The Management of Urine Storage Dysfunction in the Neurological Patient

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CHAPTER 1

GENERAL INTRODUCTION
to
THE MANAGEMENT OF URINE STORAGE DYSFUNCTION IN THE NEUROLOGICAL PATIENT

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INTRODUCTION

The human lower urinary tract (LUT), comprising the urinary bladder, the urethra and the external urethral sphincter, has two opposing functions [1]: 1) the low pressure, continent, and symptom free storage of urine which is constantly draining from the kidneys, and 2) the periodical, voluntarily controlled, unobstructed, and complete release of the stored urine.

The correct progression of each phase and particularly the switch from one phase to the other requires the orchestration of a neural network of afferent and efferent pathways involving different levels of the nervous system, i.e. peripheral autonomic and somatic nerves, spinal neurons and tracts, and finally supraspinal processes to enable voluntary control and judgement of appropriateness (**Figure 1-1**).

Hence, it is not surprising that neurological diseases or lesions that interfere with such complex neuronal control easily lead to dysfunction and / or symptoms in the LUT. Indeed, the prevalence of LUT dysfunction and symptoms in neurological conditions such as spinal cord injury (SCI), multiple sclerosis (MS), Parkinson's disease (PD), and stroke, can reach almost 100% (**Table 1-1, Table 1-2**).

Lower urinary tract symptoms (LUTS) such as urinary frequency, urgency, and incontinence or urinary retention are highly bothersome [2, 3] and severely reduce quality of life (QoL) [4] particularly in neurological patients as they often already struggle with the comorbidities of their neurological disease / lesion, such as impaired mobility. Hence, restoration of bladder function is one of the top priorities of individuals with neurogenic lower urinary tract dysfunction (NLUTD), such as SCI patients [5].

In addition, the underlying dysfunction of LUTS (**Table 1-3, Table 1-4**) can bear certain health risks. The most relevant sequelae that are associated with NLUTD are upper urinary tract (UUT) damage, i.e. impairment of kidney function, and recurrent urinary tract infections [6-14].

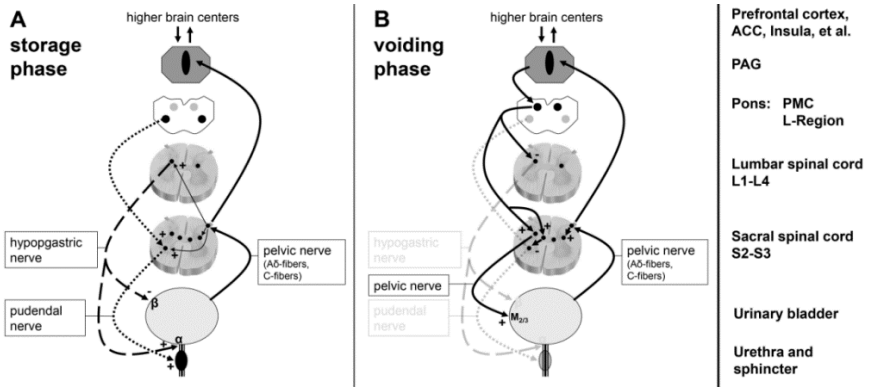

Figure 1-1 Schematic illustration of spinal cord and brain stem regions involved in lower urinary tract (LUT) control and their most relevant neuronal connection to the LUT. The illustration summarizes the findings of neurophysiological animal studies from De Groat et al. [15] and early functional neuroimaging studies in humans from Blok et al. [16]. During the storage phase (A), which normally accounts for most of the day (98%), the detrusor is relaxed and the bladder neck closed due to sympathetic tone acting on the bladder body and neck. Sympathetic fibres travel along the hypogastric nerve from the sympathetic nuclei in the intermediolateral column of the lumbar spinal cord to the LUT and provide adrenergic input to beta-receptors on intramural ganglia of the bladder body (→ relaxation) and alpha-receptors at the bladder neck (→ contraction/closure). Bladder afferents traverse through the pelvic nerve and enter the dorsal horn of the sacral spinal cord. At low filling volumes, there might be only little afferent activity and weak afferent signals might reach the PAG and diencephalic structures (e.g. thalamus), but bladder sensations do usually not reach consciousness during this state. With increasing bladder volumes, afferent activity might increase, likely due to changes in intravesical pressure and, at some degree of filling, bladder sensations will reach consciousness in the form of a first desire to void. From the sacral dorsal horn, excitatory collaterals reach the sympathetic nuclei in the lumbar intermediolateral column and the sacral frontal horn, where the motor neurons of the external urethral sphincter (EUS) are located (Onuf's nucleus), to facilitate sympathetic input to the bladder and bladder neck, and somatic input to the EUS respectively. This supports continence during increasing bladder volumes, when voiding has to be postponed. Another region thought to be responsible for continence is the pontine L-region (named L-region as it is lateral to the other relevant pontine structure named the pontine micturition centre or M-region or Barrington's nucleus), which has excitatory input to the EUS motor neurons in Onuf's nucleus and thus facilitates the elevation of the EUS tone.

If the decision to empty the bladder is made (in the higher brain centres), the periaqueductal grey (PAG) activates the pontine micturition centre (PMC) (B). The switch between L-region and PMC activation is sometimes conceived in a simplified manner as moving a lever from one programme to the other. Only one region can be activated at a time. From the PMC, strong inhibitory inputs reach the sympathetic nuclei in the intermediolateral lumbar cord to suppress the sympathetic input to bladder body and bladder neck to enable synergic micturition. Simultaneously, the PMC has strong excitatory projections to the parasympathetic nuclei in the sacral spinal cord that in turn activate the detrusor muscle via muscarinic receptors. The parasympathetic fibres travel along the pelvic nerve. In addition to the parasympathetic activation, the PMC has excitatory collaterals to inhibitory interneurons in the sacral cord that reduce the activity of EUS motor neurons, and thus facilitate EUS relaxation and synergic micturition.

Table 1-1 Prevalence of different neurogenic lower urinary tract dysfunction (NLUTD) and symptoms in multiple sclerosis (MS), Parkinson's disease (PD), multiple system atrophy (MSA), and stroke.

	MS	PD	MSA	Stroke
Prevalence of NLUTD	34-99% [17]	27-71% [18, 19]	78-96% [20]	38-94% [21, 22]
Average time interval between diagnosis of neurological disease and onset of urological symptoms [years]	5.9 (4.6-7.8) [17]	5 [23]	2 [23]	
Urinary urgency	63.4% (32-86%) [17]	33-68% [18, 19]	63% [24]	70% [21]
Urinary frequency	54.4% (25-99%) [17]	16-71% [18, 19]	45% [24]	59% [21]
Nocturia		60-86% [18, 19]	74% [24]	76% [21]
Urinary urgency incontinence	56.3% (19-80%) [17]	27% [19]	63% [24]	29% [21]
Dysuria	34.8% (6-79.5%) [17]	30% [23]	69% [23]	6% [21]
Retention / incomplete bladder emptying (PVRV > 100 mL)	35.6% (8.3-73.8%) [17]		52% [24]	48% [21]
DO	65% (43-99%) [17]	45-93% [19]	35-56% [23, 24]	36-82% [21]
DSD	35% (5-83%) [17]		47-98% (incl. bladder neck dyssynergia) [23, 24]	
Reduced compliance	2-10% [17]		31% [24]	
Detrusor hypocontractility	25% (0-40%) [17]	53% [19]	52-67% [20, 23]	33-40% [21]
Open bladder neck during filling cystometry		31% [20]	87% [20]	
Pathologic EUS-EMG		5% [20]	93% [20]	

The listed numbers reflect only gross guide values due to sparse and / or heterogeneous data form investigations using different assessment methods. PVRV post void residual volume, DO detrusor overactivity, DSD detrusor-sphincter-dyssynergia, EUS-EMG external urethral sphincter electromyogram. Table adapted from [25].

Table 1-2 Associations between injury levels and urodynamic findings in patients with spinal cord injury (SCI) based on a meta-analysis by Jeong et al. [26]

	Level of SCI				p-value*
	cervical	thoracic	lumbar	sacral	
No. of Patients	259	215	137	46	
DO [%]	65	78	49	22	< 0.001
DSD [%]	63	72	33	13	< 0.001
DU [%]	9	9	39	70	< 0.001
Normal [%]	1	2	2	9	0.002

Thoracic lesions are indicated to spinal cord level T9 or above, and injuries at the T10 through T12 levels are included in lumbar lesions. The combined suprasacral and sacral lesions have been excluded from this analysis.

* Pearson chi-square test

DO detrusor overactivity. DSD detrusor-sphincter-dyssynergia, DU detrusor underactivity. Table adapted from **[26]**.

Not by accident, renal disease and other urological complications such as urosepsis ranged among the most frequent causes of death in SCI patients until the mid 1970s whereupon neuro-urological work–up and follow-up gradually became established [27-34].

Nowadays, due to improvements in medical care, including neuro-urological management, many patients with neurological disease or trauma and NLUTD have increased their life expectancy to a level close to normal [31, 35-38]. As a consequence, not only the number of elderly individuals with NLUTD is increasing but also the time period for which they have to deal with their NLUTD. This is further potentiated by the increasing life expectancy of the general population and, consequently, age-associated, chronic degenerative neurological diseases such as PD [39, 40]. Finally, these aspects are also relevant from a uro-oncological view point as, while the incidence of bladder malignancies may not be necessarily higher in NLUTD compared to the general population, they may occur earlier and with a more rapid/aggressive progression. This can, in conjunction with the comorbidities related to the neurological disease/lesion, lead to a higher

degree of morbidity [41-43]. Thus, it is all the more important to understand how to manage NLUTD and associated complications to provide sustainable treatment and follow-up strategies.

Table 1-3 Summary of common storage symptoms that might occur due to lower urinary tract dysfunction in neurological diseases or lesions in association with their typically related urodynamic and clinical findings. Definitions of Symptoms are reproduced from the International Continence Society standardisation of terminology in lower urinary tract function [44].

Storage symptom	Most typical urodynamic and clinical findings (listed are single findings that can also occur in combination)	Typical neurological lesion site
Urinary urgency *Complaint of a sudden compelling desire to pass urine which is difficult to defer.*	- Detrusor overactivity [1, 2] - Low bladder compliance [1, 2]	1 suprasacral 2 supraspinal
Urinary frequency (increased daytime frequency, pollakisuria) *Complaint by the patient who considers that he/she voids too often by day.*	- Detrusor overactivity [1, 2] - Low bladder compliance [1, 2] - Incomplete bladder emptying / elevated post void residual volume due to hypocontractile detrusor [3, 4] or bladder outlet obstruction (anatomical: prostate enlargement, urethral stricture; functional: detrusor-sphincter-dyssynergia [1, 2])	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Nocturia *Complaint that the individual has to wake at night one or more times to void.*	- Detrusor overactivity [1, 2] - Low bladder compliance [1, 2] - Incomplete bladder emptying / elevated post void residual volume due to hypocontractile detrusor [3, 4] or bladder outlet obstruction (anatomical: prostate enlargement, urethral stricture; functional: detrusor-sphincter-dyssynergia [1, 2])	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Urgency urinary incontinence *Complaint of involuntary leakage accompanied by or immediately preceded by urgency.*	- Detrusor overactivity [1, 2] - Low bladder compliance [1, 2]	1 suprasacral 2 supraspinal
Stress urinary incontinence *Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing.*	- Urethral sphincter insufficiency [3, 4] - Bladder neck incompetence [3, 4]	3 subsacral / lumbosacral 4 peripheral

Storage symptom	Most typical urodynamic and clinical findings (listed are single findings that can also occur in combination)	Typical neurological lesion site
Mixed urinary incontinence *Complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.*	- Detrusor overactivity [1, 2] - Low bladder compliance [1, 2] **AND** - Urethral sphincter insufficiency [3, 4] - Bladder neck incompetence [3, 4]	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Continuous urinary incontinence *Complaint of continuous urinary leakage.*	- Open bladder neck and flaccid urethral sphincter [3, 4] **OR** - Overflow incontinence due to bladder outlet obstruction (anatomical: prostate enlargement, urethral stricture; functional: detrusor-sphincter-dyssynergia [1, 2]) and/or acontractile [3, 4], hyposensitive bladder [3, 4]	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Reduced or absent bladder sensation *The individual is aware of bladder filling* *but does not feel a definite desire to void or reports no sensation of bladder filling or desire to void.*	- Bladder distension during filling cystometry is not perceived or only at high volumes [1-4]	1 suprasacral (only in complete spinal cord lesions) 2 supraspinal (only in complete spinal cord lesions) 3 subsacral / lumbosacral 4 peripheral
Increased bladder sensation *The individual feels an early and persistent desire to void.*	- Bladder distension during filling cystometry is perceived early, at low volumes [1, 2].	1 suprasacral 2 supraspinal

STORAGE DYSFUNCTION OF THE LOWER URINARY TRACT IN NEUROLOGICAL PATIENTS

DETRUSOR OVERACTIVITY

One of the most relevant risk factors for developing LUTS and complications of lower and upper urinary tract, especially in neurological patients, is detrusor overactivity (DO) [7, 14, 45-47]. This term describes a condition of involuntary detrusor contractions during the storage phase that result from loss or impaired supraspinal inhibitory input to the sacral bladder reflex circuitry. This also implicates that DO can occur as a consequence of any lesion / disease affecting the suprasacral central nervous system. This makes DO one of the most common dysfunctions in neurological patients (**Table 1-1, Table 1-2**). DO can be visualised and diagnosed using filling cystometry. This specialized examination provides details on the maximum pressure amplitude during DO, the frequency and duration of DO, and the volume of DO occurrence, which are relevant parameters for a full understanding and characterization of the extent of DO. An increase in detrusor pressure during DO will usually cause a sensation of urgency, if sensory function is maintained. When pressure levels of DO exceed the sub-vesical closing pressure, the DO will result in DO incontinence. Moreover, DO has been proven to be associated with irreversible morphological alterations of the LUT and renal function impairment in the long-term [6-9, 11, 12].

The morphological alterations associated with DO include detrusor hypertrophy, trabeculation of the bladder wall, and the development of pseudo-diverticula [11]. Renal function impairment associated with DO may occur through multiple mechanisms, such as obstruction, excessive pressure exposure, vesicoureteral reflux (VUR), and recurrent infections.

Usually, the terminal distal parts of the ureters pass transversely through the bladder wall to their orifices in the trigone [48]. This intramural passage provides a flap valve mechanism with compression of the intramural ureter

parts during detrusor contraction, preventing VUR during micturition. During storage, when the detrusor is relaxed, the intramural ureter is not compressed and can thus deliver the urine into the bladder. However, in case of detrusor hypertrophy due to chronic DO, the intramural ureter parts may become constantly compressed by the hypertrophic detrusor resulting in ureteric outflow obstruction, which in the long-term will lead to dilatation of the ureters and subsequently also the pelvicaliceal system of the kidneys [11]. Such pressure-related ectasia of the UUT is associated with renal damage [11, 13].

Even prior to the development of detrusor hypertrophy, DO can become harmful to renal function if detrusor pressure increases to amplitudes above 40 cmH_2O, pressures that have been demonstrated to be associated with upper urinary tract deterioration [7, 8, 49, 50]. However, this pressure threshold of 40 cmH_2O for UUT damage is deemed controversial due to the rather low level of evidence and the clinical observation that intravesical storage pressures below 40 cmH_2O do not guarantee UUT safety but may result in even more severe UUT deterioration if tolerated over a longer period of time. Hence, the pressure level of DO alone is certainly not the only factor related to UUT deterioration but rather a mixture of pressure level, frequency of DO contractions, and duration of pressure elevation during single DO contractions [51]. Development of VUR in this context may aggravate pressure exposure and transmission to the kidneys but the absence of VUR does not prevent renal impairment in DO.

UUT deterioration due to DO may even be accelerated by recurrent urinary tract infections (UTI). Patients with LUTD such as DO are prone to develop recurrent UTI [10, 46, 52] and in conditions of altered UUT urodynamics, i.e. obstruction and VUR, such infections may reach the upper urinary tract more frequently and easily.

Table 1-4 Summary of common voiding symptoms that might occur due to lower urinary tract dysfunction in neurological diseases or lesions in association with their typically related urodynamic and clinical findings. Definitions of Symptoms are reproduced from the International Continence Society standardisation of terminology in lower urinary tract function [44].

Voiding Symptom	Most typical urodynamic and clinical findings (listed are single findings that can also occur in combination)	Typical neurological lesion site
Urinary retention *Inability to pass urine to empty the bladder. This might occur acute or chronically, complete or incomplete.*	- Hypo- or acontractile detrusor muscle [3, 4] - Bladder outlet obstruction (anatomical: prostate enlargement; functional: detrusor-sphincter-dyssynergia [1, 2])	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Urinary hesitancy *An individual describes difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine.*	- Bladder outlet obstruction (anatomical: prostate enlargement, urethral stricture; functional: detrusor-sphincter-dyssynergia [1, 2]) - Hypocontractile detrusor [3, 4]	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Urinary intermittency *An individual describes urine flow which stops and starts, on one or more occasions, during micturition.*	- Detrusor-sphincter-dyssynergia [1, 2] - Hypocontractile detrusor [3, 4]	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral
Slow urinary stream *Perception of reduced urine flow, usually compared to previous performance or in comparison to others.*	- Bladder outlet obstruction (anatomical: prostate enlargement, urethral stricture; functional: detrusor-sphincter-dyssynergia [1, 2]) - Hypocontractile detrusor [3, 4]	1 suprasacral 2 supraspinal 3 subsacral / lumbosacral 4 peripheral

DETRUSOR-SPHINCTER-DYSSYNERGIA

The development of elevated storage pressures and dysfunctional dynamics of the urinary tract due to DO may aggravate with Detrusor-Sphincter-Dyssynergia (DSD) which is frequently associated with DO specifically in neurological patients [53].

DSD is defined as a detrusor contraction concurrent with an involuntary contraction of the urethral sphincter and / or periurethral striated muscle groups. Occasionally, flow may be prevented altogether [54]. Hence, DSD may, on the symptomatic level, limit or prevent urinary incontinence but in turn contribute to significant rise of intravesical pressure due to functional subvesical outlet obstruction during a detrusor contraction. Such DSD-related intravesical pressure excesses can increase urgency or pain symptoms and, more importantly, potentiate the risks for LUT and UUT complications, the latter leading to significant renal damage in the long run [55].

Different types of DSD have been described previously [56-58]: type 1) concomitant increase in both detrusor pressure and sphincter EMG activity with sudden sphincter relaxation at the peak of the detrusor contraction, type 2) sporadic contractions of the external urethral sphincter throughout the detrusor contraction, and type 3) a crescendo-decrescendo pattern of sphincter contraction which results in urethral obstruction throughout the entire detrusor contraction. However, the clinical relevance of the different types of DSD is controversial as type distinction does not yet have any impact on treatment decision or outcome [58, 59].

AUTONOMIC DYSREFLEXIA

An acute and potentially life-threatening complication associated with DO / DSD most commonly observed in SCI patients with lesions above the thoracic (Th) level 6 is autonomic dysreflexia (AD) [60, 61]. AD is defined as an increase in systolic blood pressure (SBP) of at least 20mmHg from baseline [62]. It is based on an sympathetic overreaction due to the loss of descending central (brain stem) inhibitory pathways to the sympathetic chain causing vasoconstriction below the level of lesion and consequently a blood pressure increase [60]. This becomes especially pertinent in SCI lesions

above Th6 due to the lack of central modulation on the splanchnic nerves that usually emanate below Th5 but innervate the critical mass of blood vessels required to cause elevation of the blood pressure [60]. In response to excessive hypertension during AD, baroreceptors above the lesion level may become activated and induce a vagal-mediated bradycardia. This compensatory parasympathetic output above the level of lesion is thought to be responsible also for symptoms such as headache, flushing and sweating in the head and neck region [60]. However, AD may also occur completely asymptomatically, which makes it even more hazardous in daily life.

In addition to DO / DSD, AD can be triggered by various, often usually benign stimuli below the lesion, i.e. bladder and/or bowel distention, urinary stones or infection, skin lesions / irritations, wounds, fractures, menstruation and sexual intercourse [63]. When AD occurs, it is important and most effective to eliminate the trigger stimulus, i.e. emptying the bladder, to prevent otherwise rapid progression of AD.

RESTORATION OF URINARY BLADDER STORAGE FUNCTION

DO with or without DSD are the main causes of increased storage pressures and long-term damage to the UUT and LUT particularly in neurological patients [6-10, 12-14, 45, 46, 49]. Hence, to protect the UUT function and prevent long-term complications, it is necessary to maintain or restore low-pressure and unrestricted urinary drainage from the kidneys [64]. Depending upon the extent and severity of the neurogenic urinary storage dysfunction, this can be achieved using conservative, minimally-invasive, and / or surgical treatment options:

CONSERVATIVE TREATMENT OPTIONS

NEUROPHYSIOLOGICAL BACKGROUND

Despite the apparently more obvious cause of LUT storage dysfunction in neurological patients based on the impairment of aforementioned multilevel neuronal control, it is important to also consider the physiological mechanisms occurring within the LUT. This is of particular relevance since there are as yet no direct treatments available for most of the neurological lesions / diseases causing LUT storage dysfunction. Understanding the physiological processes in the LUT also on a receptor and neurotransmitter level, however, can help to detect useful targets for pharmacotherapy.

In previous decades, different receptors, chemical mediators and signal transduction pathways within the LUT have been discovered and described as being involved in normal and pathological LUT function [65]. Of those, the cholinergic system, including muscarinic receptors, is probably the best described and longest-known mechanism in the LUT [66, 67].

In order to contract, the detrusor requires an appropriate command, delivered by acetylcholine released from parasympathetic postganglionic nerve terminals. Acetylcholine binds to the muscarinic receptors on the detrusor and activates G-protein-related pathways that lead to smooth muscle contraction [68]. Depending on the muscarinic receptor subtype that is activated, detrusor contraction is facilitated by (1) inhibition of adenylyl cyclase via M2 receptors and subsequent decrease of intracellular cAMP, and / or (2) phospholipase c activation via M3 receptors to generate inositol triphosphate which then releases Ca^{2+} from the sarcoplasmic reticulum [68]. Since intracellular Ca^{2+} release is regarded as the main trigger for smooth muscle contraction, M3 receptors are regarded as most relevant for the initiation of voiding contractions [68].

Beyond the detrusor, muscarinic receptors of all subtypes (M1 – M5) have been found elsewhere in the LUT [66, 67]: e.g. urothelium, suburothelium, afferent nerve fibers, and autonomic postganglionic nerve endings. Their exact role and function in these locations is not yet fully established. However, there is evidence that muscarinic receptors on the postganglionic nerve endings are involved in facilitation (M1) and inhibition (M2, M4) of axonal acetylcholine release [67]. In the urothelium and suburothelium, activation of muscarinic receptors can lead to release of neurotransmitters such as adenosine triphosphate (ATP), that in turn can modulate afferent nerve- and smooth muscle activity [69].

In the context of DO, both of idiopathic and neurogenic origin, alterations of muscarinic receptor expression and sensitivity have been observed and seem to contribute to the pathophysiological process of DO: e.g. muscarinic receptors in the detrusor tissue of patients with idiopathic detrusor overactivity (IDO) and neurogenic detrusor overactivity (NDO) demonstrated increased sensitivity to stimulation, compared to healthy controls [70] and decreased suburothelial expression [71]. In the animal model, SCI seem to alter the muscarinic receptor profile on the postganglionic nerve terminals towards upregulation of M3 and downregulation of M1 receptors [72, 73].

The sympathetic counterparts of muscarinic receptors are beta-adrenoceptors. Their activation, naturally by noradrenaline release from postganglionic sympathetic neurons of the hypogastric nerve, can mediate relaxation of the detrusor and thus contribute to the restoration of bladder storage function. Beta-3-adrenoceptors seem to be the most relevant in this context [74] and recent clinical trials have resulted in approval of a beta-3-adrenoceptor agonist for the treatment of bladder overactivity including DO [75, 76] (see paragraph on beta-adrenoceptor agonists below).

In addition to classical cholinergic/adrenergic mechanisms, there are other pathways, neurotransmitters, and receptors that have been described to play a role in bladder storage (dys-)function and thus may serve as relevant treatment targets [65]: e.g. purinergic system, cannabinoid system, nerve growth factor, Rho-kinase pathway, transient receptor potential (TRP) channels, prostanoid receptors, potassium channels, and vitamin D3 receptors. So far, purinergic receptors, TRP channels, and the cannabinoid system seem to constitute the most promising targets [65].

The purinergic system is based on the principle that ATP is released from the urothelium upon stretch and binds to purinergic receptors (P2X) on suburothelial sensory nerves which mediate the sensation of bladder filling. Increased levels of ATP release or purinergic receptor expression may contribute to increased sensitivity, i.e. urinary urgency, or detrusor overactivity [65]. In the bladders of patients with NDO, increased levels of nerve fibers expressing the purinergic receptor P2X3 have been detected [77, 78]. Patients with a clinical response to intravesical vanilloid treatment with resiniferatoxin showed decreased P2X3 expression, whereas non-responders did not [77]. Similar effects were observed in response to botulinum neurotoxin A (BoNT/A) intradetrusor injections [79]. In SCI rats, which showed higher frequencies of spinal cord field potentials and non-voiding contractions compared to normal rats, application of P2X3 antagonists A-317491 and AF353 was demonstrated to reduce both parameters [80, 81].

TRP cationic ion channels are universal sensors of physical and chemical stimuli that are ubiquitous in various tissues of the human body including the LUT [82]. Their basic mechanism is to allow cationic (e.g. K^+, Ca^{2+}) influx upon stimulation, causing secondary reactions dependant on the tissue in which the TRP channel is located, e.g. depolarization with elicitation of an action potential in neurons. Within the LUT, several TRP channels have been detected in various layers (including mucosa and detrusor) and on neuronal fibers innervating the LUT. Of such TRP channels, specifically TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1 have been attributed to play a relevant role in normal and pathological LUT function [65, 82]. As with the increased purinergic receptor expression in patients with NDO, TRPV1 expression was also found to be elevated in NDO patients [83, 84]. Again, treatment with resiniferatoxin or BoNT/A intradetrusor injections was able to reduce TRPV1 expression in those patients responding also clinically to treatment [79, 83, 84]

Despite their promising effects in human studies, the evidence for intravesical treatment with vanilloids such as capsaicin and resiniferatoxin is still very limited and adverse events including pelvic pain, facial flush, worsening of incontinence, autonomic dysreflexia, urinary tract infection, and haematuria are very frequent [85]. Intravesical vanilloids are not approved for treatment in LUTD / LUTS and have largely fallen into oblivion, particularly after the propagation of BoNT/A intradetrusor injections. However, based on their action on specific LUT receptors and afferent fibers, vanilloids are still of scientific interest and may undergo a clinical revival once more tolerable solvents for their application are developed [85].

The cannabinoid system in the LUT involves two G-protein-coupled cannabinoid receptors, CB1 and CB2, their endogeneous (e.g. anandamide, 2-arachidonoylglycerol) and exogeneous (phytocannabinoids, synthetic cannabinoids) ligands, and related enzymes for biosynthesis and degradation (e.g. fatty acid amid hydrolase, monoacylglycerol lipase) [86]. Hence, effects can be elicited directly by stimulation of the cannabinoid

receptors or indirectly by inhibiting the degradation enzymes such as fatty acid amid hydrolase (FAAH). In SCI rats, treatment with the selective CB2 agonist O-1966 resulted in improved bladder function recovery which was associated with a significant reduction of inflammatory response in the spinal cord following injury [87]. In MS patients with NDO, delta-9-tetrahydrocannabinol alone or in combination with cannabidiol applied as oral capsule or spray improved symptoms such as urinary incontinence and frequency [88]. However, symptomatic improvements were not reflected urodynamically and there were mild but frequent adverse events such as UTI, dizzinesss, headache, vomiting, and worsening of dry mouth [65, 88]. Although Sativex® is an approved drug, its indication in most countries is limited to treatment of refractory spasticity in patients with advanced MS. The overall clinical evidence for the use of cannabinoids in the treatment of NLUTD is still very limited and trials applying indirect cannabinoid stimulation, e.g. use of FAAH inhibitors, for the treatment of NLUTD, are lacking.

Despite the numerous potential treatment targets identified in different animal models, of which only few are neurogenic, i.e. SCI or MS, translation of findings into humans is a major challenge. Thus, approved pharmacotherapy for LUTD / LUTS is still very limited and antimuscarinic drugs are still the mainstay of conservative therapy for bladder storage dysfunction (see paragraph below).

ANTIMUSCARINIC DRUGS

In principle, antimuscarinics act as reversible competitive antagonists that block the muscarinic receptors on the detrusor myocytes resulting in reduced detrusor excitability through acetylcholine release from parasympathetic nerve terminals [68]. Assuming urinary urgency and DO are the result of premature acetylcholine release from the parasympathetic nerves during the storage phase, the available antimuscarinic drugs will shift

the dose response curve of acetylcholine to the right, i.e. more acetylcholine is necessary to cause the same effect or symptom, resulting in the postponement or attenuation of cholinergic stress on the detrusor. Clinically, this results in the typical improvements in LUTD / LUTS such as increased warning time, larger bladder capacities prior occurrence of urgency and DO, and reduced pressure amplitudes of DO [89-95]. This competitive antagonism is a dynamic process, the efficacy of which depends *inter alia* on the available concentration of the antimuscarinic drug at the neuromuscular junction in relation to the acetylcholine concentration. Thus, high dosages of antimuscarinics may cause enough detrusor sedation to result in increased post-void residual volume (PVRV) or even urinary retention [93, 96, 97]. However, with the clinically applied and approved antimuscarinic dosages, this seems to happen rarely – at least in patients with non-neurogenic overactive bladder symptoms (OABS) [98, 99]. Nevertheless, antimuscarinics still apply a verifiable effect on storage symptoms and DO [89, 90, 95], raising the question why they seem to selectively act during the storage but not voiding phase. Certainly, antimuscarinics cannot differentiate or act differently across both phases and this observation may simply be a false conclusion, as many aspects of the pathogenesis of OABS and the interplay between muscarinic receptor expression, acetylcholine release and antimuscarinic drugs remain unknown. In addition, the treatment effect of currently available antimuscarinic drugs for LUTD / LUTS is often little greater than placebo [100] and their effect on the detrusor pressure amplitude during micturition has never been systematically analysed. This would be of relevance for our understanding of antimuscarinic action and the lack of voiding symptoms does not *per se* prove that there is no effect on detrusor contractility during voiding at all. Yet, potential relationships between antimuscarinic effects during the storage and voiding phase remain unclear, e.g. if the reduction in DO or urgency corresponds to a reduction in voiding contraction. The explanation that during micturition the expected massive neuronal release of acetylcholine cannot be countered by

antimuscarinic drugs in the approved dosages [101] appears reasonable in view of the competitive antagonistic mechanism of action of antimuscarinic drugs but still leaves unclear what happens during the storage phase causing urinary urgency and DO that *can* be alleviated by antimuscarinics. As mentioned, some premature neuronal acetylcholine “leakage” that can be covered by antimuscarinic drugs at the approved dosages may be involved, providing support to the neurogenic hypothesis of OABS [102], but non-neuronal acetylcholine release and muscarinic receptors on other tissues than detrusor may also play a role.

Recent studies in animals and isolated human bladder tissue provide evidence for acetylcholine release from sources other than the parasympathetic nerve terminals, i.e. urothelium and suburothelial myofibroblasts, and the presence of muscarinic receptors on afferent nerves [101, 103]. In addition, it has been demonstrated that antimuscarinic drugs can suppress adenosine triphosphate release form the urothelium [101, 104]. The antagonization of acetylcholine release from non-neuronal sources and the modulation of neurotransmitter release at the urothelial and suburothelial level by antimuscarinic drugs may influence localized autonomous non-micturition contractile activity [105] and afferent activity, which in consequence reduces OABS [101]. However, the detailed mechanism in humans, especially if there is a direct afferent effect of muscarinic drugs, requires further elucidation.

Although some newer antimuscarinic drugs show some selectivity for the M2 and / or M3 receptors on the detrusor, all antimuscarinic drugs for LUTD / LUTS treatment still bind to other muscarinic receptors elsewhere in the body causing, to various extents, adverse events such as dry mouth, constipation, blurred vision, somnolence, dizziness, and cognitive impairment [106]. The main route of antimuscarinic drug administration is oral, through which extended-release compared to immediate-release formulations are usually better tolerated and enable a once-daily application. Alternative administration routes, such as transdermal and intravesical

application, are available and may be an option for reducing some side effects [106].

The voluminous literature and evidence available for the use of antimuscarinic drugs is mainly related to the treatment of OABS which occurs per definition only in patients without any neurological etiology for their LUTS and for whom these drugs have been mainly developed and marketed [90, 95, 107]. However, there is also some evidence for the efficacy of antimuscarinic drugs in NDO [89, 91, 108]. In conjunction with the relatively good safety profile and tolerability, as well as being a conservative treatment strategy, are the reason antimuscarinic drugs also remain first line treatment for NDO [64]. Data on the urodynamic effects of antimuscarinics in NDO are primarily available for “older” drugs such as oxybutynin, trospium chloride, propiverine, and tolterodine and show increases in maximum cystometric bladder capacity of about 120 mL and reductions in maximum detrusor pressure amplitude of about 28 cmH_2O [91, 108]. Data for urodynamic effects of newer drugs in NDO such as darifenacin, solifenacin, or fesoterodine are scarce. Solifenacin seems to be beneficial but with somewhat less impact on maximum cystometric bladder capacity and maximum detrusor pressure [109].

For some patients with NDO, antimuscarinic drugs are not efficacious at the available dosages [108]. This may be related to the fact that current antimuscarinics as competitive antagonists cannot resist the likely massive cholinergic output from the parasympathetic nerve terminals during full-blown NDO. Here, some authors suggest the application of higher dosages either of the same or as a combination of different antimuscarinic drugs [110-114]. However, this is off-label use without sufficient evidence and adverse events might be more pronounced, decreasing the benefit / risk ratio and patient compliance with this therapy [64, 89].

BETA-ADRENOCEPTOR AGONISTS

An alternative strategy is combined treatment of an antimuscarinic drug and the newer beta-3-agonist mirabegron, aimed at achieving a synergistic effect by targeting two different receptors without exceeding approved dosing [115, 116]. In addition to a small, retrospectively-analysed case series suggesting beneficial urodynamic and clinical effects of such combination treatment [117], there is a very recently published randomized placebo-controlled trial available, concluding that mirabegron monotherapy with 50mg once daily improves both urodynamic variables and patient reported outcomes in patients with NDO [118]. However, this trial had a very short follow-up period of only 4 weeks and the main urodynamic parameters such as maximum detrusor pressure and maximum cystometric bladder capacity were not significantly improved, raising doubts as to the efficacy of mirabegron in the treatment of NDO. More comprehensive data are lacking. Moreover, mirabegron may not be a good option in the treatment of patients prone to AD due to its sympathomimetic properties, which may cause elevated blood pressure and palpitations and potentially lead to more pronounced symptoms and blood pressure elevations during AD.

PER- OR TRANSCUTANEOUS NEUROMODULATION

Neuromodulative therapies aim to modulate neuronal signals in both afferent and efferent directions, exerting their effect by fairly slowly-occurring alterations of neuronal communication and circuitry. Thus, they must be distinguished from neurostimulation aiming at a direct response, i.e. muscle contraction, upon stimulation. The exact mechanism of action of neuromodulation for LUTD / LUTS remains unknown but it is hypothesized that, in the dorsal horn of the sacral spinal cord, bladder afferent activity may be inhibited through interneurons activated by somatic sensory pathways originating in the external genitalia, perineum, lower limb and muscles of the pelvic floor via the pudendal and / or tibial nerve [119, 120]. This inhibitory

interaction between larger somatic sensory fibres and small bladder afferents (A-delta or unmyelinated C fibres) may operate in a similar way to the ‘gate control’ theory of pain [121]. Animal studies suggest that pudendal nerve stimulation can elicit two effects [122]: (1) suppression of pelvic nerve activity to the detrusor by inhibition of the sacral micturition reflex at either the afferent input or the parasysmpathetic pre-ganglionic motor neurons and (2) activation of sympathetic neurones running in the hypogastric nerves causing inhibition of the parasympathetic efferent motor neurons at the level of the pelvic ganglia.

Based on these hypotheses, the most frequently investigated sites to apply per- or transcutaneous neuromodulation for the treatment of LUTD / LUTS are the dorsal genital nerve [123] as a terminal branch of the pudendal nerve and the tibial nerve [124].

The approach of using the pudendal and tibial nerve as therapeutic targets for NLUTD goes back at least to the publication by Parker M.M. and Rose D.K. in 1937, which demonstrated reduced DO in response to pin prick stimulation at the glans penis and sole of the foot in complete traumatic SCI patients [125]. In the 1970s, initial reports of electrical stimulation of terminal branches of the pudendal nerve, mainly using anal or vaginal plugs to reduce detrusor (over)activity, were published [126, 127]. Today, clitoral / penile, vaginal or rectal electrodes to reach the pudendal nerve or its terminal branches are commercially available, but transcutaneous electrical nerve stimulation (TENS) for LUTD / LUTS treatment is not limited to the genital / rectal area and may also be applied to sacral and suprapubic sites using conventional surface electrodes [123]. For percutaneous tibial nerve stimulation (PTNS), a 34-gauge needle electrode is inserted approximately 5 cm cephalad to the medial malleolus and posterior to the tibia with a surface electrode on the arch of the foot [120]. In some more recent studies, transcutaneous tibial nerve stimulation (TTNS) has been used, which works with another surface electrode instead of the needle and thus makes it more amenable to individual home-use.

Both, TENS and PTNS / TTNS have been demonstrated to be effective on urodynamic and bladder diary parameters in patients with NLUTD [123, 124]. TENS increased maximum cystometric capacity by 4 – 163 mL, reduced maximum storage detrusor pressure by 3 – 58 cmH2O, the number of bladder emptyings / 24 h by 1 – 3, and the number of incontinence episodes / 24 h by 0 – 4 [123]. PTNS / TTNS increased maximum cystometric capacity by 49 – 150 mL, reduced maximum storage detrusor pressure by 4 – 21 cmH2O, the number of bladder emptyings / 24 h by 3 – 7, and the number of incontinence episodes / 24 h by 1 – 4 [124].

Despite these promising beneficial effects, there are very few long-term results [128] and a lack of QoL data. Larger randomized controlled trials are needed to provide reliable evidence, which might be, in addition to the handling and necessity for regular application of treatment sessions, a reason that this kind of therapy is still not very commonly used, despite the commercial availability of inexpensive devices and the fact that adverse events are almost inexistent.

INTERMITTENT SELF-CATHETERISZATION

In addition to its obvious utility in emptying the urinary bladder, it is often necessary to add intermittent self-catheterization (ISC) to the management of bladder storage dysfunction in the neurological patient in order to achieve continence. It may even represent the first choice in patients with DO incontinence provoked by a reduced functional bladder capacity prior to the occurrence of the DO incontinence due to accumulation of residual urine volume. Post-void residual volume may in particular increase with therapies aiming to restore continence by detrusor sedation to reduce or prevent DO, i.e. antimuscarinic drugs, BoNT/A intradetrusor injections and augmentation cystoplasty. If such a residual volume becomes too large and the bladder is not regularly emptied, symptoms such as urinary urgency and incontinence may persist or reoccur due to reduced functional capacity. In such cases,

ISC is today's gold standard for regularly, efficiently, and autonomously emptying the bladder. A certain degree of hand function and, in females, pelvic and lower limb mobilisation is required to adequately perform ISC and these aspects must be considered in the treatment strategy of LUTD in neurological patients.

Since its introduction in 1972 by Lapides [129], catheter models and characteristics have significantly improved and today there is a wide selection of high-tech catheters available, covering the needs of nearly every patient. More recent data and expert panels are in favour of single-use catheters with a hydrophilic coating [130, 131]. However, further evidence from prospective randomized controlled trials evaluating catheter type (hydrophilic vs. uncoated) and catheterization technique (sterile vs. clean vs aseptic; single-use vs re-use) in a broader context, including evaluation of therapy compliance, QoL, and costs are needed.

OTHER CONSERVATIVE TREATMENT OPTIONS

There are a few other alternative conservative treatment options available, such as pelvic floor muscle training [132] and intravesical electrostimulation [133, 134]. In particular pelvic floor muscle training under professional guidance is a first line conservative treatment option that should be considered if appropriate to improve LUT function. However, the level of evidence for these therapies in the treatment of NDO is very limited as randomized controlled trials are lacking. Moreover, pelvic floor muscle training and intravesical electrostimulation require at least some preserved sensory-motor function to be effective and therefore may be suitable only for a subset of patients with NDO.

MINIMALLY INVASIVE TREATMENT OPTIONS

IMPLANTABLE DEVICES FOR TIBIAL NERVE STIMULATION

To facilitate tibial nerve stimulation outside the hospital or clinic setting, implantable devices are also available [135-138]: Urgent-SQ® (formerly Uroplasty then Cogentix Medical, now Laborie, Mississauga, ON, Canada), RENOVA® (BlueWind Medical, Herzliya, Israel), and StimGuard® implantable miniature device (StimGuard, Pompano Beach, FL, USA). These devices consist of a small electromagnetic impulse receiver requiring no battery with stimulation electrodes and an external electromagnetic impulse generator. The impulse receiver with electrodes is implanted next to the tibial nerve, usually above or at the ankle, and the external impulse generator is strapped around the ankle during therapy sessions to allow wireless transmission of the stimulation signal to the implanted receiver to induce stimulation. Despite this smart approach and some decent long-term-data [135], currently available studies focus on non-neurogenic overactive bladder (NNOAB) patients and the level of evidence is generally low due to the lack of randomized controlled trials [135-137]. Hence, currently, no recommendation or conclusion on the use in neurological patients can be made.

SACRAL NEUROMODULATION

Similar to the principles described for TENS and PTNS / TTNS earlier, sacral neuromodulation (SNM) aims to modulate the activity of one of the neural pathways affecting the pre-existing activity of another neural pathway, i.e. LUT-related afferent and efferent pathways, via spinal interneurons and synaptic interaction. Available evidence suggests that both spinal reflexes and supraspinal circuits involved in LUT control are modulated in this way [139, 140].

Although SNM has been commercially available for more than 20 years, it was not initially used for NLUTD as it was believed that intact neuronal innervation was a prerequisite for SNM to be effective [141-143]. In contrast to per- or transcutaneous neuromodulation, SNM is an implantable therapy that delivers constant stimulation to the sacral nerve roots. For the purposes of LUTD / LUTS treatment, electrodes are usually placed next to the S3 root as it passes through the sacral foramen.

In a first stage, the quadripolar electrodes (tined lead, Medtronic, Minneapolis, Minnesota, USA) are placed in a minimally-invasive fashion by puncturing the 3rd sacral (S3) foramen under fluoroscopic guidance and implanting the tined lead using the Seldinger technique with a special introducer sheath [144, 145]. The procedure can be performed under local anaesthesia, which allows for evaluation of sensory responses and the anal motor response. However, sensory testing during tined lead placement for sacral neuromodulation does not necessarily improve clinical outcomes of neuromodulation [146]. Following tined lead placement, which can be performed uni- or bilaterally, electrode wires are tunnelled subcutaneously and connected to an external stimulator [144, 145]. During a subsequent test phase, different neuromodulative settings, i.e. number of active electrodes, stimulation frequency, and stimulation strength, can be evaluated with respect to treatment efficacy. If an improvement of at least 50% can be achieved with a certain parameter setting and the patient is happy to go for the full implantation, the permanent neuromodulator (Insterstim or Interstim II, Medtronic. Minneapolis, Minnesota, USA) is implanted into the gluteal subcutaneous fat tissue [144, 145].

To date, a pooled success rate of 68% in the test phase and 92% in the fully implanted condition has been described for SNM in the treatment of NLUTD [139]. Despite these very promising numbers, the current evidence is based on rather small prospective cohort studies and retrospective case series only and consequently constitutes an evidence level too low to allow a final

conclusion or recommendation [64]. The first randomized controlled trial is currently ongoing (NCT02165774) [147].

Adverse events seem to be more frequent after complete implantation than during the test phase and comprise lead migration (7%), pain at the neuromodulator implantation site (5%), infection at the neuromodulator implantation site (5%), hypersensitivity to stimulation (4%), infection at the lead site (2%), pain at the lead site (1%), lead fracture (1%), migration of the neuromodulator (1%), malfunction of the neuromodulator (1%), and others (4%) [139].

A more recent study using bilateral SNM for treatment of LUTD in patients after complete traumatic SCI demonstrated excellent results on bladder, bowel and sexual function [148]. NDO in particular could be prevented, resulting in normo-capacitive and normo-active bladders in the storage phase. This surprisingly advantageous effect was attributed to the early time point of implantation, i.e. 3 months after SCI. An early application of SNM may at least partly prevent the formation or emergence of pathological reflex circuits in the spinal cord below the lesion during the spinal shock phase that otherwise results in NDO. Also, detrusor inhibitory effects via the sympathetic hypogastric nerve may be activated or facilitated through SNM, contributing to a degree of autonomic balance below the lesion that otherwise is deranged due to the SCI [148]. However, this potentially promising approach has only been described in this publication of 10 cases and long-term, multi-center, and randomized controlled data are lacking.

Very recently, newer devices for SNM have been developed, e.g. Virtis® (Nuvectra, Plano, TX, USA) and Axonics Sacal Neuromodulation System (Axonics, Irvine, CA, USA), that provide improvements with regard to MR-compatibility and ability to recharge the implanted neurostimulator. Since none of the devices are yet approved for treatment, clinical experience is currently still very limited and data for use in NLUTD are lacking. However, initial study results appear promising, at least in NNOAB patients, not only

with respect to symptom relief but also in terms of cost-effectiveness [149-151].

BOTULINUM NEUROTOXIN A INTRADETRUSOR INJECTIONS

BoNT/A is a highly potent neurotoxin that has been in medical use for several decades in the treatment of localized motor dysfunction and muscle spasms such as blepharospasm, cervical dystonia, strabism, and hemifacial spasm [152]. Beyond motor / movement disorders, treatment of autonomic dysfunction such as sialorrhea, hyperhidrosis, and detrusor overactivity using BoNT/A injections has been explored.

The proposed general mechanism of action of BoNT/A is the irreversible cleavage of the SNAP-25 protein in the axon terminal of the neuromuscular junction. SNAP-25 is a SNARE (soluble N-ethylmaleimide sensitive fusion protein attachment receptor protein) that is responsible for the fusion of the synaptic vesicles into the synaptic membrane and subsequent release of the neurotransmitter, i.e. acetylcholine, from the vesicles into the synaptic cleft [152, 153]. The disenabling of SNAP-25 by BoNT/A prevents or reduces acetylcholine release upon arrival of an action potential at the axon terminal and hence results in a chemo-denervation of the target muscle. Depending on the applied dosage, such chemo-denervation can reduce elevated muscle tone or spasticity or even paralyse the muscle. Despite the permanent cleavage of the SNAP-25 protein, the duration of effect of BoNT/A is limited to several weeks or months depending *inter alia* on the type of targeted nerve terminal (somatic vs. autonomic) and applied dosage [153-155]. The mechanism presumed to be responsible for the reversibility of the neuroparalysis is synaptic sprouting with formation of new neuromuscular junctions [153, 154].

Due to the large molecular size, i.e. 150 kD for the core toxin alone, BoNT/A cannot be absorbed through skin or mucosa and needs to be injected to reach the target tissue. Intradetrusor injections can be applied via a flexible

or rigid cystoscope [156]. Although several aspects of the injection technique, i.e. number of injection sites, volume per injection and injection depth are still matter of discussion, the currently approved dosage and technique for the treatment of NDO implies a total dose of 200 units onabotulinumtoxinA, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor [157, 158].

There are several different BoNT/A formulations on the market, i.e. onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), incobotulinumtoxinA (Xeomin®) of which currently only onabotulinumtoxinA is approved for the treatment of NDO. However, two ongoing Phase-III studies using abobotulinumtoxinA in the treatment of NDO (NCT02660138, NCT02660359) may lead to approval of abobotulinumtoxinA in the near future.

OnabotulinumtoxinA 200 or 300 units significantly reduced the mean frequency of urinary incontinence per week by 11 episodes in patients with NDO at 6 weeks after treatment compared to placebo. In the same time, maximum cystometric capacity significantly increased on average by 145 mL and maximum detrusor pressure decreased on average by 33 cmH2O compared to placebo [159].

BoNT/A intradetrusor injections are a safe treatment with few adverse events that are mostly self-limiting such as haematuria (relative risk 1.7), injection site pain, procedure-related urinary tract infection (relative risk 1.47), and generalized muscle weakness (relative risk 2.59) [155, 159]. However, urinary retention (relative risk 5.58) can occur and needs to be explained to the patient prior to injection as it may require the use of intermittent or indwelling catheters [155, 159].

Due to the limited effect duration, repeated treatments are necessary in the majority of cases, which seems to be feasible without loss of efficacy [160-162]. Caution should be taken in regard to multidisciplinary BoNT/A treatments to prevent unintended overdosage. It is recommended to not

exceed a total dose of 360 units onabotulinumtoxin-A administered in a 3 month interval [157].

Based on the existing high-level evidence, BoNT/A intradetrusor injections are recommended as second line treatment for NDO refractory to antimuscarinic treatment [64]. Usually, prior antimuscarinic treatment is stopped shortly after BoNT/A intradetrusor injections, but may be continued as concomitant treatment in selected cases to optimize efficacy if required. Antimuscarinic treatment may be restarted once the BoNT/A effects starts to fade and symptoms recur to bridge the time until reinjection.

Similar to antimuscarinic drugs, recent basic research has revealed multiple alternative or additional sites and mechanisms of action of BoNT/A within the LUT [163]. Such alternative mechanisms include modulation of neurotransmitter and -peptide release, receptor trafficking, and neurogenesis both on peripheral but probably also at a central level [163].

Moreover, BoNT/A has been evaluated in applying intraprostatic injections, which seem to improve prostate related LUTD / LUTS [164]. This may be specifically relevant for male neurological patients who show a prostatic component in their LUTD / LUTS but in whom surgical intervention would bear increased risk of urinary incontinence [165-167].

SURGICAL TREATMENT OPTIONS

SACRAL DEAFFERENTATION (WITH / WITHOUT SACRAL ANTERIOR ROOT STIMULATION)

Considering NDO as result of an overshooting spinal reflex because of impaired or lost inhibitory control from supraspinal centers similar to musculoskeletal spasticity, transection of the afferent branch of the reflex arc

would result in the disruption of this spinal reflex and consequently abolish NDO. Sacral deafferentation is a neurosurgical procedure with the aim of transecting the dorsal S2-S5 nerve roots. It requires a laminectomy to access the spinal nerve roots and opening of the dura to microsurgically separate the ventral from the dorsal roots prior to transection [168]. An extradural approach is also possible but implies a higher risk of incomplete de-afferentiation and injury of the anterior root due to a less definite separation between anterior and posterior root segments compared to the intradural approach [169]. Intraoperative urodynamics and cardiovascular monitoring allow the functional differentiation between ventral and dorsal roots upon electrical stimulation [168]. After this procedure, a form of catheterization, i.e. ideally ISC, is required to empty the bladder.

Complete deafferentation of the S2-S5 roots can be achieved in 73-95% [168, 170, 171] resulting in an acontractile, flaccid detrusor and continence without further treatment in 83-85% [168, 171]. Moreover, coexisting AD can also be abolished with this treatment in about 59-61% [170, 171].

The main drawbacks of this treatment are the invasive and irreversible character of the procedure with the necessity of performing a laminectomy and to irreversibly transect intact nerve tissue resulting in loss of potentially preserved sensory function of the pelvis and lower limbs. Moreover, sexual function (e.g. reflex erections) and the defecation reflex will be lost. These drawbacks are the main reason why few patients are today willing to undergo such treatment.

A possibility for regaining function and to even empty the bladder through the urethra without using a catheter is to implant a sacral anterior root stimulator (SARS) after sacral deafferentation. A SARS, e.g. Finetech-Brindley bladder stimulation system, can be implanted in the same procedure following sacral deafferentation by placing special electrodes bilaterally around the anterior roots S2-S4. By placing each root in a separate electrode segment, independent control of pelvic functions is

possible, for example S3 stimulation for detrusor contraction and micturition, S3 + S4 stimulation for rectal pressure rise and defecation, and S2 stimulation to induce penile erection [168]. However, adjustments may differ on an individual level and, while the efficacy of the SARS for micturition and defecation seems to be good, it is less effective for sexual function.

Although SARS is sometimes referred to as a bladder pacemaker in the same manner as the SNM system, both procedures must be clearly distinguished. SARS is much more invasive, needs much higher amplitude of stimulation above the pain threshold, and thus has a much narrower indication, reserved to selected SCI patients.

AUGMENTATION CYSTOPLASTY

Augmentation cystoplasty is a well-established abdominal surgical procedure that aims to reduce detrusor contractility and to enlarge bladder capacity. Detrusor contractility is reduced by removing part of the detrusor or cleaving the detrusor at the dome and thereby interrupting its muscular continuity. Bladder capacity is increased by replacing or augmenting the bladder with bowel tissue. In addition, augmentation cystoplasty can be combined with a continent cutaneous urinary diversion to facilitate ISC via an abdominal site, when ISC via the urethra is impossible or difficult [172].

Although several types of gastrointestinal tissues have been used for augmentation cystoplasty [173], i.e. stomach, ileum, colon, or sigmoid, ileum is nowadays the most frequently used tissue, generally due to its slightly more advantageous properties with regard to intraoperative handling, postoperative complications, and effectiveness [173].

Using an augmentation cystoplasty for NDO treatment, reduction of MDP from 60 to 15 cmH_2O and an increase in MCC of 166–500 mL can be achieved, contributing to continence rates of 69–88% [174-178]. In addition,

augmentation cystoplasty has been described as reducing VUR [179]. Patients with concomitant neurogenic sphincter insufficiency may require a complementary, anti-stress urinary incontinence (SUI) procedure, e.g. aponeurotic sling or artificial sphincter to achieve continence.

Augmentation cystoplasty requires some hospitalisation time (2-4 weeks) but has a rather low mortality rate of 0–3.2% [173]. However, there are several moderate to severe complications that can occur in the short and long term [174-176, 178, 180]: urinary stones (6–21%), recurrent symptomatic UTI (20%) including recurrent pyelonephritis (1.5–11%), ileus (1.9–11.7%), chronic diarrhoea (7–18.6%), perforation (0.75–4%), and fistulas (0.4–1.3%). In addition, metabolic complications can occur due to altered absorption / reabsorption of metabolic products in the augmented bladder and in the shortened gastrointestinal tract. Thus, type and severity of metabolic complications largely depend on the type and length of the resected gastrointestinal tissue. Metabolic complications include: hypochloremic acidosis, lipid malabsorption, vitamin B12 deficiency and bile acid deficiency [181]. Patients with a catheterizable cutaneous derivation might experience additional complications regarding the urinary stoma [182-184]: stomal stenosis (6–15%), channel leakage (9%), false passage (6%), and stomal prolapse (5%).

Nevertheless, patient satisfaction is usually high [180], as most patients already suffered for a considerable time period from severe DO and usually had several failed treatment attempts before being considered for augmentation cystoplasty. However, only patients able and willing to perform ISC should be considered for this kind of treatment, as otherwise the patient is not gaining much from this kind of invasive therapy.

CYSTECTOMY WITH URINARY DIVERSION

If none of the aforementioned treatment options can sufficiently reduce NDO and / or significant structural alterations have already occurred, it may

become necessary to remove the entire bladder as a last resort. It is thus the most definite form of NDO treatment and requires the formation of a urinary diversion that can be constructed to be continent or incontinent.

Operative and postoperative risks and complications are similar to those of the augmentation cystoplasty. However, complete cystectomy and creation of a urinary diversion is usually more complex and time-consuming and requires the re-implantation of the ureters, which implies the risk of ureteral stenosis.

For a continent urinary diversion, different forms of pouches and neo-bladders made of detubularised bowel segments are available and can be selected depending on the patient's needs and physical preconditions and the surgeon's expertise [185, 186]. Again, it is important to consider the patient's abilities and preferences with regard to emptying the new pouch or bladder in advance.

For an incontinent urinary diversion, which is usually somewhat less complex and less prone to complications than a continent diversion, the ureters are connected to a short, detached ileum segment that is then diverted through the abdominal wall outwards and connected to the skin [187]. This form of urinary diversion is also called ileal conduit or Bricker diversion, named after Eugene M. Bricker who described this procedure for the first time [187].

As the urine is now continuously and directly draining outwards, a urine bag has to be placed on the stoma site to collect the draining urine.

Such an intervention certainly interferes with the body image of most patients, but in addition to a high probability of UUT protection from elevated pressures, it offers the possibility to independently manage urinary drainage with less expenditure of supplies and time compared to other treatment strategies that require regular catheterisation, medical treatment (antimuscarinc drugs, BoNT/A intradetrusor injections) and follow-up (urodynamic investigation).

However, changes in kidney function and morphology, stenosis of the ureteroileal and ileocutaneous junction, and bowel dysfunction are known postoperative complications [188, 189].

ALTERNATIVE TREATMENT OPTIONS FOR SELECTED PATIENTS

In principle, the reduction of elevated storage pressures in the LUT and protection of UUT can be achieved by diminishing outflow resistance to a minimum in order to guarantee sufficient urine outflow from the bladder prior to the onset of elevated pressures. However, it has to be considered that the two treatment options (a and b) mentioned below do not actually restore or maintain a low pressure reservoir but rather aim at continuous low pressure drainage, leaving the restoration of the native bladder as a reservoir unconsidered, which may work for selected patients but is also one of the main drawbacks of these treatment strategies contributing to their associated complications in short- and long-term.

a) Insertion of an indwelling catheter either transurethrally or suprapubically and left on permanent drainage would help to reduce storage pressures and post void residual urine by direct continuous low pressure drainage. However, indwelling catheters are associated with several complications such as recurrent or chronic UTI, stone formation, urethral erosion (mainly with transurethral catheters), increased risk of bladder cancer and reduction of sperm quality and motility and are hence not generally recommended [64, 190-192] but may be an option for selected patients not able to perform ISC and who are not suitable for more invasive therapies such as urinary diversion. Nevertheless, an indwelling catheter itself does not treat DO and associated complications such as AD will persist and become evident each time the catheter occludes [193]. Moreover, constant urinary drainage required here to avoid elevated

storage pressures may lead to significant loss of capacity over time and consecutive urinary leakage transurethrally and / or alongside the catheter [194].

b) Transurethral sphincterotomy plus further subvesical desobstruction if required (e.g. resection of prostate and / or bladder neck tissue), implantation of a urethral stent, or BoNT/A intrasphincteric injections (off-label use) are options for reducing outflow resistance to enable low pressure urine drainage from the LUT. Although there are several cohort studies reporting promising results for each technique, i.e. reduction of maximum detrusor pressure and PVRV as well as lower incidence of hydronephrosis and AD [53], there are specific complications such as the necessity for repeated procedures due to urethral scarring, bladder neck obstruction, inefficient urodynamic improvement, stent migration / erosion and stone formation. In addition, there are only very few randomized controlled trials available with inconclusive urodynamic data and a lack of QoL data, hampering clear recommendations [64, 195] and official approval for the use of BoNT/A in this context. Moreover, the mentioned techniques based on their principle of lowering outflow resistance will not reduce DO but lead to increased urinary incontinence and are thus mainly applicable to male patients who can wear a condom catheter to collect the urine.

RESTORATION OF URETHRAL URINE STORAGE FUNCTION

Urinary incontinence has a devastating impact on QoL as it demonstrates loss of bodily control in its most inconvenient and unpleasant way, make LUT care the most challenging issue in the patient's daily life, and can itself drive patients into depression [196-198]. Furthermore, urinary incontinence can negatively affect the skin due to frequent contact with urine and / or the necessity to wear pads or diapers which facilitates the development of wounds / ulcerations and dermal infections [199-201].

Despite the frequent association of NDO with urinary incontinence [202], adequate treatment of NDO alone may be either insufficient to prevent urinary incontinence or even evoke urinary incontinence.

Sometimes, behavioural aspects have to be considered and augmented, as even the best NDO treatment is not meant to create a low pressure and continent urinary reservoir that needs to be emptied just once daily. In this regard, the patient's expectations and post-treatment responsibilities have to be clearly discussed. Behavioral treatments such as timed voiding / catheterization or adaption of fluid intake may help to prevent urinary incontinence in patients with impaired bladder sensibility or increased evening fluid intake, respectively [203].

Nevertheless, patients with an insufficient closing mechanism at the bladder neck and / or external urethral sphincter due to a lack or impairment of neurogenic innervation of these structures will most likely suffer from neurogenic SUI. In such cases, the main treatment principle is to increase outlet resistance. Hence, prior to application of such treatments, it is absolutely mandatory that NDO is either absent or at least adequately treated to prevent high pressure conditions and consequently a risk of renal damage.

Four different types of surgical interventions can be distinguished: (1) bladder neck / urethral reconstruction, (2) injectables (e.g. bulking agents), (3) suspensions (e.g. Burch, suburethral tapes and slings), and (4) prostheses (e.g. artificial urinary sphincter).

BLADDER NECK / URETHRAL RECONSTRUCTION

Urethral lengthening in the form of an intravesical extension of the urethra using a bladder wall flap creates a valvular closure of the urethra with increasing filling of the bladder [204-208]. The original technique described by Young-Dees-Leadbetter was modified in recent decades by different urological surgeons mainly in pediatric patients with bladder extrophy [204, 209-212]. These techniques provide continence rates of 50-94% [204, 205, 209, 213, 214]. However, such bladder neck / urethral reconstructions require regular ISC to empty the bladder and often prior or simultaneous bladder augmentation to secure low pressure storage [215]. Compared to the artificial urinary sphincter (AUS), continence rates seems to be similar but with a significantly lower reoperation rate [216].

INJECTABLES

Injectables can consist of different materials (e.g. autologous fat, collagen, silicon, carbon, Teflon®, poly-acrylamide hydrogel) and are injected transurethrally below the bladder neck to create a sub-mucous cushion / bulking of the urethra that cause obstruction to withhold the urine. Despite some recent promising findings [217, 218], the current literature does not provide sufficient evidence for this kind of therapy [219] and long-term

results in patients with neurogenic sphincter deficiency seem to be rather poor [220].

SUSPENSIONS

Suspension therapies aim to restore or to improve urethral and / or bladder neck position and support, thereby enhancing the bladder neck or sphincteric closing mechanism. These are established treatment methods for female SUI [221, 222] and have recently been introduced also for male SUI [223, 224]. Alongside traditional techniques such as Burch colposuspension, there are several different forms and materials of slings and tapes available. In patients with NLUTD, the use of autologous rectus abdominis fascia slings in a pediatric or adolescent population with or without simultaneous augmentation cystoplasty has been reported most commonly, demonstrating excellent results and low complication rates [225-235]. Synthetic tapes also seem to be suitable and effective for neurogenic SUI [236-238], except where a tight sling is necessary to provide adequate continence as there is a marked increase in the erosion risk.

PROSTHESES

Prostheses for neurogenic SUI treatment comprise implantable devices that cause adjustable mechanical obstruction or closure of the urethra and / or bladder neck. Autologous prostheses for sphincter augmentation have also been successfully explored using gracilis myoplasty around the bladder neck or urethra [239-242]. The use of autologous tissue around the urethra and bladder neck may reduce the risk of infection and erosion compared to artificial implants, especially in conditions where increased tension needs to

be applied and ISC is performed. Nevertheless, an implanted pulse generator is required to stimulate the gracilis prosthesis to obtain contraction and urethral closure, respectively. Data on this procedure are scarce and, due to the rather sophisticated surgical approach, this approach is not widely-used.

Regarding artificial prostheses, two options are available, the AUS (e.g. AMS 800®, ZSI 375®) and the inflatable para-urethral balloons (ACT® / ProACT®).

Currently, the most widely-used AUS model (AMS 800®, formerly American Medical Systems, now Boston Scientific, Marlborough, MA, USA) consists of 3 major components, the inflatable cuff, the pump, and the pressure-regulating balloon. All three components are implanted and connected via special flexible but non-colliding tubes, allowing hydraulic function of the sphincter. The inflatable cuff is placed around the bulbar urethra (in men) or bladder neck (in men after prostatectomy and women or in some neurogenic indications) and connected to a control pump that is placed in the scrotum (in men) or labium majus (in women). The balloon is placed in the subperitoneal space lateral to the bladder. Activating the pump deflates the cuff by pumping water from the cuff into the balloon, from where it flows back into the cuff due to the hydraulic gradient between balloon and cuff. The re-closing of the cuff takes 2–4 minutes during which the patients can empty the bladder via spontaneous voiding or via ISC. ISC may be performed even with a closed AUS but the risk of urethral injuries may increase. The AUS is suitable for both men and women. Due to its efficacy, the AUS is today's gold standard in the therapy of SUI [224]. Patients with neurogenic SUI, in whom the natural sphincter is insufficiently working due to damage of its neuronal control, also have greatly benefited from this therapy [243]. The success rate (proportion of continent patients) in patients with neurogenic SUI lies between 23% and 91% (mean 73%) [244-251].

Frequent complications for this procedure are erosion, infection, and mechanical / device-related failure that cause a re-operation rate for revisions and / or explantations of 16% to 80% [244, 245, 247-250].

Murphy et al. compared treatment outcomes between patients with neurogenic SUI and patients with non-neurogenic SUI [246]. According to this study, patients with neurogenic SUI tend to have complications more frequently that were not related to mechanical or device-related failure [246]. Bersch et al. reported very promising long-term results of a modified AMS800 system in patients with neurogenic SUI [252]. This modified system has the advantage that it works without the pump and is thus less susceptible to device-related defects and less costly [252]. Instead of the pump, a subcutaneous port is implanted that enables postoperative adjustments of the cuff-pressure. This system also seems to have some advantage with regard to the risk of pump-erosion in wheelchair-bound female patients [252]. In addition, cuff pressure can be adjusted at any later time point via the subcutaneous port. Using cuff only AUS implantation in conjunction with an augmentation cystoplasty seems to be another alternative with very few AUS specific complications [253].

Inflatable paraurethral balloons are a relatively new minimally invasive technique that offers the advantage of postoperative adaption of the balloon size and consequently the degree of urethral obstruction [254, 255]. The balloons are placed bilaterally to the urethra at the bladder neck (in women) or at the membranous urethra (in men). Each balloon has a port that is placed into the ipsilateral scrotum or labium majus. The inflation is performed during follow-up visits with saline via the port of each balloon. Depending on the volume, the balloons cause a functional obstruction that should keep the urine within the bladder during situations of increased abdominal pressure. First time exploration of using this prosthesis in neurogenic SUI is part of this thesis.

PURPOSE, RESEARCH QUESTIONS, AND OUTLINE OF THIS THESIS

Despite the many above-mentioned therapies already in use clinically, many questions remain regarding their technical applicability, mechanism of action, and long-term outcomes. Hence, the purpose of this thesis is to contribute further insights into treatments of LUTD / LUTS in patients with a neurological disease / lesion as the underlying cause of their LUTD / LUTS. Since BoNT/A intradetrusor injections had such a seminal impact on the treatment of LUTD / LUTS over the last two decades and set off many new research projects and considerations on LUT neurophysiology, we placed a specific focus on this treatment.

The following specific research questions are addressed in this thesis:

1) What are the current therapeutic principles of LUTS in male neurological patients?

2) How does the onabotulinumtoxinA solution spread within and potentially also beyond the bladder wall after intradetrusor injections for LUTS treatment?

3) Can low dose treatment with onabotulinumtoxinA intradetrusor injections in MS patients effectively treat LUTS while sufficient voluntary micturition is maintained?

4) Does onabotulinumtoxinA cause any distant systemic effects on cardiac function following intradetrusor injections?

5) What is the evidence for and efficacy of further treatment options using BoNT/A for the therapy of male LUTS?

6) Is the adjustable continence therapy device an effective and sustainable treatment option for SUI due to neurogenic sphincter insufficiency?

The findings of the corresponding studies addressing the above mentioned research questions are critically discussed in chapter 8. Since the LUTD discussed in this thesis are a direct consequence of neurological trauma or disease which are currently neither curable nor reversible, patients with NLUTD require life-long, specialized neuro-urological care and follow-up. This thesis elucidates relevant aspects of treatment strategies for such care and follow-up. It also underlines the importance of multidisciplinary interaction between neurologists, rehabilitation physicians and urologists. In addition, translational research aspects are addressed and elaborated.

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CHAPTER 2

THE MANAGEMENT OF URINARY INCONTINENCE IN THE MALE NEUROLOGICAL PATIENT

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ABSTRACT

Purpose of review: Urinary incontinence in male neurological patients is a very frequent problem but treatment remains challenging. Thus, we summarize and highlight the latest developments in the management of urinary incontinence in this specific patient population.

Recent findings: Intermittent self-catheterization, antimuscarinics, intradetrusor injections with onabotulinumtoxinA, augmentation cystoplasty, urinary diversion, and artificial urinary sphincter are the cornerstones of the armamentarium for treating neurogenic urinary incontinence. However, with the exception of onabotulinumtoxinA intradetrusor injections, level of evidence is often low and male-specific outcomes are virtually not available.

Alternative conservative and / or minimally invasive procedures such as neuromodulation techniques and suburethral suspension devices provide promising data with apparently good safety and tolerability but still insufficient evidence lacking randomized control trials.

Summary: Standard options for treatment of urinary incontinence in neurological patients remain largely unchanged. Alternative treatment options, especially of conservative or minimally invasive character, have the potential to further broaden the therapeutic spectrum.

While a higher level of evidence is needed to assess the potential of such therapeutic approaches, randomized controlled trials in the male neurological population present a challenge. To truly advance treatment of urinary continence in male neurological patients, well-designed, multicenter studies are warranted.

INTRODUCTION

Urinary incontinence in neurological patients is a very frequent [1] and debilitating condition resulting from the profound alterations of LUT control and function caused by the neurological disorder. It should be implicitly considered that in neurological patients LUTS such as urgency may be reduced or absent because of sensory deficits, and that urinary incontinence is often the 'only' apparent symptom of relevant LUTD requiring further specialized investigation [2].

Therefore, it is of utmost importance not only to appropriately differentiate between the different types of urinary incontinence but also to understand the underlying neurological cause as it significantly influences the choice of treatment. Urinary incontinence related to NDO requires a completely different management than urinary incontinence related to isolated neurogenic sphincter insufficiency. Neglect of this principle may result not only in insufficient and inaccurate treatment but also in significant harm of the patient.

The scope of this article is to review the management of urinary incontinence in male neurological patients. However, data specifically considering the male neurological population is very rare so that we took into account neurological patients in general and referred to male-specific data whenever possible.

MANAGEMENT OPTIONS FOR URINARY INCONTINENCE IN MALE NEUROLOGICAL PATIENTS

As therapeutic principles in male neurological patients largely depend on the underlying cause of urinary incontinence, that is, mainly NDO and / or neurogenic sphincter insufficiency, the current armamentarium focuses on treating either cause or both in mixed forms. However, prior to the appliance of any form of subvesical obstruction with the intention to treat neurogenic

SUI, that is, suburethral slings, adjustable continence devices, and AUS, it is mandatory to first adequately treat DO or reduced bladder compliance as otherwise increased storage pressures can jeopardize UUT function.

An often-underestimated or neglected problem in neurological patients is concomitant problems with defecation that can interfere with LUT function and should be addressed before or concomitantly with any medical or surgical urinary incontinence therapy.

Behavioral therapy and pelvic floor exercises

Although specific studies on behavioral treatment (aiming to adapt drinking and voiding habits) in male neurological urinary incontinence are lacking, it should be part of the first-line treatment.

Behavioral regimens have to be adapted to the individual abilities and needs of the patients and suit best for patients in whom voiding function is intact and urinary incontinence is mainly due to impaired bladder sensation, cognitive, or motor deficits. However, in such cases, caregivers need to provide additional support.

Pelvic floor muscle training (PFMT) has been mainly explored within MS populations with predominantly female patients [3]. In men, PFMT is primarily used to treat postprostatectomy SUI. Nevertheless, PFMT has been shown to be beneficial in the treatment of both, stress and urgency urinary incontinence [4]. However, to be successful, voluntary pelvic floor sensorimotor control must be at least partly intact which can be a limiting factor in many neurological patients.

Catheters

ISC can improve urinary incontinence and is the gold standard in the management of neurogenic voiding dysfunction due to DSD or underactive /

acontractile detrusor. Although newer data and expert panels are in favor of single-use hydrophilic catheters in an aseptic or clean manner [5-8], the level of evidence is still low resulting in an ongoing debate on the optimal technique (sterile vs. clean vs. aseptic; single-use vs. reuse) and catheter type (hydrophilic vs. noncoated catheters) regarding the rate of UTI, urethral lesions, cost-effectiveness, and health-related QoL (HRQoL) [9-13].

Recent articles focused on the impact of ISC on HRQoL [14], patient's adherence to ISC [15], and preferences regarding catheter design [13, 16] including male-specific data [17, 18].

Indwelling catheters can be effective in treating urinary incontinence and especially suprapubic catheters might be an option for highly selected populations, such as tetraplegic patients [19]. However, indwelling catheters are not recommended for routine long-term treatment because of the associated complications such as acute and chronic UTI, stone formation, urinary leakage / incontinence, erosion of meatus and urethra, fistula formation, reduction in bladder capacity, and compliance (with continuous drainage) [20-22].

Condom catheters [23] or other external appliances such as drip collectors can help to control urinary incontinence and make it socially more acceptable.

Drugs

The first-line drug treatment for NDO and subsequent urinary incontinence are antimuscarinics, that is, oxybutynin, trospium chloride, tolterodine, solifenacin, darifenacin, propiverine, and fesoterodine. Efficacy and safety of antimuscarinics are well described for the non-neurogenic overactive bladder population [24, 25] but less conclusive for patients with NDO because of a limited and very heterogeneous body of studies [26]. Nevertheless, antimuscarinics were demonstrated to significantly improve

patient-reported and urodynamic outcome compared with placebo in the NDO population [26]. However, a significant improvement of urinary incontinence could not be demonstrated [26]. The current results are mainly based on data from SCI or MS populations and conclusions cannot be readily extended to other neurological diseases, such as stroke or PD. Furthermore, effects on bladder compliance, UUT function, and HRQoL were usually not assessed and long-term data of antimuscarinics in neurological patients are very limited [26, 27].

Although some large clinical trials could demonstrate statistically significant efficacy differences between several antimuscarinics, such differences seem to remain rather marginal from a clinical viewpoint and could not be demonstrated for the NDO population [26, 28]. Differences in the safety and tolerability profiles seem to be more relevant and should be considered when choosing an antimuscarinic drug for a specific patient, especially considering central nervous side-effects [28, 29].

Dose-escalating mono or combination therapy can be an option for NDO patients, requiring higher doses as urodynamic parameters could be significantly improved compared with standard dose treatment [27, 30]; however, high-evidence level studies are lacking.

A recent, but rather small, study comparing the immediate and extended release forms of propiverine for NDO demonstrated better continence rates using the extended release form [31]. Transdermal or intravesical antimuscarinic applications are alternative options that may help to increase bioavalability and reduce adverse events due to the circumvention of the intestinal first pass metabolism [32], but clinical data for the use in adult NDO patients are still very limited.

Other drugs, such as phosphodiesterase inhibitors or beta-adrenergic receptor agonists, seem to become future alternatives [33, 34] but have not yet been investigated for the treatment of urinary incontinence in neurological patients.

External neuromodulation

Of the different potential treatment modalities available, tibial nerve stimulation either percutaneously (PTNS) or transcutaneously (TTNS) seems to be the currently most promising and investigated method. However, the mainstay of available data are from non-neurogenic overactive bladder patients [35, 36], but some recent studies also provided data from neurological patients, that is, MS and PD [37-44]. However, randomized controlled trials (RCT) are lacking for PTNS and TTNS in the neurological population, and there are currently no long-term data or systematic data on HRQoL available. Nevertheless, the benefits of PTNS and TTNS are clearly the almost inexistent adverse events and the non-invasiveness that allows performance of diagnostic measures, such as repeated magnetic resonance imaging (MRI) or home-based therapy (for TTNS).

Intradetrusor injections with botulinum toxin

On the basis of the results of the two recent Phase III studies [45, 46], intradetrusor injections using onabotulinumtoxinA received Food and Drug Administration approval in 2011 for the treatment of urinary incontinence due to NDO in adults who have an inadequate response to or are intolerant of antimuscarinics. Intradetrusor injections with BoNT/A have been demonstrated to be safe, well tolerated and to significantly improve urodynamic parameters [47, 48], reduce LUTS [47], and improve QoL [49, 50]. Daily urinary incontinence episodes can be reduced by 63% [47]. These effects seem to occur regardless of concomitant antimuscarinics or neurological disorder, that is, MS or SCI [51]. However, data on the use of BoNT/A intradetrusor injections in neurological patients other than SCI and MS are scarce but there may be an indication [52].

Injections require a cystoscopic (rigid or flexible) intervention that needs to be repeated every 6–9 months [53]. The procedure can be performed in

local anesthesia in most NDO patients. There is, however, still controversy about the best technique.

Long-term data confirm the efficacy of onabotulinumtoxinA beyond multiple intradetrusor injections [54, 55], and cost-effectiveness seems to be superior to best supportive care [56]. If the durability of onabotulinumtoxinA is greater than 5 months, intradetrusor injections seem to be more cost-effective in the treatment of refractory NDO than augmentation cystoplasty [57].

Permanent neuromodulation with implanted electrodes

Initially, considered as unsuitable for the treatment of LUT dysfunction in neurological patients due to the impaired neuronal innervation, SNM has yet been demonstrated to be a promising treatment option for NDO [58, 59]. However, there is a lack of RCTs, and it is unclear which neurological patient is most suitable for SNM [58].

Remarkably, early bilateral SNM during the phase of spinal shock phase could prevent NDO and subsequent urinary incontinence in complete SCI patients [60]. However, long-term results are pending and the exact mechanism of action is not well understood [61]. Nevertheless, as the method is generally appealing because of its minimally invasive and fully reversible technique, well designed and adequately powered studies are highly warranted.

Sacral deafferentation with or without anterior root stimulator

This technique, also known as posterior rhizotomy, has to be strictly distinguished from the aforementioned SNM as sacral deafferentation is a specialized surgical intervention that aims to abolish NDO by transection of the afferent part of the sacral reflex arc and is not reversible. Although highly effective with up to 83% continence rates [62], if complete transection of the sacral roots S2-S5 can be achieved, it is preserved for a highly selected and

well informed group of SCI patients who accept the inevitable and permanent loss of any potentially preserved sensation of the pelvis and lower limbs and sexual function (e.g., reflex erections) [63]. In combination with a sacral anterior root stimulator (Finetech-Brindley bladder stimulation system) patients can regain control of micturition and even improve erectile and defecation function. An additional benefit is that sacral deafferentation can effectively abolish AD.

However, this procedure is nowadays less frequently performed because of effective but less-invasive alternatives, such as onabotulinumtoxinA intradetrusor injections. Thus, new data are scarce. One current retrospective study is available reporting continence rates of 23% 15 years after sacral deafferentation and anterior root stimulator implantation but also 84 cases of complications requiring surgical intervention among 137 patients [64].

Augmentation cystoplasty

Although there are no RCT, augmentation cystoplasty is a recommended and established treatment option for intractable urinary incontinence due to NDO but requires major abdominal surgery with interposition of an intestinal segment (usually ileum) into the bladder and / or partial replacement of bladder by an intestinal substitute, and should be preserved for patients in whom conservative or less invasive treatment options failed to achieve an adequate level of continence [65, 66]. Importantly, this treatment should only be offered to patients who are able and willing to perform ISC. Augmentation cystoplasty can be combined with a continent catheterizable cutaneous urinary diversion to facilitate ISC in patients with limited dexterity. Recent long-term data confirm previous data on efficacy demonstrating sustained improvements in both, urodynamic parameters and symptoms [67-70].

A less-invasive version of bladder augmentation is detrusor myectomy (autoaugmentation) with lower surgical burden and complication rates, but efficacy seems to be inferior to augmentation cystoplasty [71-73].

Urinary diversion

In highly selected patients cystectomy with urinary diversion becomes necessary. Cystectomy in contrast to augmentation cystoplasty requires the reimplantation of the ureters, which basically implies the risk of ureteral stenosis.

For continent urinary diversion different techniques have been described [74, 75]. Regular ISC is required subsequently and specific complications include stomal stenosis, channel leakage, false passage, and stomal prolapse [75, 76]. However, there is less alteration of body appearance than with incontinent diversion that is usually indicated if ISC is impossible or patient compliance is inadequate.

A recent case series in MS patients with advanced refractory NDO demonstrated an effective treatment of LUTD and associated problems with an improvement in HRQoL following incontinent urinary diversion [77]. However, the complication rate was high (55%) and the authors consider urinary diversion as an effective but rather last resort treatment option for neurogenic urinary incontinence.

Bulking agents

Although bulking agents have been mainly used for the treatment of SUI in women, there are also studies in men with rather discouraging results, especially in the long term [78, 79]. RCT are lacking and from the available data, bulking agents cannot be considered a durable treatment especially for more severe forms of SUI, which may be the reason that there are no current data in adult male neurological patients.

Suspension therapy

Suburethral slings or tapes become more and more popular for the treatment of male SUI as a minimally invasive option, and different types have been introduced with success rates of 54–80% [80]. In male patients with neurogenic SUI mainly autologous fascia slings, often in combination with bladder augmentation, have been investigated predominantly in pediatric populations but also in adults, demonstrating favorable results and low complication rates [81-83]. Synthetic tapes are up-to-date rarely investigated in male neurological patients. Currently, only one small study presents promising data from a mixed adult and pediatric male neurological population treated with the AdVance sling [84]. RCT and data on long-term follow-up are lacking.

Implants for stress urinary incontinence

Adjustable periurethral balloons might be an option in highly selected patients, but there is only one study in a mixed population of patients with neurogenic SUI demonstrating rather fair results [85].

The AUS is the gold standard for the treatment of SUI and has also been investigated in the adult male neurological population demonstrating a high efficacy of 23–100% (mean 70%) continent patients [83]. However, frequent complications are erosion, infection, and mechanical / device-related failure that cause a reoperation rate for revisions and / or explantations of 7–100% [83]. Comparing complication rates between neurogenic and non-neurogenic patients revealed that patients with neurogenic SUI tend to have more frequently complications that were not related to mechanical or device-related failure [86].

A recent study suggested a less costly and less fragile alternative for SCI patients replacing the pump with a subcutaneous port to adjust cuff pressure also postoperatively and to omit the necessity to repetitively activate the

pump [87]. The two most recent studies report on long-term outcomes, demonstrating persistent efficacy in 74% of patients up to 10 years [88], and on the feasibility to implant the AUS using the daVinci robot [89].

However, RCT are actually lacking and the best site for cuff placement in male neurological patients is still a matter of debate. In male neurological patients, assessment of the ejaculatory status can be relevant as AUS placement at the bladder neck level may allow patients to achieve antegrade ejaculation [83].

CONCLUSION

Management of urinary incontinence in male neurological patients is challenging and will usually require a combination of different treatment options. Although the therapeutic armamentarium has been increased during the last decades providing new possibilities for clinicians and patients, the level of evidence is often low. Moreover, current findings are mainly from MS and SCI patients without gender-specific outcomes limiting generalization of the results.

The established cornerstones of neurogenic urinary incontinence therapy, such as ISC, antimuscarinics, intradetrusor onabotulinumtoxinA injections, augmentation cystoplasty, urinary diversion, and AUS, have not substantially changed. There is a clear interest in conservative and further minimally invasive therapeutic options, such as neuromodulation, either applied from external or via implantable devices, and suburethral suspension systems. Recent data are promising but further research is urgently needed. RCT for assessing efficacy and safety of different therapies for urinary incontinence in male neurological patients are a challenge and well-designed multicenter studies are highly warranted.

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CHAPTER 3

A MORPHOLOGICAL EVALUATION OF BOTULINUM NEUROTOXIN A INJECTIONS INTO THE DETRUSOR MUSCLE USING MAGNETIC RESONANCE IMAGING

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ABSTRACT

Objectives: Although BoNT/A intradetrusor injections are a recommended therapy for NDO, refractory to antimuscarinic drugs, a standardisation of injection technique is missing. Furthermore, some basic questions are still unanswered, as where the toxin solution exactly spreads after injection. Therefore, we investigated the distribution of the toxin solution after injection into the bladder wall, using MRI.

Methods: Six patients with NDO were recruited. Three of six patients received 300 U of onabotulinumtoxinA + contrast agent distributed over 30 injection sites (group 1). The other three patients received 300 U of onabotulinumtoxinA + contrast agent distributed over 10 injection sites (group 2). Immediately after injection, MRI of the pelvis was performed. The volume of the detrusor and the total volume of contrast medium inside and outside the bladder wall were calculated.

Results: In all patients, a small volume (mean 17.6%) was found at the lateral aspects of the bladder dome in the extra peritoneal fat tissue, whereas 82.4% of the injected volume reached the target area (detrusor). In both groups there was a similar distribution of the contrast medium in the target area. A mean of 33.3 and 25.3% of the total detrusor volume was covered in group 1 and 2, respectively. Six weeks after injection, five of six patients were continent and showed no DO in the urodynamic follow-up. No systemic side effects were observed.

Conclusions: Our results provide morphological arguments that the currently used injection techniques are appropriate and safe.

INTRODUCTION

BoNT/A injections into the detrusor muscle are a recommended therapy for NDO, when antimuscarinic drug therapy failed or is not tolerated [1-4]. BoNT/A injections have been successfully used to treat NDO worldwide and further indications and therapy options are currently explored [5-8]. The toxin is injected into the detrusor muscle via a cystoscopic approach, either flexible or rigid. The injection needle, which can be of different length and diameter, is stabbed into the bladder wall, followed by the injection of the toxin and the retraction of the needle. This is usually performed at multiple sites of the bladder wall, depending on the technique and amount of toxin, chosen for therapy [3, 9]. Target structure of the toxin is the detrusor muscle, as its main mechanism of action is at the neuromuscular junction [10, 11]. However, detrusor thickness is variable and depends on several factors such as gender, age, bladder filling volume and the presence of neurogenic lesion or obstruction [12, 13]. Although injection is performed under cystoscopic guidance, injection depth can only be estimated by the surgeon. Therefore, it remains difficult to estimate exactly in which layer the toxin is injected and where it spreads out. The sole visual control could be a bulging of the bladder wall after injection. If a big transparent bleb forms, the injection was probably superficial in the mucosa, if a slight bulging of bladder wall tissue can be observed the injection was probably in the detrusor layer. But very often, no bulging can be observed at all and it remains a very insecure sign of a correct injection.

Although the injection of BoNT/A is frequently used to treat NDO, no standardisation of technique exists [9, 14, 15]. There are repeatedly reports of treatment failures, even in those patients, who formerly showed an excellent treatment response to BoNT/A [16-18]. Not all treatment failures can be explained properly and one reason for this might be a variation in the amount of toxin that reaches its target area.

Therefore, it was our purpose to investigate for the first time, the distribution of the toxin solution after injection into the bladder wall, using MRI. Since we previously investigated the use of two different injection schemes (10 vs. 30 injection sites), which showed similar clinical results [14], we were also interested to observe the morphological outcome of both injection schemes.

Due to our long term experience with the use of BoNT/A in the treatment of NDO and our favourable results in those years [19, 20], we expected most of the toxin to be found in the detrusor. Nevertheless we also expected some toxin outside the detrusor, as perforation cannot be completely excluded using the cystoscopic approach. As a secondary outcome measure we evaluated the urodynamical data before and after BoNT/A injection to be able to correlate the clinical outcome with the morphological evaluation of the toxin distribution.

MATERIALS AND METHODS

After approval of the local ethics committee, a patient sample was recruited in the neuro-urological out-patient clinic of the SCI centre at the Balgrist University Hospital.

Inclusion criteria were: urodynamically proven NDO, failure to treatment with antimuscarinic drugs, minimum age of 18.

Exclusion criteria: allergy to BoNT/A or to MRI contrast agents, any existing malignancy in the bladder or urethra, UTI, pregnancy, breastfeeding, incapability or unwillingness to perform ISC, coagulation disorders or intake of anticoagulant drugs, impaired renal function, myasthenia gravis, pacemaker, Lambert–Eaton syndrome, medication with aminoglycosides (or other drugs with impact upon neuromuscular transmission), any ferromagnetic metal implants or compounds in or at the body.

Prior to inclusion, all patients were informed about the character of the study, both verbally and in writing and each patient had to provide written informed consent.

Pre-treatment evaluation consisted in physical examination, medical history, cystomanometry, blood chemistry, urine sediment and culture. Infections were treated according to germ resistance before examination or injection and all patients received antibiotic prophylaxis for 3 days, starting 1 day before injection and ending 1 day after injection.

Local anaesthesia using electromotive drug administration of 2% lidocain was applied in patient 2 because of preserved bladder sensibility due to an incomplete SCI (**Table 3-1**) [21].

The BoNT/A injections were performed at the bladder base and dome in a standardised manner by the same surgeon in all patients, using a rigid cystoscope (19 or 22 Fr) and a 22 G (=0.7 mm) needle with a length of 8 mm. Not the full needle length was inserted into the bladder wall during injection. Instead, the needle was retracted up to half its length, depending on the injection angle. The used BoNT/A compound in this study was BOTOX® (Allergan AG, Lachen, Switzerland).

The first group (group 1) of patients received 300 U of BOTOX®, distributed over 30 injection sites each 1 ml BoNT/A solution [3]. A second group (group 2) received 300 U of BOTOX®, distributed over ten injection sites each 1 ml BoNT/A solution [14]. For group 1, 300 U of BOTOX® were diluted in 27 ml 0.9% saline + 3 ml gadopentate. For group 2, 300 U of BOTOX® were diluted in 9 ml 0.9% saline + 1 ml gadopentate. The paramagnetic MRI contrast agent gadopentate (Magnevist®, Schering AG, Berlin, Germany) was mixed into the BoNT/A solutions to detect the distribution of the injections in the following magnetic resonance (MR)-scans, which were performed in a 1.5 T Avanto Siemens Magnetom. Prior to scanning, the bladder of all patients was emptied and filled with 200 ml 0.9% saline to achieve a standardised filling during MR scanning.

A T1 fast low angle shot (FLASH) 3D with fat saturation was used in the MR evaluation including the following specifications: TR: 4 ms, TE: 1.7 ms, flipangle: 12°, matrix: 256 x 256, FOV: 200 mm, slice thickness: 2.9 mm, NEX (Acquisitions): 2.

Using the freehand tool of the MR-software, the following regions of interest (ROIs) were selected: (1) the area of contrast agent within the detrusor muscle, (2) the area of contrast agent outside the detrusor and (3) the whole detrusor itself. Once a ROI was defined, the software automatically calculated the area in square millimetres. The 3D acquisition technique enabled the generation of volume data by multiplying the previously measured ROIs of each slice with the slice thickness. The distribution of gadopentate after injection was calculated and evaluated by two different radiologists who were blinded to the injection protocol. A urodynamic control visit was scheduled for each patient 3 months after injection and the urodynamic outcome measures were compared with those before BoNT/A injection.

RESULTS

Six patients with spinal cord injury and subsequent NDO could be included (**Table 3-1**). All injections could be performed without any clinically evident adverse events and none of the patients felt discomfort or pain. Only in patient 6, the injection procedure itself was difficult because of an increased spasticity of the lower limb. No systemic side effects were observed in any patient directly after the injection or during follow-up. Bleeding from the injection sites was minimal and stopped shortly after retracting the needle.

The average delay between the end of the BoNT/A injection and the start of the first MR-sequence was 17.5 min, ranging from 10 to 32 min. Mean examination time in the MR-scanner was 25 min, ranging from 17 to 42 min.

In none of the patients, contrast agent could be detected intraperitoneal, which would be highly suspicious for a penetration into the peritoneum. Furthermore, no contrast agent was found in other organs like the rectum or pelvic muscles. In all six patients, fractions of the contrast agent could be detected outside the bladder wall, located in the perivesical fat, mainly at the lateral aspects of the bladder dome either on one or both sides. In one patient, contrast agent was also found beyond the bladder base, in another patient beyond the middle part of the bladder dome. The average spreading distance of contrast agent from the outer margin of the detrusor was 16 mm.

The mean total detrusor volume of all subjects was 156.4 cm^3. The mean contrast enhanced detrusor volume of all subjects was 46.3 cm^3 (29.3% of the mean total detrusor volume). The mean amount of contrast enhanced volume outside the detrusor was 8.7 cm3 (17.6% of the mean total contrast enhanced volume). Accordingly, 82.4% of contrast agent was found within the detrusor (**Table 3-1)**.

In group 1, the mean total detrusor volume was 199 cm^3. The mean volume of detrusor, found to be contrast enhanced, was 62.8 cm^3 (33.3% of the mean total detrusor volume in group 1). The mean amount of contrast enhanced volume outside the detrusor was 10.7 cm^3 (14.3% of the mean total contrast enhanced volume). Accordingly, 85.7% of contrast agent was found within the detrusor (**Table 3-1**).

In group 2, the mean total detrusor volume was 113.7 cm^3. The mean volume of detrusor, found to be contrast enhanced, was 29.9 cm^3 (25.3% of the mean total detrusor volume in group 2). The mean amount of contrast enhanced volume outside the detrusor was 6.6 cm^3 (20.8% of the mean total contrast enhanced volume). Accordingly, 79.2% of contrast agent was found within the detrusor (**Table 3-1**).

Table 3-1 Patients characteristics, urodynamic parameters before and after treatment, and the results of the magnet resonance imaging analysis of all six patients

	P 1	P 3	P 5	P2	P 4	P 6
Age	34	34	41	82	67	18
Sex	male	male	male	female	male	female
Level of SCI	Th11	Th6	Th6	Th7	Th10	Th10
ASIA impairment scale	A	A	A	C	A	A
Urodynamic parameters before treatment						
Max. bladder capacity [ml]	217	300	222	217	200	249
Max. Detrusor pressure [cmH_2O]	69	46	41	37	48	27
Incontinence / Urine leak	yes	yes	yes	yes	yes	yes
Treatment						
Units of Botox®	300	300	300	300	300	300
No. injection sites	30	30	30	10	10	10
Urodynamic parameters after treatment						
Max. bladder capacity [ml]	381	500	500	186	500	440
Max. Detrusor pressure [cmH_2O]	57	10	8	36	11	10
Incontinence / Urine leak	no	no	no	yes	no	no
MR imaging analysis						
Volume detrusor [cm^3]	217.16	253.95	126.02	64.55	198.3	78.27
Volume contrast medium (total) [cm^3]	101.53	61.2	57.74	14.51	56.57	38.53
Volume contrast medium inside detrusor [cm^3]	85.6	52.97	49.76	11.52	54.08	24.11
Volume contrast medium outside detrusor [cm^3]	15.93	8.23	7.98	2.99	2.49	14.42

P patient, SCI spinal cord injury, ASIA American Spinal Injury Association, MR magnetic resonance, Th thoracic spine

In five of six patients, the BoNT/A injections showed to be effective. Before treatment, all six patients had NDO in their urodynamic examination. The average volume at which the first DO could be observed was 234.2 ml. The

maximum detrusor pressure was on average 44.7 cmH_2O. Five of six patients had urinary incontinence (**Table 3-1**).

After the BoNT/A injections, four of six patients had no DO up to 500 ml and were continent. In patient 1 bladder capacity at least increased from 217 to 381 ml and the maximum detrusor pressure decreased from 69 to 57 cmH_2O (**Table 3-1**). Patient 2 showed no improvement in the follow-up cystometry, although he reported improvement. This patient had the lowest percentage of detrusor volume covered by the contrast agent (**Table 3-1**).

Due to the spastic limb contractions in patient 6, shifts in the penetration depth of the needle might have incidentally occurred. When analysing this patient's data we found that nearly 40% of the applied contrast agent was located beyond the detrusor (**Table 3-1**).

All patients would agree to a second injection, when the effect of the last injection fades.

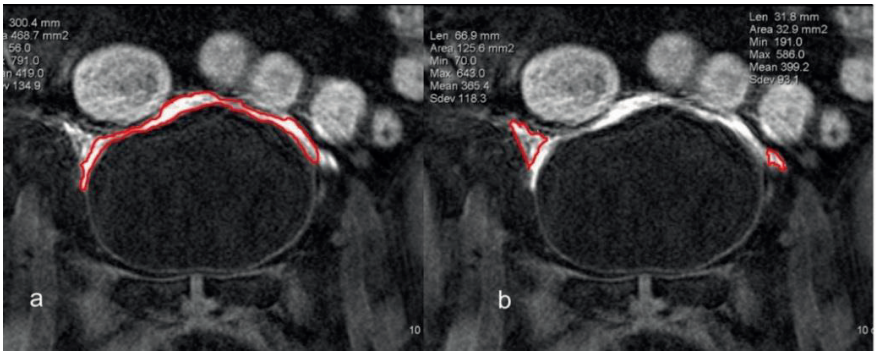

Figure 3-1 An exemplary coronal slice of the magnet resonance imaging of the lower pelvis, showing the urinary bladder in the middle of the image. The contrast agent, appearing in white, can be found for the most part within the detrusor (a) and to some extent outside the detrusor in the perivesical fat tissue (b) (the areas were encircled in *red* for better visibility)

DISCUSSION

The aim of this study was to investigate the distribution of the BoNT/A solution, after injection into the bladder wall. Our data show, that using the previously described and most widely used injection technique with 30 or 10 injection sites [3, 14], most of the applied volume spreads inside the detrusor. Only small amounts were found outside the detrusor, almost exclusively in the fat tissue at the lateral aspects of the bladder dome.

That 82.4% (average of all 6 subjects) of the injected BoNT/A-gadopentate solution were detected inside the detrusor, met our expectations. In regard with the clinical improvement of the patients, these results show that the used techniques are accurate and efficient.

Due to the fact, that contrast agent could be detected outside the detrusor, it has to be assumed that the injection needle perforated the detrusor during some of the injections. This is probably not uncommon following detrusor injections via a cystoscopic approach, as the surgeon can only estimate the relation of needle length to detrusor thickness. These two factors, e.g. needle length and detrusor thickness, are most crucial in regard to injection depth. One can now assume that the surgeon could choose the needle length according to the detrusor thickness, which can be measured using ultrasound at a defined filling level [12]. This measurement, however, might not be very reliable during cystoscopic BoNT/A injection, as filling volumes and therefore detrusor thickness is likely to change during cystoscopy due to diuresis and more likely due to the regular use of flushing and draining of saline. Additionally, detrusor thickness might not be the same throughout the bladder, although investigated by Kuzmic [22], who found per individual the same detrusor thickness in all parts of the bladder wall. This is probably true for healthy subjects but might be completely different for patients with NDO.

Perforation might not be the only mechanism contributing to the extravesical amount of contrast medium. A diffusion of the BoNT/A-gadopentate solution outside the bladder cannot be excluded in principle. Although one would

expect a more homogeneous and broader extravesical accumulation of the contrast medium and not only at certain areas as shown in **Figure 3-1**.

The amount of the injected BoNT/A-gadopentate solution found outside of the bladder wall in the present study seemed to be low enough, not to cause any systemic side effects or to compromise the effect of the toxin on the bladder. Most of the intradetrusor contrast agent was found in the bladder base and dome, since this are the locations we injected. When descriptively comparing the two different treatment modalities (30 vs. 10 injection sites) there was a similar amount of contrast agent found in the target area (85.7 vs. 79.2%) and a similar percentage coverage of detrusor volume with the contrast agent (33.3 vs. 25.3%). Although both groups cannot be compared statistically due to the small sample size, this finding can still be seen in agreement with the study from Karsenty et al. [14], who found no difference in clinical efficacy and safety using 10 compared to 30 injection sites with the same amount of BoNT/A.

In general, it remains still unclear, how much detrusor tissue should be covered to gain the best dosage / effect ratio of BoNT/A. One would assume that a distribution of BoNT/A covering most of the detrusor body might cause the greatest effect. In the present study an average of only about 30% (mean of all patients) of detrusor muscle was covered with contrast agent. Nevertheless, a sufficient effect of the BoNT/A treatment could be observed, which is well comparable with the success rates reported in former studies [6, 7]. Therefore, it might not be necessary to cover the whole detrusor with BoNT/A, to achieve good clinical results.

An exact explanation why 30% detrusor coverage with BoNT/A are sufficient enough to produce the reported clinically significant improvements cannot be given with this study. A possible reason eventually underlying these results might be areas of detrusor tissue, which are more important for detrusor contraction and increase of local reflex activity than other areas after SCI [23]. Treatment of those areas with BoNT/A might be sufficient enough to

reduce detrusor contractions in NDO patients, regardless of the total amount of detrusor area covered. Experimental studies in neonate and SCI rats showed that spontaneous contractile activity originated in the urothelium-suburothelium near the bladder dome [23, 24]. This spontaneous activity, unlike activity in normal adult rat bladders, is highly organised, i.e. starting at the dome, followed by the bladder body further contracting towards the bladder outlet. These organised contractions resulted in high amplitudes (10–20 cmH2O). Increased expression of gap junctions seems to play a role in this coordinated contraction in neonate and SCI bladders, which gives the impression, that the bladder works partially like a “functional syncytium” [24].

In addition, BoNT/A is not only inhibiting the efferent pathway by preventing neuronal acetylcholine release but also modulating the afferent pathway due to its effect on receptors and neurotransmitter release from the urothelium and suburothelium, which probably adds to the efficacy of the toxin in the treatment of DO [25-27].

Disruption of such organised synergic contractions and of the urothelial and suburothelial para- and autocrine signalling by an area of 30% of the total detrusor, due to intradetrusor injection of BoNT/A at and around the bladder dome might not completely abolish detrusor contractions (**Table 3-1**), but prevent complete and / or large amplitude contractions arising from the bladder dome. This is probably sufficient enough to prevent incontinence and cause satisfying clinical results. Interestingly, two studies mainly using injections at the bladder base reported a significant lower rate of complete continent patients with NDO compared to other studies injecting BoNT/A in base and dome [7, 28, 29].

Further investigations are necessary to evaluate the degree of detrusor coverage with BoNT/A compared with the clinical outcome. Presumably there is an optimal ratio between the amount and the degree of distribution of BoNT/A inside the detrusor and the clinical outcome, which is worth to be

discovered. Using MRI in conjunction with contrast enhanced BoNT/A solution, might be a very useful tool to perform this investigation.

There are, however, limitations of the used investigation method. First limitation is that during the injection procedure there might be some volume leaking out of the injection site into the bladder lumen. We consider this volume as extremely low, as the needle diameter is very small and most injection sites will clot shortly after removing the needle, which is in accordance with the experience of Schulte–Baukloh, who investigated toxin back flow from the injection site using a dye. He found, although not specifically quantified, that none to extremely little dye / toxin is flowing back from the injection sites [30]. Quantification of a dye (e.g. methylene blue) in the bladder irrigation fluid requires at least a photometric device, which was not readily available in our clinic. The group around Helmut Madersbacher and Gustav Kiss from the University of Innsbruck very recently performed such a photometric evaluation and found out that only 1.96–19.2 U (median 5.5 U) of 170–400 U BoNT/A are lost due to back flow after injection (personal communication, annual meeting of the German Urological Association in Stuttgart, 24–27 Sep 2008).

Second limitation might be measurement errors. Although most borders could be clearly distinguished, extravesical fluid may not have perfectly smooth borders. Manual determination of the region of interest introduces an additional small error. These errors were minimised by having two senior radiologists experienced in quantitative assessments of MR images performing the evaluations in consensus. The remaining error is small in comparison to the measured volumes.

Third limitation is the number of six patients, which is too small to receive data for reliable statistics, but besides monetary constraints (expensive MRI-examinations) the focus of this study was to demonstrate morphological aspects of the injection technique for the first time. The used MRI technique is well suited to demonstrate the morphologic situation after injecting the

detrusor, but a short delay between injection and obtaining the pictures is mandatory because of fast diffusion and venous backflow of the contrast agent.

At least, it has to be considered that we cannot demonstrate the localisation of the BoNT/A itself, but only the localisation of the contrast agent. Although BoNT/A is not residing just at the injection site [31], it probably diffuses much slower and less far as gadopentate, due to the higher molecular weight of 150 kDa compared to the 835 Da of gadopentate. In our study (with a mean delay of 17.5 min after injection) renal excretion of contrast agent could already be seen in all patients.

CONCLUSION

Using the previously described injection techniques, a mean of 82.4% of the injected BoNT/A-gadopentate solution can be found within the detrusor. However, a perforation with the needle tip and injection into the perivesical tissue could not be prevented. Treatment with 10 or 30 injection sites seem similar regarding the distribution of contrast agent in or outside the detrusor. In consideration of the clinical improvements of the patients, our results provide further arguments that the currently used injection techniques are appropriate and safe. Further studies are necessary to explore the optimal ratio between the amount and the degree of dissemination of BoNT/A inside the detrusor and the clinical outcome.

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CHAPTER 4

THE EFFECT OF BOTULINUM TOXIN TYPE A ON OVERACTIVE BLADDER SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS: A PILOT STUDY

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ABSTRACT

Purpose: Patients with MS often experience OABS. High dose BoNT/A intradetrusor treatment is effective but often results in urinary retention and urinary diversion via a catheter. In this pilot study we evaluated whether only 100 units onabotulinumtoxinA would significantly decrease OABS in patients with MS without impairing pre-treatment voluntary voiding.

Materials and Methods: Included in our study were 12 patients with MS who had OABS such as urgency, frequency and / or urgency incontinence. The treatment effect was evaluated using data on 3 consecutive visits, that is before, and a mean ± SD of 46.2 ± 11.9 and 101 ± 21 days after intradetrusor injection of 100 units Botox®, including the results of cystometry and uroflowmetry at visits 1 and 2, and uroflowmetry alone at visit 3. Patients completed a 3-day voiding diary for all 3 visits.

Results: Maximum bladder capacity significantly increased and maximum detrusor pressure decreased. Daytime and nighttime frequency, urgency and pad use significantly decreased. PVRV significantly increased initially but decreased until 12 weeks. Median time to re-injection due to recurrent overactive bladder symptoms was 8 months.

Conclusions: Overactive bladder treatment in patients with MS using 100 units OnabotulinumtoxinA intradetrusor injections seems to be effective and safe. Despite slightly impaired detrusor contractility most patients still voided voluntarily without symptoms. Thus, 100 units OnabotulinumtoxinA may be a reasonable treatment option for OABS in patients with MS who still void voluntarily.

INTRODUCTION

LUTD is common in patients with MS and can severely impair QoL in addition to the restrictions already experienced due to the neurological disease [1-4]. Of the patients 10% are already affected by detrusor and sphincter disorders at the initial MS diagnosis [1]. Initial symptoms of LUTD are often irritative, such as urgency and frequency, but incontinence or urinary retention also occurs often [1]. In the MS course the prevalence and severity of these symptoms inevitably increase and up to 75% of patients with MS experience bladder problems during the disease course [3-5]. A point is commonly reached at which patients with MS do not tolerate first line antimuscarinic treatment or find the effects insufficient to treat OABS and second line treatment becomes necessary [6].

BoNT/A is an effective second line treatment for OABS in neurogenic cases. Most often a dose of 300 units is chosen when using OnabotulinumtoxinA for intradetrusor injection [7]. However, patients with MS often present with initial PVRV and treating them with 300 units OnabotulinumtoxinA may probably result in high PVRV or urinary retention, requiring ISC or an indwelling catheter [1, 6-8]. This is often not satisfactory in patients with MS who are still ambulatory and voluntarily empty most of the bladder capacity.

Recently 100 units OnabotulinumtoxinA were noted to effectively alleviate OABS in non-neurogenic cases without causing urinary retention or a significant increase in PVRV [9, 10]. To our knowledge there is as yet no proof that 300 units OnabotulinumtoxinA are needed to efficiently treat OABS in MS cases. Drug treatment usually starts with a low dose that can be increased as needed, rather than with a high dose.

The aims of our study were to (1) investigate whether intradetrusor injections of only 100 units OnabotulinumtoxinA would sufficiently treat OABS in patients with MS and 2) observe whether 100 units OnabotulinumtoxinA would prevent urinary retention and, thus, provide the possibility of avoiding or decreasing the frequency of de novo ISC. We hypothesized that 100 units

OnabotulinumtoxinA would alleviate OABS in our MS population but efficient, symptom-free voluntary voiding would still be possible.

MATERIALS AND METHODS

After receiving approval from the local ethics committee we recruited patients with MS who consulted our neuro-urology department for treatment of LUTS. Study inclusion criteria were a proven diagnosis of MS; OABS with or without incontinence, as documented by 3-day voiding diary, with at least 3 urgency episodes in 3 days that were refractory to at least 2 antimuscarinic agents, each ingested for 1 month; treatment naïve status to BoNT/A before the first consultation at our department; preserved voluntary voiding or voluntary voiding as the only way of bladder emptying; ability and willingness to perform ISC; and written informed consent. Study exclusion criteria were neurological diseases other than MS, MS relapse 6 months before or during the evaluation period, previous LUT surgery or malignancy and previous BoNT/A treatment.

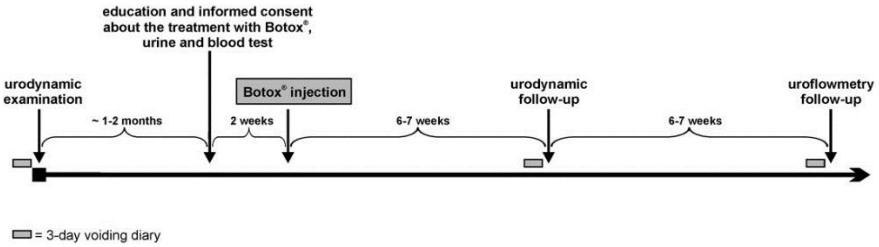

Figure 4-1 Study course

All patients had to complete 5 visits, including initial urodynamic evaluation at visit 1, blood and urine test before BoNT/A intradetrusor injection at visit 2, Botox® intradetrusor injection at visit 3, post-treatment urodynamic evaluation 6 to 7 weeks after injection at visit 4 and uroflowmetry follow-up

12 to 14 weeks after injection at visit 5 (**Figure 4-1**). At visits 1, 4 and 5 a 3-day voiding diary was completed (**Figure 4-1**).

BoNT/A intradetrusor injection at visit 3 was done with a 19Fr or 22Fr rigid cystoscope and a 22 gauge 0.7 mm needle 8 mm long. Only half of the needle was inserted. Each patient received 100 units OnabotulinumtoxinA diluted in 10 ml 0.9% saline and distributed over 10 injection sites at 1 ml each. Local anesthesia of the bladder mucosa was achieved with 50 ml 2% lidocaine / 8.4% bicarbonate solution instilled into the bladder for 10 minutes before injection.

Evaluated outcome parameters were maximum detrusor pressure ($pDet_{max}$), maximum cystometric capacity (MCC), bladder volume at first desire to void (FDV) on video cystometry at visits 1 and 4; voided volume, maximum flow rate (Q_{max}), PVRV on uroflowmetry at visits 1, 4 and 5; daytime and nighttime frequency, incontinence episodes, urgency episodes and number of pads used on voiding diary at visits 1, 4 and 5. All outcome parameters were defined according to the International Continence Society standardization of terminology [11].

We also assessed the extended disability symptom scale (EDSS) in all patients to provide information on individual impairment (**Table 4-1**) [12]. The EDSS range is 0.0—normal neurological examination to 10.0—death from MS and it quantifies the disability in 8 functional systems. Procedure pain and patient satisfaction were evaluated using 2 visual analogue scales (VAS) with a range of 1—no pain or complete dissatisfaction to 10—worst pain or maximum satisfaction.

Patients were eligible for re-injection on demand but not before 3 months after the previous injection. The reinjection appointment was scheduled by patients when OABS recurred.

Video cystometry outcome parameters were statistically compared between visits 1 and 4 using the nonparametric Wilcoxon signed ranks test with $\alpha = 0.05$. Uroflowmetry and voiding diary outcome parameters were statistically

compared among visits 1, 4 and 5 using the nonparametric Wilcoxon signed ranks test but due to multiple comparisons α = 0.025.

Table 4-1 Patient demographics

Patient No. - Gender	Age [years] at BoNT/A injection	Age [years] at MS diagnosis	EDSS
1 - F	43	35	3.0
2 - F	58	41	3.0
3 - F	60	45	4.5
4 - F	39	27	5.5
5 - F	50	20	6.0
6 - F	62	29	6.0
7 - F	51	34	7.5
8 - M	50	33	6.0
9 - F	43	37	4.5
10 - F	65	35	3.0
11 - F	59	52	6.0
12 - F	38	21	4.5
Mean ±SD	51.5 ±9.3	34.1 ±9.3	5.0 ±1.5

BoNT/A botulinum neurotoxin A, EDSS extended disability symptom scale, MS multiple sclerosis

RESULTS

One man and 11 women with a mean ± SD age of 50.7 ± 10 years met all study inclusion and exclusion criteria, and were evaluated (**Table 4-1**). Mean time between visits 3 and 4 was 44.1 ± 10.6 days and between visits 3 and 5 it was 113.8 ± 61.4 days. Before visit 2 no patient performed ISC.

All patients showed OABS on 3-day voiding diary at visit 1, although some had normal video cystometry results. No patient had VUR before or after treatment. DO with incontinence was observed on cystometry in 7 patients before and in 3 after Botox® application.

Mean MCC significantly increased in 9 patients from 352.6 ml at visit 1 to 538.8 ml at visit 4 (p = 0.008). The remaining 3 patients already had an initial MCC of about 600 ml. However, comparison of all 12 MCCs between visits 1 and 4 revealed a significant increase (p = 0.034, **Figure 4-2**). Mean volume at FDV increased significantly from 340.3 ± 233 ml at visit 1 to 453.1 ± 200 ml at visit 4 (p = 0.05). In all patients $Pdet_{max}$ decreased significantly from a mean of 38.0 cmH_2O at visit 1 to 16.3 cmH_2O at visit 4 (p = 0.004, **Figure 4-3*A***).

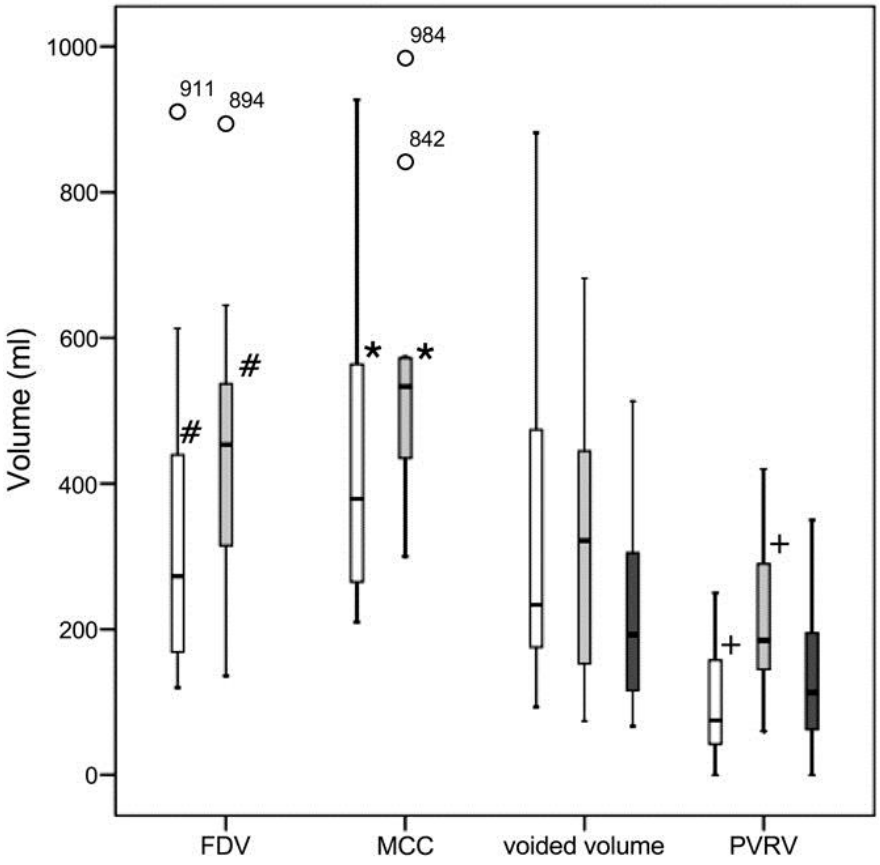

Figure 4-2 Volume at FDV and MCC at visits 1 (open bars) and 4 (light gray bars), and voided volume and PVRV at visits 1, 4 and 5 (dark gray bars) in all patients. Box plots indicate minimum, 25% percentile, median, 75% percentile and maximum. Pound sign indicates p = 0.05. Asterisk indicates p = 0.034. Plus sign indicates p = 0.003.

Voiding diary data showed a significant decrease in frequency, urgency episodes and pad use from visits 1 to 4 (**Table 4-2, Figure 4-4**). This significant decrease was sustained up to visit 5 (**Table 4-2, Figure 4-4**). We noted a significant decrease in nocturia from visits 1 to 4 (**Table 4-2, Figure 4-4**). However, this significant decrease was not sustained up to visit 5, although mean nighttime frequency was still lower at visit 5 than at visit 1 (**Table 4-2**). The mean number of incontinence episodes decreased continuously from visits 1 to 5 but we noted no significant difference between visits in the number of incontinence episodes (**Table 4-2, Figure 4-4**).

We found no significant differences between visits in voided volume and Q_{max}, although each parameter seem to slightly decrease from visits 1 to 5 (**Table 4-2**, **Figure 4-2**, and **Figure 4-3*B***). PVRV significantly increased from visits 1 to 4 (**Table 4-2**, **Figure 4-2**). However, until visit 5 PVRV decreased back toward baseline values and we noted no significant difference between visits 1 and 5 (**Table 4-2**, **Figure 4-2**).

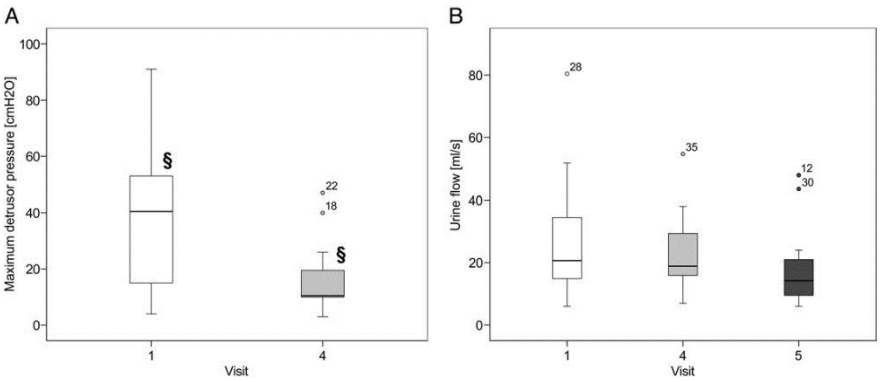

Figure 4-3 *A*, Pdet max during filling cystometry in all patients at visits 1 and 4. *B*, Qmax during uroflowmetry in all patients at visits 1, 4 and 5. *ml/s*, ml per second. Box plots indicate minimum, 25% percentile, median, 75% percentile and maximum. § indicates p = 0.004

After visit 3 ISC was needed only in 2 patients once to twice daily on demand. One patient needed a suprapubic catheter. The need for ISC was based on symptoms, eg persistent OABS or recurrent UTI, and not related to

a certain PVRV. The mean incidence of symptomatic UTI was 1.0 ± 1.1 at 12 months before BoNT/A injection and 1.1 ± 1.4 between BoNT/A injection and re-injection. Other adverse events were mild self-limited hematuria in 6 patients and mild self-limited injection site pain in 8. The mean VAS pain score in those cases was 2.8 ± 1.9 points.

The mean VAS satisfaction score in all patients was 7.3 ± 2.1. Ten of 12 patients agreed to be treated with BoNT/A again. Of those 10 patients 1 was lost to further follow-up and 9 required re-injection after a mean of 11 ± 6.1 months (median 8, range 5 to 22). The 2 patients who did not agree to re-injection were not satisfied with the treatment outcome, although 1 showed significant improvement in the urodynamic and voiding diary parameters.

Table 4-2 Three-day voiding diary and uroflowmetry results in 12 patients at visits 1, 4, and 5.

		Visit 1 [mean ±SD]	Visit 4 [mean ±SD]	p Value vs Visit 1*	Visit 5 [mean ±SD]	p Value vs Visit 1*
No. voids	Daytime	11.4 ±3.5	7.1 ±2.1	p = 0.002	8.5 ±2.6	p = 0.004
	Nighttime	2.4 ±1.4	1.3 ±1.2	p = 0.005	1.9 ±2.0	p = 0.107
No. episodes / day	Incontinence	3.8 ±5.1	1.9 ±3.2	p = 0.041	1.0 ±1.4	p = 0.214
	Urgency	9.1 ±5.7	2.8 ±3.8	p = 0.013	4.4 ±5.2	p = 0.008
No. pads / day		1.9 ±09	0.8 ±0.8	p = 0.020	0.7 ±0.9	p = 0.011
Uroflowmetry	Voided vol. (mL)	337.4 ±256.5	330.8 ±186.2	p = 0.875	221.3 ±132.4	p = 0.239
	Qmax (mL/s)	27.9 ±21.0	23.1 ±13.2	p = 0.530	18.7 ±13.5	p = 0.055
	PVRV (mL)	98.3 ±77.6	222.1 ±113.2	p = 0.003	135.2 ±94.8	p = 0.328

PVRV post void residual volume, *α = 0.025

DISCUSSION

Our study showed significant improvement in all cystometric and voiding diary parameters except incontinence episodes after intradetrusor injection of only 100 units OnabotulinumtoxinA. Currently only 2 studies are available of the effect of BoNT/A intradetrusor injections in a pure MS population and each describes the effect of 300 units [6, 13]. Direct comparison of the studies by Schulte- Baukloh [13] and Kalsi [6] with our study remains difficult and no direct conclusion can be drawn about which dose is more effective. However, somewhat similar results were observed in cystometric parameters at 4 to 6-week follow-up, and for voiding diaries at 4 to 6 and 12 to 16-week follow-up. Nevertheless, decreased daytime and nighttime frequency, incontinence and urgency appear more pronounced and persistent in the study by Kalsi [6] than in our series. Moreover, in our study the mean number of urgency episodes, and mean daytime and nighttime frequency showed a tendency to increase again after 12-week follow-up, although urgency episodes and daytime frequency remained significantly decreased compared to before treatment. Our follow-up was only until 12 weeks after treatment and the median interval after which patients requested re-injection was 8 months. This shows that from the patient viewpoint the effect of 100 units OnabotulinumtoxinA lasted for a period comparable to that in the study by Kalsi [6].

Our results show that intradetrusor injections of 100 units OnabotulinumtoxinA alleviated OABS significantly in our MS population. However, 100 units OnabotulinumtoxinA do not preserve initial detrusor contractility and cannot generally prevent the need for de novo ISC or even urinary diversion via a catheter. PVRV increased significantly, and mean Q_{max} and voided volume decreased, although not significantly. BoNT/A intradetrusor injections may most often cause a higher incidence of de novo ISC and increased PVRV in patients with neurogenic OABS but not or only rarely in those with NNOAB presumably due to the already neurologically compromised process of bladder emptying, e.g. DSD, in the neurogenic

OABS population [6]. However, that observation may be biased or influenced by the use or omission of a certain PVRV threshold at which to start ISC as well as the potential difference of those thresholds among studies. A recent study using 200 units OnabotulinumtoxinA in patients with NNOAB showed quite a high number with de novo ISC with a PVRV threshold requiring ISC at 200 ml regardless of symptoms [14]. Thus, using or not using a PVRV threshold for ISC and its level can significantly influence the study outcome. In our series we did not use a fixed PVRV threshold for ISC but rather focused on symptomatology.

To our knowledge there is yet no evidence-based consensus of PVRV threshold use, although experts on this topic from the United Kingdom seems to be ahead [15]. The suggested United Kingdom consensus of a 100 ml PVRV cutoff for ISC regardless of symptoms is straightforward and seems to be reasonable treatment since full functional bladder capacity is available in the storage phase due to complete bladder emptying by ISC [15]. Also, all patients in whom BoNT/A intradetrusor treatment is planned should be encouraged to learn ISC since increased PVRV or even urinary retention are known risk factors [7, 14, 16]. However, ISC done at least 4 to 6 times daily only because of a certain PVRV is not evidence-based and can be discussed critically. Moreover, it may not meet the individual expectations and needs of a patient with OAB.

In regard to this issue daily practice may legitimately differ from the protocol in prospective studies. To our knowledge no current study provides enough evidence to establish a certain PVRV threshold. A recent literature review stated that PVRV greater than 300 ml may be considered to favor UTI development [1]. Another group noted in a series of patients with stroke that PVRV greater than 150 ml seems to be an independent risk factor for UTI [17]. None of our patients had PVRV greater than 200 ml at 12-week follow-up or an increased incidence of UTI. Only 1 patient, who was 1 of the 2 requiring ISC twice daily, had a PVRV of 350 ml.

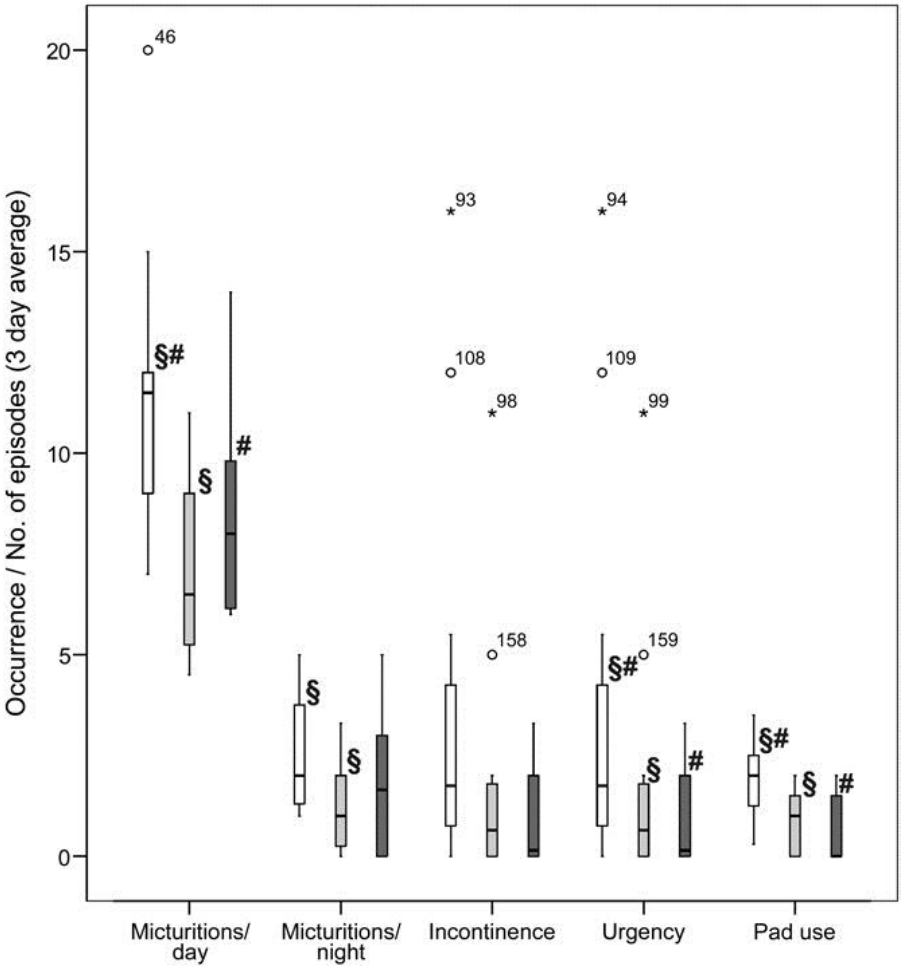

Figure 4-4 Three-day VD results in all patients at visits 1 (open bars), 4 (light gray bars) and 5 (dark gray bars) regarding daytime (§ indicates p = 0.002 and # indicates p = 0.004) and nighttime (§ indicates p = 0.005) frequency, incontinence, urgency (§ indicates p = 0.013 and # indicates p = 0.008) and pad use (§ indicates p = 0.02 and # indicates p = 0.011). Box plots indicate minimum, 25% percentile, median, 75% percentile and maximum of 3-day averages.

When OABS are satisfactorily treated, no recurrent UTI develops, no VUR is present and patients can still sufficiently empty the bladder without symptoms, it may be justified to omit or decrease the frequency of ISC. However, regular follow-up investigations remain mandatory since the consequences of sustained high PVRV on the UUT in this population have

not yet been specifically assessed. In this context α-receptor-antagonists may be an option to decrease outflow resistance and, thus, PVRV in these patients. In our study 100 units OnabotulinumtoxinA intradetrusor injections enabled most patients to omit or at least decrease ISC to a minimum without symptoms.

Since OABS development and severity can be quite heterogeneous in the MS population [1], a more rational approach would be to first start at a low dose and increase the dose during the treatment course according to symptoms and the treatment effect, as it is usually done with most other forms of drug therapy.

Potential limitations of this study are 1) our small number of patients, which is probably the cause of the high SD in some outcome parameters and the subsequent lack of significance, e.g. incontinence episodes, and 2) uroflowmetry and voiding diary follow-up was only up to 12 weeks, limiting information on the real duration of efficacy. Nevertheless, our pilot study presents promising first results of a different approach to OABS treatment in patients with MS and BoNT/A use in this context.

CONCLUSIONS

100 units OnabotulinumtoxinA seemed to be effective and safe for OABS in our MS study group due to significantly decreased urgency episodes, daytime and nighttime frequency, pad use and $Pdet_{max}$, and significantly increased MCC. However, initial detrusor contractility was not maintained since PVRV increased significantly and Q_{max} decreased. Nevertheless, most patients were able to remain on voluntary voiding without symptoms. The median time to when patients requested re-injection due to OABS relapse was 8 months. Results favour a treatment approach starting with a low BoNT/A dose with the possibility of increasing the dose, when applicable. This may be a reasonable OABS treatment in patients with MS who still void voluntarily.

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CHAPTER 5

EFFECTS OF ONABOTULINUMTOXINA ON CARDIAC FUNCTION FOLLOWING INTRADETRUSOR INJECTIONS

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ABSTRACT

OnabotulinumtoxinA intradetrusor injections are considered a highly effective localized therapy for refractory DO. However, despite evidence for distant systemic effects of onabotulinumtoxinA, little is known on potential systemic side effects following intradetrusor injections. Given that onabotulinumtoxinA is a highly potent toxin this is an important safety issue specifically with regard to repeat injections and parallel treatments with BoNT/A. Hence, it was the purpose of this prospective study to investigate, using heart rate variability (HRV) analysis, whether onabotulinumtoxinA causes systemic effects on cardiac function following intradetrusor injections.

Patients with NDO and age-matched healthy controls were recruited. Concomitant medication and diseases affecting the cardio-vascular system were exclusion criteria. A 3-channel resting electrocardiogram (ECG) was recorded in supine position for 15 min during four consecutive visits: 1) two weeks prior onabotulinumtoxinA intradetrusor injections, 2) 10min prior injections, 3) 30 min after injections, and 4) 6 weeks after injections. NDO patients received intradetrusor injections (300 units Botox®) between visits 2 and 3. The control group had no intervention.

Short-term (5 min) HRV analysis included assessment of frequency and time domain parameters. Statistical analysis was performed using ANOVA with repeated measures and the t-test. Due to multiple comparisons, α was corrected to 0.0125 (Bonferroni method).

Twelve healthy volunteers (5♀, 7♂; 46 ± 12 years old) and 12 NDO patients (5♀, 7♂; 46± 13 years old) completed all measurements. Comparing both groups, resting heart rate was significantly higher in the patients group at visit 4 only. No further significant differences in time and frequency domain parameters were discovered.

Within the NDO group, standard deviation of the normal to normal intervals (SDNN) in the ECG demonstrated a significant decrease (1.70 to 1.53ms, p=0.003) from visit 3 to 4, whereas the total power (TP) significantly

increased (3.05 to 3.29 ms2, p = 0.009) from visit 2 to 3. This increase subsided until visit 4.

Study limitations: single treatment investigation under resting conditions only.

In conclusion, onabotulinumtoxinA intradetrusor injections do not seem to affect resting state cardiac function. Short-term changes such as total power might rather result from natural cardio-vascular responses to the procedure itself (e.g. discomfort, stress). Further detailed investigations also under physical stress and repeated injections are necessary to fully exclude systemic cardiac side effects of onabotulinumtoxinA intradetrusor injections.

INTRODUCTION

DO is a urodynamic finding that can be the underlying cause of bothersome LUTS such as urinary urgency and / or incontinence. Furthermore, DO may cause irreversible alterations to morphology and function of the urinary tract, including in its worst case renal failure [1]. First line treatment of DO is usually with antimuscarinics and just recently also a β3 adrenergic receptor agonist has been approved for this indication [1].

However, antimuscarinics and / or β3 adrenergic receptor agonists might not be sufficient to adequately reduce DO. In such cases, a second line treatment option is onabotulinumtoxinA intradetrusor injections [1]. The efficacy of onabotulinumtoxinA intradetrusor injections has been proven previously and the safety profile seems to be beneficial [2, 3]. However, most studies reporting on safety concentrated on adverse events related to the injection procedure itself, i.e. UTI, bleeding, pain, or the local effects on the bladder, i.e. urinary retention. Distant effects after intradetrusor injections have not yet been reported or investigated systematically [4].

However, there is evidence that BoNT/A causes effects related but not necessarily limited to its action on cholinergic nerve terminals elsewhere in the body than at the site of injection [5, 6]. One important neuromuscular structure that might be affected by distant effects following injection of BoNT/A is the heart [7-11]. By blocking acetylcholine release form the autonomic nerve terminals, BoNT/A can affect 1) parasympathetic control on the sinoatrial and atrioventricular node of the heart through the vagal nerve [12] and 2) the preganglionic sympathetic innervation of the heart [11, 13]. Both, sympathetic and parasympathetic influence on the heart can be assessed using HRV analysis. During normal sinus rhythm, the heart rate physiologically varies from beat to beat as a result of the dynamic interplay between the multiple physiologic mechanisms that regulate the instantaneous heart rate [14]. HRV reflects the ability of the cardio-vascular system to rapidly adapt to changing needs in response to a broad range of

internal and external stimuli and conditions and thus, is a measure of cardiac and overall health [15]. A reduced HRV has been associated with a poor prognosis of cardio-vascular disease, an increased risk of incident myocardial infarction, cardiovascular mortality, and death from other causes in the general population [16].

Considering that onabotulinumtoxinA is a highly potent neurotoxin and that leakage into the circulation cannot be prevented or excluded during intradetrusor injections, it was the purpose of this study to investigate the potential effects of onabotulinumtoxinA on cardiac function after intradetrusor injections using HRV assessment.

From the anticholinergic mechanism of onabotulinumtoxinA and previous findings [7, 9, 10, 12, 17, 18], we would expect a reduced HRV following interdetrusor injection.

SUBJECTS AND METHODS

This is a prospective, controlled, single center study. The study was performed according to the declaration of Helsinki, approved by the local ethics committee and registered at https://www.clinicaltrials.gov (NCT identifier: NCT01337024). All subjects provided written informed consent prior to study inclusion.

Subjects

Patients with NDO eligible for treatment with onabotulinumtoxinA intradetrusor injections and age matched (±5 years) healthy controls were recruited.

Inclusion criteria for patients: age ≥ 18 years, urodynamically proven NDO refractory to antimuscarinic treatment. Inclusion criteria for healthy subjects: age ≥ 18 years, good physical and mental health.

Table 5-1 Demographic data of patients with neurogenic detrusor overactivity and age-matched healthy control subjects.

Patient / Subject No. – Gender – Age [years]	Neurological lesion / disease	ASIA impairment scale / level of lesion	Duration of lesion / disease [years]
1 – M – 36	Spinal cord inury	A / Th5	18
2 – M – 39	Spinal cord inury	A / Th6	17
3 – F – 43	Multiple sclerosis	-	21
4 – M – 43	Spinal cord inury	A / Th5	4
5 – M – 38	Spinal cord inury	A / Th6	8
6 – F – 71	Spinal cord inury	A / Th3	24
7 – M – 51	Spinal cord inury	C / Th4	7
8 – F – 47	Spinal cord inury	C / L4	3
9 – M – 63	Spinal cord inury	D / C1	3
10 – F – 58	Multiple sclerosis	-	33
11 – F – 38	Spinal cord inury	A / L2	27
12 – M – 22	Meningomyelocele		22
Healthy controls			
1 – M – 35	None	-	-
2 – M – 34	None	-	-
3 – F – 48	None	-	-
4 – M – 48	None	-	-
5 – F – 41	None	-	-
6 – M – 67	None	-	-
7 – M – 51	None	-	-
8 – F – 50	None	-	-
9 – M – 62	None	-	-
10 – M – 54	None	-	-
11 – F – 36	None	-	-
12 – F – 27	None	-	-

ASIA American Spinal Injury Association, C cervical, L lumbar, Th thoracic

Exclusion criteria: pregnancy or lactation, any diseases of the cardiovascular system (e.g. cardiac arrhythmia, myocardial infarction, surgery), as well as cardiac pacemaker and medication with impact to cardiac function (e.g. beta-blockers, antiarrhythmic drugs), and medication influencing thyroid function; use of antimuscarinic therapy within 10 days prior to the first measurement; previous BoNT/A treatment within the last 12 months prior to the first measurement.

Additional exclusion criteria for healthy subjects only: any current health problem or concomitant medication.

Electrocardiogram (ECG) recordings

The measurements were performed in a quiet separate examination room at constant room temperature and each subject / patient had a 30 – 35 min rest period to adjust to environment and setting. All subjects / patients were instructed to avoid caffeine, smoking, and meals at least 2 h before measurements.

Just prior to each measurement, subjects / patients were instructed to refrain from closing their eyes, moving or talking, or to intentionally control breathing.

Subsequently, a 3-channel resting ECG was recorded in a comfortable supine position with empty bladder for 15 minutes during four consecutive visits: 1) 2 weeks prior to onabotulinumtoxinA intradetrusor injections, 2) 10 min prior to injections, 3) 30 min after injections, and 4) 6 weeks after injections.

To reduce a confounding effect of pain from the onabotulinumtoxinA injection procedure on the HRV measurement, all patients rated their pain level on a VAS before and after injection treatment. Only when the post-injection pain VAS score reached the baseline value, the post-injection ECG was recorded.

The healthy control group had their ECG recordings at identical time intervals. The recordings of each subject / patient were performed at the same day times as the initial recording (visit 1).

Table 5-2 Heart rate variability outcome parameters (mean ±SD) from all 4 consecutive visits of both groups, patients undergoing onabotulinumtoxinA (onaBTA) intradetrusor injections for treatment of neurogenic detrusor overactivity (n = 12) and age-matched healthy controls (HC, n = 12). All HRV parameters were generated from 5-minutes time intervals and, except resting heart rate (rHR), log10 transformed. The p-values result from a t-test analysis between both groups. Due to multiple comparisons α was corrected to 0.0125 for all values (Bonferroni method).

		rHR [bpm]	VLF [ms²]	LF [ms²]	HF [ms²]	LF/HF	TP [ms²]	RMSSD [ms]	SDNN [ms]
Visit 1	**ona-BTA**	71 ±15	2.46 ±0.4	2.50 ±0.4	2.29 ±0.6	1.13 ±0.2	2.96 ±0.4	1.45 ±0.4	1.59 ±0.3
	HC	65 ±10	2.55 ±0.4	2.37 ±0.4	2.32 ±0.4	1.03 ±0.1	2.95 ±0.4	1.39 ±0.3	1.53 ±0.2
	p value	0.203	0.608	0.413	0.876	0.16	0.974	0.707	0.584
Visit 2	**ona-BTA**	73 ±17	2.66 ±0.3	2.51 ±0.5	2.27 ±0.6	1.15 ±0.2	3.05 ±0.4	1.49 ±0.4	1.65 ±0.2
	HC	62 ±9	2.56 ±0.3	2.54 ±0.4	2.33 ±0.5	1.12 ±0.2	3.00 ±0.3	1.41 ±0.2	1.57 ±0.2
	p value	0.062	0.489	0.857	0.808	0.79	0.769	0.552	0.316
Visit 3	**ona-BTA**	69 ±14	2.90 ±0.4	2.77 ±0.4	2.51 ±0.6	1.13 ±0.2	3.29 ±0.3	1.57 ±0.3	1.70 ±0.1
	HC	60 ±8	2.61 ±0.3	2.49 ±0.4	2.42 ±0.5	1.04 ±0.2	3.05 ±0.3	1.53 ±0.3	1.64 ±0.2
	p value	0.074	0.053	0.131	0.674	0.247	0.046	0.795	0.454
Visit 4	**ona-BTA**	73 ±10	2.63 ±0.4	2.42 ±0.5	2.12 ±0.7	1.18 ±0.2	3.04 ±0.4	1.32 ±0.3	1.53 ±0.2
	HC	61 ±9	2.80 ±0.4	2.55 ±0.5	2.46 ±0.5	1.05 ±0.2	3.22 ±0.4	1.51 ±0.3	1.62 ±0.2
	p value	0.004	0.312	0.575	0.181	0.073	0.257	0.134	0.278

HC healthy controls, HF high frequency, LF low frequency, LF/HF low frequency / high frequency ratio, onaBTA onabotulinumtoxinA, rHR resting heart rate, RMSSD Root Mean Square of the Successive Differences, SDNN standard deviation of the NN intervals, TP total power, VLF very low frequency.

OnabotulinumtoxinA intradetrusor injections

All included patients with NDO received 300 units onabotulinumtoxinA (Botox®) diluted in 30 mL saline and injected at 30 different sites sparing the trigone using a rigid or flexible cystoscope as described previously [19].

Local intravesical anesthesia was applied with 60 mL buffered lidocaine solution (30 mL of 2% lidocaine and 30 mL of 8.4% sodium bicarbonate) instilled 15 – 20 minutes prior to onabotulinumtoxinA injection.

HRV analysis

From the 15 minutes ECG recording, the middle 5 minutes were used for HRV analysis which was performed using SOLEASY™(Alea Solutions, Zürich, Switzerland) as follows: a) detection of r-waves in the ECG, b) calculation of the RR intervals and generation of discrete event series (DES), c) calculation of power spectra from DES d) calculation of the integral of very low frequency (VLF), low frequency (LF) and high frequency (HF) ranges. From these frequency domain parameters the total power (TP = VLF + LF + HF) and the LF/HF ratio were calculated.

For the time domain analysis, the mean heart rate at rest (rHR), the standard deviation of the normal to normal (NN or RR, i.e. interval between two R peaks) intervals (SDNN), and the root mean square of the sum of differences between adjacent NN intervals (RMSSD) were calculated.

For more details and background on HRV previous publications elsewhere are recommended [14, 15, 20].

Outcome measures

The primary outcome parameter was TP, as a general indicator for both, sympathetic and parasympathetic autonomic nervous system activity on the heart.

Secondary outcome parameters were VLF, LF, HF, LF/HF, rHR, RMSSD, and SDNN.

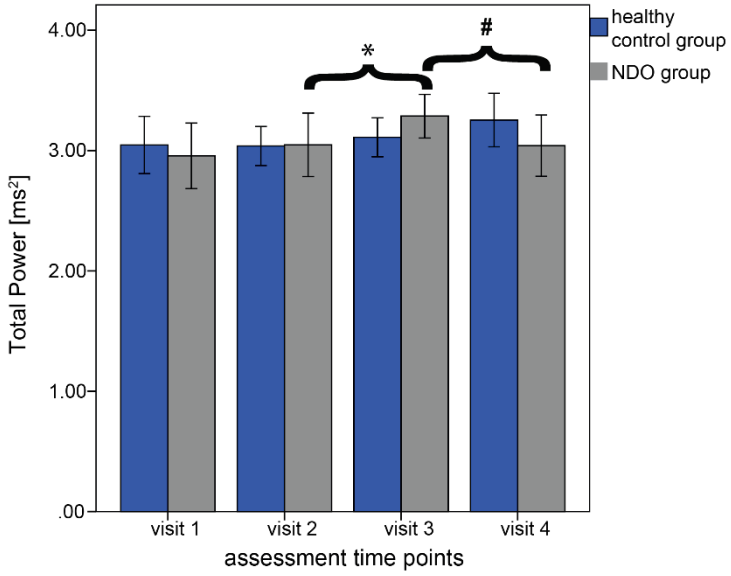

Figure 5-1 Total power (TP, in ms^2) during the four consecutive visits for the control (blue bars) and the neurogenic detrusor overactivity (NDO, grey bars) group. In the NDO group, there was a significant (*p = 0.009) increase in TP from visit 2 to 3 and significant (#p = 0.003) decrease from visit 3 to 4.

Statistical analysis

All data, except rHR, were log10 transformed. Statistical analysis was performed using IBM SPSS Statistics 17.0 and ANOVA with repeated measures to analyse differences within each group, i.e. between visits, and the t-test to analyse differences between both groups. Due to multiple comparisons, α was corrected to 0.0125 (Bonferroni method). All values are presented as mean ± standard deviation (SD).

RESULTS

Twelve patients with NDO (46 ± 13 years old; 5 females, 7 males) and 12 healthy subjects (46 ± 12 years old; 5 females, 7males) were included and completed all investigations (**Table 5-1**). The cause of NDO was SCI (n = 9), MS (n = 2), and spina bifida (n= 1) (**Table 5-1**).

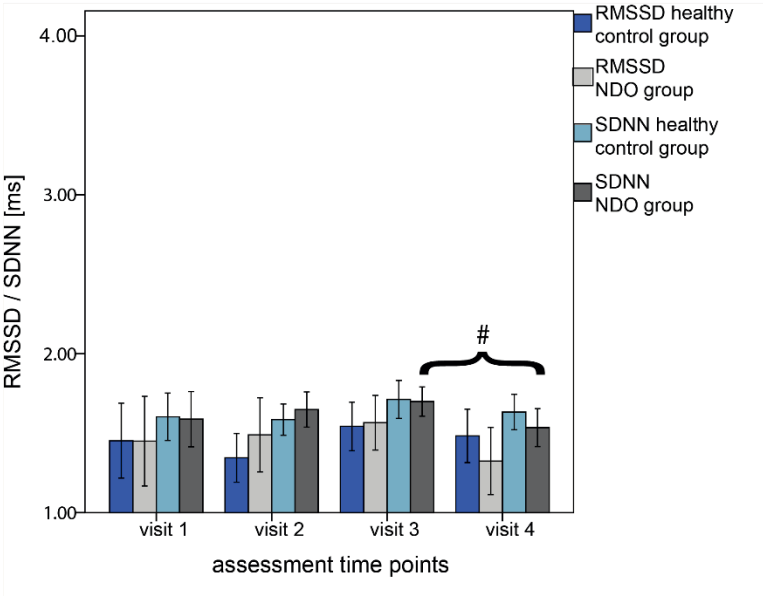

Figure 5-2 Root mean square of the successive differences (RMSSD, in ms) and standard deviation of NN intervals (SDNN, in ms) during the four consecutive visits for the control (blue bars) and the neurogenic detrusor overactivity (NDO, grey bars) group. In the NDO group, SDNN decreased significantly (#p = 0.003) from visit 3 to 4.

HRV parameters

Within the control group there were no significant changes of any HRV parameter throughout the four visits.

Within the NDO patient group there was a significant increase (p= 0.009) in TP from visit 2 to 3 and a significant decrease (p=0.003) from visit 3 to 4 (**Table 5-2**, **Figure 5-1**). The SDNN parameter decreased significantly

(p=0.003) from visit 3 to 4 (**Table 5-2**, **Figure 5-2**). There were no further significant changes of HRV parameters throughout the four visits.

Comparing both groups during all visits revealed a significant difference (p=0.004) in rHR at visit 4 (**Table 5-2**, **Figure 5-3**). There were no further significant differences of HRV parameters between groups (**Table 5-2**, **Figure 5-2**, **Figure 5-4**, **Figure 5-5**).

DISCUSSION

The main findings of this study are a temporary increase of TP and decrease of SDNN following onabotulinumtoxinA whereas rHR demonstrated a generally higher level in patients than in healthy controls. All other HRV parameters, i.e. VLF, LF, HF, LF/HF, RMSSD, did not show differences between visits, i.e. before vs after onabotulinumtoxinA injections, or groups.

Considering previous findings from studies on the effect of botulinum toxin on the cardiac autonomic function [7, 10, 17, 18, 21-23], effects seem to be predominantly HRV depressive, i.e. decrease in coefficient of variation of heart rate [7], R-R interval variation [21], RMSSD [10, 18, 23], TP [10], and SDNN [10, 17, 18], and / or parasympatholytic [12, 24], i.e. increase in rHR [10, 18, 22, 23] and decrease of parasympathetic related test outcomes such as 30:15 ratio [17, 22], E/I ratio [10, 17, 22], and Valsalva ratio [17, 22]. In line with that, animal studies in dogs demonstrated a significant reduction and even elimination of parasympathetic related bradycardia and atrial fibrillation, respectively, following BoNT/A injections into pericardial fat pads [11, 13]. An attenuation of parasympathetic modulation on the heart has also been described in studies on the autonomic cardiac effects of botulism, reporting significant declines of parasympathetic test parameters that lasted longer than in sympathetic tests [17], elevated rHR, and LF/HF ratio [22].

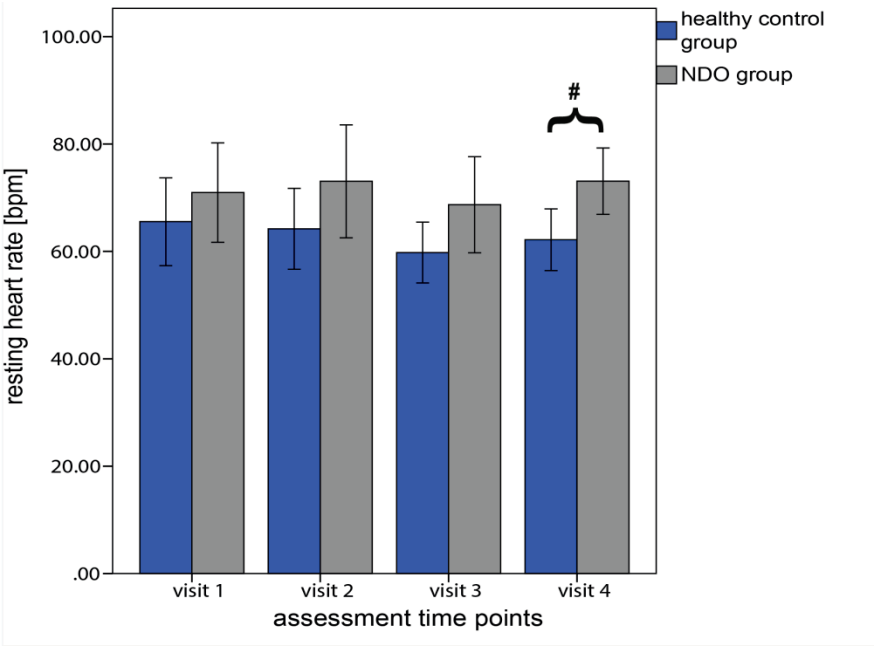

Figure 5-3 Resting heart rate (rHT, in bpm) during the four consecutive visits for the control (blue bars) and the neurogenic detrusor overactivity (NDO, grey bars) group. Comparing the control versus the NDO group, there was a significant difference (#p = 0.004) in rHR at visit 4.

However, there is also a study reporting significant bradycardia after high dose intravenous BoNT/A application in different animals, i.e. mice, rats, rabbits, and dogs, with electrocardiogram alterations across all species indicating conduction defects, i.e. prolongation of the P-R, QRS, and Q-T intervals. In dogs, bilateral vagotomy and / or atropine could not prevent the bradycardia and ECG changes [9]. In addition, bradycardia and ECG changes were also observed in the isolated animal hearts, suggesting on the one hand that those effects are independent from respiratory related conditions and on the other hand that botulinum toxin A seems to act on local cardiac conducting structures such as artrioventricular junction, His bundle, and Purkinje fibers [9].

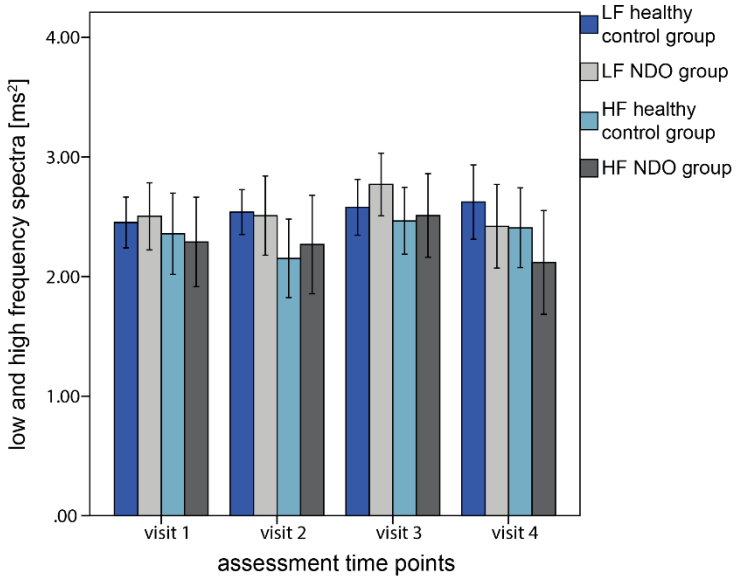

Figure 5-4 Low frequency spectrum (LF, in ms^2) and high frequency spectrum (HF, in ms^2) during the four consecutive visits for the control (blue bars) and the neurogenic detrusor overactivity (NDO, grey bars) group.

In our study we could not observe such HRV reductive and / or parasympatholytic effects as described previously, despite investigating resting conditions only under which vagal tone prevails and variations in heart rate are largely dependent on vagal modulation [20] which would then be specifically susceptible to attenuation by BoNT/A.

In contrary, the observed temporary increase in TP from visit 2 to 3 in the patient / onabotulinumtoxinA group would rather indicate an increase in HRV since TP constitutes from the sum of the frequency domain parameters VLF, LF, and HF and reflects the overall autonomic activity on the heart including sympathetic (main contributor to the LF component) as well as parasympathetic (main contributor to the HF component) cardiac modulation [14, 15]. In this context it is noteworthy that, although not significantly, the mean values of VLF, LF, and HF increased from visit 2 to 3 in the patient group suggesting a rather uniform than a single component driven change of

TP. In their sum, such insignificant changes of all frequency domain parameters might contribute to the eventually statistically significant outcome of TP. In addition, TP values were not different between patient and control group and compared to normative values from subjects of the same age group [25] the TP values of our patients fluctuated within a normative range. Hence, attributing this temporary change in TP to an effect of onabotulinumtoxinA appears rather unlikely.

A confounding factor that can affect HRV and might contribute to the observed transient TP changes shortly after onabotulinumtoxinA injections is the use of the lidocaine based local anesthesia prior to the injections. However, lidocaine causes very different and quite opposite changes of HRV than isolated TP increase [26, 27], making an effect of lidocaine in this context unlikely.

The significant decrease in SDNN could be related to the onabotulinumtoxinA treatment. However, looking at the values, significance mainly results form a preceding SDNN increase until visit 3 that returns just below baseline value at visit 1 without significant difference to the baseline value.

The significant difference between groups in rHR at visit 4 results most probably from the continuously higher rHR in the patient group compared to the healthy control group which nearly became already significant at visit 2. Slight rHR decrease in the control group and slight rHR increase in the patient group at visit 4 were sufficient to cause the statistical significance whereas each group demonstrated a quite stable rHR throughout all visits. Since most patients suffered from SCI, the higher rHR in the patient group might be a consequence of the altered autonomic nervous system function in such patients [28].

In summary, we did not find relevant HRV changes related to onabotulinumtoxinA intradetrusor injections neither within the treated patient group nor in comparison with the untreated age-matched healthy control

group. To the best of our knowledge, this is the first study on the relationship of onabotulinumtoxinA intradetrusor injections and autonomic cardiac control. There are some studies that investigated the effect of BoNT/A on cardiac autonomic function using HRV before and after injections for the treatment of cervical dystonia [7, 8, 10, 29, 30], spastic hemiplegia [31], and other dystonic conditions [8, 10]. However, the results are conflicting on weather BoNT/A injections have an effect on autonomic cardiovascular function [7, 8, 10] or not [29-31]. Comparison amongst studies remains very difficult and needs to be done with caution due to the different injection doses, injection sites, BoNT/A formulations, and primary HRV endpoints used. Moreover, time point of HRV assessment in relation to BoNT/A injections as well as the course of treatment, i.e. single primary treatment vs. chronic repeated treatment might be additional and essential factors influencing study outcome. Post treatment measurements followed mainly within 10 days to 6 weeks after BoNT/A injections.

In our study we re-assessed the patients 6 weeks after onabotulinumtoxinA injections since this is the usual interval within which onabotulinumtoxinA is expected to show full efficacy on the detrusor. However, an earlier occurrence of transient effects might be missed whereas 30 min after onabotulinumtoxinA (visit 3) might be too early to observe any onabotulinumtoxinA related effects [8, 32]. Regarding the treatment course, our patients had previous onabotulinumtoxinA treatments but not within 12 months prior to the first HRV measurement. Nevertheless, we cannot fully exclude a sustained onabotulinumtoxinA effect on autonomic cardiac control from previous injections. In this context it is noteworthy that in two of three studies, that demonstrated effects of BoNT/A on HRV, only treatment naive patients were included (in the third study, patient status was not indicated) [7, 8] although short-term (14–45 days) re-injections were necessary to record significant effects. This might suggest on the one hand a dose dependent effect of BoNT/A on cardiac autonomic control and on the other hand that patients with repeat BoNT/A injections might no longer show acute

effects on HRV potentially due to an already altered baseline. In contrary, Nebe et al. investigated treatment naive patients only as well but did not find any BoNT/A effect on HRV [29]. Moreover, in our patient group, potential chronic adaptations of the cardiac autonomic control due to previously repeated onabotulinumtoxinA injections must be subtle enough not to result in any difference compared to the healthy control group.

Despite using a quite high dosage of 300 units onabotulinumtoxinA compared to the studies indicating BoNT/A effects on HRV (20–130 units onabotulinumtoxinA or 500 units abobotulinumtoxinA), we could not confirm effects of onabotulinumtoxinA on HRV which is in line with the most recent study on this topic using 600 units of incobotulinumtoxinA for treatment of spastic hemiplegia in stroke survivors without significant post treatment effects on HRV [31]. A possible explanation could be a less extensive spread of onabotulinumtoxinA after intradetrusor injections compared to injections into striated muscle as suggested by a pilot study of Schnitzler et al. using single fiber electromyography to assess the neuromuscular jitter as sign of distant neuromuscular effects in 21 patients after 300 units onabotulinumtoxinA intradetrusor injections for NDO [33].

In view of the rather sparse body of literature in contrast to the many unclarified aspects on distant effects of BoNT/A after injection treatments further investigations on this topic are indicated to improve the knowledge and patient safety regarding side effects of one of the most potent neurotoxins, that is frequently used in neurorehabilitation.

Limitations of the study are: A) Focus on resting state HRV investigations only. Assessment of cardiovascular parameters under functional tasks such as tilt or exercise might have revealed different results. B) Investigation of single treatment only. No conclusions possible on the effect of repeated injections which might have altered the outcome of HRV measurements, specifically if performed at short intervals, i.e. ≤3 months. C) Post-treatment assessment of onabotulinumtoxinA effects on HRV at only two time points.

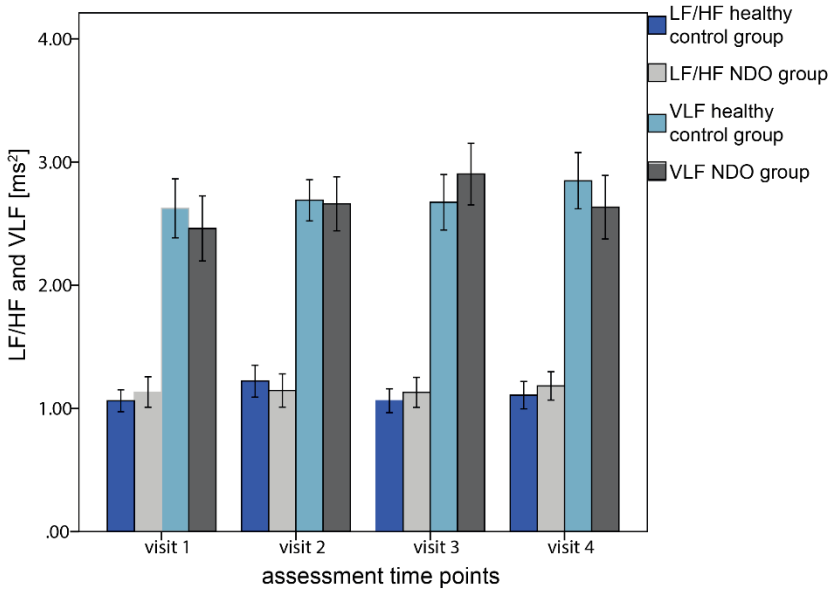

Figure 5-5 Low frequency/high frequency (LF/HF) ratio and very low frequency spectrum (VLF, in ms^2) during the four consecutive visits for the control (blue bars) and the neurogenic detrusor overactivity (NDO, grey bars) group.

In conclusion, this is the first study assessing the effects of onabotulinumtoxinA intradetrusor injections on autonomic cardiac function including 4 visits (two before and two after treatment) to control for natural fluctuations in HRV and using a healthy control group.

Our findings indicate that onabotulinumtoxinA intradetrusor injections (300 units Botox®) do not affect the resting autonomic nervous system control of cardiac function. This is highly relevant in regard to treatment of DO in patients with altered autonomic cardiac control and might influence the choice of treatment in regard to alternative treatments with systemic side effects on the heart [34]. Studies including HRV measurements under physical stress and after repeated onabotulinumtoxinA intradetrusor injections are desirable future tasks.

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CHAPTER 6

BOTULINUM NEUROTOXIN A FOR MALE LOWER URINARY TRACT SYMPTOMS

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ABSTRACT

Purpose of review: LUTS related to benign prostatic hyperplasia (BPH) affects a large number of male patients from 45 years onward, increasing with age. Routine medical treatment is mainly limited to plant extracts, a-blockers, and 5-areductase inhibitors. Although all types of drug have a proven efficacy, they often do not sufficiently treat all aspects of LUTS related to BPH. Thus, there is a need for alternatives. Intraprostatic injections with BoNT/A seem to be a promising alternative. The purpose of this review is to summarize the most recent findings from basic science and clinical studies in relation to BoNT/A application in BPH-related LUTS, thereby providing insight into the putative mechanism of action, the rationale for the use of BoNT/A in BPH-related LUTS, and the clinical outcomes.

Recent findings: There is some evidence that BoNT/A intraprostatic injections affect both, the static and dynamic component of BPH-related LUTS by reducing the prostate volume and by downregulation of α-1A-adrenoreceptors. Clinical trials demonstrated an easy and minimally invasive intraprostatic application of BoNT/A with a favourable safety profile. Efficacy seems to be good with significant improvements for several months in symptoms, urinary flow rate and reduction in postvoid residual, prostate volume, and also prostate-specific antigen in some studies.

Summary: BoNT/A seems to be a promising alternative in the treatment of BPH-related LUTS with a good tolerance and safety profile. However, the level of evidence is still low and further randomized controlled studies are mandatory.

INTRODUCTION

BoNT/A, long been used by neurologists for the treatment of focal spasticity of striated skeletal muscles, has been introduced into the field of urology in 1988 for the treatment of Detrusor- Sphincter-Dyssynergia [1]. In 2000, the first BoNT/A application in the smooth detrusor muscle in patients with NDO was described [2], followed in 2003 by the first results on the injection of BoNT/A into the prostate gland for the treatment of benign prostate hyperplasia (BPH) [3].

BoNT/A is a 150-kDa molecule, consisting of a heavy and a light chain. The known mechanism of action on striated skeletal muscles is the inhibition of acetylcholine release at motoric axon terminals [4, 5]. Thus, it causes a flaccid muscle paralysis, which is however of limited duration (months) due to resprouting of the axon terminals. Therefore, regular reinjection becomes necessary [4].

Basic research on the mechanism of action of BoNT/A in the human and animal urinary bladder rapidly provided evidence of additional BoNT/A effects, including modulation of urothelial and suburothelial receptor expression and neurotransmitter release [6].

Recent research on BoNT/A injections into the prostate revealed further mechanisms of action of BoNT/A and reported promising results for the therapy of LUTS due to BPH (LUTS / BPH).

This review summarizes and highlights the most recent findings in basic and clinical research on the use of BoNT/A for LUTS / BPH.

BASIC SCIENCE AND PROPOSED MECHANISM OF ACTION

BPH-related LUTS are commonly characterized by a static component related to prostate overgrowth, and by a dynamic component related to an increase in bladder neck / prostatic / urethral smooth muscle cells (SMC)

contractile tone. Current pharmacological treatment options target each component separately. Indeed, 5-α-reductase inhibitors (5-ARI) cause prostate tissue shrinkage, thereby targeting the static component, while prostatic / urethral SMC relaxation is achieved by α-1-adrenergic receptor blockers.

Prostatic SMC tone is mainly controlled by sympathetic innervation while prostate size is under both sympathetic and parasympathetic innervation influences [7]. As BoNT/A could act on both sympathetic and parasympathetic innervation [8], it makes sense to investigate the use of BoNT/A to impact both static and dynamic components of LUTS / BPH. However, preclinical studies supporting such effects are scarce.

Effects of botulinum neurotoxin type A on the static component of benign prostatic hyperplasia-related lower urinary tract symptoms

Most of the animal studies have provided evidence that intraprostatic BoNT/A toxin injections induce prostate size reduction in animals [9-13]. Silva et al. [13] performed intraprostatic injections of saline or 10 units onabotulinumtoxinA in adult male Wistar rats, and reported a significant 30% lower prostate weight 1 week after intraprostatic onabotulinumtoxinA injections compared to vehicle injections. Nishiyama et al. [12] also reported a significant lower prostate weight of, respectively, 36 and 22% at 1 and 4 weeks after intraprostatic injection of a newly purified neurotoxin issued from BoNT/A (when compared to saline injection).

The main concern with these preclinical data is the fact that they were conducted in normal rats. To date, the only published work performed in an experimental model of BPH in dogs does not report any significant effect of BoNT/A on prostate weight [14]. Nevertheless, these results need to be interpreted cautiously since they were obtained from only two animals in each experimental group.

Therefore, there is a need for more preclinical data to better investigate the effects of intraprostatic BoNT/A on prostate size in an experimental model of BPH.

Mechanisms of action of botulinum neurotoxin type A on the static component of benign prostatic hyperplasia-related lower urinary tract symptoms

The best characterized mechanism of action of BoNT/A induced reduction of prostate volume is the promotion of apoptosis that has been described in both humans [15] and animals [9, 10, 12-14].

Silva et al. [13] reported that apoptosis rate is clearly enhanced in adult rat prostate 1 week following 10 units intraprostatic onabotulinumtoxinA injection. Interestingly, this study showed that parasympathetic denervation may not participate to this proapoptotic effect while sympathetic innervation restoration by phenylephrine reduced apoptosis rate by 60%. Prostate atrophy [9, 11, 12, 14, 16] and decreased proliferation rate [9] have also been identified in rat and dog prostates treated with BoNT/A. Indeed, using a purified BoNT/A, Nishiyama et al. [12] observed histologically a partial atrophy of the prostate gland 1 week following intraprostatic injection in rats. Such an atrophy characterized by acini dilation and epithelial cells flattening was generalized to all parts of the prostate 4 weeks following injection. However, in human prostate, no sign of prostate atrophy could be identified following intraprostatic BoNT/A injection [15].

It is therefore likely that intraprostatic BoNT/A-induced prostate tissue shrinkage involves the enhancement of apoptosis rate. However, the possible involvement of decreased proliferation rate and/or tissue atrophy in the beneficial effects of intraprostatic BoNT/A still need to be confirmed in human BPH tissue.

Table 6-1 Injection techniques and protocols of different studies on intraprostatic botulinum toxin A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	Injection route / guidance tool	Needle size	No. of injections	Dose [units] / product / dilution [units/ml]	Anaes-thesia	Antibiotic prophylaxis
Maria et al. 2003 [3]	Trans-perineal / TRUS	22 G, 9 cm	2 (1 per lobe à 2 ml)	200 / Botox® / 50	none	n/a
Chuang et al. 2005 [15]	Trans-perineal / TRUS	21 G, 20 cm	2 (1 per lobe à 2 ml)	100 / Botox® / 25	i.v. sedation with 50 mg propofol	Cafazolin 1 g i.v. perioperative
Kuo 2005 [17]	Trans-urethral / cystoscope	23 G	10	200 / Botox® / 10	Light i.v. general anaesthesia	7 days post treatment antibiotic prophylaxis
Chuang et al. 2006 [18]	Trans-perineal / TRUS	21 G, 15 or 20 cm	2 for PV < 30 ml (1 per lobe à 2 ml), 4 for PV > 30 ml (2 per lobe à 2 ml)	100 for PV < 30 ml, 200 for PV > 30 ml / Botox® / 25	i.v. sedation for first 20 cases only, none thereafter	n/a
Park et al. 2006 [19]	Trans-perineal / TRUS	22 G, 15 cm	2 (1 per lobe)	100 for PV < 30 ml, 200 for PV between 30-80 ml, 300 for PV > 80 ml / Botox® / 25 for PV < 30 ml, 33.3 for PV > 30 ml	none	n/a
Silva et al. 2008 [20]	Transrectal / TRUS	21 G, 20 cm	4 (2 per lobe à 2 ml)	200 / Botox® / 25	none	ciprofloxacin 500 mg bid for 7 days post treatment
Brisinda et al. 2009 [21]	Trans-perineal / TRUS	22 G, 9 cm	2 (1 per lobe à 2 ml)	200 / Botox® / 50	none	n/a
Kuo et Liu 2009 [22]	Trans-perineal / TRUS	n.a.	2-3 (1 per lobe + 1 additional in median lobe if applicable)	200-600 / Botox® / n/a	Local or light i.v. general anaesthesia	Ciproxin 1 g daily for 3 days

Study	Injection route / guidance tool	Needle size	No. of injections	Dose [units] / product / dilution [units/ml]	Anaes-thesia	Antibiotic prophylaxis
Silva et al. 2009 [23]	Transrectal / TRUS	21 G, 20 cm	4 (2 per lobe à 2 ml)	200 / Botox® / 25	none	ciprofloxacin 500 mg bid for 7 days post treatment
Nikoobakht et al. 2010 [24]	Trans-perineal / TRUS	20 G	2 for PV < 30 ml (1 per lobe à 2 ml), 4 for PV > 30 ml (2 per lobe à 2 ml)	300 for PV < 30 ml, 600 for PV > 30 ml / Dysport® / 75	local	Cefazoline 1g i.v. pretreatment and ciprofloxacin 500 mg bid for 7 days post treatment

b.i.d. (lat. bis in die) twice daily, n/a not available, PV prostate volume, TRUS transrectal ultrasound.

Effects of botulinum neurotoxin type A on the dynamic component of benign prostatic hyperplasia-related lower urinary tract symptoms

Lin et al. [11] reported the consequences of intraprostatic BoNT/A injections on prostatic / urethral SMC tone. In dogs, while intraprostatic injection of 100 units onabotulinumtoxinA did not have any effect, 200 units reduced both in-vitro prostate strips contractile responses to KCl, phenylephrine and electrostimulation, and in-vivo urethral pressor responses to i.v. norepinephrine [11]. It is to be noted that these experiments have been performed in dogs without prostate enlargement and that the effects of intraprostatic BoNT/A on prostatic / urethral SMC reactivity in an experimental model of BPH has not been reported to date.

Mechanisms of action of botulinum neurotoxin type A on the dynamic component of benign prostatic hyperplasia-related lower urinary tract symptoms

It has been reported that intraprostatic onabotulinumtoxinA down regulates the expression of α-1A-adrenoreceptor within rat prostate [9]. Since an

overall nine-fold increase in α-1A-adrenoreceptor has been observed in BPH compared with normal prostate [25], and α-1A-adrenoreceptors antagonists are successfully used to relieve prostatic / urethral obstruction associated with increased SMC contractile tone in BPH, the downregulation of prostatic α-1A-adrenoreceptors expression following intraprostatic BoNT/A injection [9] represents a strong rationale for using such a treatment for symptomatic BPH. This is further supported by Lin et al. [11] who demonstrated that, in dogs, intraprostatic 200 units onabotulinumtoxinA injection reduced the contractile activity of the prostate when observed 1 month after injection. In this study, it was suggested that two mechanisms could be responsible for such an effect: an impaired release of norepinephrine from adrenergic nerves and an impaired contractile machinery of stromal SMC. Prostate SMC vacuolization was observed and constitute a plausible explanation for the in-vitro decreased contractile response of prostate tissue to KCl. However, it is still needed to determine whether this effect lasts over time or constitutes an irreversible cellular toxic effect. Interestingly, it has also been demonstrated that the cleavage of SNAP-25 (a component of the SNARE complex) by BoNT/A light chain increased outwards potassium currents channels in oesophageal SMC [26]. This effect would tend to hyperpolarize the membrane and thereby decrease smooth muscle tone, since potassium channels constitute an important component of SMC contractile machinery. Studies are however needed to identify such an effect in prostate SMC.

FINDINGS FROM CLINICAL STUDIES: FROM TECHNIQUE TO INDICATIONS

In patients, intraprostatic BoNT/A injections exert beneficial effects on BPH-related bladder dysfunction that are linked to prostatic urethral obstruction relief [reduction of the International Prostate Symptom Score (IPSS) voiding symptoms component], but also to bladder dysfunction by itself (reduction of IPSS storage symptoms component). Indeed, the decrease in storage

symptoms component of IPSS accounts for 20–55% of total IPSS reduction following intraprostatic BoNT/A injection [19, 27].

Three formulations of BoNT/A are currently commercially available, namely Botox® (Allergan, Irvine, California, USA), Dysport® (Ipsen, Paris, France), and Xeomin® (Merz, Frankfurt am Main, Germany). They mainly differ in their envelope proteins covering the BoNT/A molecule and in the application dosage. None of them is yet licensed for the treatment of LUTS or BPH. Thus, application of BoNT/A for LUTS / BPH remains off-label use.

Technique and dosage

In most studies a transperineal injection route with transrectal ultrasound guidance has been described (**Table 6-1)**, but transrectal and transurethral application routes have been also used [17, 23, 24]. Usually a 20– 22G needle is used to perform one to two injections per lobe either without or under local or light general anaesthesia. A total of 200U Botox® in different dilutions are most frequently used, although there is no rationale for this, as dose finding studies are still missing.

Efficacy

The most frequently used outcome parameters to evaluate the efficacy of BoNT/A intraprostatic injections on LUTS / BPH are the IPSS or the American Urological Association Symptom Index (AUA-SI) (**Table 6-2**), QoL-Index (QoL-I), Q_{max}, prostate volume, PVRV and serum levels of prostate-specific antigen (PSA) (**Table 6-2**).

The first and still only RCT on the efficacy of BoNT/A for LUTS / BPH was published by Maria et al. in 2003 [3]. This trial investigated 30 50–80-year-old patients with moderate to severe BPH symptoms (**Table 6-3**). Patients were either injected with 200 units onabotulinumtoxinA or saline. AUA-SI, Q_{max}, prostate volume, serum PSA level, and PVRV were evaluated at

baseline, 1, 2, 6, and 12 months after injection with unblinding after 2 months [3]. BoNT/A injections demonstrated significant improvements in all study parameters at 1 and 2 months post-treatment (65% improvement in AUA-SI and 51% decrease of serum PSA) (**Table 6-2**). In contrast, placebo did not show any differences to baseline, which is remarkable as placebo usually shows some effect that can reach up to 30% in randomized controlled trials using a-blockers for BPH [28, 29]. Follow-up at 6 and 12 months demonstrated persistent efficacy up to 12 months in all parameters (**Table 6-2**). This study represents the starting point of human studies.

Similar results in a similar study population were reported by Brisinda et al. in 2009 [21] (**Table 6-3**). In a prospective open-label study, 77 patients received 200 units onabotulinumtoxinA. At 1 and 2 months AUA-SI, Q_{max}, prostate volume, serum PSA level, and PVRV were significantly improved. Retreatments with 200 units were possible, if patients reported no improvements. After the first treatment 71% of patients reported significant improvements. The results remained stable up to 30 months [21]. However, 43 reinjections were performed during that time.

In 2006, Chuang et al. [18] reported on the effect of a prostate size-related onabotulinumtoxinA dosing (100 units for <30 ml and 200 units for >30 ml) in 41 BPH-patients who failed treatment with 5-ARI and / or a-blocker, **(Table 6-1, Table 6-3**). Significant improvements were observed in IPSS, QoL-I, Q_{max}, and prostate volume up to 12 months with slightly greater changes of parameters in the 200 units group [18] (**Table 6-2**). This later observation might be due to the fact that 200 units were used in larger prostates, which provides a larger impact area and a larger margin for improvements. PVRV showed significant improvements only at 3 months in the 100 units group and at 1, 2, and 3 months in the 200 units group [18].

Table 6-2 Efficacy results of different studies on intraprostatic botulinum neurotoxin A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	Time after BoNT/A injection [months]	No. of patients improved / treated	IPSS / AUA-SI: BL ➔ FU (p-value)	Q_{max} [ml/s]: BL ➔ FU (p-value)	PVRV [ml]: BL ➔ FU (p-value)	PV [ml]: BL ➔ FU (p-value)	QoL-I: BL ➔ FU (p-value)	Serum PSA [ng/ml]: BL ➔ FU (p-value)
Maria et al. 2003 [3]	1	11 / 15	23.2 ➔ 10.6 (0.00001)	8.1 ➔ 14.9 (0.00001)	126.3 ➔ 49.6 (0.00001)	52.6 ➔ 23.8 (0.00001)	n/a	3.7 ➔ 2.1 (0.00006)
	2	13 / 15	23.2 ➔ 8.0 (0.00001)	8.1 ➔ 15.4 (0.00001)	126.3 ➔ 21.0 (0.00001)	52.6 ➔ 16.8 (0.00001)	n/a	3.7 ➔ 1.8 (0.00001)
	6	17 / 19	23.2 ➔ 9.1	8.1 ➔ 14.6	126.3 ➔ 24.2	52.6 ➔ 21.0	n/a	3.7 ➔ 2.1
	12	17 / 19	23.2 ➔ 8.9	8.1 ➔ 15.0	126.3 ➔ 24.0	52.6 ➔ 20.5	n/a	3.7 ➔ 2.3
Chuang et al. 2005 [15]	1	16 / 16	18.8 ➔ 8.9 (0.0001)	7.3 ➔ 11.8 (0.0001)	67.7 ➔ 25.1	19.6 ➔ 17.0 (0.0014)	3.8 ➔ 2.1 (0.0001)	0.8 ➔ 0.72
	3	16 / 16	18.8 ➔ 7.9 (< 0.05)	7.3 ➔ 11.9 (< 0.05)	67.7 ➔ 27.3	19.6 ➔ 16.7 (< 0.05)	3.8 ➔ 1.9 (< 0.05)	n/a
	6	16 / 16	18.8 ➔ 7.4 (< 0.05)	7.3 ➔ 12.5 (< 0.05)	67.7 ➔ 26.4	19.6 ➔ 16.9 (< 0.05)	3.8 ➔ 1.8 (< 0.05)	n/a
	10	16 / 16	18.8 ➔ 9.0 (< 0.05)	7.3 ➔ 12.6 (< 0.05)	67.7 ➔ 26.8	19.6 ➔ 16.4 (< 0.05)	3.8 ➔ 2.1 (< 0.05)	n/a
Kuo 2005 [17]	3	7 / 10	n/a	7.6 ➔ 9.9 (0.02)	243.0 ➔ 53.9 (0.002)	65.5 ➔ 45.9 (0.001)	n/a	n/a
	6	10 / 10	n/a	7.6 ➔ 11.6 (0.05)	243.0 ➔ 36.8 (0.005)	65.5 ➔ 49.6 (0.009)	n/a	n/a

Study	Time after BoNT/A injection [months]	No. of patients improved / treated	IPSS / AUA-SI: BL → FU (p-value)	Q_{max} [ml/s]: BL → FU (p-value)	PVRV [ml]: BL → FU (p-value)	PV [ml]: BL → FU (p-value)	QoL-I: BL → FU (p-value)	Serum PSA [ng/ml]: BL → FU (p-value)
Chuang et al. 2006 [18]	1[a]	31 / 41	18.7 → 9.8 (0.001) 19.3 → 9.5 (0.001)	7.9 → 12.0 (0.001) 7.0 → 10.3 (0.001)	64.1 → 35.7 (0.3) 161.7 → 45.2 (0.02)	21.1 → 18.0 (0.001) 54.3 → 46.3 (0.001)	3.9 → 2.1 (0.001) 4.1 → 2.0 (0.001)	n/a
	3[a]	n/a	18.7 → 8.1 (< 0.05) 19.3 → 8.3 (< 0.05)	7.9 → 12.7 (< 0.05) 7.0 → 9.8 (< 0.05)	64.1 → 24.1 (< 0.05) 161.7 → 37.6 (< 0.05)	21.1 → 18.0 (< 0.05) 54.3 → 45.0 (< 0.05)	3.9 → 2.0 (< 0.05) 4.1 → 2.2 (< 0.05)	n/a
	6[a]	n/a	18.7 → 7.3 (< 0.05) 19.3 → 5.2 (< 0.05)	7.9 → 12.7 (< 0.05) 7.0 → 11.9 (< 0.05)	64.1 → 38.5 161.7 → 45.5 (< 0.05)	21.1 → 17.5 (< 0.05) 54.3 → 45.3 (< 0.05)	3.9 → 1.4 (< 0.05) 4.1 → 1.8 (< 0.05)	n/a
	12[a]	n/a	18.7 → 9.0 (< 0.05) 19.3 → 8.3 (< 0.05)	7.9 → 13.4 (< 0.05) 7.0 → 11.1 (< 0.05)	64.1 → 40.0 161.7 → 93.6	21.1 → 17.0 (< 0.05) 54.3 → 47.2 (< 0.05)	3.9 → 1.8 (< 0.05) 4.1 → 2.4 (< 0.05)	n/a
Park et al. 2006 [19]	1[b]	18 / 26 21 / 26	24.2 → 18.5 (0.001) 24.3 → 17.5 (0.001)	9.1 → 10.1 10.2 → 11.4	108.1 → 82.2 137.4 → 95.5	47.9 → 44.1 (0.001) 46.6 → 42.4 (0.009)	4.6 → 3.4 5.0 → 3.3	n/a
	3	39 / 52	24.3 → 16.9	9.6 → 11.1	122.7 → 80.7	47.2 → 41.0	4.8 → 3.2	n/a
	6[c]	21 / 23	24.0 → 14.7	7.4 → 9.4	108.7 → 59.4	47.5 → 40.8	4.7 → 3.0	n/a

Study	Time after BoNT/A injection [months]	No. of patients improved / treated	IPSS / AUA-SI: BL ➔ FU (p-value)	Q_{max} [ml/s]: BL ➔ FU (p-value)	PVRV [ml]: BL ➔ FU (p-value)	PV [ml]: BL ➔ FU (p-value)	QoL-I: BL ➔ FU (p-value)	Serum PSA [ng/ml]: BL ➔ FU (p-value)
Silva et al. 2008 [20]	1	16 / 21	n/a	retention ➔ 9.0	retention ➔ 80.0	70.0 ➔ 57.0 (0.006)	n/a	6.0 ➔ 5.8
	3	17 / 21	n/a	retention ➔ 10.3	retention ➔ 92.0	70.0 ➔ 47.0 (< 0.05)	n/a	6.0 ➔ 5.0 (0.04)
	6[c]	9 / 10	n/a	retention ➔ 11.4	retention ➔ 66	59.0 ➔ 50.0 (0.02)	n/a	6.5 ➔ 6.3
Brisinda et al. 2009 [21]	1	41 / 77	24.1 ➔ 12.6 (0.00001)	8.6 ➔ 13.1 (0.01)	92.1 ➔ 80.3 (0.01)	54.1 ➔ 47.2	n/a	6.2 ➔ 4.8 (0.03)
	2	55 / 77	24.1 ➔ 8.7 (0.00001)	8.6 ➔ 16.5 (0.00001)	92.1 ➔ 40.6 (0.002)	54.1 ➔ 30.9 (0.00001)	n/a	6.2 ➔ 3.0 (0.00001)
	6	n/a / 77	24.1 ➔ 10.4	8.6 ➔ 13.2	92.1 ➔ 34.3	54.1 ➔ 24.3	n/a	6.2 ➔ 3.6
	12	n/a / 77	24.1 ➔ 14.0	8.6 ➔ 11.4	92.1 ➔ 64.7	54.1 ➔ 32.0	n/a	6.2 ➔ 4.1
	18	n/a / 77	24.1 ➔ 9.2	8.6 ➔ 16.0	92.1 ➔ 30.0	54.1 ➔ 24.2	n/a	6.2 ➔ 2.9
	24	n/a / 77	24.1 ➔ 10.1	8.6 ➔ 15.0	92.1 ➔ 32.0	54.1 ➔ 27.1	n/a	6.2 ➔ 2.6
	30	n/a / 77	24.1 ➔ 11.1	8.6 ➔ 14.5	92.1 ➔ 27.1	54.1 ➔ 26.9	n/a	6.2 ➔ 3.1
Kuo et Liu 2009 [22]	6[d]	n/a	16.5 ➔ 11.1 (< 0.05) 18.2 ➔ 9.2 (< 0.05)	9.4 ➔ 10.5 8.4 ➔ 10.2 (< 0.05)	65.3 ➔ 85.7 92.7 ➔ 102.2	83.4 ➔ 81.6 89.7 ➔ 79.8 (< 0.05)	3.57 ➔ 2.93 (< 0.05) 4.11 ➔ 2.22 (< 0.05)	5.74 ➔ 3.89 5.94 ➔ 5.80
	12[d]	n/a	16.5 ➔ 9.4 (< 0.05) 18.2 ➔ 8.9 (< 0.05)	9.4 ➔ 10.7 8.4 ➔ 10.7 (< 0.05)	65.3 ➔ 68.5 92.7 ➔ 113.7	83.4 ➔ 76.6 (< 0.05) 89.7 ➔ 76.8 (< 0.05)	3.57 ➔ 2.53 4.11 ➔ 2.04	5.74 ➔ 4.14 5.94 ➔ 3.87

Study	Time after BoNT/A injection [months]	No. of patients improved / treated	IPSS / AUA-SI: BL → FU (p-value)	Q_{max} [ml/s]: BL → FU (p-value)	PVRV [ml]: BL → FU (p-value)	PV [ml]: BL → FU (p-value)	QoL-I: BL → FU (p-value)	Serum PSA [ng/ml]: BL → FU (p-value)
Silva et al. 2009 [23]	1	11 / 11	n/a	retention → 11.3	retention → 73.0	82.2 → 68.7	n/a	6.7 → 6.6
	3	11 / 11	12.3	11.3 → 12.0	73.0 → 82.0	82.2 → 59.1	3.3	6.7 → 5.1
	6	11 / 11	12.3 → 10.0	11.3 → 12.3	73.0 → 55.0	82.2 → 49.0	3.3 → 2.4	6.7 → 5.1
	12	11 / 11	12.3 → 10.8	11.3 → 11.4	73.0 → 64.0	82.2 → 63.8	3.3 → 3.0	6.7 → 5.4
	18	11 / 11	12.3 → 11.3	11.3 → 10.5	73.0 → 58.0	82.2 → 73.0	3.3 → 3.2	6.7 → 5.9
Nikoobakht et al. 2010 [24]	1[e]	n/a	16.2 → 9.9 (0.004) 19.7 → 10.2 (< 0.001)	6.5 → 12.7 (0.005) 6.3 → 12.6	37.2 → 21.1 50.7 → 25.0 (< 0.001)		3.2 → 2.3 3.6 → 2.4 (< 0.001)	
	6[e]	n/a	16.2 → 9.0 (0.001) 19.7 → 7.8 (< 0.001)	6.5 → 14.2 (0.001) 6.3 → 13.6 (< 0.001)	37.2 → 20.5 50.7 → 10.7 (< 0.001)	27.3 → 21.6 (0.001) 46.6 → 28.8 (< 0.001)	3.2 → 1.8 (0.001) 3.6 → 1.9 (< 0.001)	1.9 → 1.4 2.8 → 1.8 (0.036)
	12[e]	n/a	16.2 → 9.1 (0.003) 19.7 → 8.4 (< 0.001)	6.5 → 13.2 (0.002) 6.3 → 14.0 (< 0.001)	37.2 → 16.1 50.7 → 16.3 (< 0.001)		3.2 → 2.0 (0.005) 3.6 → 1.9 (< 0.001)	

AUA-SI American Urological Association Symptom Index, BL baseline, BoNT/A botulinum neurotoxin type A, FU follow-up, IPSS International Prostate Symptom Score, Q_{max}, maximum urinary flow rate, n/a not available, PSA prostate-specific antigen, PVRV postvoid residual volume, QoL-I quality of life index. P values indicate significance level in comparison to baseline values.

a Outcome parameters are indicated for 100 (upper values) and 200 (lower values) units Botox® separately.

b Outcome parameters are indicated for the BoNT/A group (upper values) and the BoNT/Aþa-blockers group (lower values) separately.

c The indicated mean baseline values represent only those patients who participated in this follow-up.

d Outcome parameters are indicated for the combined medication group (upper values) and the BoNT/A group (lower values) separately.

e Outcome parameters are indicated for the group with prostate volume <30 ml (upper values) and the group with prostate volume >30 ml (lower values) separately.

The first results using Dysport on LUTS / BPH were recently reported by Nikoobakht et al. [24] in a prospective open-label study. A population of 72 males was included using similar inclusion criteria as Maria et al. (**Table 6-3**). Follow-up was 12 months with intermediate evaluation at 1 and 6 months. IPSS, QoI-I, PVRV, and Q_{max} were evaluated at each follow-up visit. Serum PSA, prostate volume, urine analysis, and urine culture were evaluated at 6 months only [24]. All parameters significantly improved from 1 up to 12 months in the whole study population with a magnitude of effect that is comparable to the one observed by Maria et al. (**Table 6-2**). Like Chuang et al. [18], Nikoobakht et al. [24] treated different prostate sizes with different dosages of BoNT/A (**Table 6-1**). Subgroup analysis showed again differences in the outcome analysis in means that BoNT/A was more efficient in patients with larger prostates regarding the reduction in prostate volume, PSA, and PVRV and the increase in Q_{max} (**Table 6-2**) [18, 24].

Special indications

Several studies already investigated the use of BoNT/A for LUTS / BPH in special indications, like especially small or large prostates, poor surgical candidates, and as add-on treatment to α-blocker and 5-ARI. The findings are summarized below.

Small prostates

In a small population (n=16), Chuang et al. [15] reported the efficacy of 100 units onabotulinumtoxinA as a second-line treatment following α-blocker therapy in patients with small prostate volumes (<30 ml) and a Q_{max} less than 12 ml/s (**Table 6-3**). IPSS, Q_{max}, prostate volume, and QoL-I were significantly improved from 1 up to 10 months (**Table 6-2**). Mean PVRV was markedly reduced but standard deviations were probably too large to reveal any significance.

Table 6-3 General characteristics of different studies on intraprostatic botulinum neurotoxin A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study	No. of patients	Mean age [years] ±SD (range)	Patient characteristics / Inclusion criteria	Control group or comparison group	LoE
Maria et al. 2003 [3]	30	68.8 ±4.4 (50-80)	AUA-SI > 8, Q_{max} < 15 ml/s, voiding volume > 150 ml, enlarged PV on DRE	placebo	1b
Chuang et al. 2005 [15]	16	66.3 ±2.8 (n.a.)	PV < 30 ml, Q_{max} < 12 ml/s, inadequate response to alpha-blocker therapy for > 1 month	none	3
Kuo 2005 [17]	10	75.2 ±9.7 (48-92)	Acute or chronic urinary retention, severely difficult urination, large PVRV, failure of treatment with finasteride and alpha-blocker for > 1 year, poor surgical candidates	none	3
Chuang et al. 2006 [18]	41	69.1 ±7.1 (n.a.)	IPSS of ≥ 8, Q_{max} < 12 ml/s, inadequate response or failure to tolerate alpha-blockers and/or 5-ARI. All had a benign DRE and a PSA level of < 4 ng/ml, or a PSA level of 4–10 ng/ml but with a biopsy that showed no malignancy	none	3
Park et al. 2006 [19]	52	66.4 ±8.3 (45-84)	Urinary obstruction symptoms as determined by the IPSS and an enlarged prostate gland on digital rectal examination. All patients were treated with an alpha-blocker with or without a 5-ARI at least one month before this study.	BoNT/A + alpha-blockers	3
Silva et al. 2008 [20]	21	80.0 ±2.0 (65–92)	High risk patients not suitable for prostate surgery, history of indwelling catheter for > 3 months due to urinary retention refractory to alpha-blocker. At time of inclusion none of patients was taking 5-ARI or alpha-blocker.	none	3
Brisinda et al. 2009 [21]	77	67.9 ±3.6 (n/a)	AUA-SI > 8, Q_{max} < 15 ml/s, minimum voided volume > 150ml, enlarged prostate gland on DRE	none	3

Study	No. of patients	Mean age [years] ±SD (range)	Patient characteristics / Inclusion criteria	Control group or comparison group	LoE
Kuo et Liu 2009 [22]	60	74.9 ±8.3 (n/a)	IPSS > 8, combined 5-ARI and alpha-blocker treatment at full doses > 12months with symptom progression (occurrence of acute urinary retention or increased IPSS by > 4) or unsatisfactory therapeutic outcome (persistent difficult urination with either Q_{max} <12ml/s and/or PVRV > 100ml)	Combined medical treatment (5-ARI + alpha-blocker)	3
Silva et al. 2009 [23]	11	81.7 ±2.6 (61-92)	High risk patients not suitable for prostate surgery, history of indwelling catheter for > 3 months due to urinary retention refractory to alpha-blocker. At time of inclusion none of patients was taking 5-ARI or alpha-blocker.	none	3
Nikoobakht et al. 2010 [24]	72	63.5 ±8.5 (49-80)	Enlarged PV in DRE, serum PSA < 4ng/ml, IPSS > 8, Q_{max} < 12ml/s, and normal renal function tests. For serum PSA between 4 and 10ng/ml, free PSA was measured and the patient was included if free PSA was within the normal range (i.e. 0.02–0.5 ng/ml)	none	3

5-ARI 5-a-reductase inhibitor, AUA-SI American Urological Association Symptom Index, BoNT/A, botulinum neurotoxin type A; DRE, digital rectal examination, IPSS International Prostate Symptom Score, LoE level of evidence, QMAX maximum urinary flow rate; n/a, not available, PSA prostate-specific antigen, PVRV postvoid residual volume.

Poor surgical candidates for benign prostatic hyperplasia surgery

Kuo [17] treated 10 patients with 200 units onabotulinumtoxinA who had severe obstruction but were poor candidates for surgery due to co-morbidities (**Table 6-3**). Results were rated excellent, if spontaneous voiding occurred in patients with urinary retention or if patients had improvements in voiding pressure, Q_{max}, and PVRV of more than 25% from baseline values. At 6 months, eight of 10 patients had excellent results and two patients

showed improvement. Follow-up at 3 and 6 months demonstrated significant improvements in Q_{max}, PVRV, and prostate volume (**Table 6-2**).

In a similar population of 21 males (poor surgical candidates with urinary retention and indwelling catheters), Silva et al. [20] reported 2008 about the short-term results of intraprostatic injections of 200 units onabotulinumtoxinA. At 3 months post injection, 17 of 21 patients were able to voluntarily empty their bladder with a Q_{max} of 10.3 mL/s and mean PVRV less than 100 mL (**Table 6-2**). Prostate volume decreased significantly from 1 up to 6 months [20].

In 2009, Silva et al. [23] reported on the long-term results of a small subgroup (n=11) of their initial evaluation [20]. Follow-up was 18 months, and although IPSS, PVRV, prostate volume, QoL-I, and serum PSA seemed to slowly increase after 6 months, prostate volume remained still significantly below baseline values and patients remained on voluntary voiding up to 18 months [23] (**Table 6-2**). A total of 200 units onabotulinumtoxinA seem to be a valuable alternative treatment for patients who are not suitable for surgery because of poor general condition. Especially the fact that indwelling catheters could be omitted after the treatment in most of the patients is of great value for the patient.

Add-on treatment in patients with large prostates

Park et al. [19] investigated in 52 patients with LUTS / BPH the effect of BoNT/A alone and in combination with α-blocker for 4 weeks. Both groups showed significant improvements in IPSS and prostate volume after 1 month with sustained effects up to 6 months in those patients who participated in the follow-up (**Table 6-2**). Q_{max}, PVRV, and QoL-I were not improved at any follow-up. The only difference in both groups was demonstrated for IPSS-5 (weak stream) in favour of the BoNT/A and α-blocker group, which was interpreted as relative reinforcement of the adrenergic influence by the anticholinergic effect of BoNT/A [19].

Kuo and Liu [22] investigated the effect of BoNT/A on LUTS / BPH in patients with ongoing but not sufficient treatment with α-blockers and 5-ARI combination therapy since more than 12 months (**Table 6-3**). Sixty patients were either assigned to receive 200 units onabotulinumtoxinA add-on intraprostatic injection or continued medical therapy (control group) [22]. Additional injections were allowed after 2 months with increasing doses up to 600 units, if initial treatment results were not satisfactorily [22]. Although onabotulinumtoxinA treatment could significantly reduce IPSS, QoI-I, and prostate volume and increase Q_{max} at 6 months, no significant differences versus the control group were observed at 12 months regarding prostate volume, IPSS, QoL-I, Q_{max}, and PVRV. The only significant difference was observed regarding QoL-I at 6 and 12 months, showing a difference of small amplitude in favour of onabotulinumtoxinA treatment [22]. In regard to both, the study by Park et al. [19] and Kuo and Liu [22], add-on treatment with BoNT/A to α-blocker and / or 5-ARI treatment seems not to result in additional benefits. However, study design, patient number and power of both studies seem not appropriate to finally conclude on an add-on effect of BoNT/A. Future trials should probably include a run-in period and try to determine if previous medical treatment might influence responding rate.

Adverse events

Only very few and generally mild and self-limited adverse events were reported in some studies (**Table 6-4**). Adverse events that occurred were gross haematuria, urinary retention and acute prostatitis [15, 22, 24]. In some studies post-op indwelling catheter for up to 4 weeks were applied routinely [20, 23] (**Table 6-4**). Whether this is generally necessary remains questionable and requires further investigation.

Although various treatment strategies for BPH may impact sexual dysfunction (ejaculatory and erectile disorders) [30], only one yet unpublished clinical trial has examined the effects of intraprostatic BoNT/A

on sexual function and reported a significant improvement of ejaculatory function without any change in erectile function [31]. Thus, further studies are needed to investigate the effects of intraprostatic BoNT/A on bladder function and to validate its safety on sexual function.

Onset and duration of effect

In summary of the above-mentioned 10 clinical studies [3, 15, 17-24], mean onset of action seems to be around 3.5 weeks (range 1–6 weeks) after injection. The mean duration seems to be 11.9 months (range 3–30 months). However, none of those studies was designed to evaluate the exact onset and duration of effect on LUTS after intraprostatic BoNT/A injection. In most studies onset and duration was dependent on the follow-up scheme. Some studies even performed early reinjections in patients with insufficient outcome after first injection [21, 22] thereby influencing the study outcome and analysis of effect duration. Thus, studies investigating the exact start and duration of effect are lacking. This is important to be able to estimate cost-effectiveness. In relation to this, dose finding studies, investigations on repeated injections, and studies specifically investigating the impact of the treatment on the QoL using adequate QoL-questionnaires are also missing.

Ongoing studies

There are currently three active but not yet recruiting phase II studies registered at ClinicalTrials.gov investigating efficacy and / or safety of BoNT/A intraprostatic injections for the treatment of BPH-related LUTS. One is a randomized dose comparison study and two are randomized placebo-controlled trials. Interestingly, in one study (NCT00284518), the injection route of BoNT/A has been changed from transperineal to transrectal, showing that there is still an ongoing discussion about the best route of application. There is also a phase II randomized active control study

investigating intraprostatic BoNT/A injections for chronic prostatitis and / or chronic pelvic pain syndrome. Last but not least, there is a randomized, placebo-controlled phase II study currently recruiting that investigates the influence of intraprostatic BoNT/A injections on semen quality.

Table 6-4 Adverse events in different studies on intraprostatic botulinum neurotoxin A injections for benign prostatic hyperplasia-related lower urinary tract symptoms

Study / Author	Adverse events	Catheterization after injection
Maria et al. 2003 [3]	none	n/a
Chuang et al. 2005 [15]	Transient and mild dysuria and haematuria in 3 patients during the first 24h post treatment	For 1 week in 1 patient with indwelling catheter
Kuo 2005 [17]	none	3 patients needed ISC for 2 weeks post-op
Chuang et al. 2006 [18]	none	Only in patients with indwelling catheter
Park et al. 2006 [19]	none	n/a
Silva et al. 2008 [20]	none	Foley catheter for 1 month in all patients
Brisinda et al. 2009 [21]	none	n/a
Kuo et Liu 2009 [22]	In totally 50 injections, transient acute urinary retention occurred after three(6%),gross haematuria after seven(14%)and acute prostatitis after one(2%) injection	n/a
Silva et al. 2009 [23]	none	Foley catheter for 1 month in all patients
Nikoobakht et al. 2010 [24]	Self-limited gross hematuria in 3 patients (4.2%)	n/a

ISC intermittent self-catheterization

CONCLUSION

There is a rationale for the use of intraprostatic BoNT/A to impact both static and dynamic components of LUTS / BPH. Further preclinical data are needed to better investigate these effects and the exact mechanisms of action of BoNT/A within the prostate. Clinical studies show very promising

results with significant symptom relief in the majority of treated patients. The application technique is easily feasible and seems to have a low-risk profile with only rare or mild adverse events. However, the level of evidence is still very low and in view of that BoNT/A intraprostatic injections are still off-label use, no general recommendation for the BPH population can be given. There is still very little information on exact onset and duration of effect, on the dose–effect relation, on changes in QoL, on comparison to other or placebo treatment, and on adverse events on sexual function and semen quality. The results of ongoing controlled trials have to be awaited to increase the level of recommendation.

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CHAPTER 7

TREATMENT OF NEUROGENIC STRESS URINARY INCONTINENCE USING AN ADJUSTABLE CONTINENCE DEVICE: 4-YEAR FOLLOW-UP

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ABSTRACT

Purpose: We evaluated the long-term safety and efficacy of an adjustable continence device (ACT® or ProACT®) in male and female patients with neurogenic SUI (nSUI).

Materials and Methods: Data on patients consecutively treated with implantation of an adjustable continence device due to nSUI were reviewed from the start of our experience to the current 4-year follow-up.

Results: We reviewed data on 13 male and 24 female patients with nSUI due to different forms of pelvic nerve or spinal cord lesions. Mean ± SD age at implantation was 46.2 ± 17.4 years. Of the patients 92% performed ISC. The device was implanted bilaterally using general and local anesthesia in 16.2% and 83.8% of cases, respectively. From before implantation to 48-month follow-up the mean number of urinary incontinence episodes decreased from 6.1 ± 2.4 to 2.8 ± 3.1 and the mean number of pads used per 24 hours decreased from 4.2 ± 2.7 to 2.2 ± 2.2. Of the patients 54.5% indicated more than 50% improvement of SUI symptoms after 48 months, of whom 38.9% indicated complete continence. Adverse events included erosion / migration, device infection or failure, implantation site pain, bladder stone formation and difficult ISC.

Conclusions: Implantation of the ACT® / ProACT® device in patients with nSUI is minimally invasive and safe. It can significantly improve nSUI in the long term. Thus, it might be a reasonable option for patients who are not willing, not suitable or not yet ready for more invasive surgery, such as AUS or fascial suspension sling placement.

INTRODUCTION

Neurogenic lesions, e.g. SCI or peripheral lesions of nerve fibers innervating the LUT, can cause nSUI due to sphincter and / or bladder neck insufficiency. Managing neurogenic sphincter deficiency remains a therapeutic challenge since to our knowledge there is no available medical treatment. Moreover, most patients must perform ISC to empty the bladder and are at higher risk for complications of any prosthetic implant used for continence [1].

The current, most frequently used surgical options for nSUI are an AUS [2, 3] or an obstructing fascial sling [4-6]. However, these procedures require open abdominal and pelvic surgery using general anesthesia and do not provide the opportunity for postoperative adjustment. Some patients do not desire or feel uncomfortable with an AUS or they do not have the dexterity to use such an implant. Others might not be good candidates for more invasive surgery or they might need additional continence support after previous surgery, i.e. fascial sling placement. Moreover, in patients with nSUI it would be desirable to have an adjustable continence device that allows for adaptation in regard to changes in continence function without undergoing further surgery or changing the implant.

The ACT® / ProACT® device offers such adjustable continence support for male [7-10] and female [11] patients. The device consists of 2 balloons that are implanted in minimally invasive fashion on each side of the urethra. Small subcutaneous titanium ports allow refilling or deflation at any time. Good mid-term results with a 52% to 80% continence rate were achieved in non-neurogenic SUI populations with sphincter deficiency [7, 9-12]. However, long-term results of more than 2 years have been reported only for single cases.

There is no available information on using ACT® / ProACT® for nSUI. Thus, to our knowledge we retrospectively investigated for the first time the safety

and efficacy of the ACT® / ProACT® device in male and female patients with nSUI.

PATIENTS AND METHODS

Data on patients who were consecutively treated at our clinic (Department of Urology, Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, University Paris VI) with implantation of the ACT® or ProACT® adjustable continence device due to nSUI were reviewed from the start of our experience up to the current 4-year follow-up to determine long-term results. The frequency of ISC, urinary incontinence episodes (UIEs) and pad use was evaluated from follow-up data and compared to preoperative values. In addition, balloon volume, operative and postoperative adverse events, and patient reported treatment outcomes were evaluated from follow-up data.

Statistical analysis was performed as applicable between pre-implantation and follow-up data using the Wilcoxon signed rank test with SPSS® 17.0.

RESULTS

A total of 13 male and 24 female patients with nSUI were treated with ACT® / ProACT® at our clinic. Mean ± SD age at implantation was 46.2 ± 17.4 years. Of the 37 patients 19 had paraplegia at Th3 or below, 7 had spina bifida, 4 had cauda equina syndrome and 1 each had poliomyelitis, syringomyelitis, lumbar stenosis, multiple sclerosis, tetraplegia, pelvic polytrauma and peripheral nerve lesion following major pelvic surgery, each with subsequent nSUI (**Table 7-1**).

A total of 14 patients received 1 or more previous urological treatments for nSUI, 21 underwent or were currently being treated for concomitant NDO and 5 received previous urological treatment for reasons other than nSUI or NDO (**Table 7-1**). Before implantation, the micturition mode was ISC and

voluntary micturition in 34 and 3 patients, respectively. Additionally, 6 male patients used a condom catheter between ISC.

Urodynamic data before implantation revealed a mean maximum cystometric capacity of 424 ± 147 ml, a mean maximum detrusor storage pressure of 20.2 ± 11.3 cmH_2O and a mean bladder compliance of 37.7 ± 21.8 ml/cmH_2O. Mean urethral closure pressure was 22.6 ± 13.2 cmH_2O. DO or poor bladder compliance was not detected on pre-implantation cystometry, which was a prerequisite for the procedure. SUI was noted in each patient during pelvic examination.

All implantations were performed bilaterally under cystoscopic and fluoroscopic control by the same surgeon (ECK). All patients received prophylactic antibiotics at surgery. The detailed implantation technique was described previously [9-11]. The mean volume injected during implantation was 2.0 ± 0.3 and 1.9 ± 0.4 ml for the right and the left balloon, respectively. Mean operative time was 25 ± 2.4 minutes.

In 6 patients the procedure was performed under general anesthesia. All other patients tolerated implantation well under local anesthesia. Mean hospital stay was 1.5 days (range 1 to 2). However, this reflects an administrative rather than a medical reason.

During surgery or the postoperative hospital stay, a labial / scrotal hematoma developed in 2 patients, which was surgically removed in 1. In 3 patients small intraoperative urethral perforations resulted in immediate balloon repositioning on the side of the perforation and Foley catheter placement for 24 hours.

Follow-up was performed at 3, 6, 12, 24 and 48 months. Due to incomplete and missing data, 1 patient data set was excluded from further analysis. Thus, the data sets of 36 patients were used for follow-up analysis. By 48 months another patient was lost to follow-up and 1 each had died of esophageal cancer and cardiac arrest. Thus, at 48-month follow-up 33 patient data sets were available.

Table 7-1 Patient characteristics, previous and current urological treatments

Pt No. – Gender – Age [years] at implantation	Neurologic lesion (cause)	ASIA impairment scale/level of lesion	Previous urological treatments	Current urological treatments
1 – F – 72	Poliomyelitis		none	none
2 – F – 41	Paraplegia (infection)	A/Th9	Ileum bladder augmentation, suburethral sling from muscel fascia	oral oxybutynin
3 – F – 33	Paraplegia (vascular)	-/L5	none	oral oxybutynin
4 – F – 36	Paraplegia (trauma)	A/Th10	Botulinum toxin intradetrusor injections, Ileum bladder augmentation, trans vaginal tape	none
5 – M – 25	Syringomyelitis		none	oral oxybutynin
6 – M – 42	Spina bifida		Ileum bladder augmentation	none
7 – F – 49	Spina Bifida		Vesico-ureteral-reflux repair	none
8 – M – 69	Cauda-Equina-Syndrome (t)		Urethral stent, sacral neuromodulation	oral oxybutynin
9 – F – 55	Paraplegia (trauma)	A/Th12	trans vaginal tape	none
10 – F – 72	Cauda-Equina-Syndrome (Ca surgery)		sacral neuromodulation	none
11 – F – 37	Peripheral nerve lesion following major pelvic surgery		sacral neuromodulation	none
12 – M – 30	Spina bifida		Ileum bladder augmentation	none
13 – F – 68	Lumbar stenosis		Ileum bladder augmentation, trans vaginal tape	oral oxybutynin
14 – F – 46	Multiple sclerosis		Ileum bladder augmentation + continent urinary diversion, suburethral sling from muscle fascia	oral oxybutynin
15 - F – 32	Spina bifida		none	none
16 – F – 30	Paraplegia (trauma)	A/Th12	none	oral oxybutynin
17 – F – 26	Pelvic polytrauma		AMS800 (’88 – ’05), Ileum bladder augmentation, vesico-ureteral-reflux repair	none
18 – M – 62	Paraplegia (Ca surgery)	A/L1	Radical prostaectomy	oral oybutynin
19 – M – 55	Cauda-Equina-Syndrome		Orchiectomy	none

Pt No. – Gender – Age [years] at implantation	Neurologic lesion (cause)	ASIA impairment scale/level of lesion	Previous urological treatments	Current urological treatments
20 – M – 53	Paraplegia (trauma)	A/Th11	Ileum bladder augmentation, sphincterotomy	oral oxybutynin
21 – F – 58	Paraplegia	-/Th12	Promontofixation, bladder neck closure	oral oxybutynin
22 – F – 14	Spina bifida		Sigmoid cystoplasty, bladder neck reconstruction	none
23 – F – 46	Paraplegia (trauma)	A/Th11	Trans vaginal tape, hysterectomy, promontofixation, Ileum bladder augmentation + Mitrofanoff catherizable stoma	oral oxybutynin, intradetrusor injections with botulinum toxin
24 – F – 56	Paraplegia	A/Th12	Ileum bladder augmentation + Mitrofanoff catherizable stoma, trans vaginal tape	oral oxybutynin
25 – F – 64	Paraplagia (Ca surgery)	C/Th3	none	none
26 – F – 27	Paraplegia (trauma)	A/L1	suburethral sling from muscle fascia	none
27 – F – 83	Spina bifida		none	none
8 – F – 76	Cauda-Equina-Syndrome (Ca surgery)		none	none
29 – M – 36	Paraplegia (trauma)	D/Th12	none	none
30 – M – 30	Paraplegia (trauma)	A/Th12	vesico-ureteral-reflux repair, bladder stone extraction	none
31 – M – 71	Paraplegia (trauma)	A/Th10	none	none
32 – M – 36	Paraplegia (trauma)	A/Th10	none	none
33 – M – 44	Paraplegia (trauma)	A/L5	none	oral oxybutynin
34 – F – 41	Paraplegia (trauma)	A/L4	Promontofixation, trans vaginal tape	none
35 – F – 23	Spina bifida		Pippi-Salle procedure, trans vaginal tape	none
36 – M – 35	Tetraplegia		Urethral stent, urethrotomy	oral oxybutynin
37 – F – 35	Paraplegia (trauma)	B/L3	Promontofixation, trans vaginal tape	oral oxybutynin

F = female, M = male, ASIA = American Spinal Injury Association, L = lumbar, Th = thoracic

Table 7-2 lists balloon volume, the frequency of ISC, UIEs and pad use, and patient reported treatment outcomes. The micturition mode did not change in any patient postoperatively.

A total of 74 adverse events involved the 2 balloons or the balloon on only one side. Therefore, adverse events are not presented per patient but rather per balloon (**Table 7-3**). Overall, we noted device erosion/migration for 15 of the 74 balloons (20.3%), device infection for 5 (6.8%), implantation site pain for 5 (6.8%), and device failure (i.e. balloon leakage), bladder stone formation and difficult ISC for 2 each (2.7%). Balloons eroded / migrated more frequently into the urethra than into the bladder (13 vs 2 of 15). Adverse events were generally mild and only temporary due to easy, timely balloon explantation as an outpatient procedure without anesthesia. In cases of infection additional treatment with oral antibiotics was sufficient.

The number of patients who required or asked for device explantation was 5 of 36 (13.8%) at 3 months, 4 of 36 (11.1%) at 6 months, 2 of 36 (5.5%) at 12 months, 4 of 36 (11.1%) at 24 months and 9 of 33 (27.3%) at 48 months (**Table 7-3**). In 11 patients devices were only temporarily explanted and could be successfully re-implanted after 3 to 24 weeks (**Table 7-3**). Thus, the device was permanently explanted by the end of the 48-month follow-up in 13 of 33 patients (39.4%). Reasons for permanent removal were adverse events and the inefficacy of nSUI treatment.

Of the patients with permanently removed devices 4 underwent AUS implantation, 3 were treated with bladder neck closure combined with continent cutaneous urinary diversion and 2 received an ileal conduit.

DISCUSSION

The implantation of adjustable paraurethral balloons significantly decreased the number of UIEs and pad use in patients with nSUI. However, only 21% of patients attained complete continence and 39.4% required permanent

explantation of the device after 4 years of follow-up. Nevertheless, greater than 50% improvement was reported by 67.6% and 64.8% of patients, including those who achieved complete continence, at 1 and 2 years of follow-up, respectively.

Table 7-2 Results on ballon volume, frequency of intermittend self-catheterization (ISC), urinary incontinence episodes (UIE), pad use, and patient reported outcome at baseline and follow-up after 3, 6, 12, 24, and 48 months.

	Baseline	Follow-up (months)				
		3	6	12	24	48
Mean ± SD balloon vol (ml):						
right		2.8 ±1.1	3.6 ±1.6	3.7 ±1.8	3.9 ±2.1	4.1 ±2.2
left		3.0 ±0.8	3.6 ±1.5	3.9 ±1.7	4.2 ±2.0	4.3 ±2.0
Mean ± SD No./24 hrs:						
ISCs	5.4 ±1.7	5.1 ±1.6,	5.0 ±1.7	5.2 ±1.7	5.2 ±1.9	5.6 ±1.7
UIE	6.1 ±2.4	3.9 ±3.2	4.1 ±2.9	3.1 ±3.4	3.2 ±3.4	2.8 ±3.1
p Value*		0.001	0.002	< 0.001	< 0.001	0.001
Pad use	4.2 ±2.7	2.3 ±2.2	2.4 ±2.3	1.8 ±2.0	2.4 ±2.5	2.2 ±2.2
p Value*		0.001	0.004	0.001	< 0.001	0.004
No. pt reported (%):		36	36	36	36	33
complete continence		6 (16.7)	6 (16.7)	7 (19.4)	5 (13.8)	7 (21.2)
50% or greater improvement		14 (39.0)	17 (47.2)	18 (50.0)	19 (52.8)	11 (33.3)
treatment failure or less than 50% improvement		16 (44.4)	11 (30.5)	8 (22.2)	7 (19.4)	2 (6)
permanent device explantation		0	2 (5.6)	3 (8.3)	5 (13.9)	13 (39.4)

* = significant different vs baseline

Previous groups that investigated the efficacy of the adjustable continence device in female and post-prostatectomy SUI cases reported a success rate

of 52% to 80% (proportion of completely continent patients) [7, 9-12]. However, in the latter studies non-neurogenic patients had at least some sphincter and pelvic floor function remaining. In our patient population sphincteric and pelvic floor function was absent, explaining the discrepancy in efficacy rates between the current and previous studies. The type of neurological lesion might have influenced the results but this could not be statistically demonstrated in our study due to our small, mixed study population. However, according to daily clinical experience the degree of disability / mobility seems to be more important for the therapeutic outcome than the type of neurological lesion because there is high variability in nSUI severity even for the same type of neurological lesion.

Usually, postoperative adjustment is necessary to optimize the effect on urinary continence. Best outcomes were reported after 4 or 5 refillings [9]. In our patients refilling was done more rapidly during the first 6 months to achieve continence more quickly. Further refilling was needed less frequently and performed more cautiously to prevent trouble with ISC.

The most common intraoperative and postoperative complications using the adjustable continence device reported in the current literature are erosion in 2.5% to 7.5% of cases, urinary retention in 1.2% to 6.3%, migration in 3.8% to 5.6%, perforation in 2.5% to 18%, therapy failure in 2.5%, and urinary tract infections in 1.9% to 5% [7-12]. Other complications, such as wound infection in 0.6% to 8% of cases, implantation site pain in 0.6% to 15%, de novo urgency in 5% and device / material failure in 0.6% to 4% were less common [11] except in the study by Gilling et al. [7]. In most cases complications were described as mild and quickly correctable. The reported explantation rate is between 8% and 58% [7-11]. Within 12 months after explantation successful reimplantation could be performed in most cases [11, 12].

Complication and explantation rates in our study of the ACT® / ProACT® device in an nSUI population are well within the ranges reported in the current literature. However, urinary retention is less relevant in our nSUI

population of patients, who perform ISC. The fact that 92% of our patients performed ISC and 37.8% of them had undergone previous SUI surgery seems not to have negatively affected our complication rate.

Table 7-3 Adverse events in 74 ballon cases during follow-up

Follow-up (months)	No. Ballons*					No. Pts / No. Ballons	
	Errosion / Migration (site)	Infection (type)	Pain	Device failure	Other (cause)	Removal	Re-implantation
3	4 (urethra)	2 (device)		1 (balloon leak)		5 / 7	3 / 3
6	6 (5x urethra, 1x bladder)					4 / 7	3 / 5
12	1 (bladder)	1 (orchido-epidydi-mitis)	2		3 (2x bladder stone, 1x difficult ISC)	2 / 4	1 / 2
24	2 (urethra)	1 (device)	2	1 (balloon leak)	1 (difficult ISC)	4 / 7	3 / 5
48	2 (urethra)	1 (device)	1			9 / 17	1 / 1
Totals	**15**	**5**	**5**	**2**	**4**	**24 / 42**	**11 / 16**

*No patient had urethral stricture. ISC intermittend self-catheterisation

Concomitant NDO that is not treated or insufficiently treated can adversely influence the complication rate and study outcome in our patient population. Thus, in neurogenic cases it is important to strictly determine whether urinary incontinence is related to NDO or whether it is true SUI due to sphincter and / or bladder neck insufficiency [13]. This distinction can only be made by urodynamic investigations using filling cystometry, as in our study. All of our

patients had cystometric parameters within the normal range and no DO. Those known to have NDO were under adequate treatment.

Other surgical therapies for SUI include bulking agents, suburethral or bladder neck slings / tapes and AUS implants. Bulking agents comprise different products of different materials, eg collagen, autologous fat, silicon, carbon, polytetrafluoroethylene and polyacrylamide hydrogel. Due to initially rather low therapeutic success and sparse data [14], this therapy form is not well established. There are hardly any investigations of the application of bulking agents for nSUI. Two studies in children with nSUI showed rather unsatisfactory results [15, 16]. Almost all bulking agents migrate, or cause erosion or granulomas [14, 17]. Re-injections are frequently required for adequate efficacy [14].

Autologous suspension slings, i.e. rectus fascia, are often used for female and male nSUI with a complete continence rate of 66.6% to 69.2% (mean 68.3%) in the adult population [4-6] and 14% to 95% (mean 68.4%) in the pediatric population [18-20]. However, most sling procedures are performed in combination with augmentation cystoplasty, which potentially contributes to the beneficial outcome of nSUI [19].

Although most patients with nSUI performed ISC, studies of autologous fascia slings in adult and pediatric patients with nSUI show only a few, less severe adverse events than those reported for tape and sling implantation in the more general SUI population [21, 22]. Two available studies show midterm and long-term outcomes of tension-free vaginal tape implantation in an adult female nSUI population with continence in 83.3% at 2 years [23] and in 77% at 10 years [13].

The AUS is used in men and less frequently in women [24, 25]. Due to its high efficacy in terms of the continence rate of 58% to 88% (proportion of completely continent patients), today it is the gold standard treatment for male SUI [26]. Patients with nSUI, in whom an AUS is an established treatment option, have also largely benefited from this therapy [24]. The

success rate (proportion of completely continent patients) for nSUI is reportedly between 23% and 91% (mean 73%) [2, 27-30].

However, the AUS is expensive and requires a somewhat complex surgical procedure that may be associated with significant complication and revision rates [12]. Common complications are erosion, infection and mechanical / product related failure, causing an overall 16% to 80% revision and explantation rate [2, 28-30]. Murphy et al compared treatment outcomes between patients with nSUI and those with non-neurogenic SUI [27]. According to those results, patients with nSUI seem to have non-mechanical / non-product related complications more frequently, which was attributable to a higher rate of previous LUT surgeries in patients with nSUI. ISC and wheelchair dependency potentially also contribute to the higher complication rate in neurogenic cases.

Despite the rather average effectiveness in our study, special circumstances in patients with nSUI must be considered, such as complete sphincter insufficiency and a yawning bladder neck, i.e. in those with spina bifida. However, the adjustable balloons offer certain advantages. 1) Application is safe with few intraoperative and immediate postoperative complications even in neurogenic cases with previous LUT surgery. 2) The short, minimally invasive procedure allows for fast healing and a short hospital stay or even ambulatory treatment. 3) There is quick, uncomplicated ambulatory adaptation of balloon volumes according to patient needs [9]. 4) In contrast to slings / tapes or bulking agents, balloons can be explanted as ambulatory surgery using local anesthesia in case of adverse events with the option of re-implantation at 3 months. 5) Balloon implantation or explantation does not limit the implantation of other continence devices, i.e. an AUS, at a later time.

Although to our knowledge this is the first study evaluating the efficacy and safety of the ACT® / ProACT® system in an nSUI population, certain limitations must be considered. 1) Our study was not a randomized,

prospective study. Nevertheless, our data are representative of everyday clinical practice. 2) Patient reported outcomes were not obtained anonymously from questionnaires but from chart reviews. 3) QoL before and after implantation was not systematically assessed and, therefore, could not be evaluated.

CONCLUSIONS

ACT® / ProACT® implantation in patients with nSUI can be performed as a short, minimally invasive procedure. The safety profile is good with intraoperative and postoperative complications that are self-limited or easily manageable, even in neurogenic patients who mainly performed ISC and / or underwent previous SUI surgery. Efficacy seems to be somewhat limited, probably due to the severity of the continence deficiency in neurogenic patients. Nevertheless, UIEs and pad use were significantly decreased throughout the 4-year follow-up. The ACT® / ProACT® system appears to be an interesting alternative for nSUI, especially for patients who need additional continence support after previous nSUI surgery or those who are not willing, not suitable or not yet ready for more invasive surgery.

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CHAPTER 8

GENERAL DISCUSSION

GENERAL DISCUSSION

The adequate management of urine storage dysfunction in the neurological patient is highly relevant for the patient's QoL and general health. A thorough diagnostic workup is essential in order to understand the type of dysfunction and underlying mechanism, to effectively treat the LUTS / LUTD and to prevent (further) deterioration of upper and lower urinary tract function. Early diagnosis and prevention are important, as, once deterioration of morphology and function of lower and upper urinary tract has occurred, it is usually not reversible and further, sometimes invasive treatment efforts may become necessary to alleviate symptoms and to avoid sequelae and further urinary tract damage.

Today, a level of patient care has been reached that allows the prevention of fatal courses of urinary tract deterioration and the provision of some reasonable improvements in the QoL. Neuro-urological research and practice has, in recent decades, certainly contributed to the significantly improved life expectancy of SCI patients.

However, still many aspects of human LUT (patho)physiology and the mechanisms of action of different, often extant therapies are only poorly understood or entirely unknown. Hence, further research, basic and clinically oriented, is crucial for improving health care for LUTS / LUTD in the neurological patient.

In this thesis, current LUTS / LUTD treatments in neurological patients have been investigated and assessed with regard to the aforementioned research questions with a specific focus on BoNT/A intradetrusor injections (chapters 3-6) using clinical studies (chapters 3-5, 7) and comprehensive literature reviews (chapters 2 and 6). In this chapter, the findings of the investigations reported in chapters 2-7 are discussed in a broader context of neuro-urological health care and in view of the most recently available insights into the management of urine storage dysfunction in the neurological patient.

THERAPEUTIC PRINCIPLES OF URINARY INCONTINENCE IN NEUROLOGICAL PATIENTS

Urinary incontinence in the neurological patient is essentially related to one of the following dysfunctional patterns, which may occur either isolated or in combination with each other: a) DO which may cause sudden intravesical pressure increase that overcomes the subvesical resistance and consequently results in overactivity incontinence, b) sphincter insufficiency lowering the subvesical resistance and the ability to voluntarily prevent or interrupt urinary outflow, resulting in stress urinary incontinence and / or aggravated overactivity incontinence in case of coexisting DO and c) hypo- or acontractile detrusor resulting in accumulation of PVRU and potentially overflow incontinence.

Although the initial intention of our review was to highlight male-specific data, we extended our review to neurological patients in general because, on the one hand, male-specific data are very scarce and, on the other, all the dysfunctional patterns mentioned above apply equally to both male and female patients (**Chapter 2, [1]**).

Effective treatment of urinary incontinence in patients with NLUTD is based on the treatment of the underlying dysfunctional pattern a) to c). To detect which of these patterns applies and to understand the cause of the incontinence, urodynamic investigation, i.e. filling cystometry with subsequent pressure-flow study, is mandatory. Only such urodynamic investigation allows the positing of a complete diagnosis and the selection of appropriate treatments. In addition to the urodynamic outcome, which also provides an estimate of the risk for upper urinary tract damage, treatment selection depends on the severity of symptoms. In general, the more advanced the dysfunction and the morphological alterations are, the more invasive the treatment requirements become.

Treatment options for the dysfunctional patterns a) and b), i.e. neurogenic DO and sphincter insufficiency, are described in detail in **chapters 1 and 2**.

In addition, a specific treatment option for stress urinary incontinence due to neurogenic sphincter insufficiency is highlighted and discussed in **chapter 7**. Hence, the main focus of the following discussion will be placed on the dysfunctional pattern c), i.e. neurogenic detrusor hypo- or acontractility.

Neurogenic detrusor hypo- or acontractility may typically result from subsacral or peripheral neuronal lesions [2] related to e.g. trauma, pelvic surgery, or progressive polyneuropathy. Suprasacral lesions may also result in an acontractile detrusor, e.g. during the spinal shock phase after SCI but also in cases of isolated lesions affecting the efferent pathway such as in multiple sclerosis [3]. Although less frequently, supraspinal lesions, e.g. stroke, Parkinson's disease, multiple sclerosis, tumors, hemorrhage, may also cause detrusor hypo- or acontractility, most probably related to a disturbed or disrupted connection to the pontine micturition center, preventing its activation and thus the induction of micturition [3-6].

A rather extraordinary, yet poorly understood, form of LUT dysfunction, including detrusor underactivity with a supposed supraspinal component, is "isolated" urinary retention that particularly occurs in younger women without any overt neurological dysfunction and is often referred to as Fowler's Syndrome [7]. The currently best-established working hypothesis is that a poorly relaxing sphincter causes increased urethral afferent activity, which inhibits bladder afferent signaling and leads to poor bladder sensation and detrusor underactivity, i.e. an exaggerated guarding reflex [8]. Alongside other potentially implicated etiological factors such as autonomic dystonia, hormonal dysfunction, opiate use and psychological stress, a supraspinal component is likely, supported by recent neuroimaging studies and may also explain the extremely good treatment response to sacral neuromodulation [9-12].

Diseases such as diabetes mellitus may cause detrusor hypocontractility by damaging pre- and postsynaptic efferent and afferent fibers in diabetic polyneuropathy. In addition, diabetes mellitus may also cause reduced substrate supply to the detrusor by vascular damage or even direct

myogenic damage and bladder wall remodeling due to hyperglycemia-related oxidative stress [13-16].

Finally, acute, prolonged bladder overdistension or chronic bladder outlet obstruction can cause detrusor damage *inter alia* due to changes in cellular architecture and local ischemia, resulting in hypo- or acontractile detrusor [17, 18].

Detrusor hypo- or acontractility can frequently result in a chronic post-void residual volume, particularly in male patients who naturally require a higher detrusor pressure to empty their bladder due to the prostate and longer urethra [19]. Subsequently, this may lead to overflow incontinence during accumulation and a reduced functional capacity causing higher urinary day- and nighttime frequency.

CATHETERIZATION

Detrusor hypo- or acontractility may appear simple to treat using a form of catheterisation. However, not all patients are able or willing to perform the recommended gold-standard ISC and may end up with an either transurethral or suprapubic indwelling catheter [20, 21]. Although the EAU guidelines on neuro-urology recommend the use of ISC and to avoid indwelling catheters whenever possible with grade A, the corresponding level of evidence supporting this recommendation is only 3 [22]. Indeed, there is no single RCT adequately comparing indwelling versus ISC for long-term bladder management [23, 24] despite the importance and daily clinical relevance of this topic.

In fact, catheter-associated urinary tract infections are among the most common healthcare-associated infections with excess morbidity and health care costs [25-28]. This is all the more concerning considering the increasing antimicrobial resistance of many uropathogenic bacteria [29-32].

Certainly, even indwelling catheters can be useful tools in the management of NLUTD and may also serve as a reasonable long-term solution for selected patients [33-35], however, they should be used advisedly and the indication should be evaluated carefully and reevaluated during regular follow-up contacts. In patients with neurogenic bladder dysfunction after SCI, indwelling catheters have been identified as the most prevalent risk factors for urinary tract infection [36-39] and prior studies have demonstrated that patients are at higher risk for upper and lower urinary tract deterioration with indwelling catheters [40-49]. More recent studies report that complications and urinary tract deterioration in those using suprapubic catheters achieved similar morbidity profiles compared to ISC, which is probably related to improvements or more consistent implementation of DO treatment, appliance of closed loop systems and regular and more frequent follow-up including catheter changes, bladder washing regimes, and improved catheter material / fabrication [21, 50]. Nevertheless, infection rates are still considered to be higher with indwelling catheters [22, 36, 37, 51] which is why efforts have been made to improve catheter material by coating or impregnating the catheter with antiseptic or antimicrobial substances such as silver alloy and nitrofurazone. However, available studies do not provide sufficient evidence that catheters coated or impregnated with antimicrobial substances significantly reduce the incidence and frequency of catheter associated urinary tract infections [27, 38, 52, 53].

Thus, the best approach for preventing catheter associated UTIs is still to avoid unnecessary use of indwelling catheters and to reduce the time period during which the catheter is used by removing it as early as possible [27].

In addition to the higher risk of UTIs, there are other relevant complications of indwelling catheters such as encrustation, stone formation, blockage, urinary leakage, urethral stricture, genitourinary trauma, fistula formation and reduced bladder capacity and compliance (with continuous drainage) [28, 49, 54-61]. Due to the longer and sinuous urethra, male patients may be

more prone to traumatic complication of long-term indwelling transurethral catheter which may be avoided using a suprapubic catheter [62, 63].

Although still rare, development of bladder malignancies has been reported to be more prevalent in patients managed with long-term indwelling catheters [55, 64-68] possibly based on the catheter-associated chronic inflammatory and mechanical stress to the urothelium [44, 69].

Another aspect that seems to be negatively affected by the use of indwelling catheters, in particular transurethral catheters, is health-related QoL [70, 71]. ISC seems to provide less impairment or even improvements in QoL compared to other forms of catheterization [72]. However, individual barriers and preferences must be considered and patient-tailored instruction and education as well as periodical follow-up are important for long-term compliance [73-75]. More female than male patients may have difficulties in adequately introducing the catheter, especially when wheelchair-bound or with lower limb spasticity or poor visual or hand function [75, 76]. In such conditions, a catheterizable cutaneous continent urinary diversion composed of an abdominal continent stoma with or without combined enterocystoplasty can facilitate self-catheterization to maintain independent bladder management [77-79].

There are different types of catheters (hydrophilic vs non-coated catheters) and methods (clean vs sterile and single-use vs multi-use) and, due to an insufficient body of evidence, it is still a matter of debate as to which is preferred [80-83], although some newer data favour single-use hydrophilic catheters in regard to urinary tract infection and urethral trauma [84-86]. There are discrepant data on cost-effectiveness [87, 88] and very few data on QoL, two very important aspects that need better consideration in further randomized controlled trials.

NEUROMODULATION

Of course, not requiring a catheter to empty the bladder is the ideal, but also most challenging, aim in neurogenic urinary retention. Sacral neuromodulation has been demonstrated to be effective in the treatment of non-obstructive urinary retention, i.e. hypo- or acontractile detrusor, in male and female patients [89]. However, most previous studies reported results from populations with a mixed etiology of the hypo- or acontractile detrusor, i.e. neurogenic, myogenic, or even a combination of both [90-92]. The rationale for using sacral neuromodulation in patients with neurogenic urinary retention is to modulate disease- or lesion-specific pathologically-altered spinal reflexes and brain networks by stimulation of afferent pathways to restore at least some physiological function [93-95]. Similar to the supposed inhibitory effect on inappropriate activation of the ‘‘guarding reflex’’ (i.e., the spinally mediated reflex whereby the urethral sphincter contracts to prevent urinary incontinence on a sudden increase in intravesical pressure) in patients with Fowler’s syndrome [93], DSD, which is a frequent cause of incomplete micturition in patients with neurogenic urinary retention, may be diminished, whereas a normalized pattern of brainstem activity may contribute to improved detrusor contractility [11].

Although specific data on neurological patients treated with sacral neuromodulation for chronic urinary retention are promising, success rates seem to be slightly lower than for the treatment of urgency and urgency incontinence [93]. In general, RCTs in neurological patients are still lacking and it is unclear which population of neurological patients benefits most from sacral neuromodulation and which does not [93]. Nevertheless, sacral neuromodulation is a fairly minimally invasive procedure that is fully reversible and whose efficacy can be individually tested prior to complete implantation of the stimulator. The exact mechanism of action of sacral neuromodulation in this context is unknown but may be related to the transmission of ascending signals to the LUT control centers in the spinal

cord and supraspinal regions that modulate efferent output from those centers to the pelvic organs [96].

INTRAVESICAL ELECTRIC STIMULATION

In contrast, intravesical electric stimulation is thought to act by direct stimulation of the intramural motor system, resulting in local muscle contractions which promote vegetative afferent activation with consecutive central stimulation leading to improved bladder sensation and more coordinated, stronger detrusor contractions [97]. Despite initially promising results, mainly in pediatric populations with NLUTD due to meningomyelocele, [98-100] there is only one RCT available showing no beneficial effect on micturition [101]. In addition, the enormous time and effort required of therapist and patient in relation to the relatively limited treatment outcome has led to scarce application of this treatment currently. There is no recommendation in current EAU guidelines [22].

SUBVESICAL DE-OBSTRUCTION

In male patients, TURP prior to sacral neuromodulation may optimize outcome and even TURP alone has been shown to be sufficient in DU conditions for attaining voluntary micturition or at least reducing the risk of acute urinary retention in the short and medium term [89]. Of course, male patients with NLUTD may also have prostate-related bladder outlet obstruction and may benefit from surgical de-obstruction [102]. However, prior to performing such irreversible surgery in neurological patients, intact urethral sphincter function needs to be verified. If in doubt from the clinical examination, sphincteric needle EMG of the urethral or anal sphincter should be performed [103, 104]. This can be particularly relevant in the context of differentiation between NLUTD from Parkinson's disease vs multiple system atrophy (**Table 1-1**) [105, 106]. If still in doubt, or there is any sign of

sphincter deficiency, TURP should be omitted due to the elevated risk of postoperative incontinence [107-110]. In such cases, ISC may be the better alternative [111]. Using a temporary prostatic stent to simulate TURP is an option for avoiding unpleasant surprises and to evaluate which patient would benefit most from a TURP as permanent solution [112].

Although bladder outlet obstruction is difficult to objectify in urodynamics of patients with hypo- or acontractile detrusor, a urodynamic workup to evaluate current detrusor contractility is mandatory, especially prior to choosing surgical treatment options [113, 114]. However, while an acontractile detrusor is fairly precisely defined as lack of any contraction during urodynamic studies [115] hypocontractile detrusor is a less-precisely defined term due to the lack of and difficulty in defining urodynamic cut-off values for normal and abnormal, i.e. hypocontractile, reduced detrusor contraction strength [18, 116]. Nevertheless, to fully understand the dynamics behind the symptoms and to create precedents for future comparison, urodynamic investigations are indispensable, as they are the only tool to allow diagnosis and quantification of detrusor hypo- and acontractility [113, 114]. In addition, recently developed nomograms have been demonstrated to allow better quantification of the relationship between detrusor contractility and bladder outlet obstruction in male patients [117].

NEUROPROSTHESIS

A very sophisticated treatment for regaining detrusor control of voluntary micturition in NLUTD is the implantation of an electrical neuroprosthesis. Currently, the only established neuroprothesis for the LUT is the sacral anterior root stimulator, also known as the Fintech-Brindley neurostimulator, which produces direct electrical stimulation of the efferent fibers in the anterior root to induce detrusor contraction [118-121]. Such devices can significantly contribute to improvements in quality of life and continence [122, 123]. However, it should be reserved for a highly-selected patient population,

since it requires prior sacral deafferentation (posterior rhizotomy) with permanent loss of any potentially preserved sensation of the pelvis and lower limbs and sexual function. Thus, patients with complete, chronic (≥ 1 year after SCI) tetra- or paraplegia are most suitable for an anterior root stimulator as they would suffer the least functional loss from posterior rhizotomy due to their pre-existing neuronal lesion. Instead, they gain from abolished or at least significantly reduced autonomic dysreflexia and detrusor overactivity incontinence and independent bladder management even with impaired hand function [124]. This latter aspect applies particularly to male tetraplegic patients who cannot transfer to a toilet but can use a condom catheter to drain the voided urine or paraplegic patients who can independently transfer to a toilet seat for micturition using the anterior root stimulator.

SPREAD AND DIFFUSION OF BOTULINUM TOXIN A AFTER INTRADETRUSOR INJECTION

Since the first BoNT/A intradetrusor injections for the treatment of NDO in SCI patients at Balgrist University Hospital, Zürich, Switzerland in 1998, its use has become widespread as a minimally-invasive treatment option [125]. Last but not least, this is also related to the simple administrative route using a rigid and, later, also a flexible cystoscope [126]. Although BoNT/A has been used in the treatment of local striated muscle dystonias decades before application into the detrusor [127], the main difference and novelty with intradetrusor injections was the use in a smooth, autonomically innervated muscle. Fortunately, for NDO patients, BoNT/A intadetrusor injections yield a significantly longer duration of action (~ 8 months) than injections in striated muscle (~ 3 months) [128]. In addition to this, as yet unexplained, phenomenon, many aspects regarding the injection technique and mechanism of action also await elucidation.

So far, protocols of different injection locations, number of injections, volumes / concentrations per injection and injection depths have been used [129, 130]. Due to the lack of reliable comparative data on different injection techniques, there is not yet a single best technique. However, the phase III studies for approval of BoNT/A in the context of NDO describe a technique using 300 or 200 units of onabotulinumtoxinA in 30 injections of 1 mL each with an injection depth of 2 mm sparing the trigone [131, 132]. Since 300 units did not show any clinically relevant benefit over 200 units, the currently approved standard dosage for NDO treatment is 200 units, resulting in a concentration of 6.66 units per mL per injection [131, 132].

Nevertheless, different physicians may still use “their” technique and the number of injection sites in particular is a matter of discussion as fewer injection sites may be equally effective but less traumatic and faster [133-136]. Those latter aspects are of relevance as the BoNT/A injections have emerged as an out-patient or office-based procedure under local anesthesia [126, 134]. The reason for the fairly equivalent treatment effect observed despite using different numbers of injection sites may be the injection-related spread and naturally-occurring diffusion within the target tissue [134, 137, 138]. In this context, injection depth may be relevant as the degree of spread and diffusion may differ between different bladder wall layers, i.e. suburothelium vs detrusor. However, injection depth is less easily controlled than number of injection sites and it remains unclear how an injection depth of exactly 2 mm can be guaranteed and reproduced as suggested by the phase III NDO trials [131, 132]. Certainly, needle length is an option for controlling injection depth but individual bladder wall properties and filling-dependent thickness during the procedure can influence the final injection depth and injected tissue layer. In particular, patients with NDO in whom existing morphological alterations such as bladder wall trabeculation has occurred may no longer show equal bladder wall thickness. Visual feedback is unreliable and may be only useful during pure suburothelial injections

[139]. The latter have been demonstrated to be effective but not superior to conventional intradetrusor injections [139].

To visualize how BoNT/A spreads and diffuses within the bladder wall after intradetrusor injection, we added the contrast medium gadopentate to the BoNT/A solution (300 units onabotulinumtoxinA) and perfomed MR scans to measure the extent of contrast medium enhancement within the bladder wall (**Chapter 3**). Our findings indicate that the onabotulinumtoxinA / gadopentae solution spreads not only within the bladder wall but also beyond. We found small amounts of contrast medium (17.6 %) outside the bladder wall in the perivesical fatty tissue at the lateral aspects of the bladder dome [140]. This extravasation of contrast medium outside the bladder wall is most likely due to perforation of the injection needle through the bladder wall which in turn may be related to the relatively long needle tip (8mm) used in our study. Using a shorter needle, as nowadays recommended [130], may have prevented external leakage, but this remains to be clarified. Another related factor may be bladder volume during the procedure, which was not standardized but adapted to the individual procedure-related condition. BoNT/A leakage beyond the bladder wall may be responsible for adverse events in adjacent organs, e.g. the bowel. Reported adverse events on bowel function following BoNT/A intradetrusor injections seem to be rare [129, 141, 142]. On the other hand, specific bowel-related adverse events have never been systematically investigated.

Interestingly, the mean contrast-enhanced detrusor volume did not exceed one-third of the total detrusor volume. Nevertheless, 5 of 6 patients had a subjectively and urodynamically sufficient effect with a mean reduction of maximum storage detrusor pressure of 27 cmH2O and mean increase in maximum bladder capacity of 225 mL [140]. Hence, it does not seem necessary to cover the full or even 50% of detrusor to achieve relevant clinical improvements. However, there was a trend towards a positive correlation between the percentage of detrusor coverage and urodynamic improvements, i.e. the more detrusor volume enhanced with contrast as a

representation of the onabotulinumtoxinA distribution, the larger was the reduction in maximum detrusor pressure and increase in bladder capacity. The one patient who did not benefit from the BoNT/A treatment showed the least detrusor volume coverage with contrast medium (17.84 %) indicating limited distribution of BoNT/A as potential reason for the lack of clinical and urodynamic efficacy.

Regarding the number of injection sites, i.e. 10 vs. 30, there was a slightly larger percentage of detrusor coverage with contrast medium in the group treated with 30 injection sites (33.3 % vs 25.3 %) [140]. This small difference between both groups was also reflected in the urodynamic improvements with larger detrusor pressure decreases (-27 cmH2O vs -18.3 cmH2O) and bladder capacity increases (214 mL vs 153 mL) in the group treated with 30 injection sites. However, the total study group was too small to perform a reliable subgroup analysis and the inferior mean values in the group treated with 10 injections were mainly driven by the one patient who did not benefit from the BoNT/A treatment. Considering recent literature regarding the number of injection sites, there seems to be no relevant difference between the standard amount of injections and the reduced number of injection sites [133, 134, 136]. More evidence is needed to clarify this. In this regard, injection volume / dilution as well as location of injection are important factors that need to be considered as they can significantly affect spread / diffusion and consequently treatment outcome [143]. Multiple smaller injections are generally considered to provide a more even distribution and less spread beyond the target muscle compared to one or very few larger bolus injections [143, 144]. In terms of location, sparing the trigone has become the commonly used and currently approved technique [131, 132] although the initial fear of consecutive VUR could be disproven [145-148] and recent randomized trials even suggest a better treatment outcome in NDO and IDO using intradetrusor injections that include the trigone [147-149]. Considering that afferent nerve terminals are particularly dense within the trigone, there is also a neurophysiological rationale and explanation for

injecting the trigone and obtaining a superior treatment effect [150]. However, in addition to the still poorly-understood effect and mechanism of action of injecting specific areas of the bladder, i.e. trigone or bladder dome, there is also evidence for unexplained primary and secondary treatment failures and treatment discontinuation [142, 151-155], which require a more systematic analysis than currently available to better understand the causes. In this regard, toxin spread beyond the bladder but also backflow into the bladder from the injection site may play a role [138]. Increased backflow, which may, again, depend on injection volume, injection depth, and bladder wall tension in relation to the degree of bladder volume / filling during injection, can cause loss of toxin and, consequently, reduced efficacy.

Hence, prior to performing repeated injections, increasing dosage or switching to another formulation or BoNT type in case of treatment failure, it might be worthwhile to first clarify if application precision is adequate, i.e. the ability to bring the toxin to the right location in the right amount. This is poorly investigated but highly relevant in regard to optimizing risk / benefit and cost / effect ratios.

Different formulations of BoNT/A, i.e. onabotulinumtoxin vs abobotulinumtoxin, may display different spread and diffusion characteristics, i.e. more migration using abobotulinumtoxin [156, 157], which could at least partly explain the more frequent observation of generalized muscle weakness with abobotulinumtoxin [141, 158]. However, such findings need to be observed with some caution as the applied dose and dilution affect spread and diffusion of BoNT/A and controversy as to the real dose equivalence between different BoNT/A formulations complicates a reliable comparison resulting in conflicting study outcomes [159].

Despite that our study has limitations in regard to sample size and the fact that gadopentate cannot fully replicate the diffusion of BoNT/A as it is not attached to the BoNT/A molecule and may have different diffusion characteristics, it is the first study to provide a more detailed insight into the

behavior of the BoNT/A-solution after bladder wall injection. Further studies using radio- / isotopic- labeled BoNT/A molecules and appropriate imaging such as scintigraphy, PET-CT, or MR-spectroscopy can improve our understanding on the pathways and dynamics of BoNT/A diffusion within the human bladder wall after injection [160]. In addition, distant spread and migration beyond the bladder including retrograde axonal transport could be monitored and quantified. Such novel insights in accordance with standard clinical parameters would contribute to a better understanding of mechanism of action, treatment failures and distant / systemic adverse events. Moreover, visualization of diffusion characteristics in relation to area-specific injections, i.e. trigone or bladder dome only, could help in clarifying and understanding differences in location-specific diffusion and effects. It could be imagined, for example, that trigone-only BoNT/A injections mainly act by central desensitization via retrograde axonal transport to the dorsal root ganglion [160] and less by the classic mode acting on the neuromuscular junction resulting in a predominant sensory effect, i.e. reduction of urgency with a relatively lower effect on detrusor contractility and voiding function [161, 162].

In conclusion, understanding where toxin distributes after injections into the bladder wall and what it does at the sites it reaches is key to better application precision and control of safety and efficacy. Precise application will permit precise dosing and consequently limit wasting of toxin and the risk of adverse events such as elevated post void residual urine (PVRU) or urinary retention resulting in *de novo* ISC, which still counts among the most frequent adverse events after BoNT/A intadetrusor injections [163-165].

EFFECT OF LOW-DOSE BOTULINUM TOXIN A ON OVERACTIVE BLADDER SYMPTOMS IN PATIENTS WITH MULTIPLE SCLEROSIS

The issue of PVRU elevation and *de novo* ISC is most relevant in patients with OABS and, less frequently, in patients with NDO who more often already perform ISC due to the usually more severe impairment of bladder control and the commonly NDO associated pattern of DSD.

However, although NDO / DSD are relevant and frequently-encountered dysfunctional patterns in NLUTD, they do not represent the underlying urodynamic pattern of all LUTS in neurological patients. Moreover, there is quite a large population of neurological patients, in particular MS or PD patients, who may not require or are unable or unwilling to perform ISC [20, 166, 167]. Unwillingness or reservations in performing ISC may be due to several factors such as fear of infection and pain, previous negative experiences with attempts to perform ISC and the feeling of losing another body function adding to the already preexisting disease related disabilities and causing further separation from a normal and enjoyable life [168]. Despite the fact that most reservations and fears about ISC can be addressed and overcome by adequate education, instruction and follow-up [73, 168], it would still be most desirable to alleviate detrusor overactivity and associated symptoms such as urinary incontinence and urgency without causing or increasing urinary retention.

Prior to our study presented in **chapter 4** [169], NDO refractory to antimuscarinic drugs was usually treated with onabotulinumtoxinA using 300 units [129] and, since the recent phase III RCTs, with 200 units in the majority of cases [131, 132]. However, treatment of NDO using 300 units onabotulinumtoxinA most likely results in urinary retention or at least significantly elevated residual urine requiring ISC.

In contrast, treatment of OABS in patients without a clear neurological cause for their symptoms using only 100 units of onabotulinumtoxin A resulted in

significant symptomatic improvement without impairing voiding function [170]. Clearly, this is also at least partly related to the different etiology and characteristics of neurogenic vs non-neurogenic LUTD. Nevertheless, we were interested if a dose reduction of onabotulinumtoxinA to 100 units for the treatment of NDO in MS patients would also be effective without impairing voluntary micturition. Therefore, we applied the same protocol used in patients with idiopathic OABS [170] in a group of MS patients. In keeping with our hypothesis, we observed alleviation of NDO and associated symptoms. However, voiding function was also affected, showing decreased voided volume and Q_{max} and increased PVRU [169]. Hence, our treatment goal was not fully achieved, although only two patients needed ISC once to twice daily while one patient needed a suprapubic catheter.

Yet the decision as to who requires ISC and when, can, but not necessarily must, be related to a predefined PVRU threshold and thus may significantly affect the outcome of different studies [165]. This leads us to the still unsettled and ongoing debate on how much PVRU is too much and requires treatment. In our view, a strict and inflexible PVRU threshold does not appear to be reasonable and our preferred patient-tailored approach is also now becoming recognized in the more recent literature [171]. PVRU itself is not harmful considering that the bladder is specifically designed and lined to store urine. Moreover, there seems to be no clear or significant correlation between PVRU and symptomatic urinary tract infections in non-neurogenic LUTD [172-174]. However, this may be different in patients with NLUTD [175, 176] who usually present with more severe LUTD and in whom PVRU often causes symptoms that are bothersome and / or harmful and thus require treatment. Such symptoms include all kinds of storage symptoms but also recurrent urinary tract infections. PVRU can also be the reason for persistence of LUTS despite treatment due to loss of functional bladder capacity.

Hence, it may be more reasonable to decide on the necessity and frequency of ISC based on the symptoms rather than a fixed threshold which is anyway not yet firmly established [174-176].

In conclusion, dose reduction of onabotulinumtoxinA to 100 units for the treatment of NDO does not completely prevent impairment in voiding, probably due to the pre-existing and persisting pattern of NLUTD, i.e. persistence of DSD in our MS patient group. Nevertheless, the positive treatment effect was comparable to studies using 200 units, whereas the increase in PVRU was less pronounced [169], contributing to a lower rate of ISC. Unfortunately there is not yet a prognostic clinical or urodynamic tool that would allow for a reliable prediction of the BoNT/A dose required for each patient [177]. However, to provide a more tailored treatment for the individual patient, it may be worthwhile to follow a more stepwise treatment approach starting with lower doses of BoNT/A and to increase the dose only if urodynamically or symptomatically indicated. Larger RCTs considering cost-effectiveness and QoL of low-dose BoNT/A applications in NDO treatment are highly warranted. Such trials should also allow subgroup analysis regarding mobility and dexterity since most previous trials presented mixed neurological etiologies of NDO such as MS, SCI, and PD although each of them has a different disease course with different concomitant disabilities and support requirements.

In favor of a stepwise approach aiming to apply only as much BoNT/A as actually required, it may be necessary to also reconsider the fact that BoNT/A is the most powerful available neurotoxin and should be used with appropriate caution, especially in view of the increasing number of medical indications and consequently higher chance of multiple or parallel treatments [178]. This is also of relevance in view of the limited control of injection precision and spread beyond the bladder (**chapter 3**, [140]).

SYSTEMIC EFFECTS OF BOTULINUM TOXIN A AFTER URINARY BLADDER INJECTIONS

Considering our findings from **chapter 3**, spread and / or diffusion of BoNT/A can reach beyond the bladder wall and may cause systemic side effects [140, 144, 179]. Distant effects related to diffusion, leakage into the circulation and retrograde axonal transport has been previously described for BoNT/A applied in striated muscles [180-183]. Reviewing the literature on BoNT/A intradetrusor injections, mainly procedure- and detrusor-related adverse events have been reported with almost no systemic side effects [141, 165] except for some scarce reports on generalized muscle weakness in a few patients [184, 185]. However, “not reported“ does not necessarily mean “not present”, especially when distant effects have not yet been assessed systematically. There is no rationale that such distant effects should occur after injections in striated muscle only but not in smooth muscle. Indeed, a very recent investigation on retrograde transport of radiolabelled BoNT/A after bladder injections in rats demonstrated traces of the BoNT/A in the intestine and stomatch in addition to within the bladder and L6-S1 dorsal root ganglion [160]. Furthermore, the reports of patients with generalized muscle weakness after BoNT/A intradetrusor injections [184, 185] resemble those patients with contralateral weakness and fatigue after high-dose BoNT/A poststroke spasticity management [186, 187].

Based on its primary mechanism of action, BoNT/A frequently also affects, in addition to the neuromuscular junction of striated muscles, the autonomic nervous system [188-190]. An important neuromuscular structure under autonomic control is the heart and previous investigations have demonstrated that BoNT/A injections can cause distant effects on cardiac autonomic function [190-195]. Such autonomic and cardiovascular effects may be subtle and remain subclinical but reliable data, especially in the long-term, are lacking.

Therefore, we assessed in the study described in **chapter 5,** for the first time, potential distant effects of onabotulinumtoxinA intradetrusor injections on the autonomic nervous system using heart rate variability (HRV) [196]. HRV analysis is an inexpensive and easily applicable tool to assess even subtle alterations of autonomic control on cardiac function including vagal and sympathetic components [188, 197, 198]. HRV is based on ECG recording that can be easily performed prior to and during follow-up after BoNT/A treatment. In this first study including a control group and 4 measurement timepoints, i.e. 2 weeks and 10 minutes prior and 30 minutes and 6 weeks after onabotulinumtoxinA intradetrusor injections, we could not detect any significant HRV changes [196]. However, we investigated resting conditions only and cannot expand our conclusion to situations of physical stress. Furthermore, all patients were treatment-naïve without parallel treatment for other indications. Hence, BoNT/A distant effects on autonomic cardiovascular function need to be further elucidated also in conditions of physical stress and under repeated and / or parallel treatments. The latter is of particular relevance since dose-dependent effects on autonomic cardiac function has been reported [192, 194].

There are currently three known routes by which BoNT/A can reach distant sites: 1) diffusion or spread into neighboring tissue, 2) retrograde axonal transport, and 3) hematogenic distribution by leakage into the circulation [144]. In addition, indirect reorganizational effects on the CNS related to its effect on the neuromuscular synapse and muscle spindles have been described [144, 199]. The most realistic route by which BoNT/A reaches the heart following bladder injections is hematogenic spread [144]. Retrograde axonal transport could be another possibility but, although transsynaptic transmission of BoNT/A has been demonstrated in animal models [200, 201], the potential route from the bladder to the heart in humans remains questionable and may be too long to reach the heart prior to inactivation of the toxin [199]. BoNT/A binds with high affinity to peripheral cholinergic nerve terminals and is thus quite rapidly removed from the circulation. At the

heart, BoNT/A can affect a) parasympathetic control on the sinoatrial and atrioventricular node by acting on vagal nerve terminals and b) sympathetic control by acting on preganglionic nerve terminal in the sympathetic chain [195, 202, 203].

In addition to effects on the heart after BoNT injections for striated muscle dystonia, there are also reports of systemic side effects on other autonomously-innervated organs including the bladder, e.g. urinary retention, [183, 194]. Such autonomic side effects seem to be more pronounced with BoNT/B than with BoNT/A [194, 204]. Although BoNT/B has been proposed as alternative treatment to BoNT/A-resistant DO [205, 206], the more pronounced autonomic side effects and significantly shorter effect duration render its use the exception [207, 208]. Moreover, BoNT/B seems to be highly antigenic, particularly in patients who are immunoresistant to BoNT/A, resulting in cross-reactivity which may explain the rapidly progressive unresponsiveness after a few treatments [183].

Cardiovascular monitoring in the context of NLUTD is not only useful for assessing potential adverse events of different treatments in neuro-urology or to identify patients at risk for certain treatments affecting the CV system but also to duly detect acute complications such as autonomic dysreflexia.

Monitoring of treatment-related adverse cardiovascular effects not only concern BoNT/A but also antimuscarinic drugs [209-212] and beta-3-receptor agonists which are occasionally applied in NDO treatment in higher doses than approved [213-215] or in combination with each other [216, 217]. Increased dosing or combined therapy of antimuscarinics and beta-3-receptor agonists may increase cardiovascular adverse events.

Although AD should occur less frequently and less intensively after NDO treatment using BoNT/A due to the reduction of NDO that usually triggers AD [218, 219], severe AD may occur during the cystoscopic injection procedure [158, 220]. Hence, to adequately assess onset and severity of autonomic dysreflexia or other cardiovascular events, e.g. micturition

syncope, during urological procedures such as urodynamics or cystoscopy, continuous recording of blood pressure and heart rate, at the least, is mandatory, especially in all patients with evident or suspected suprasacral spinal cord lesions [220-222]. Other measures of autonomic function such as HRV that can be derived even retrospectively from the ECG, can supplement cardiovascular monitoring as needed. Since essential parts of the LUT, e.g. the detrusor and bladder neck, are exclusively autonomously innervated, further insights into autonomic function during urodynamics may help to add previously missing pieces to the puzzle and to better understand certain symptoms and dysfunction [223-228].

INTRAPROSTATIC APPLICATION OF BOTULINUM TOXIN A FOR TREATMENT OF MALE LOWER URINARY TRACT SYMPTOMS

In addition to the distant and central effects of BoNT/A mentioned above, increasing evidence suggests that BoNT/A causes other additional effects within the LUT than just smooth muscle paralysis. Of special interest are the properties and effects of BoNT/A on LUTS related to prostatic enlargement and / or obstruction. Currently only a few pharmacological treatment options are available, i.e. plant extracts, alpha-blockers, and 5-alpha-reductase inhibitors that have proven but somewhat limited efficacy [229-231]. This also bears relevance to the neurological male patient, as it can be challenging to differentiate the proportions of prostatic and neurogenic involvement in the LUTS as presented [116, 232]. TURP in case of failure of conservative treatment may still be an option in selected neurological patients [102]. However, if neurogenic sphincter deficiency is present and hidden behind an anatomical cause and / or NDO is not adequately treated, post-TURP urinary incontinence may occur [107-110].

There are two prostatic components proposed to be involved in LUT dynamics and consequently also in the development of LUTS; a static

component related to prostate growth and a dynamic component related to the contractile tone of the smooth muscle cells in the prostate and prostatic urethra. Since the static component is under parasympathetic and sympathetic and the dynamic component under sympathetic influence [233], both components may be susceptible to BoNT/A intraprostatic injections due to its chemo-denervative properties that can modulate the autonomic prostatic innervation [234, 235].

In **Chapter 6** we reviewed the current evidence on the mechanism of action of BoNT/A on the static and dynamic prostatic component and its application and efficacy in clinical practice [236].

At the level of animal research, it has been demonstrated that the effect of BoNT/A on the static component is related to prostatic apoptosis [237-242]. This would well explain the observed prostatic atrophy by means of reduced prostate size and weight in rats and dogs [237-241, 243, 244]. The mechanism by which BoNT/A may induce prostatic apoptosis is not yet fully understood but it is proposed that BoNT/A activates apoptotic pathways in the prostate through sympathetic outflow impairment [242]. This is mainly based on the observation that phenylephrine administration after BoNT/A injection into the gland, which is expected to replace the normal neuronal sympathetic drive impaired by the neurotoxin, prevents the apoptotic reaction [242].

However, most animal studies were performed on normal rats, not using specific BPH-models, and there are conflicting results relating to the occurrence of prostatic atrophy in humans [245-248].

Regarding the effect of BoNT/A on the dynamic prostatic component, it has been demonstrated that BoNT/A downregulates the expression of alpha-1A-adrenoreceptors in the rat prostate [237]. This represents a strong argument to use BoNT/A intraprostatic injections for the treatment of enlarged prostate-related LUTS as alpha-1A-adrenoreceptor expression has been

found to be significantly increased in BPH compared to normal prostate tissue [249].

In line with these considerations, Lin et al. demonstrated reduced in-vivo urethral pressure responses to i.v. norepinephrine and reduced contractility of in-vitro prostate strips in response to KCL, epinephrine and electrostimulation after intraprostatic injection of 200 units onabotulinumtoxinA [243]. The underlying mechanism is suggested to be two-fold: a) impaired release of norepinephrine from adrenergic nerves and b) impaired intracellular contractile machinery in smooth muscle cells due to increased expression of outward current potassium channels as has been demonstrated to occur after SNAP-25 cleavage in oesophageal smooth muscle cells [250].

In clinical practice, BoNT/A can be injected into the prostate via three routes, transperineal, transrectal, and transurethral. Transperineal and transrectal ultrasound guided routes have been most frequently used [236, 251] of which the transperineal approach may be less prone to infections [235]. Intraprostatic injections are performed using a 20-22 G, 15-20 cm long needle and 2-4 injections per side with typically 200 units diluted in 4 mL [235]. Other dosages ranging from 100-300 units and dilutions have been used and the few existing dose-ranging studies do not provide reasonable evidence in favor of one dosage over another [235]. The mean onset of action seems to be around 3.5 weeks (range 1-6 weeks) and the mean duration 12 months (range 3-30 months) after injection but further, more specific, data on the onset and duration are required to further verify these time specifications in relation to the dosage [236]. Adverse events include gross hematuria, urinary retention and acute prostatitis which seem to be more procedure- than BoNT/A-related, as placebo injections showed no difference in adverse events compared to BoNT/A [248]. However, other important potential adverse events such as the effect of BoNT/A intraprostatic injections on sexual function have not been evaluated systematically. There is only one non-RCT reporting no effect on sexual

function following BoNT/A intraprostatic injections [252]. Despite promising results in initial trials, recent RCTs and meta-analyses do not provide evidence for significant differences with intraprostatic injections with BoNT/A compared to placebo [235, 248]. Nevertheless, at the current stage of understanding, the processes within the prostate after BoNT/A injections and the influence of the prostate and its functional and structural alterations on LUTS are still obscure, therefore it is too early to omit BoNT/A intraprostatic injections as a treatment option. It may serve as therapy in a selected patient population such as poor surgical candidates [253]. More basic knowledge on the physiological and pathophysiological processes of the prostate on LUT function and LUTS is required to address clear hypotheses and design adequate clinical trials.

TREATMENT OF STRESS URINARY INCONTINENCE ASSOCIATED WITH NEUROGENIC SPHINCTER DEFICIENCY

Despite efficient treatment for DO, urinary incontinence may persist due to sphincter deficiency. The motor neurons of the external urethral sphincter are located in the ventral part of the anterior sacral horn between S1 and S3, an area also called Onuf's nucleus [254]. These neurons send their axons via the pudendal nerve to the EUS. Hence, any damage at or below the sacral level or of the pudendal nerve can result in sphincter deficiency. In addition to patients with iatrogenic nerve damage due to pelvic surgery, patients with spina bifida constitute a population that is often affected by neurogenic sphincter deficiency [255].

Pelvic floor muscle training may be a conservative treatment option, but only in patients with at least some preserved voluntary EUS control, which is, however, typically lost or severely impaired in nSUI. Since there is no effective medical therapy for nSUI, treatment is mainly limited to surgical

solutions. However, the level of evidence of surgical treatments for nSUI is generally low due to the lack of RCTs [256].

Of the available surgical treatment options for nSUI (see **chapter 1** and **2**), urethral suspension using autologous fascia or synthetic slings and the artificial urinary sphincter have been most commonly and successfully used [256]. The use of autologous fascia slings requires abdominal surgery and is therefore frequently used in combination with bladder augmentation for treatment of concomitant NDO. Synthetic slings can be applied less invasively in a single procedure but may be prone to higher postoperative morbidity and complication rates [257-259]. In addition, explantation of synthetic slings in case of complications, i.e. infection, pain, and erosion, can be challenging. Therefore, in patients requiring a tight sling to virtually close the urethra when supplied with a catheterizable diversion, synthetic materials should not be used.

The implantation of an artificial urinary sphincter system is a very effective therapy for nSUI, but, due to the more sophisticated approach, is associated with a higher rate of complications and reoperations [256]. Neurogenic patients in particular seem to have a higher risk of non-mechanical device failure, e.g. device infection and cuff erosion [260]. This may be related to the fact that many patients with NLUTD perform ISC which causes higher mechanical strain on the urethra and consequently any peri-urethral implant with the risk of erosion and perforation. Correspondingly, cuffs or slings placed at the bulbar urethra resulted in a higher rate of complication when compared to implantation at the bladder neck [256]. Despite introduction of a simplified AUS with the possibility of postoperative adjustment of cuff pressure that seems to cause less complications and revisions [261], we were interested in investigating an adjustable device that is simple to implant but also simple to explant in case of complications.

Our results show that using the ACT® and ProACT® devices for treatment of nSUI in female and male neurological patients, respectively, incontinence

episodes were significantly decreased from 6.1 ±2.4 to 2.8 ±3.1 at 48 months follow-up (**chapter 7**, [262]). However, only a fairly small proportion (21%) of patients gained full continence. This may be at least partly related to the heterogeneous study population including patients with complete and incomplete SCI, MS, surgical trauma to the pelvis, and meningomyelocele, resulting in different degrees of incontinence. Nevertheless, the number of fully continent patients remained stable throughout 4 years follow-up and more than half of patients had a ≥ 50% improvement in their incontinence.

Although these results are inferior compared to those of AUS and slings, the ACT® / ProACT® devices combine certain advantages [262]: 1) Application is safe with few intraoperative and immediate postoperative complications even in neurogenic cases with previous LUT surgery. 2) The short, minimally-invasive procedure allows for fast healing and a short hospital stay or even outpatient treatment. 3) Outpatient adjustment of balloon volume according to the patient's needs is quick and uncomplicated. 4) In contrast to slings / tapes or bulking agents, balloons can be explanted as an outpatient surgical procedure using local anesthesia in case of adverse events with the option of reimplantation at 3 months. 5) Balloon implantation or explantation does not preclude the implantation of other continence devices, ie an AUS, at a later stage.

Although there are limited data on the use of ACT® / ProACT®, particularly after failed previous incontinence surgery [263, 264], there are currently no data available on the efficacy and safety of multiple subsequent ACT® / ProACT® implantations in the same patient group. Animal studies in dogs have demonstrated that a fibrous capsule of variable thickness and well-organized layers of mature collagen develops around the device components which can be considered a typical and predictable foreign body reaction towards the device [265, 266]. Such fibrotic capsules may persist after explantation and, on the one hand, contribute to prolonged efficacy despite explantation but may also interfere with subsequent implantations at the same location and adjustment of balloon volume.

In conclusion, the ACT® / ProACT® device seems to be a valuable treatment option for nSUI in patients unwilling, unable or unsuitable for more invasive procedures or more complex implants, albeit for rather mild to moderate incontinence. The aforementioned low level of evidence for treatments of nSUI certainly applies also to this retrospective cohort study but it remains the only study on the use of ACT® / ProACT® in nSUI. Thus, first RCTs on this relevant topic would be highly appreciated.

Independent of the surgical technique or device used or determined to be the best, NDO has to be excluded or appropriately treated prior to and again after surgery or implantation. Not following this principle may put the UUT in jeopardy, as with persistent or *de novo* DO combined with improved subvesical continence mechanisms, intravesical pressures will raise even higher during DO.

CONCLUSIONS AND FUTURE PERSPECTIVES

There is a range of conservative and invasive treatment options available for the management of urine storage dysfunction in neurological patients, of which ISC, antimuscarinic drugs, intradetrusor BoNT/A injections, augmentation cystoplasty, urinary diversion, and AUS still represent the therapeutic cornerstones. Although this has not changed much recently, BoNT/A intradetrusor injections as a minimally-invasive therapy have contributed to reduce the large gap between conservative pharmacological and invasive surgical treatments.

BoNT/A intradetrusor injections are readily applicable as an outpatient procedure and have a favorable efficacy / safety profile without evidence of significant distant or systemic effects, for instance on resting state cardiac function. However, elevated PVRV or even urinary retention is an issue in neurological patients. Adjustments of dosing, i.e. starting with a lower dose, can alleviate PVRV and allows for some adaptation of therapy to individual patient requirements according to symptom severity and urodynamic outcomes. Nevertheless, the precision of application using current techniques is limited and spread of BoNT/A beyond or outside the target tissue may reduce efficacy and affect adjacent organs such as the rectum. Moreover, the potential auxiliary mechanisms of BoNT/A on the afferent neuronal pathways need further elucidation. Other therapeutic indications of BoNT/A such as intraprostatic injections for LUTS related to BPH have a scientific rationale but still lack convincing clinical evidence and thus may currently serve as an off-label alternative for poor surgical candidates only.

In contrast to NDO, effective treatment of urinary incontinence due to neurogenic sphincter deficiency much more frequently requires reconstructive or prosthetic surgery. The ACT® / ProACT® device may be a minimally-invasive option for mild to moderate incontinence due to neurogenic sphincter deficiency with the possibility of post-operative adjustment in an outpatient setting. In case of complications, the device is

easily explanted under local anesthesia without limiting the potential for (re)implantation of the same or other continence devices at a later stage.

Although modern neuro-urological work- and follow-up have contributed to significant improvements in life-expectancy and QoL for many neurological patients affected by NLUTD, the management of urine storage dysfunction in the neurological patient is still a challenge and often requires a combination of treatments or multidisciplinary treatment approaches. This is, on the one hand, due to frequently-occurring co-disabilities caused by the underlying neurological lesion / disease but, on the other, also due to the limitations of the currently available treatments. It is, for example, still a major difficulty to effectively reduce or abolish DO in the storage phase without compromising detrusor contractility in the voiding phase and to effectively treat DSD or detrusor underactivity without using catheters.

This may be in turn related to (1) the complex multilevel neurogenic control of the LUT that is still not fully understood in detail and (2) our still incomplete comprehension of the mechanisms of action, best patient selection, and reasons for treatment failures in available therapies such as neuromodulative treatments and BoNT/A intradetrusor injections. In addition, there are major difficulties in transferring findings and conclusions from the numerous available in-vitro and animal models to humans. This is mainly due to many models only focusing on just one specific mechanism, disregarding other mechanisms compensating for a specific system failure. This advocates for more models following an integrative, system-based physiological approach. Then again, there is a distinct lack of adequate and reliable assessment tools and biomarkers to objectively investigate functional and structural correlates of LUTD / LUTS and their treatment in more detail directly in humans.

To better address in the future the challenges in the management of urine storage dysfunction in neurological patients, further research should not only focus on discovery of new treatment targets but also strive to amplify our

knowledge and understanding of currently existing therapies. This will help to more effectively use therapies that are already available to our patients.

Our own results and findings from animal studies [140, 160] have shown that BoNT/A intradetrusor injections involve spread and migration of the toxin beyond the LUT. In addition, there are, on the one hand, known yet unexplained primary and secondary treatment failures of BoNT/A intradetrusor injections and, on the other, auxiliary effects of BoNT/A that are not yet fully understood. Therefore, the following research questions should be addressed next: Are we always able to apply the toxin to the right location, i.e. detrusor muscle, in the right amount / concentration? How relevant is the exact BoNT/A application for a favorable treatment outcome? To which locations and through which pathways does the toxin migrate after intradetrusor injections?

To address these questions and to understand to where the toxin exactly migrates and where potential auxiliary effects may be exerted would require tracing of the toxin, which is challenging *in vivo*. Methods such as radio- / isotopic-labeling of the toxin in combination with specific imaging techniques such as scintigraphy, PET-CT, or MR-spectroscopy may be applicable but require further exploration and evaluation. Nevertheless, the ability to visualize and monitor the distribution of BoNT/A within the target tissue, i.e. detrusor muscle, and to correlate how relevant this is in relation to the treatment outcome will be of special importance for patients who did not show the expected response to their BoNT/A treatment and may provide relevant information on how to prevent such treatment failures including reconsideration of application technique and precision. BoNT/A tracing will help to explore methods of more targeted application that may reduce the number of treatment failures and prevent more invasive treatments. Future alternatives to injections, e.g. simple instillation using a carrier [267], can be assessed in regard to the real diffusion behavior, i.e. if BoNT/A is diffusing into the muscle or even beyond or mainly remains at the mucosal level.

Both BoNT/A intradetrusor injections and antimuscarinic drugs are thought to act in a manner supplementary to their conventional mechanism of action on LUT afferents. This is of relevance, as alterations of LUT afferent function seem to play an important role in the pathophysiology of LUTD / LUTS. However, to quantify and understand alterations of function and integrity of LUT afferents related to neurological disease or lesion and treatments, it is mandatory to provide a reliable and objective assessment of LUT afferents in humans. LUT sensory evoked potentials, as recently investigated by our group [268, 269], may be such a tool to objectively assess LUT afferent function in more detail. Methodological considerations are currently being studied in larger groups of healthy subjects and first investigations in neurological patients will follow to evaluate diagnostic potential (NCT02272309).

Such a tool may finally also contribute to the understanding of the effect of neuromodulation on LUT afferents. In conjunction with functional and structural neuroimaging, sensory evoked potentials may provide an essential piece in the puzzle of how to improve our knowledge on the mechanism of action of neuromodulation on spinal and supraspinal neuronal LUT control.

Considering that the underlying cause of LUTD is a neurological lesion or disease that in most cases cannot be completely cured or reversed, treatments using implantable neuro-prosthesis or non-implantable neuromodulation or -stimulation to control or modulate neurogenic tissue to bridge or compensate for neurological defects appear to be most promising and worthwhile to invest more research efforts in the future [95, 270]. Currently, neuromodulative therapies appear to be the only option that would allow alleviation of NDO and DSD without impairing a preserved voluntary voiding contraction. However, except for exploring and using sacral neuromodulation also for neurogenic LUTD, not much has changed or advanced in regard to this technique during the last two decades. The same applies to the only available LUT neuroprosthesis, the Brindley Finetech anterior root stimulator. In this regard, a broader and more profound

collaboration between neuroscientists, engineers and urologists would be highly desirable and would inspire and promote development on this seminal sector.

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CHAPTER 9

- SUMMARY
- NEDERLANDSE SAMENVATTING
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SUMMARY

Neurogenic lower urinary tract (LUT) dysfunction is a frequent sequela to neurological disease or trauma with devastating consequences to patients' general health and quality of life (QoL). Since the causative neurological condition usually cannot be cured or reversed and even with a less progressive or putative "stable" neurological disease / lesion, the LUT dysfunction (LUTD) may worsen, patients require life-long, specialized neuro-urological care and follow-up.

This thesis describes important aspects of urine storage dysfunction in neurological patients and their current treatment options with a special focus on therapies using botulinum neurotoxin A (BoNT/A). The studies presented in this thesis contribute novel insights into the management of LUT dysfunction (LUTD) / LUT symptoms (LUTS) in neurological patients and provide starting points for future research.

Chapter 1 provides a comprehensive overview of the neurophysiological background of LUT function and the LUT related pathophysiological changes occurring as a result of neurological disease or trauma. Epidemiological data are presented and both urodynamic and clinical findings are matched with the related symptoms and typical neurological lesions. Finally, currently available treatment options are summarized with a focus on restoration of bladder and urethral urine storage function.

Chapter 2 presents a literature review on the management of urinary incontinence in the male neurological patient, highlighting the most recent and relevant publications related to this topic. The cornerstones of urine storage dysfunction management in neurological patients, such as intermittent self-catheterization (ISC), antimuscarinic drugs, intradetrusor BoNT/A injections, augmentation cystoplasty, urinary diversion, and artificial urinary sphincter, are largely unchanged. However, with the exception of onabotulinumtoxinA intradetrusor injections, the level of evidence for many therapy options is quite low. In addition, current findings are mainly derived

from multiple sclerosis and spinal cord injury patients without gender-specific outcomes, limiting generalization of the results.

Chapter 3 describes a first-of-its-kind study in humans on the distribution of the onabotulinumtoxinA solution mixed with gadopentate using MR imaging after intradetrusor injections. The onabotulinumtoxinA / gadopentate solution showed spreading within the bladder wall, but also beyond, as 17.6 % of contrast medium was found outside the bladder wall in the perivesical fatty tissue. Although the mean contrast enhanced detrusor volume did not exceed one-third of the total detrusor volume, 83% of patients demonstrated sufficient efficacy of the treatment. However, a larger area of detrusor coverage appears to result in a larger reduction of maximum detrusor pressure and a greater increase in bladder capacity.

Chapter 4 reports, for the first time, a study using low dose, i.e. 100 units, onabotulinumtoxinA intradetrusor injections to treat neurogenic detrusor overactivity (NDO) in patients with multiple sclerosis. The aim was the reduction of overactive bladder symptoms (OABS) to a satisfactory level without causing impaired voiding, which would require ISC. Our results showed that treatment with 100 units significantly reduced all symptoms. However, post void residual volume (PVRV) initially increased, requiring 16% of patients to use ISC twice daily and one patient to have a suprapubic catheter. The main difficulty in interpreting these results is the lack of PVRV cut-off values indicating when to start with ISC. It is, however, questionable if such a cut-off value is really needed and clinically useful, as the decision as to when to use ISC should be made based on symptoms. This would allow more patient- and QoL-oriented management.

Chapter 5 describes a study investigating systemic, distant effects of onabotulinumtoxinA on cardiac function after intradetrusor injections for the treatment of NDO. Resting electrocardiogram was recorded for 15 minutes from patients and age-matched healthy controls during 4 consecutive visits. Patients received 300 unit onabotulinumtoxinA intradetrusor injections

between visits 2 and 3. The recorded electrocardiograms were evaluated, including the time and frequency domain parameters of heart rate variability (HRV) analysis. Despite a short-term increase in total power (TP) between visits 2 and 3 in the patient group, no further alterations of resting state cardiac function were observed. The observed changes in TP are a rather positive sign, indicating elevated HRV, potentially in response to procedure-related discomfort, and were not different compared to the healthy group or to normative values from the literature.

Chapter 6 provides a review on the current pre-clinical and clinical evidence for intraprostatic BoNT/A injections to treat LUTS related to benign prostatic enlargement (BPE). There is some evidence that intraprostatic BoNT/A injections affect both the static and dynamic component of BPE-related LUTS by reducing prostate volume and the number of alpha-adrenoceptors. The reduction of prostate volume seems to be mainly related to apoptosis and glandular atrophy. Despite the rather simple and apparently safe application technique and initially promising clinical results, the current level of evidence is still surprisingly low. Hence, randomized controlled trials are required to provide more reliable recommendations on BoNT/A treatment for this indication.

Chapter 7 presents a first-of-its-kind investigation into the use of an adjustable continence device (ACT®, ProACT®) to treat stress urinary incontinence due to neurogenic sphincter insufficiency. The majority of patients (92%) used ISC as the main mode of bladder emptying. The ACT® / ProACT® device was implanted under local anesthesia in most cases (84%). Complete continence was achieved in 21% of patients, at least 50% improvement or more was achieved in 54% of patients, and 6% of patients had less than 50% improvement after 48 months follow-up. Permanent device explantation was performed in 40% of patients after 48 months follow-up due to insufficient efficacy and / or adverse events such as erosion / migration, infection, pain, and device failure. Explantation is safe and relatively easy and can be performed in an outpatient setting in most cases.

Although the efficacy seems to be lower compared to previous studies, most likely due to the severity of continence deficiency in our neurogenic population, the safety profile is good with minor, mainly self-limiting intraoperative and postoperative complications. The ACT® / ProACT® device seems to be a reasonable option for treating neurogenic stress urinary incontinence in patients who have minor symptoms and / or are not willing, not suitable or not yet ready for more invasive surgery.

Chapter 8 comprises the general discussion in which all aforementioned studies of this thesis are critically discussed in the context of the current literature. Generally, we have an improved understanding on the pathophysiological processes that alter LUT function in consequence to neurological disease and trauma. However, we still have an incomplete understanding of mechanisms of action, best patient selection, and reasons for treatment failure of currently-applied therapies such as sacral neuromodulation and BoNT/A intradetrusor injections. BoNT/A revolutionized the treatment of NDO and helped to reduce the gap between conservative drug treatment and invasive surgery. Despite its success and widespread use, the full potential and range of BoNT/A application in the LUT has not yet been fully exploited.

Future research should thus not only focus on the discovery of new treatment targets, which may take decades to become a genuine treatment option, but also on the exploration of the full potential and possibilities of treatment options that are currently available. Enabling real-time visualisation of BoNT/A distribution after intradetrusor injections in vivo would allow a better comprehension of the distribution and locations of action of the toxin within the human LUT and adjacent structures. This may also help to clarify reasons for treatment failures and strategies to prevent them. Objective and quantitative assessment of human LUT afferents, e.g. using LUT sensory evoked potentials, would allow more detailed evaluations of the changes in the afferent system in LUTD / LUTS conditions. This may create a better understanding of the mechanism of action of therapies

targeting the LUT afferents such as antimuscarinics, BoNT/A, and neuromodulative therapies. The latter and the more sophisticated neuroprostheses have great potential in bridging or compensating for neurological deficits and restoring LUT function. However, more efforts are necessary to make meaningful advances and interdisciplinary collaboration between neuroscientists, engineers, neurologists, rehabilitation physicians, and urologists is crucial to this endeavour.

NEDERLANDSE SAMENVATTING

Neurogene disfunctie van de lage urinewegen (LUT) is een vaak voorkomend gevolg van neurologische ziekten en trauma en heeft zeer ingrijpende consequenties voor de algemene gezondheid van patiënten en hun kwaliteit van leven. Gegeven het feit dat de neurologische conditie veelal niet kan worden genezen en de disfunctie van de lage urinewegen zelfs bij minder progressieve of vermeend „stabiele“ neurologische ziekte gewoonlijk progressief is, is levenslange gespecialiseerde neuro-urologische zorg en follow-up noodzakelijk.

Dit proefschrift beschrijft belangrijke aspecten van een verstoorde urine opslag bij neurologische patiënten en de nu voor handen zijnde behandelopties hiervoor, met speciale aandacht voor Botuline neurotoxine A (BoNT/A) injecties. De studies die in dit proefschrift worden gepresenteerd dragen bij aan nieuwe inzichten in het omgaan met de verstoring van de functie van de lage urinewegen en de gerelateerde symptomen (LUTS) in neurologische patiënten. Daarnaast wordt aangegeven welke nieuwe onderzoeksinitiatieven ontwikkeld kunnen worden voor deze problematiek.

Hoofdstuk 1 schetst een beeld van de neurofysiologische controle van de lage urinewegen en de veranderingen die kunnen optreden als gevolg van neurologische ziekte of trauma van het centrale of perifere zenuwstelsel. Epidemiologische data worden gepresenteerd in combinatie met urodynamische en klinische bevindingen in de context van de specifieke neurologische laesies. Tot slot worden momenteel beschikbare behandelopties samengevat met de focus op herstel van de opslagfunctie van de lage urinewegen.

Hoofdstuk 2 geeft een overzicht van de beschikbare literatuur over de aanpak van urine-incontinentie bij de mannelijke neurologische patiënt. De meest recente publicaties worden besproken betreffende intermittente zelfkatheterisatie (ISC), antimuscarinerge medicatie, BONT/A injecties in de blaasspier (detrusor), augmentatie cystoplastiek, urineweg afleiding met

darm en de kunstmatige sluitspierprothese. Het bewijs van de effectiviteit van bovenstaande therapieën is over het algemeen laag behalve voor BONT/A detrusor injecties. De bevindingen zijn overigens wel hoofdzakelijk gebaseerd op studies met patiënten met multiple sclerose (MS) of een dwarslaesie zonder verschil te maken tussen mannen en vrouwen. Dit beperkt de toepasbaarheid in de algemene populatie.

Hoofdstuk 3 beschrijft een eerste studie bij mensen waarin met behulp van een MRI gekeken werd naar de verspreiding van een oplossing van onabotulinumtoxine A gemengd met het MRI contrastmiddel gadopentate na injecties in de detrusor. Van deze oplossing bleek 17,6 % niet in de blaas terecht te komen maar in het omgevende vetweefsel. Hoewel de patiënten in minder dan een derde van de blaas de geïnjecteerde botuline toxine met MRI contrast lieten zien, werd toch in 83% van de patiënten een positief effect van de behandeling gevonden. Wel bleek dat een groter behandeloppervlak geassocieerd was met een grotere blaascapaciteit postoperatief.

Hoofdstuk 4 presenteert de resultaten van een studie waarbij voor de eerste keer een lage dosis van 100 units onabotulinumtoxine A is gebruikt voor de behandeling van neurogene detrusor overactiviteit in MS patiënten. Het doel van deze studie was om de symptomen van een overactieve blaas adequaat te reduceren en minder patiënten zouden worden gezien met een residu na mictie waarvoor katheterisatie nodig zou zijn. Er werd vastgesteld dat de symptomen significant verbeterden na de behandeling, maar 16 % van de patiënten moesten 2 x per dag katheteriseren en 1 patiënt had een suprapubische katheter nodig. Doordat er geen algemeen geldende afkapwaarde bestaat voor het residu waarop gekatheteriseerd moet worden, is een conclusie moeilijk. De vraag blijft of een afkapwaarde nodig is en of niet beter zou kunnen worden beslist aan de hand van klinische symptomen. Dit laatste is een praktische aanpak en leidt wellicht tot een betere kwaliteit van leven.

Hoofdstuk 5 beschrijft een studie naar systemische en specifieke effecten van onabotulinumtoxineA op hartfunctie na blaasinjecties. Een ECG in rust werd opgenomen gedurende 15 minuten bij patiënten en bij gezonde controles gedurende 4 opeenvolgende bezoeken. Tussen visite 2 en 3 werd bij de patiënten een behandeling met intradetrusorinjecties met onabotulinumtoxine A gegeven. Behalve een kortdurende periode met hogere kracht (TP: total power) tussen visite 2 en 3 konden geen veranderingen worden gezien in Hart rust functie. De TP-verhoging zijn juist een positief teken van verhoogde hartritme variabiliteit mogelijk gerelateerd aan procedure of ongemak, deze bevinding is niet anders dan wat bij gezonde proefpersonen of in de literatuur wordt gezien.

Hoofdstuk 6 is een overzicht van de huidige preklinische en klinische data betreffende de behandeling van LUTS en benigne prostaat hyperplasie met intraprostatische BoNT/A injecties. Er is enig bewijs dat BONT/A invloed heeft op, zowel de statische en dynamische component van de aan benigne prostaat vergroting gerelateerde LUTS door het verkleinen van het prostaatvolume en door het verlagen van het aantal alfa receptoren. De volumereductie lijkt vooral te wijten aan apoptose en klier atrofie.

Hoofdstuk 7 beschrijft een eerste onderzoek naar het gebruik van de aanpasbare continentie behandeling middels ACT® en PRO ACT® ballonnetjes voor de behandeling van stress incontinentie bij neurogene sluitspier dysfunctie. Het grootste deel van de onderzochte patiënten paste intermittente katheterisatie toe om de blaas te ledigen. De ballonnetjes konden worden ingebracht onder lokale anesthesie bij 84% van de patiënten. Volledige continentie werd bereikt bij 21% van de patiënten, ten minste 50% verbetering werd gezien bij 54% van de patiënten en 6 % had minder dan 50 % verbetering na 48 maanden follow-up. Permanente explantatie was geïndiceerd bij 40 % wegens te weinig effect of ongewenste nevenwerking zoals erosie, migratie, infectie of pijn. Explantatie is eenvoudig en veilig en kan in de meerderheid van de gevallen poliklinische gebeuren.

Hoewel het therapeutisch effect minder is dan bij eerdere studies, wat waarschijnlijk het gevolg is van ernstiger incontinentie in deze populatie, is het veiligheidsprofiel van deze procedure goed met meestal beperkte complicaties. Daarom is de ACT en PRO ACT een realistische optie voor de behandeling van neurogene stress incontinentie voor patiënten met beperkte symptomen die geen of nog geen invasieve chirurgische behandeling willen of kunnen ondergaan.

Hoofdstuk 8 is de algemene discussie. Hierin worden alle hiervoor besproken studies kritische bediscussieerd in de context van momenteel beschikbare literatuur. De pathofysiologische processen die de functie van de lage urinewegen veranderen als gevolg van neurologische ziekte of trauma zijn beter bekend. Toch is er nog een onvolledig begrip van werkingsmechanismen, patiënt selectie technieken en redenen voor het toch regelmatig falen van huidige therapie zoals neuromodulatie en BoNT/A behandeling.

BoNT/A heeft de behandeling van neurogeen blaaslijden revolutionair veranderd en heeft de kloof overbrugd tussen conservatieve medicamenteuze therapie en invasieve chirurgie. Ondanks het succes van deze therapie zijn nog niet alle mogelijkheden en toepassingen van deze therapie op de lage urinewegen te volle benut.

Daarom zal toekomstig onderzoek niet alleen nieuwe behandeldoelen en soorten moeten onderzoeken, maar ook zullen alle mogelijkheden met momenteel beschikbare therapieën verder moeten worden geperfectioneerd en benut. De gelijktijdige visualisatie in vivo tijdens BoNT/A injecties zou een beter inzicht kunnen bieden in de verdeling en de plaats van injectie. Dit kan zorgen voor betere injectietechniek en falen van behandelingen voorkomen. Objectief en kwantitatief in kaart brengen van afferente zenuwen van de lage urinewegen door bijvoorbeeld Evoked Potentials van de Lage Urinewegen kan meer inzicht geven in normale en pathologische condities van het afferente systeem bij LUTS. Dit kan ook helpen bij het begrijpen van werkingsmechanismen van andere therapieën zoals antimuscarinica,

BoNT/A en neuromodulatie. Deze laatsten en gesofisticeerde neuro-prosthetische toepassingen hebben een enorme potentie LUT functie te corrigeren vooral door het overbruggen of compenseren van neurologische afwijkingen. Hiervoor is interdisciplinaire samenwerking nodig tussen neurowetenschappers, technische ingenieurs, neurologists, revalidatieartsen en urologen.

ZUSAMMENFASSUNG IN DEUTSCH

Funktionsstörungen des unteren Harntraktes sind häufige Folge neurologischer Erkrankungen oder Verletzungen der versorgenden zentralen und / oder peripheren Nervenbahnen mit verheerenden Folgen für die Gesundheit und Lebensqualität der betroffenen Patienten. Da die zugrundeliegende neurologische Erkrankung oder Verletzung meist nicht geheilt werden kann und selbst bei gering progressiven oder vermeintlich „stabilen“ neurologischen Erkrankungen / Verletzungen eine Verschlechterung der Funktionsstörung des unteren Harntraktes eintreten kann, ist eine lebenslange, spezialisierte neuro-urologische Nachsorge notwendig.

Die vorliegende Dissertation beschreibt die wesentlichen Aspekte und aktuellen Behandlungsoptionen von Harnspeicherstörungen bei neurologischen Patienten wobei der Fokus auf Therapien mit Anwendung von Botulinum Neurotoxin A (BoNT/A) liegt. Die in dieser Dissertation enthaltenen Studien leisten einen Beitrag zu neuen Erkenntnissen in der Behandlung von neurogenen Funktionsstörungen und Symptomen des unteren Harntraktes und liefern relevante Ansatzpunkte für zukünftige Forschungsprojekte auf diesem Gebiet.

Kapitel 1 vermittelt eine umfassende Übersicht über die neurophysiologischen Grundlagen der Funktion des unteren Harntraktes sowie der pathophysiologischen Veränderungen dieser Funktion als Folge eines neurologischen Traumas oder Erkrankung. Es werden sowohl epidemiologische Daten präsentiert als auch typische urodynamische Befunde mit der entsprechenden klinischen Symptomatik und der zugrundeliegenden neurologischen Erkrankung / Verletzung gegenübergestellt. Zudem wird ein Überblick über die zurzeit verfügbaren Therapieoptionen mit Fokus auf die Wiederherstellung einer adäquaten Harnspeicherfunktion gegeben.

Kapitel 2 präsentiert das Ergebnis einer ausgiebigen Literaturrecherche zur Behandlung von Harninkontinenz bei männlichen Patienten mit neurologischer Erkrankung. Die Grundstöcke der Therapie von Harnspeicherstörungen bei neurologischen Patienten wie z.B. intermittierender Selbstkatheterismus, antimuskarinerge Medikamente, BoNT/A Intradetrusorinjektionen, Harnblasenaugmentation, operative Harnableitung und Schliessmuskelprothese, haben sich im wesentlichen nicht verändert. Dennoch sind die Evidenzniveaus der meisten Therapien mit Ausnahme von BoNT/A Intradetrusorinjektionen immer noch gering.

Zudem basieren die aktuellen Erkenntnise im Wesentlich auf Daten von Patienten ausschliesslich mit Querschnittlähmung oder Multipler Sklerose ohne Angaben geschlechtsspezifischer Befunde, wodurch eine Generalisierung bzw. Übertragbarkeit der Resultate auf andere Patientengruppen eingeschränkt ist.

Kapitel 3 berichtet über die Ergebnisse einer erstmaligen Studie zur Untersuchung der in vivo Verteilung der BoNT/A-Lösung nach Intradetrusorinjektionen. Dazu wurde das BoNT/A mit Gadolinium-basiertem Kontrastmittel gemischt und nach den Intradetrusorinjektionen eine MRT Untersuchung durchgeführt. Dabei zeigte sich, dass die BoNT/A / Gadolinium-Mischung sich sowohl in der Blasenwand als auch ausserhalb verteilt. 17.6% der Kontrastmittelmenge wurde im perivesikalen Fettgewebe identifiziert. Obwohl das kontrastierte Detrusorvolumen maximal ein Drittel des gesamten Detrusorvolumens ausmachte, zeigten 83% der Patienten eine suffiziente Therapiewirkung. Dennoch lies sich ein Trend erkennen, bei dem eine grössere Abdeckung des Detrusors mit der BoNT/A / Gadolinium-Lösung in einer stärkeren Reduktion der maximalen Detrusordrücke und höheren Blasenkapazität resultierte.

Kapitel 4 beschreibt eine Studie bei der erstmals eine niedrige BoNT/A Dosis, d.h. 100 Einheiten Botox®, zur Therapie der neurogenen Detrusorüberaktivität bei Patienten mit Multipler Sklerose eingesetzt und

evaluiert wurde. Mit Verwendung der niedrigen Dosis sollte die nachteilige Wirkung der Therapie auf die Harnblasenentleerung vermieden bzw. zumindest reduziert werden, bei gleichzeitig guter Wirkung auf die Detrusorüberaktivität und die konsekutive Drang- und Inkontinenzsymptomatik. Die Ergebnisse zeitgen, dass mit 100 Einheiten Botox® eine signifikante Abnahme von Detrusorüberaktivität sowie Drang- und Inkontinenzsymptomen erzielt werden konnte. Allerdings kam es initial zu einem Ansteig der postmiktionellen Restharnmengen, so dass in 16% der Patienten ein Selbstkatheterismus 2x/d und in einem Fall die Versorgung mit einen suprapubischen Katheter notwendig wurde. Eine wesentliche Schwierigkeit bei der Interpretation dieser Resultate ist das Fehlen einer einheitlichen Restharnschwelle ab der mit dem intermittierendem Selbstkatheterismus begonnen werden sollte. Es ist jedoch andererseits fraglich ob ein strikter Schwellenwert für den klinischen Alltag geeignet ist und nicht vielmehr eine symptombasierte Entscheidung das bessere Vorgehen wäre im Sinne der Lebenqualität.

Kapitel 5 beschreibt eine Studie bei der mittels Herzfrequenzvariabilitätsanalyse systemische Nebenwirkungen auf die Herzfunktion durch BoNT/A nach Intradetrusorinjektionen untersucht wurden. Dazu wurde bei Patienten und altersgleichen gesunden Probanden ein Ruheelektrokardiogramm über 15 Minuten an vier konsekutiven Visiten aufgezeichnet. Zwischen Visite 2 und 3 erhielten die Patienten 300 Einheiten OnabotulinumtoxinA in den Detrusor. Die aufgezeichneten Elektrokardiogramme wurden in Hinblick auf Parameter der Zeit- und Frequenzdomäne der Herzfrequenzvariabilitätsanalyse ausgewertet. Ausser einem kurzzeitigen Anstieg der Herzfrequenz-Gesamtpower zwischen den Visiten 2 und 3 in der Patientengruppe konnten keine weiteren Veränderungen der kardialen Ruhefunktion beobachtet werden. Die Zunahme der Gesamtpower ist als Zeichen für einen leichten Anstieg der Herzfrequenzvariabilität positiv zu werten und möglicherweise durch interventionsbedingte Beschwerden oder Anspannung verursacht. Im

Vergleich zwischen Patienten und gesunden Probanden zeigte die Gesamtpower keinen Unterschied und lag auch im Rahmen der beobachteten Erhöhung stets im Normbereich.

Kapitel 6 beinhaltet eine Übersichtsarbeit zur Anwendung von BoNT/A in der Therapie von Symptomen des unteren Harntraktes, die mit einer gutartigen Vergrösserung der Prostata assoziiert sind. Es wird die präklinische als auch klinische Datenlage beschrieben. Dabei zeigten sich Hinweise für eine Wirkung des BoNT/A sowohl auf die statische als auch dynamische Komponente der prostatabezogenen Beschwerden des unteren Harntraktes. Dies scheint einerseits über die Reduktion des Prostatavolumens durch eine BoNT/A induzierte Apoptose und durch eine verminderte Expression von Alpha-Adrenorezeptoren zu erfolgen. Trotz der relativ einfachen und weitgehend sicheren Applikation, mit guten initialen Erfolgen, ist das Evidenzniveau noch immer sehr gering, so dass nun randomisierte, kontrollierte Studien folgen müssen.

Kapitel 7 zeigt die Ergebnisse einer erstmaligen Untersuchung zur Anwendung eines paraurethralen, justierbaren Kontinenzsystems (ACT® / ProACT®) bei neurogener Belastungsharninkontinenz. Die Mehrzahl der untersuchten Patienten (92%) führte zur Harnblasenentleerung den intermittierenen Selbstkatheterismus durch. Die Implantation der ACT® / ProACT® Prothesen erfolgte in den meisten Fällen (84%) in Lokalanästhesie. Nach 48 Monaten konnte eine mindestens 50%ige Verbesserung in 54% der Patienten erzielt werden, davon 21% mit vollständiger Kontinenz. 6% der Patienten hatten weniger als 50% Verbesserung und in 40% der Patienten musste das Kontinenzsystem explantiert werden auf Grund von fehlender Effektivität oder Nebenwirkungen wie Arrosion / Migration, Infektion und Schmerz. Die Explantationen liessen sich sicher und meist einfach im ambulanten Setting durchführen. Obwohl die Effizienz der ACT® / ProACT® Prothese im Vergleich zu Daten aus vorherigen Studien bei nicht-neurogener Belastungsharninkontinenz in unserer Cohorte etwas geringer war, bedingt

durch die ausgeprägtere Funktionsstörung mit Sphinkterinsuffizienz bei den neurologischen Patienten, konnte ein gute Anwendungssicherheit festgestellt werden mit wenigen, meist selbstlimitierenden und nicht schwerwiegenden Nebenwirkungen. Die ACT® / ProACT® Prothese scheint insbesondere für Patienten geeignet, die eine milde bis moderate neurogene Belastungsinkontinenzsymptomatik aufweisen und / oder für die invasivere Optionen ungeeignet oder nicht gewünscht sind.

Kapitel 8 beinhaltet die allgemeine Diskussion, in der alle vorhergehenden Kapitel und entsprechenden Studien dieser Dissertation kritisch und im Kontext der aktuellen Literatur diskutiert werden.

Obwohl wir mittlerweile ein verbessertes Grundverständnis von den pathophysiologischen Prozessen, die zu den Funktionsstörungen des unteren Harntraktes nach neurologischer Erkankung oder Trauma führen, haben, besteht eine nur unzureichende Kenntnis über die genauen Wirkmechanismen, die ideale Patientenselektion und Gründe für Therapieversagen bei aktuell bereits angewendeten Behandlungen wie Sakrale Neuromodulation und BoNT/A Intradetrusorinjektionen. BoNT/A hat die Behandlung der therapierefraktären neurogenen Detrusorüberaktivität in den letzten Jahrzehnten revolutioniert und die grosse Lücke zwischen konservativ medikamentöser Therapie und offen chirurgischer Lösungen erheblich verringert. Trotz dieses Erfolges und der weitläufigen Anwendung, wurde das volle Potential dieser Therapie bislang noch nicht ausgeschöpft.

Daher sollten sich zukünftige Forschungsbestrebungen nicht immer nur auf die Entdeckung neuer potentieller Therapieziele fokussieren, die möglicherweise noch Jahrezehnte bis zur klinischen Anwendbarkeit benötigen, sondern auch dazu beitragen, die bisherigen Therapieoptionen deutlich besser zu verstehen, um das volle Potential dieser Therapien ausnutzen zu können.

In vivo echtzeit Visualisierung der BoNT/A Ausbreitung nach Intradetrusorinjektionen würde ein besseres Verständnis der Verteilung

innerhalb und ausserhalb des unteren Harntraktes ermöglichen. Durch ein solches Verfahren könnten sich möglicherweise auch Gründe für ein Therapieversagen feststellen lassen und Optimierungen der Injektionstechnik vorgenommen werden.

Die objektive, quantitative Evaluation der afferenten Bahnen des unteren Harntraktes mittels sensorisch evozierter Potentiale kann dazu beitragen, dass die Rolle der afferenten Fasern und Bahnen im Rahmen von Funktionsstörungen des unteren Harntraktes besser verstanden wird und der Wirkungsmechanismus von Behandlungen, die auf die afferenten Bahnen des unteren Harntraktes abzielen (z.B. antimuskarinerge Medikamente, BoNT/A, neuromodulative Therapien) genauer verstanden und evaluiert werden kann.

Aus therapeutischer Sicht haben neuromodulative Verfahren und Neuroprothesen (z.B. Brindley-Finetech Stimulator) das grösste Potential durch Überbrückung und / oder Kompensation von neurologischen Defiziten eine Restauration der Funktion des unteren Harntraktes zu erreichen. Um diesbezüglich in Zukunft relevante Fortschritte zu erzielen, ist eine verstärkte interdisziplinäre Zusammenarbeit von Neurowissenschaftlern, Ingenieuren, Neurologen, Rehabilitationsmedizinern und Urologen essentiell.

VALORISATION

Neurological disorders or lesions can readily impair LUT function due to its dependency on complex, multilevel neuronal control. The overall prevalence of neurological disorders and lesions impairing LUT function is very high and affects millions of people worldwide. The most common neurological disorders typically associated with LUTD are multiple sclerosis, Parkinson's disease, and cerebrovascular disease with a world-wide crude prevalence per 100'000 population of 20-100, 100-200, and 500-1000, respectively [1]. In addition there are hereditary and acquired spinal cord lesions such as spina bifida, and traumatic and non-traumatic (e.g. ischemic, infectious, malignancy related) spinal cord injuries with world-wide crude prevalence rates of 30-40 per 100'000 pregnancies [2], 30-130 per 100'000 population, and 40-120 per 100'000 population, respectively [3]. Finally, there is a large group of patients suffering from peripheral nerve damage secondary to diabetes mellitus or pelvic surgery.

Depending on the extent and progression, all these neurological diseases and lesions cause LUTD / LUTS in at least 15% and up to 99% of affected patients [4, 5], making NLUTD a frequent health problem with an enormous economic burden for every healthcare system. This becomes even more obvious considering that almost none of the underlying neurological diseases or lesions are curable, which makes life-long neuro-urological follow-up a necessity.

NLUTD may occur immediately or during the course of a neurological disease leading to (1) additional psychological burden due to embarrassment, depression, and eventually social isolation related to LUTS such as urinary frequency and incontinence and (2) physical damage such as skin ulcers, recurrent urinary tract infections, and renal impairment [4].

Adequate management and follow-up of NLUTD is thus mandatory for improving quality of life and preventing secondary damage to health.

Although this principle appears obvious, it still lacks sufficient implementation in many healthcare systems [6].

This thesis provides, on the one hand, a comprehensive overview of the neuropathophysiological background and current management of NLUTD and, on the other, several first-of-its-kind studies on important but previously unknown clinical aspects of currently available treatments for NLUTD. The chosen focus on BoNT/A intradetrusor injections in this thesis is due to its revolutionary impact on NLUTD management. Prior to BoNT/A intradetrusor injections, patients refractory to antimuscarinic treatment were restricted to surgery, e.g. bladder augmentation, ileal conduit. Nowadays, BoNT/A intradetrusor injections have significantly improved the QoL of many patients with NLUTD and helped to protect their upper urinary tract function without major surgery. However, despite the benefits of this treatment, many aspects of BoNT/A intradetrusor injections remain unknown and require further investigation before we can fully explore and utilize the true potential of this drug.

The output of this thesis may help to (1) raise awareness of urologists, neurologists, and rehabilitation physicians of the importance of diagnosis, treatment, and follow-up of NLUTD, (2) optimize the use of BoNT/A intradetrusor injections for NLUTD in multiple sclerosis and other neurological patients, (3) improve treatment of neurogenic stress urinary incontinence in neurological patients, and (4) stimulate new research into the use of BoNT/A in the treatment of NLUTD to improve its benefit / risk ratio and explore proposed accessory effects to make the full treatment potential of BoNT/A available.

Hence, this thesis provides new treatment concepts for NLUTD but also suggests new pathways and targets for further research specifically on BoNT/A injections within the LUT. The great advantage of exploiting and optimizing treatments that are already on the market and approved, as

presented in this thesis, is the direct availability and applicability for our patients.

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LIST OF ABBREVIATIONS

AD	autonomic dysreflexia
ARI	Alpha reductase inhibitor
ATP	adenosine triphosphate
AUA-SI	American Urological Association Symptom Index
AUS	artificial urinary sphincter
BoNT/A	botulinum neurotoxin A
BPH	benign prostatic hyperplasia
DU	detrusor underactivity
DES	discrete event series
DO	detrusor overactivity
DSD	detrusor-sphincter-dyssynergia
ECG	Electrocardiogram
EDSS	extended disability symptom scale
EMG	electromyogramme
EUS	external urethral sphincter
FDV	first desire to void
HF	high frequency
HRV	heart rate variability
IDO	idiopathic detrusor overactivity
IPSS	international prostate symptom score
ISC	intermittent self-catheterisation
LF	low frequency
LUT	lower urinary tract
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
MCC	maximum cystometric capacity
MR	magnetic resonance
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSA	multiple system atrophy

nSUI	neurogenic stress urinary incontinence
NDO	neurogenic detrusor overactivity
NLUTD	neurogenic lower urinary tract dysfunction
NNOAB	non-neurogenic overactive bladder
OABS	overactive bladder symptoms
PD	Parkinson's disease
pDetmax	maximum detrusor pressure
PFMT	pelvic floor muscle training
PSA	prostate specific antigen
PTNS	percutaneous tibial nerve stimulation
PVRV	post void residual volume
Qmax	maximum Flowrate
QoL	quality of life
RCT	randomized controlled trials
rHR	resting heart rate
RMSSD	root mean square of the sum of differences between adjacent NN intervals
SBP	systolic blood pressure
SCI	spinal cord injury
SDNN	standard deviation of the normal to normal (NN or RR, i.e. interval between two R peaks) intervals
SMC	smooth muscle cell
SNM	sacral neuromodulation
SUI	stress urinary incontinence
TP	total power
TRP	transient receptor potential
TTNS	transcutaneous tibial nerve stimulation
UIE	urinary incontinence epidsodes
UTI	urinary tract infection
UUT	upper urinary tract
VAS	visual analogue scale
VLF	very low frequency
VUR	vesico-ureteral reflux

CURRICULUM VITAE AND LIST OF PUBLICATIONS

Ulrich Meinhard Ferdinand Laurenz Mehnert was born on August 11th, 1977 in Herne, Germany. Following graduation from secondary school (Gymnasium Altlünen, Lünen, Germany), he served during his compulsory 12-month civil service as an emergency medical assistant in the German Red Cross. Thereafter, he studied medicine at the University of Ulm, Germany, from 1998 to 2004. Subsequently, Ulrich completed a 4-month clinical internship at the Texas Heart Institute, Houston, Texas, USA and in the Departments of Urology and Plastic & Reconstructive Surgery at the Yale-New Haven Hospital, New Haven, Connecticut, USA.

In 2005, he earned his MD (Dr. med.) with magna cum laude from the University of Ulm. In the same year, Ulrich started his urology residency in the Department of Urology and Pediatric Urology at the University Medical Center Schleswig-Holstein, Kiel, Germany. During this time, he became increasingly involved and interested in urodynamics and functional urology.

In 2006, he was granted a research fellowship at the University of Zürich, Switzerland with a focus on clinical neuro-urology. From 2006 to 2009, he completed several investigator-initiated and sponsored studies in the field of neuro-urology using different research methods such as urodynamics, neurophysiological assessments, and functional neuroimaging. Alongside his research activities, Ulrich also worked as resident in the neuro-urological unit of the Spinal Cord Injury Center at Balgrist University Hospital, Zürich, Switzerland.

In 2010, he continued his surgical training in the Department of Urology at Pitié-Salpêtrière University Hospital, Sorbonne University, Paris, France with focus on methods of surgical therapy in neuro-urological patients. From 2011 to 2014, Ulrich completed his urology residency in the department of Urology and Neuro-Urology at the Marienhospital Herne, Ruhr University Bochum, Herne, Germany and obtained the specialist title in urology in 2014. In the same year, he became Fellow of the European Board of

Urology (FEBU) and re-joined the neuro-urology team at Balgrist University Hospital, Zürich, Switzerland where he is currently working as consultant urologist.

Alongside his clinical commitments, Ulrich Mehnert is vice-chairman of the Swiss Continence Foundation, treasurer of the International Neuro-Urology Society, and member of several national and international societies. He is the author of more than 50 publications in peer-reviewed medical journals and is the principal investigator / main applicant of several research grants (including from the Swiss National Science Foundation) and a reviewer for several medical journals.

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