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How botulinum toxin in neurogenic detrusor overactivity can reduce upper urinary tract damage?

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Abstract

Intradetrusor injections of botulinum toxin are the cornerstone of medical treatment of neurogenic detrusor overactivity. The primary aim of this treatment is to ensure a low pressure regimen in the urinary bladder, but the mechanisms leading to long-term protection of the urinary tract remain poorly understood. In this paper, we highlight the potential benefits of intradetrusor injections of botulinum toxin regarding local effects on the bladder structures, urinary tract infections, stone disease, vesico ureteral reflux, hydronephrosis, renal function based on a comprehensive literature review.

Key words: Botulinum toxin; Urinary tract infection; Kidney function; Neurogenic detrusor overactivity; Hydronephrosis; Urolithiasis

Core tip: Intradetrusor injection of botulinum toxin prevent damage of the upper urinary tract *via* several potential mechanisms including reduction of bladder pressure, urothelium and suburothelium modifications, sensory receptors expression, and hypoxia reduction. These data could explain the favourable effects of intradetrusor injection of botulinum toxin on urinary tract infections, stone disease, vesico ureteral reflux, hydronephrosis, renal function.

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INTRODUCTION

Neurogenic lower urinary tract dysfunction is a highly prevalent disease, impairing significantly patient's quality of life, and results in a huge medico-economic burden[1]. In particular, neurogenic detrusor overactivity (NDO)

is a common feature in the context of neurological diseases, resulting most of the time in urgency, increased frequency and urge urinary incontinence (UUI)[2]. NDO (which can be associated with sphincter dyssynergia) is also at high risk of upper urinary tract deterioration in the long term, because of high bladder pressure, low BC and low bladder capacity. A bladder pressure > 40 cmH_2O has indeed been stated as the major urodynamic warning for upper urinary tract deterioration[3]. This increase in bladder pressure can be due to NDO but also to detrusor sphincter dyssynergie in itself, that may need a specific treatment. The current review will only deal with the effect of botulinum toxin injection in the detrusor to treat NDO.

The management of NDO has two aims. While patients often focus on symptom relief (especially UUI), another objective is the long term protection of the upper urinary tract, in order to preserve renal function. To achieve these goals, NDO management must restore a continent, low pressure reservoir without vesico ureteral reflux (VUR), along with an adequate capacity and a good compliance. The first line treatment of NDO is antimuscarinics but many patients do not respond to antimuscarinics therapy, and require further treatment[4].

Intradetrusor injections of botulinum toxin are one of the options available in patients who do not respond to medical therapy. This approach has now been approved and is extensively used for NDO management[5]. Two types of botulinum toxin are available on the market: Abobotulinum toxin-A (Dysport) and onabotulinum toxin-A (Botox). Whilst the clinical efficacy of the treatment has been assessed in well-designed prospective studies and meta-analyses, the long term effect on prevention of upper urinary tract disease such as urinary tract infections (UTIs), VUR, hydronephrosis, stones, and chronic kidney disease is not fully understood yet.

The aim of this review was to summarize available evidence about how botulinum toxin can prevent upper urinary tract disease in a context of NDO.

EVIDENCE SYNTHESIS

Bladder effect

Urodynamic data: In addition to relief of lower urinary tract symptoms, intradetrusor injections of botulinum toxin have been shown to substantially modify the results of urodynamic studies in patients with NDO. Schurch *et al*[6] in 2000, for the first time, injected 300 UI of botulinum-A toxin (Botox) in the detrusor of 21 patients with spinal cord injury (SCI) who had UUI by DO refractory to antimuscarinics. At 6 wk, 17 out of 19 patients (89.4%) had complete continence. The overall mean reflex volume (RV) significantly increased from 215 ± 90.4 mL before the injections to 415.76 ± 211.1 (P = 0.016) after the injections. The mean maximum cystometric bladder capacity (MCC) significantly increased from 296 ± 145.2 to 480 ± 134.1 (P = 0.016), respectively. There was also a significant decrease after treatment in mean maximum detrusor voiding pressure (MDP) from 65.6 ± 29.2 cm water to 35 ± 32.1 (P = 0.016). Mean post-void residual urine volume (PVR) catheterized at the end of the urodynamic examination increased significantly from a mean of 261.8 ± 241.3 mL to 490 ± 204.8 (P = 0.016).

Following this first proof of concept, a number of other trials have investigated the changes in UDS after Intradetrusor injections of botulinum toxin. Through another prospective randomized, placebo controlled, double-blind, multi-center in 2005, Schurch *et al*[7] have found no significant difference between 200UI and 300UI of onabotulinum toxin A injections. However this comparative study was focused on incontinence episodes as a primary endpoint and do not allow conclusion about the comparison of urodynamic features. Reitz *et al*[8] in a prospective, open labeled study, used 300 U of Botox in the detrusor of 231 neurologic patients [167 SCI, 11 MS, 22 myelomeningocele (MMC)]. The evaluation was made at 12 and 36 wk. At 12 wk, the mean MCC increased significantly from 272 to 420 mL (P < 0.0001) while the mean MDP decreased from 61 cmH_2O to 30 cmH_2O (P < 0.0001). The mean bladder compliance (BC) also increased significantly from 32 mL/cmH_2O to 72 mL/cmH_2O and the mean PVR increased from 236 to 387 mL (P < 0.0001). At 36 wk, the results were quite similar although the mean BC was not significantly different from baseline (32 mL/cmH_2O to 51 mL/cmH_2O). These urodynamic data were correlated with a rate of 132 (73.3%) patients fully continent at 12 wk.

In a long term follow-up of 17 SCI patients at 6 years after 300 UI botulinum-toxin A injections, Giannantoni *et al*[9] in 2009 showed persistent urodynamics modifications. The unhibited detrusor contraction (UDC) first volume increased significantly from 213 ± 40.8 at baseline to 344 ± 32.6 at 4 mo, 365.4 ± 49.7 at 1 year, 410.8 ± 60.2 at 3 year, 413.7 ± 58.9 at 6 years (P < 0.001 between baseline and 6 years follow-up). Correspondingly the UDC maximum pressure decreased from 97.6 ± 32.4 to 23.8 ± 10.8 at 6 years (P < 0.01) whereas maximum cystometric capacity increased from 243 ± 64.7 to 420.8 ± 55.7 (P < 0.001).

The results are quite similar with Abobotulinum toxin A (Dysport). Del Popolo *et al*[10] in 2008 have retrospectively evaluated three Dysport doses (500 U, 750 U and 1000 U) in 199 patients with SCI and NDO refractory to antimuscarinics. The evaluation was made at 3, 6 and 12 mo. The mean MCC increased significantly from 226 to 407 mL after the first injection and was still at 380 after seven injections while the mean BC significantly increased from 27 mL/cmH_2O to 41 mL/cmH_2O after one and seven injections. There was no significant difference between all doses. In 2010, our team has reported the comparison of two Dysport doses (500 U and 750 U) in a prospective, double-blind, randomized, comparative trial[11]. Seventy-seven patients were included, 49 had SCI, 18 had MS and 11 had other neurological causes. At four weeks, the mean MCC increased from 242 to 434 mL with Dysport 500 U and from 180 to 423 mL with Dysport

750 U. The BC also increased from 32 to 37 mL/cmH_2O and from 23 to 59 mL/cmH_2O for Dysport 500 U and 750 U respectively. There were no significant differences between two groups.

These studies highlight the important urodynamic modifications induced by intradetrusor botulinum toxin injections.

Pathophysiology: Botulinum toxin act at the neuromuscular junction level by temporarily blocking acetylcholine (Ach) presynaptic release from parasympathetic nerves. It induces a paralysis of the detrusor smooth muscle that induce urodynamic changes and symptoms relief.

Serotype type A cleaves the SNAP-25 protein complex which plays an important role in the fusion of neurotransmitter-filled transmitter vesicles with the plasma membrane and their release during exocytosis. This induces an highly specific blockage of acetylcholine release at the neuromuscular junction of somatic and autonomic presynaptic nerve terminals[12].

Those fragments of SANP-25 protein complex are detectable in the bladder for longer periods that would be expected in striated muscle[13]. However, this motor effect does not entirely explain all the bladder changes. In fact, at the bladder level, BoNT/A seems to have a role in modulating both efferent and afferent neurologic activity, *i.e.*, both motor and sensitive fibers[14].

Apostolidis *et al*[15] showed that BoNT/A injections for human DO decrease sensory receptors P2X3 and TRPV1 levels in suburothelial nerve fibers. Those sensory receptors are overexpressed in neurological bladder suburothelium and are believed to play a role in sensory signal transduction in normal animal bladder[16]. At 4 and 16 wk after BoNT/A intradetrusor injections in 38 patients (22 with neurologic DO and 16 with idiopathic DO, there was a significant decrease in P2X3-immunoreactive and TRPV1-immunoreactive (-IR) ($P < 0.0004$ and $P < 0.0008$, respectively), when significant improvements were observed in clinical and urodynamic parameters. P2X3-IR and TRPV1-IR fibers decrease were significantly correlated with reduction of urgency episodes at 4 and 16 wk ($P < 0.0013$ at 4 wk and $P < 0.02$ at 16 wk), but not maximum cystometric capacity or detrusor pressures.

Conte *et al*[17] also showed that, after BoNT/A injections for detrusor overactivity, patients with Parkinson disease or SCI, significantly reduced at MCC, the expected soleus Hoffman reflex (H reflex) inhibition, whereas in those with SCI, it turned the H reflex facilitation into a slight inhibition. This reflex (basically defined as a reflectory contraction of muscle after stimulation of the related sensory fibers) tests the afferent information from the bladder (C and Aδ fibers) that modulates the spinal motoneuron excitability. Those results highlight the fact that BoNT/A might influences H reflex modulation at MCC by reducing bladder afferent signalling.

However, motor effect seems to play a major role in increasing MCC and BC and decreasing MDP significantly. It creates a low pressure bladder during filling and storage phases. The ureteral outlet may be affected by a bladder pressure over 40 cmH_2O or by a BC under 10 mL/cmH_2O leading to upper urinary tract functional obstruction[3]. Prolonged periods of elevated detrusor pressure during bladder filling or voiding have been found to put the upper urinary tract at risk[18]. Primary aim of therapy in patients with such problems is conversion to a low pressure bladder during filling even if this leads to incomplete emptying and the need to supplement emptying with catheterization.

Effect on UTIs

Clinical results: The impact of intra-detrusor botulinum toxin injections on UTIs has been investigated in various clinical trials. Gamé *et al*[19] in 2008 has evaluated the impact of BoNTA 300 U on symptomatic UTIs (sUTIs). sUTIs were defined by the association of bacteriological criteria and symptoms such as fever, intensification of spasticity, intensification of autonomic hyperreflexia, pain and worsening of the neurological status. Of the thirty patients, 15 had SCI, 14 had MS and 1 had myelitis. All had at least one episode of sUTIs during the 6 mo prior to the injection (mean number 1.79 ± 0.39 per patient). At 6 mo, the number of sUTIs decreased significantly (0.2 ± 0.41) ($P = 0.003$) with only three patients having sUTIs (one pyelonephritis, one prostatitis, one orchitis). Of those three patients, two had SCI and one suffered from MS and they were those in whom BoNTA injections had the least effect on urodynamic changes. The overall incidence of bacteriuria was 43%.

In 2009, GIannantoni *et al*[9], at 6 years follow-up of 300 U botulinum toxinA injections, in 17 SCI patients, reported a decreased in UTIs episodes from 6.7 ± 2.1 per year at baseline to 1.6 ± 1.3 at 4 mo, 3.3 ± 2.1 at one year, 1.7 ± 2.0 at 3 years and 1.8 ± 0.5 at 6 years ($P = 0.001$ between baseline and 6 years). However the definition of symptomatic UTI used in the trial is not specified.

Cruz *et al*[20], evaluated in 2011 the safety of onabotulinumtoxinA, in a randomized, double-blind, controlled study *vs* placebo. 275 patients (121 SCI, 154 MS) were randomized in three groups (92 to placebo, 92 to onabotulinumtoxinA 200 U, and 91 to onabotulinumtoxinA 300 U). The mean rate of UTI was similar between all treatment groups, including placebo, in the SCI population (50%, 52%, 56.4% for placebo, 200 U and 300 U groups) whereas in the MS population, it was higher in the onabotulinumtoxinA groups compared with placebo (32%, 58%, 70% for placebo, 200 U and 300 U groups). Twelve percent, 30%, and 42% of patients in the placebo, onabotulinumtoxinA 200-U, and 300-U groups respectively, initiated CIC after the first injection. However, this level 1 study presented a major pitfall, that is the absence of clear definition of UTIs. Indeed the authors confused symptomatic UTIs (with clinical signs, including fever, and a positive urine culture) and asymptomatic bacteriuria (colonization), that is obviously increased by the high rate of self catheterization. In another level 1

study, Ginsberg *et al*[21] evaluated the safety of BoNTA in a randomized, double blind, controlled placebo trial in 416 patients (227 MS, 189 SCI). Two doses of Botox were used (200 U and 300 U). At 12 wk evaluation, the most frequent adverse effects reported were UTI and urinary retention. In MS population, the rate of UTI was higher after BoNTA than placebo (51% and 50% in 300 U and 200 U groups *vs* 28% for placebo) while it was similar in all groups in patients with SCI (42%, 48%, 50% in placebo, 200 U, 300 U groups respectively). But again, the authors disclosed that there was no clear definition between symptomatic and asymptomatic UTIs, so these studies cannot results in valuable hypotheses.

In a more focused study, Kuo *et al*[22] reported in 2011, among 132 onabotulinumA 200 U injections in 33 SCI patients, nine episodes of febrile UTIs (6.8%) and 37 (28%) episodes of asymptomatic UTI. Herschorn *et al*[23] in 38 patients with SCI and 19 with MS found a similar rate of UTI between placebo and 300 UI of onabotulinum A: 55 and 57% respectively. However, he didn't separate MS and SCI patients. Jia *et al*[24] in 2013 found similar results in men with SCI receiving 300 U of botox. The mean number of sUTIs prior to surgery was 1.49 ± 1.43 per patient over 6 mo and decreased to 0.78 ± 0.96 (P = 0.023) at 6 mo post-operatively. However, the overall sUTIs frequency had the tendency to decrease in patients who developed two or more UTIs before injection and to increased in patients who presented one or zero UTI before injection. The sUTIs included two acute epidymitis episodes. The others were acute pyelonephritis.

Physiopathology: UTIs are a major cause of morbidity and one of the main reason for hospitalization in neurologic patients[25]. It must be distinguished from asymptomatic bacteriuria, which is not threatening for the patient. One important confounder in clinical studies about intradetrusor injections of botulinum toxin is that treated patients often practice self catheterization, that increases the risk of *asymptomatic bacteriuria*. But the overall rate of *symptomatic* UTIs is thought to be decreased.

In the neurogenic patient, there are some structural and physiological factors that can be related to an increased risk of UTIs including: Over-distention of the bladder, vesicoureteral reflux, high pressure voiding, large post-void residuals, presence of stones in the urinary tract, and outlet obstruction (detrusor- sphincter dyssynergia, urethral stricture, enlarged prostate)[26]. The method of bladder drainage has also a strong influence on UTI. The use of clean intermittent catheterization (CIC) has permitted to significantly overall decrease the mean rate of UTI in patients with neurological disorders[26], despite the fact that CIC are associated with asymptomatic bacteriuria[27].

Botulinum toxin injections and CIC (when needed) result in both a low pressure bladder regimen and minimal post-void residual, that are two conditions lowering the risk of symptomatic UTIs. Indeed, the major factor of UTI is DO (eventually combined with outflow obstruction) which induce maximum detrusor pressure[28], resulting in reduced blood flow as shown by animal models[29]. Focal bladder hypoxia is associated with further deterioration of the detrusor function and fibrosis[30,31], and has been postulated to favor adherence of bacteria to the urothelium[32].

Many other mechanisms have been proposed as key factors influencing occurrence of UTIs (Figure 1). Wöllner *et al*[33] have shown that BoNT/A had a no direct antibacterial effect. Thirunavukkarasusx *et al*[34] demonstrated a high modulation of genes and pathway involved in neuroinflammatory, focal adhesion, cell adhesion molecules and gap junctions genes in intestinal epithelial cells lines treated with botulinumtoxinA. Although it has not been studied, there might be the same effects in the urothelium that could decrease bacterial adhesion.

Moreover, the symptoms of UTI presented by neurological patients may be induced by a local inflammation arising from the local release of inflammatory mediators such as substance P (SP), neurokinin A, glutamate and calcitonin gene-related peptide (CGRP) from afferent nerves. Bacteria could cause a direct stimulation of afferent A-delta and C-fibres with an increased release of those neurotransmitters inducing dysuria, urgency, frequency and general symptoms such as malaise, fever and increased spasticity. *In vitro*[35] and *in vivo*[36] analysis have shown an effect of botulinum toxin in reducing glutamate release and decreasing pain. This might alleviate bladder symptoms and the awareness of sUTI by the patients. Furthermore, CGRP is a potent vasodilator, and SP enhances vascular permeability. These substances are involved in the physiological control of blood flow. The potential effect of botulinum toxin on modulation of inflammation and sensory pathways and its potential influence on UTIs occurrence remains to be elucidated.

EFFECT ON UPPER URINARY TRACT

Effect on VUR and hydronephrosis

VUR causes UTI, hydronephrosis and alters the upper urinary tract by mechanically delivering infected urine to the renal pelvis. BoNTA injections have been postulated as having a positive influence on VUR through various ways.

Clinical data: Very few studies have evaluated the impact of BoNTA on VUR and renal pelvis dilatation. To our knowledge, no studies have ever reported on VUR nor renal pelvis dilation induced by botulinum toxin as a primary outcome. Classically, trigonal injections are avoided owing to the potential risk of precipitating VUR from inhibition of the active trigonal antireflux mechanism. Nevertheless, according to the literature review by Davis *et al*[37] in 2015, no study have shown new onset of RVU nor worsening of preexisting RVU, induced by trigonal injections.

In the opposite, RVU treated by BoNTA injections

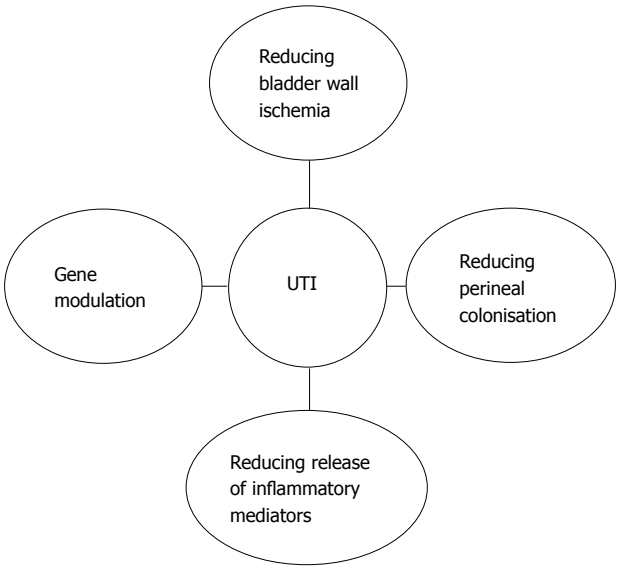

Figure 1 Pathophysiological explanation of how botulinum toxin A might decrease urinary tract infection occurrence. UTI: Urinary tract infection.

has been described. In a randomized, single-blinded study, Abedl-Meduig[38] compared initial detrusor *vs* combined detrusor-trigone 300 IU BTX-A injections in 38 adults with SCI and refractory neurogenic urinary incontinence due to NDO. At baseline 2 patients in the detrusor arm had unilateral grade 2 and 3 VUR while 2 in the combined arm had unilateral grade 1 and 3 VUR, respectively. At week 8 no patient had new onset VUR or upgrading of preexisting VUR. Mascarenhas *et al*[39] in 2008, performed trigonal injections in 21 neurological patients (12 SCI, 8 viral myelitis, 1 MS), 20 had no VUR previous to the injection and 1 had VUR grade Ⅱ unilateral. At 8 wk evaluation, no cases of *de novo* VUR were detected and the patient with preinjection VUR had complete resolution of the reflux. For Gamé *et al*[19] who used 300 U of BOTOX in 30 neurologic patients, 6 patients had VRR previously to the injections, and only 2 had one reflux remaining after the injections. But the difference was not significant. None of them had infections after treatment. Giannantoni *et al*[9] in 2009 studied 17 SCI patients with DO. Three had VUR of grade Ⅲ prior to treatment. At one year post injection, no one had persistent VUR.

Arrabal-Polo *et al*[40] in 2012 have presented the case of a children non neurologic who presented a primary reflux and was successfully treated with botulinum toxin after failure of endoscopic treatment (Deflux and Macroplastique).

Giannantoni *et al*[9], detected on kidney and bladder ultrasound, bilateral and monolateral renal pelvis dilatation in six and five patients, respectively, before the injection. At for weeks after the 300 U Botox injection, the dilatation disappear in all patients. Those results were maintened at 3 and 6 years follow up. In Mascarenhas study[39], of 21 neurological patients, four (19.0%) had mild hydronephrosis and one (4.8%) had moderate hydronephrosis at baseline. Postoperative ultrasound after 8 wk of BoNTA injections, showed no hydronephrosis in 20 (95.2%) patients and mild hydronephrosis in 1 (4.8%, $P = 0.125$).

Pathophysiology: The occurrence of VUR result from different mechanisms which defines whether reflux is considered as primary or as secondary. In general, VUR is considered primary if there is a deficiency of the uretero-vesical junction (UVJ). Secondary reflux is caused by overwhelming of the normal function of the UVJ. Bladder neurological dysfunction is often the root cause of secondary reflux[41]. Chronic increases in intravesical pressure resulting from bladder outlet obstruction or detrusor overactivity can distort bladder architecture and UVJ. It can cause herniation of the bladder mucosa through the weakest point of the hiatus above the ureter and produce a "Hutch diverticulum" and secondary reflux[42].

Uretero-hydronephrosis is also induced by high bladder pressure. Thus, reducing bladder pressure by botulinum toxin may improve VUR and hydronephrosis. Although low bladder pressure is achieved, a major deterioration of the UVJ might lead to persistent VUR. Indeed, increase wall tension in the ureter might lead to a significant decrease in smooth muscle perfusion and cause ischaemic lesion in the ureter[43].

This emphasizes the importance to control the bladder pressure at the initial stage of an overactive neurogenic bladder in order to avoid secondary damages on bladder and upper urinary tract. These data also point out the potential interest, notably in children, of an urodynamic evaluation as primary VUR can be due to an anatomical defect but also a severe voiding dysfunction, especially if bilateral.

Effect on bladder and renal stone

Clinical data: No study has evaluated the relationship between botulinum toxin and renal stones. Only Wefer *et al*[44] in 2010 reported less than 6 patients out of 214 (2.8%) presenting bladder stones. However he was not able to determine wether these disorders was BoNTA treatment related. Ginsberg *et al*[21] reported in 2012, out of 416 patients, only one case of bladder stone formation after 300 U botox injection.

Pathogenesis: Renal and bladder calculi are an important source of morbidity for patients with neurogenic bladder. The incidence of renal stones in neurogenic patient is about 6.8%[45] higher than in the common population. Old series have reported that most of the calculi were of struvite, induced by UTI[46]. However, more recent trials have established that stones may also be of metabolic origin. For instance, Matlaga *et al*[47] in 2005 has evaluated 32 renal calculi in a population of MMC and SCI, and found only 37.5% of struvite calculi and 62.5% of metabolic calculi. This modification of the origin of the stones might be due to a decrease in UTI in neurological population over the years, due to improvement of the urinary conditions in those patients.

By decreasing the mean rate of UTI and UUT

Table 1 Urinary tract infections after botulinum toxin injections in contemporary series

Ref.	Type of toxin	Patients	sUTI before injections	sUTI after injection	*P*	Bacteriuria % (*n*)	Symptomatic and asymptomatic UTI after injections	*P*
Gamé *et al*[19], 2008	Botox 300 UI	30 15 MS 14 SCI 1 Myelitis	1.79/pp/6 mo	0.2/pp/6 mo	0.003	43		
Giannantoni *et al*[9], 2009	Botox 300 UI	17 SCI	6.7/pp/yr	1.8/pp/yr	0.001			
Cruz *et al*[20], 2011	Placebo Botox 200 UI 300 UI	154 MS					Placeb: 32% 200 UI: 58% 300 UI: 70%	$P < 0.05$ (*vs* placebo)
Cruz *et al*[20], 2011	Placebo Botox 200 UI 300 UI	121 SCI					Placebo: 50% 200 UI: 52.6% 300 UI: 56.4%	
Kuo *et al*[22], 2011	Botox 200 UI	33 SCI		6.80%		28 (37)		
Herschorn *et al*[23], 2011	Placebo Botox 300 UI	57 38 SCI 19 MS					Placebo: 55% 300 UI: 57%	
Ginsberg *et al*[21], 2012	Placebo Botox 200 UI 300 UI	227 MS					Placebo: 28% 200 UI: 51% 300 UI: 50%	
Ginsberg *et al*[21], 2012	Placebo Botox 200 UI 300 UI	189 SCI					Placebo: 42% 200 UI: 48% 300 UI: 50%	
Jia *et al*[24], 2013	Botox 300 UI	SCI 41	1.49/pp/6 mo	0.78/pp/6 mo				

sUTIs: Symptomatic urinary tract infections; SCI: Spinal cord injury.

dilatation, BoNTA injections may lead to decrease the incidence of struvite calculi but further studies are warranted.

Patients with neurogenic bladder are at increased risk of bladder stone formation. According to Chen *et al*[45], within 10 years after SCI, 15% to 30% of patients will have formed at least one stone. The risk of forming a subsequent stone quadruples when a patient has already formed one stone[48]. Furthermore, the manner in which the bladder is managed in SCI appears to have a significant impact on the risk of stone formation. One large study of over 450 patients noted that the use of CIC was associated with a significant reduction in the risk of bladder stone formation, with an annual risk of 0.2%, compared with 4% in those patients managed by a chronic indwelling catheter[48].

CIC in patients treated by BoNTA might be beneficial for decreasing bladder stones formation. In the opposite, in patients who were not using CIC previously to the injections, there might be and increase risk of developing bladder calculi. However, this remains hypothetical and needs to be further established by dedicated, well performed clinical trials.

Effect on chronic kidney disease

Clinical data: In a long term follow-up of 17 patients during 6 years after 300 U of botulinum injections, Giannantoni *et al*[9] didn't show any impairment of renal function. Kuo *et al*[21] evaluated the impact of botulinum toxin 200 U on renal function in 33 patients with supra sacral SCI. Videourodynamic and 99mTc-DTPA renal scanning for glomerular filtration rate (GFR) were performed at screening and every 3 mo during 24 mo of assessment. Onabotulinum toxin injections were repeated every 6 mo. GFR significantly decreased throughout the treatment course (96.27 ± 22.50 at baseline *vs* 83.51 ± 23.96 at 24 mo, $P = 0.028$). There was no significant change in mean serum Cr levels during the same period (0.623 ± 0.183 *vs* 0.675 ± 0.175, $P = 0.802$).

In 2014, the same team[49] evaluated the effect of 300 U *vs* 200 U of onabotulinum toxinA on renal function in 72 SCI patients. During the follow-up period, the changes in GFR from baseline to all time points did not differ significantly within each group or between the two groups. At baseline, the GFR was 94.2 ± 22.1 mL/min and 84.2 ± 19.6 mL/min in 200-U and 300-U groups, respectively. At the end-point, the GFR was 90.5 ± 24.2 mL/min and 88.0 ± 28.2 mL/min in the 200-U and 300-U groups, respectively.

There were no significant difference between 300 U group and 200 U group ($P = 0.197$) neither between group with compliance > 30 and group with low compliance (< 30).

Four patients had improved their renal function (2 in 200 U and 2 in 300 U group) at the end of the study. Inhibited detrusor contracture decreased significantly after the second detrusor injection of 300-U of onabotulinumtoxinA compared to that in the 200-U group.

Pathophysiology: The ultimate consequence of all upper urinary tract complications in neurological patients is the impairment of renal function. Although bladder management methods have evolved in recent decades, chronic renal insufficiency remains a significant cause of morbidity and it is one of the major concern to have in mind when treating those patients[50].

In urodynamics studies, a bladder pressure > 40 cmH_2O mostly due to detrusor hyperreflexia and low BC are the major risk factors for renal damage in SCI patients[3]. However, CIC, antimuscarinic therapy, and regular urodynamic monitoring have been reported to reduce the risk of renal failure[51].

These studies show that renal function remains stable when patient have urodynamics modifications after botulinum toxin injections but without significant improvement (Table 1). However, the median term in follow-up of these series may be a limit for renal function study. The neurological disorder in also an important point to consider and SCI patients are more at risk of renal deterioration than multiple sclerosis patients. It highlights the fact that patients must be followed carefully on long term after botulinum injections.

Early and repeated detrusor onabotulinumtoxinA injections could therefore be beneficial to SCI patients before upper urinary tract deterioration.

An explanation why detrusor botulinum injection may not improve renal function is that anatomical renal damages may be irreversible, and also that renal deterioration may be caused by other factors. In particular, SCI patients are at higher risk to develop cardiovascular disease than others[52]. Many other confounding factors in neurological patients can induce renal impairment such as, diabetes, obesity, lipid disorders, metabolic syndrome, and disturbances of the autonomous nervous system, which may result in blood pressure abnormalities, arrhythmias and cardiac disease[51,53].

All these factors have to be taken into account when evaluating the long-term impact of on kidney function in the neurological patients. For the moment, this has not been correctly assessed and BoNTA are postulated as protective for the urinary tract in the long term, mainly through indirect benefits.

CONCLUSION

Botulinum toxin injections regulate urodynamic parameters in a context of neurogenic OAB. It furthermore may have a positive effect on UTIs, but this has to be put in perspective with the increased use of CIC. There is also an anticipated positive effect of BoNTA injections on hydronephrosis, VUR and stone disease, but with a weaker level of evidence. Long term effects on renal function are also probably positive, but this parameter remains multifactorial.

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