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Chapter

Quality of Life in Neurogenic Bladder Patients and Improvement after Botulinum Toxin Injection

Giovanni Palleschi and Antonio Cardi

Abstract

Various neurogenic conditions may determine an altered function of the bladder and urethral sphincters leading to urinary symptoms. Among these symptoms, loss of urine is considered the most bothersome, and recent literature has proposed that urinary incontinence and poor quality of life should be considered as associated conditions. Urinary incontinence is responsible for reducing the enjoyment of life, including loss of self-confidence and limitation of social activity; it is also associated with anxiety, depression, and deterioration in sexual life, and reduced physical activity. Conservative treatments represent a first-line therapeutic approach to neurogenic urinary disorders, followed by oral medications. However, these treatments often do not provide complete recovery from symptoms, especially from urinary incontinence. Onabotulimun toxin A has proven to be safe and effective for treating neurogenic urinary incontinence and its use is associated with a strong improvement of patients' quality of life. Furthermore, this treatment lowers the risk of severe complications to the upper urinary tract, reducing the need for hospitalization. Quality of life improvement as well as clinical efficacy must be considered targets of the therapy, and the use of onabotulimun toxin A for treating neurogenic urinary incontinence reaches both these goals.

Keywords: neurogenic urinary incontinence, quality of life, onabotulinum toxin A

1. Introduction

Various neurogenic conditions are responsible for lower urinary tract symptoms (LUTS) which further worsen the quality of life (QoL) of patients. In most cases, LUTS onset follows a neurogenic diagnosis by several years, while in certain disorders (i.e., parkinsonism) the urologic disease can sometimes precede neurogenic symptoms. However, in all cases, LUTS represent a significant problem for neurogenic patients, especially for those suffering from physical limitations, such as spinal cord injured (SCI) ones. In addition, LUTS of neurogenic origin is often secondary to a bladder-sphincteric dysfunction which can lead to severe complications and, therefore, must be early and properly managed. The aim of treatment is to restore adequate bladder filling and emptying processes, preventing severe complications, especially to the upper urinary tract (renal failure), and improving QoL. Various therapeutic

options are today available for neurogenic LUTS, varying from conservative approaches (behavioral treatment, physical therapy) to pharmacologic oral medications (antimuscarinics, beta-3- agonists, alpha-blockers). Among LUTS, urinary incontinence (UI) is the most bothersome and, in the neurogenic bladder (NGB), is often severe because it is the consequence of neurogenic detrusor overactivity (NDO), which is characterized by involuntary bladder contractions. Conservative treatments and first-line therapeutic options often fail to provide complete recovery from neurogenic UI. In these cases, the international guidelines therapeutic algorithms suggest the use of mini-invasive treatments, including onabotulinum toxin A (BoTA) which has proven to be effective in restoring urinary continence, improving urodynamic parameters, and ameliorating QoL. This chapter aims to report the current knowledge about the relationship between neurogenic disorders and LUTS, their impact on patients' QoL, and how they improve after administration of BoTA, as shown by large cohort studies provided by literature.

1.1 Neurogenic bladder: Definition and epidemiologic data

Neurogenic bladder refers to bladder dysfunction secondary to neurologic disease affecting any point of the complex neuronal circuit, which can ultimately compromise safe bladder filling and emptying [1]. Various pathologic conditions of the central and peripheral nervous system can lead to altered bladder and urethral sphincter function, and consequently, many people suffering from the neurogenic disease can develop LUTS. Epidemiological data available show that, in the United States, NGB has been found in 40–90% of patients with multiple sclerosis (MS), in 37–72% of patients with parkinsonism, and 15% of patients with stroke [2, 3]. In the same country, it is estimated that 70–84% of patients with SCI have at least some degree of bladder dysfunction, which is also frequently seen in patients with spina bifida, associated with vesicoureteral reflux in 40% of children and UI in 60.9% of young adults [4]. Less common scenarios for NGB may include diabetes mellitus (due to autonomic neuropathy involving the bladder), unintended sequelae following pelvic surgery, and cauda equina syndrome resulting from lumbar spine pathology [5]. More specific epidemiological data are provided by studies on neurogenic UI. A meta-analysis of five studies showed that men who suffered a stroke were at increased risk for UI with a pooled odds ratio 0f 2.68 [6]. Other reports showed that men who had a stroke presented an increased risk for UI with an odds ratio ranging from 7.1 to 8.26 [7, 8]. These studies reported that among UI sufferers, the stroke survivors had a higher prevalence of UI compared to controls (17% vs. 9%). Poorer data are provided by Literature regarding neurogenic UI in women. However, various studies analyzed the association between UI and dementia in females. Even if data in some cases are controversial, in a 9-year follow-up of 1453 women aged 65 years and over enrolled in a US HMO, diagnosed dementia was strongly associated with an incident diagnosis of UI (odds ratio of 3.0, ranging from 2.4 to 3.7, 95% CI) [9]. Given the strength and consistency of association with prevalent and incident UI, and given that treatment for reversible dementia can improve UI, a causal role seems certain [9, 10]. Among NGB patients are those suffering from the non-neurogenic neurogenic bladder (the Hinman syndrome), a pathological condition characterized by the uncoordinated activity of the lower urinary tract muscles. In these patients the contraction of the sphincter during voiding and overactivity of the detrusor muscle may lead to urinary frequency and incontinence, reproducing a neurogenic voiding pattern that can determine complications to the bladder wall like those secondary to NGB [11].

NGB is responsible for symptoms of both the bladder filling and voiding phase. Symptom association and severity are strongly related to the site of the neural system involved by the pathophysiological mechanisms of the specific neurogenic condition. Therefore, it is important for clinicians, caregivers, and patients, to gain adequate knowledge of bladder neurophysiology and pathophysiology of NGB.

1.2 Neural control of the bladder and pathophysiology of neurogenic bladder

Bladder dysfunction secondary to a neurogenic disease can be classified considering the location of the neurologic lesion in the nervous system [12]. This type of classification has the most clinical utility to manage patients with NGB from diagnosis to treatment. Neural control of the bladder and urethral sphincters is extremely complex. However, the different areas of the central and peripheral nervous system play specific and highly defined roles during the bladder filling and emptying. Various studies, including urodynamic investigations, neurophysiologic tests, and advanced imaging techniques (PET, functional MRI) allowed the precise identification of the parts of the nervous system that are activated during the different phases of the micturition cycle. The storage phase of the micturition cycle (bladder filling) is maintained by inhibition of parasympathetic activity, and consequent active relaxation of the bladder mediated by the sympathetic system acting on beta 3 adrenoceptors of the detrusor muscle. During the bladder filling, the sympathetic and pudendal nerve mediated contraction of the urethral sphincters prevents urine leakage under normal conditions. Sensory information from the bladder triggers the micturition reflex leading to bladder emptying. This phase is characterized by the inhibition of the pudendal nerve and suppression of sympathetic activity [13]. Consequently, the detrusor muscle contracts while the pelvic floor muscles and the urethral sphincters relax. When the bladder afferent pathways (from the peripheral pudendal nerves to the spinal cord, and through mesencephalus) stimulate the cerebral cortex, the detrusor center of this region allows micturition to begin or delay [14]. The micturition starts with the external urethral sphincter relaxation, induced by the cerebral cortex, and the detrusor contraction stimulated by the sacral micturition center (located at the spinal cord level S2 to S4) through the pelvic nerves which release acetylcholine to the muscarinic receptors of the detrusor muscle [13, 14]. During the micturition, the simultaneous relaxation of the external sphincter, when the detrusor contracts, is under the control of the pontine micturition center. Therefore, various areas of the nervous system, located in different sites, exert specific control on the bladder and urethral sphincters. In the case of neurogenic disorders, functional changes of detrusor-sphincter complex, clinical signs, and symptoms related, will depend on the site involved by the disease and to the loss of its specific function, as reported in the following scheme.

Lesions above the brain stem: Specific damage in this area causes the loss of the inhibitory control exerted by the cerebral cortex on bladder reflex. As consequence, the detrusor muscle develops uncontrolled function (detrusor overactivity, onset of detrusor involuntary contractions). This altered function may be responsible for the following symptoms: urinary frequency (increase of number of micturitions), urinary urgency (a sudden, compelling urge to urinate), and UI (loss of urine) [15]. In these patients, bladder sensation can be normal to decreased. The urinary sphincters should be synergistic with the bladder (they normally relax when the bladder contracts). Thus, high bladder pressures should not develop and the risk of kidney damage is low.

Complete suprasacral spinal cord lesions: When the lesion is located at the spinal cord above the sacral level, the bladder and sphincter do not receive the control exerted by the cerebral cortex and from the pontine centers. Therefore, the bladder develops uncontrolled activity but, in addition, the urethral external sphincter paradoxically contracts during detrusor activation (dyssynergia), due to the absence of neural mechanisms which provide synergy located in the pontine micturition center [16]. Patients suffering from disorders involving this area may develop the same symptoms of those affected by lesions above the brain stem, but the consequence of sphincter contraction is the high pressure inside the bladder with the risk of vesico-ureteral reflux and obstructive bladder voiding with incomplete bladder emptying (poor micturition flow, intermittent flow, urinary retention). Sensation to bladder filling can be normal to decreased. If the lesion is located above T6, the patient may experience autonomic hyperreflexia, which is represented by a constellation of signs/symptoms in response to noxious or non-noxious stimuli below the injury level, including an increase in blood pressure > 20 mmHg above baseline, and may include one or more of following signs and symptoms: headache, flushing and sweating above lesion level, vasoconstriction below lesion level, or dysrhythmias.

Sacral spinal cord lesions: When the sacral level and its micturition center are involved, the bladder reflex is disrupted and patients experience detrusor areflexia. Depending on the type and extent of neurologic injury, decreased bladder compliance may occur during filling. An open smooth sphincter area may result but the striated sphincter may exhibit varied types of dysfunction, although this area usually maintains a resting sphincter tone and cannot be controlled voluntarily [2]. Sensation to bladder filling can be normal to decreased. Therefore, patients express inability to void the bladder with consequent urinary retention, increased risk of urinary infections, bladder stones formation, and hydronephrosis.

Distal to the spinal cord lesions: When this part of the nervous system is damaged, also in these patients the functional alteration leads to detrusor areflexia. However, the smooth sphincter is likely incompetent, and the striated sphincter may exhibit a fixed residual tone that cannot be relaxed voluntarily. Sensation to bladder filling can be normal to decrease [2].

The loss of physiological nervous control of the bladder function causes symptoms that may have a negative impact on a patient's lifestyle and quality of life. While symptoms of the voiding phase may benefit from pharmacological treatment or, in severe cases, from catheterization which can be self-administered at specific time intervals, storage bladder symptoms can hardly limit social interaction, especially when UI is present.

1.3 Onabotulinum toxin type A for treatment of NGB

Treatment of NGB aims to prevent complications to the lower and upper urinary tract secondary to bladder-sphincter dysfunction and consequently improve symptoms and patients' QoL. Major complications of NGB are represented by urinary infections, urinary stones, vesicoureteral reflux, and renal failure. Clinical assessment is based on symptom evaluation, physical examination, renal and bladder ultrasound, and specific instrumental tools, especially flowmetry and urodynamic investigation combined with urethral sphincter electromyography. These tools allow to establish the type and severity of bladder-sphincter dysfunction and to choose treatment. As above reported, UI is the most bothersome symptom. When clinical and urodynamic assessment allows diagnosing NDO as the cause of low bladder

compliance and symptoms such as urinary urgency and UI, treatment has the goal to reduce involuntary bladder contractions thus achieving a stable detrusor function (also inducing bladder areflexia). When treatment is effective, intravesical pressure is reduced, and consequently, the risk of vesicoureteral reflux and UI is lower or completely recovered. Various therapeutic options are today available to cure NDO. Based on International Consultation on Incontinence (ICI) algorithms, a conservative approach, followed by oral administration of drugs is recommended as initial management for UI of neurogenic origin, associated with CIC in case of significant post-void residue [17]. Recommended oral drugs are considered antimuscarinics and beta-3-agonists. However, when these therapeutic options fail, the ICI specialized management algorithm suggests BoTA injections into the detrusor muscle for NDO and into the urethral sphincter for bladder-sphincteric dyssynergia. Botulinum toxin causes muscle relaxation (flaccid paralysis) because it binds, at presynaptic level, high-affinity sites on the cholinergic nerve terminals decreasing the release of acetylcholine. After its administration, presynaptic vesicles cannot release the acetylcholine in the synaptic space and consequently, the muscle does not contract. Currently, four different formulations of botulinum toxin, three BTX-A and one botulinum toxin B (BTX-B) are commercially available in Europe and USA: onabotulinumtoxin A / BoTA (Botox, A, Allergan Inc., Irvine, USA) abobotulinumtoxinA (Dysport, Ipsen Limited, Paris, France), incobotulinumtoxinA (Xeomin, Merz Pharmaceutical Raleigh, USA) and rimabotulinumtoxinB (Neurobloc/Myobloc, Solstice Neuroscience Inc., San Francisco, USA). However, adequate clinical data are available only on both BoTA and abobotulinumtoxin B as a treatment option for NDO [18]. Therefore, Literature and international guidelines provide recommendations only for these two formulations to treat NGB, specifically NDO [19]. These two formulations are not interchangeable and of course have different dosing [20], as it's generally accepted that a dosage of 200–300 U of BoTA is comparable with 500–750 U of abobotulinumtoxin [21]. However, further studies have clearly shown that there are no better outcomes comparing both 750 U of abototulinumtoxin and 300 U of BoTA to 500 U abobotulinumtoxin or 200 U BoTA respectively [21, 22]. Although comparative studies are rare and no studies are available comparing different BTX types in the field of urology, in one small non-randomized cohort study on 26 patients, replacement with abobotulinum after the failure of the first injection with BoTA has been proven to be effective [23]. For this reason, a conversion factor between BoTA and abobotulinumtoxin of 1:2.5 has been suggested by Grosse et al., even if this assumption was not scientifically proven and it's believed that a variable conversion rate of the two toxins between 1:2 and 1:3 is applicable [24]. Although both these products are commonly used in real clinical practice, the only FDA-approved dose and formulation for urological application is 200 U of BoTA. Intradetrusor administration of BoTA is performed under local or general anesthesia, using a rigid or flexible cystoscope. A special needle (maximum depth 4 mm) allows to perform the administration of the toxin, usually subdividing the total dose (200 U) in twenty different sites of the bladder, avoiding the bladder dome (to prevent the risk of extra-vesical diffusion) and the trigone (to prevent the risk of vesicoureteral reflux). Large evidence of the safety and efficacy of BoTA on NDO is provided by the literature. A recent review performed by L.F. Cooley and S. Kielb reported long-term data from clinical trials and real-life studies, which show that patients with NDO and detrusor sphincter dyssynergia benefit significantly from intradetrusor BoTA injection with regard to the following parameters: improved voided volume, improved bladder pressure and urodynamic outcomes, reduced incidence of urinary tract infections, and improved QoL [1]. The most important studies

providing high-quality data are those from Cruz (2011) and Ginsberg (2012) [25, 26]. In these placebo-controlled protocols, the population in both trials was represented by patients suffering from MS and SCI, with urodynamic evidence of NDO, and submitted to BoTA intradetrusor injections (200 or 300 U). The positive results shown by these studies were confirmed by Kennelly et al. who conducted a 3-year prospective study in 396 patients with SCI and MS to assess long-term efficacy of BoTA injections for NDO [27]. Data on detrusor-sphincter dyssynergia are not so strong and consistent as seen with NDO because outcomes come from low-powered studies. However, a recent meta-analysis of BoTA use in SCI patients suffering from detrusor-sphincter dyssynergia did point to the potential efficacy of this approach with an average decrease from 251.8 mL to 153 mL of post-void residue up to 6 months post-BoTA injection as well as a reduction in sequelae of urinary tract infections and need for CIC in some studies [28]. BoTA is injected on the external urethral sphincter usually through the transperineal way under transrectal ultrasound guidance, and in some cases using electromyography support.

1.4 Quality of life in patients with NGB and improvement after BoTA injection

Restoring the adequate quality of life should be considered a goal of treatment as significant as the recovery from the disease. QoL is what patients experience on a day-to-day basis and is one of the key considerations when they are involved in choices about their medical care [29]. Quality of life was defined in 1947 by the World Health Organization as a "state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity" [30]. In neuro-urology, treatments aim to correct bladder-sphincteric dysfunction to both prevent severe complications to the urinary tract and improve QoL. However, in daily clinical practice (even more so in the past) QoL has been wrongly interpreted as a secondary consideration with respect to the treatment of bladder dysfunction with serious urologic complications and the preservation of renal function. In recent years, especially since 2010, various studies have been published reporting objective data collected by specific patient-reported outcome measures. These studies clearly show how QoL changes during neurologic diseases when bladder symptoms develop [29]. It is important to assess and understand how a person's life is affected by bladder changes that can accompany the neurologic disease, especially UI because this evaluation is directed to target the therapy most effectively. Despite it being one of the fundamental aspects of neuro-urology, there has been not much research on QoL differences across bladder management choices; this fact may represent a limit for the assessment of specific therapeutic algorithms which optimize the relationship between clinical success and QoL improvement for the patient [31]. In fact, while literature provides considerable data to support the improvement of functional outcomes of treatments for NGB (i.e. bladder augmentation), there is a much smaller body of studies supporting objective improvements in QoL [31]. A large amount of research has been focused on the identification of specific QoL tools for neurogenic bladder function after SCI. Best et al. conducted a systematic review of literature published from 1950 to 2015 on this topic and found 42 studies including 24 QoL outcome tools (ten objective, fourteen subjective) [32]. This important review concluded the existing outcome measures representative of the three major domains of QoL as "Achievements", "Utility", and "Subjective well-being". The Authors explain that both objective and subjective measures are important in SCI, concluding that the only validated condition-specific outcomes that show sensitivity to NGB are the QLI-SCI (Quality of Life in Spinal Cord Injury) and Qualiveen, while the SF-36

questionnaire provides a valid assessment of objective QoL in SCI. There are some specific studies regarding QoL of neuro-urologic patient sub-categories. In these papers, the authors point out the importance of using dedicated and validated tools to investigate objective and subjective aspects, including psychometric evaluations. Catherine Browne et al. in 2015 provided a report on QoL for people with MS [33]. Bladder dysfunction has been described in approximately 75% of people with MS [34] and therefore, in this study, participants were recruited from one branch of the Multiple Sclerosis Society of Ireland using purposive sampling techniques [35]. Patients from this cohort (19 subjects, 11 females and 8 males) suffered from at least one urinary symptom: involuntary leakage of urine, voiding frequency (>8), nocturia, voiding dysfunction such as hesitancy, straining, poor stream. Outcomes from this investigation showed that bladder dysfunction creates a sense of disruption and loss for people with MS, interfering with daily activities. One of the most important factors conditioning lifestyle was the unpredictability of bladder symptoms, especially urinary urgency which drives UI. In patients suffering from MS, as other people are affected by neurological impairment, bladder dysfunction is magnified due to other co-occurring symptoms; specifically, physical limitations heighten LUTS in terms of mobility issues creating problems in managing urinary frequency and urgency, often leading to UI. In fact, this study showed that also in MS patients, UI represents the most bothersome symptom associated with emotional consequences also because fear of leaking urine in public may be greater than the distress caused by the leakage of urine itself [36]. Urinary incontinence is prevalent also in SCI individuals. In fact, more than 80% of these subjects experience NGB resulting from neurological impairments that determine NDO +/− sphincter dyssynergia or detrusor areflexia [37]. Spinal cord injury patients are at high risk of complications due to the development of vesicoureteral reflux (in case of detrusor-sphincter dyssynergia and consequent high intra-vesical pressures) or high bladder residual volumes (due to areflexia). These conditions may be responsible for urinary infections, hydronephrosis, finally leading to chronic renal failure, thus requiring strong medical intervention which also can contribute to lifestyle changes. For this reason, NGB remains the most important issue in QoL of patients with SCI, apart from physical movement, and it requires an aggressive attitude towards urinary management in order to improve QoL. As previously reported generically for NGB and SCI patients, the Qualiveen questionnaire has proven to adequately assess disease aspects of limitations, constraints, fears, and feelings [38]. Lundqvist et al. found that UI reduced self-reported QoL among individuals with SCI [39]. The same findings were reported by Westgren and Levi, who described lower QoL in SCI subjects with bladder problems with respect to controls [40]. When the bladder is properly managed, LUTS improve, renal function is preserved, and the person with SCI can enjoy a much healthier life [41]. This outcome has been seen especially when significant improvement in urinary continence has been restored and reported as better body image perception and independence [28]. A significant rate of SCI patients practices self-catheterization to void the bladder due to areflexia, which can be a direct consequence of the spinal lesion or the effect of treatment (antimuscarinics or bladder injections with BoTA). Long-term clean intermittent catheterization (CIC) was first promoted in the 1970s by Lapides et al. [42] and became the standard procedure for managing the NGB of SCI patients [43]. Studies on QoL of patients using CIC show that it has many beneficial effects, which include reduced morbidity and mortality, improved body image, and guaranteed improved self-esteem [44]. These outcomes are even more positive when the use of CIC is associated with a complete recovery of UI (when patients are totally dry), as provided in a large rate of

SCI patients by BoTA administration [45]. These outcomes in SCI submitted to CIC are supported by other studies. Fuminicelli et al. showed that in the Brazilian and Portuguese populations of SCI patients, QoL scores improved in those using CIC because of better independence, self-confidence, social relationship, and access to work activities [46]. The same authors performed a review on the topic including 13 high-quality studies (from the initial 2945 examined) examining QoL assessment in patients with NGB secondary to different disorders (SCI, MS, Parkinson's disease, cerebrovascular accident, brain tumors, infection by HTLV-I, neuroschistosomiasis). The report concluded that CIC offers considerable changes in the NGB patients' living activities, modifying social routines, professional activities, and sexuality, among other areas. However, also in this review, an important concept is the significant role of the recovery from UI to achieve a "dry-status" of the patient using CIC, therefore enhancing the role of proper treatments for the neurogenic UI, as BoTA injections [46]. Intravesical BoTA is a safe and generally well-tolerated procedure because it can be performed under local, regional, or general anesthesia and it requires short operative time. This aspect is important for ensuring good patient acceptance of this treatment which can generally be repeated over time. Quality of life outcomes in patients injected with BoTA has been considered in the most important trials since 2011. Francisco Cruz et al. reported a significant reduction of UI episodes and improvement of urodynamic parameters in 275 patients with NDO after BoTA injection during a multicenter, double-blind, randomized, placebo-controlled trial [47]. This cohort was interviewed during the study by means of Incontinence Quality of Life (I-QOL) questionnaire. Final results showed that among patients submitted to BoTA, 38% and 39,6% respectively submitted to 200 and 300 U were fully dry versus only 7,6 of those in the placebo arm. This clinical finding was associated with a significant improvement of I-QOL total summary scores at 6 weeks from treatment in patients injected, despite the incidence of adverse events (urinary tract infections and urinary retention). Specifically, the total I-QOL score improved from 24.4 to 25.1 in subjects injected with 200 BoTA U, and from 24.3 to 25.9 in those injected with 300 U, while subjects in the placebo group presented a worse score (decreased from 11.7 to 8.6). In the long-term, multi-center, double-blind, randomized, placebo-controlled trial conducted by Ginsberg et al., patients were followed up to 52 weeks. In this protocol, patients were evaluated every 6 weeks after the first 3 months from the first injection of 200 or 300 U, until re-treatment [48]. As shown in the previous trial, also in this study good QoL outcomes were associated with urodynamic improvement. Cystometric measures improved both in SCI and MS subjects, without significant difference between the active dose groups (200 or 300 U). Each BoTA dose significantly improved the I-QOL summary score at week 6 compared with placebo and this result was maintained through week 12 in the overall population with increases from baseline of 9 in the placebo arm, 31 and 33 points in the BoTA 200 and 300 U groups (p < 0.001). The most important side effects reported in this trial were UTI and the need of CIC. However, the change from baseline I-QOL score was analyzed in patients who did not perform CIC at baseline to determine whether subsequent initiation of CIC influenced QoL. In these patients, the I-QOL improvement was similar whether they did or did not begin CIC after treatment. The authors commented in the discussion that the onset of BoTA action was rapid and sustained with a duration of effect time approximately of 9 months, probably influencing the positive effect also on I-QOL scores. Particularly, the positive effect of BoTA on recovery of continence is crucial for these patients. Satisfaction with life has been shown to be significantly lower among neurogenic patients with continence problems and the use of BoTA is often required by these

subjects because they frequently discontinue antimuscarinics due to failure of response, side effects, or unmet treatment expectations [47]. Sussman et al. in 2012 randomized patients to intradetrusor placebo or BoTA 200 and 300 U. The Patient Report Outcomes included I-QOL to assess Health Related Quality of Life, the 16-item modified Overactive Bladder-Patient Satisfaction with Treatment Questionnaire (OAB-PSTQ) to assess treatment satisfaction, and Patient Global Assessment to assess treatment goal achievement [48]. Patients of the 200 and 300 U groups had improvement of I-QOL scores significantly greater compared with placebo. Improvements were reported in the avoidance/limiting behavior, psychosocial impact, and social embarrassment domain ($p < 0.01$). As observed in other trials, there were no clinically relevant differences between BoTA dose groups for the effects on total I-QOL domain scores. A significant association was then found between UI frequency and improvement of HRQoL. Also, OAB-PSTQ showed that patients treated with BoTA were somewhat or very satisfied with treatment compared to unsatisfied patients of the placebo group. These results were observed in patients regardless of the need for CIC after BoTA injection. Consequently, the final PGA measures indicated that the majority of patients treated with BoTA improved in symptoms, QoL, activity limitations, and overall emotions related to their bladder problems at weeks 6 and 12, and this improvement was maintained or continued to improve during the follow-up. Good outcomes can be achieved in NGB when proper assessment is performed (based on standardized symptoms and QoL questionnaires, clinical assessment, instrumental evaluation by urodynamics). In addition, it is important to follow international guidelines to establish treatment starting as soon as possible to prevent complications and worsening of the bladder-sphincteric dysfunction. In fact, a positive effect of continuous care intervention on the QoL of NGB patients with SCI was observed [49]. The goal of continuous care intervention is to maintain continence, prevent urological complications, and preserve upper urinary tract function to make bladder management compatible with the person's lifestyle and environment [50]. In patients submitted to BoTA injections, continuous care intervention may be an important method of re-assessment over time to suggest the need of instrumental re-evaluation and re-treatment. A significant part of continuous care is represented by training for CIC and adequate suggestions which prevent infections. It was observed that continuous care interventions contribute to improve the QoL of patients after 3 months. This is the consequence of better bladder management with regard to urinary system complications.

2. Conclusions

Patients suffering from neurogenic disorders adapt to physical and social limitations. The effect of physical disability of illness cannot be understood if QoL aspects of importance for the individual are not taken into consideration. When urinary symptoms and bladder-sphincteric dysfunction develop, these patients have a significant worsening of their QoL. This report clearly shows that UI is the most bothersome symptom to manage in this population and that it is associated with a hard negative impact on QoL. Recovery of continence allowed by intradetrusor injection of BoTA provides a great QoL improvement which is parallel to the bladder-sphincteric functional modification. This result is supported by various multicentric, randomized, placebo-controlled trials with a specific evaluation of QoL by means of standardized and highly recommended patients' report outcomes. These studies guarantee

that good outcomes are maintained over time despite the need to start CIC. For this reason, BoTA injections are strongly recommended by International Guidelines in these patients. In the future, the authorized use of different types of botulinum toxin for urological use is expected, extending the indication to the pediatric population. Furthermore, large multi-center studies are warranted to design specific protocols which should guide clinicians in managing NGB patients who need re-treatments (in terms of time intervals and BoTA dosing), and which can support the management of subjects who are refractory to BoTA, replacing it by different toxins. However, considering that QoL can be influenced by diverse factors and not only by treatments, it is important to remember that family support, adjustment and coping, productivity, self-esteem, financial stability, education, and physical and social environments must also be assessed and considered in NGB individuals.

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