed with thermosensitive hydrogel for improved delivery of toxin.

Table 1
Characteristics of Clinical studies on injection free onaBoNT-A

Studies reported in the literature on liquid instillation of onaBoNT-A in OAB, IC/PBS and children.

Study	Delivery Approach	No. of Patients	Study design	Dose of onaBoNT-A
Petrou et al ³³	DMSO	25 OAB	Open label study	300IU instillation
Kuo et al 2014 ⁴⁹	Liposomes	24 OAB	double-blind randomized parallel controlled study of OAB	200IU instillation
Chuang et al ⁵⁰	Liposomes	62OAB	2-center, double-blind, randomized, placebo controlled study of OAB	200IU instillation
Ahmadi et al ⁵⁴	EMF	15 children	Open label study of Myelomeningocele and refractory neurogenic detrusor overactivity	10 IU/kg instillation
Stav et al ⁵³	Hydrogel	15 IC/PBS	Open label study of IC/PBS	200 IU instillation