Review

Botulinum toxin A for the Treatment of Overactive Bladder

Po-Fan Hsieh 1, Hung-Chieh Chiu 1, Kuan-Chieh Chen 2, Chao-Hsiang Chang 1,3 and Eric Chieh-Lung Chou 1,3,*

1 Department of Urology, China Medical University Hospital, Taichung 40447, Taiwan; phdoublem@yahoo.com.tw (P.-F.H.); b101091082@tmu.edu.tw (H.-C.C.);
urology8395@yahoo.com.tw (C.-H.C.)
2 Department of Surgery, China Medical University Hospital, Taichung 40447, Taiwan;
kuanchieh_c@hotmail.com
3 School of Medicine, China Medical University, Taichung 40402, Taiwan
* Correspondence: ericchou66@yahoo.com.tw; Tel.: +886-4-2205-2121 (ext. 4439)

Academic Editor: Hann-Chorng Kuo
Received: 29 January 2016; Accepted: 24 February 2016; Published: 29 February 2016

Abstract: The standard treatment for overactive bladder starts with patient education and behavior therapies, followed by antimuscarinic agents. For patients with urgency urinary incontinence refractory to antimuscarinic therapy, currently both American Urological Association (AUA) and European Association of Urology (EAU) guidelines suggested that intravesical injection of botulinum toxin A should be offered. The mechanism of botulinum toxin A includes inhibition of vesicular release of neurotransmitters and the axonal expression of capsaicin and purinergic receptors in the suburothelium, as well as attenuation of central sensitization. Multiple randomized, placebo-controlled trials demonstrated that botulinum toxin A to be an effective treatment for patients with refractory idiopathic or neurogenic detrusor overactivity. The urinary incontinence episodes, maximum cystometric capacity, and maximum detrusor pressure were improved greater by botulinum toxin A compared to placebo. The adverse effects of botulinum toxin A, such as urinary retention and urinary tract infection, were primarily localized to the lower urinary tract. Therefore, botulinum toxin A offers an effective treatment option for patients with refractory overactive bladder.

Keywords: botulinum toxin A; overactive bladder; detrusor overactivity

1. Introduction

Overactive bladder (OAB) is a clinical diagnosis defined by the International Continence Society as “urgency, with or without urge incontinence, usually with frequency and nocturia” [1]. The overall prevalence of OAB was 12%–17% in the general population and it poses a great impact on daily activities and quality of life (QOL) [2–5]. In contrast to the clinical diagnosis of OAB, detrusor overactivity (DO) is a urodynamic observation characterized by involuntary detrusor contraction during the filling phase which may be spontaneous or provoked [1]. There is a substantial overlapping between OAB and DO, and DO is generally regarded as a major underlying physiology of OAB [6]. The standard treatment for OAB starts with patient education and behavior therapies. Among pharmacologic treatments, antimuscarinic agents are widely used but associated with adverse effects such as dry mouth, constipation, and blurred vision [7,8]. Due to the bothering side effects, the long-term adherence was consequently very low for antimuscarinic agents (12.0% to 39.4% at 12 months and 0% to 16% at 36 months) [9]. Beta3-adrenoceptor agonist is an alternative to antimuscarinic...
agents. The efficacy was similar among beta3-adrenoceptor agonists and antimuscarinic agents, but beta3-adrenoceptor agonists produce less rates of dry mouth and constipation [7].

Botulinum toxin was first isolated from *Clostridium botulinum* by van Ermengem [10]. There were seven serotypes of botulinum toxin, and botulinum toxin A (BoNT/A) was used most frequently in the urologic field. The efficacy of BoNT/A in treating OAB has been supported by literatures [11–13]. Currently both AUA and EAU guidelines suggested that intravesical injection of BoNT/A should be offered to patients with urgency urinary incontinence (UUI) refractory to antimuscarinic and beta3-adrenoceptor agonist therapy, and the FDA approved dose was 100 U of BoNT/A for idiopathic detrusor overactivity (IDO) and 200 U for neurogenic detrusor overactivity (NDO) [7,14]. In this article we will review the mechanism of BoNT/A in the treatment of OAB and evaluate randomized, placebo-controlled trials for the applicability of BoNT/A in IDO and NDO.

2. Mechanism of Action

BoNT/A is composed of a 100 kDa heavy chain polypeptide and a 50 kDa light chain polypeptide, as is joined via a disulfide bond [15]. The initially-proposed mechanism of BoNT/A was that by attachment of the heavy chain to the protein receptor SV2 on axon terminals, the toxin could enter the neuron by endocytosis [16]. Then the light chain cleaves synaptosomal-associated protein (25 kDa) (SNAP-25), a protein from the soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) family. As a result, the fusion of neurosecretory vesicles and release of acetylcholine (Ach) from presynaptic nerve terminals are blocked [17]. With inhibition of Ach release, the effect on suburothelial afferent and detrusor parasympathetic nerve endings was abolished, which was similar to the action of anticholinergic agents [8,18]. However, emerging studies indicated that BoNT/A also exerts complex inhibitory effects on other neurotransmitters, neuropeptides, and receptors mediating neurotransmission [19]. In a rat model, BoNT/A injection was shown to reduce capsaicin or ATP-induced contraction frequencies and amplitudes [20]. Patients with DO had increased expression of the capsaicin receptor TRPV1 and purinergic receptor P2X3 in the suburothelial nerve fibers, and intradetrusor injection of BoNT/A resulted in decreased levels of these sensory receptors [21–23]. The change in P2X3 immunoreactivity was correlated with improved sensation of urgency in patients with intractable neurogenic or idiopathic DO [23]. Besides, women with DO had increased densities of suburothelial substance P (SP) and calcitonin gene related peptide (CGRP) immunoreactive fibers [24]. BoNT/A injection could reduce the release of CGRP with improvement in the intervals between bladder contractions in a rat model [25]. Inhibition of SP by BoNT/A would reduce the activation of TRPV1 and P2X3 receptors in suburothelium and detrusor muscle via decreased activation of NK1 receptors as was shown in a guinea pig model [26]. In addition, intravesical BoNT/A leaded to neurotrophic growth factors (NGF) deprivation up to 3 months, which was correlated with clinical response in patients with DO [27,28]. Last but not least, a recent study showed that there was a significant accumulation of the radiolabelled BoNT/A in the lumbosacral dorsal root ganglia following intradetrusor injection in rats [29]. In other words, BoNT/A works through not only localized peripheral mechanism but also a CNS effect through retrograde axonal transport.

In summary, it was proposed that the action of BoNT/A on human overactive bladders followed a sequential mechanism [19]. First, the immediate effect of BoNT/A is inhibition of vesicular release of Ach, ATP, and SP and the axonal expression of TRPV1 and P2X3, leading to peripheral denervation [18,30,31]. Second, after SNAP-25 was cleaved by BoNT/A, this exocytosis inhibitor could persist for a long time (up to 40 days in a mouse model) [17]. Third, through retrograde transport into CNS BoNT/A would result in attenuation of central sensitization, leading to further peripheral desensitization.
3. Application of Botulinum Toxin A

3.1. Idiopathic Detrusor Overactivity

Radziszewski et al. conducted the first trial of BoNT/A for patients with IDO. All seven patients became continent after treatment with 300 U of BoNT/A [32]. In November 2015, we searched randomized, placebo-controlled trials of BoNT/A on Pubmed using the keywords “Botulinum toxin A” and “detrusor overactivity”. Relevant literature in the reference lists were also reviewed. Finally, eleven randomized, placebo-controlled trials of BoNT/A for IDO to date were identified and summarized in Table 1 [33–43]. The definition of refractory IDO/OAB varied among studies. Most studies enrolled patients with OAB symptoms inadequately responded to anticholinergic therapy or those who had intolerable side effects [33,35,37–43]. Failed behavioral modification in addition to anticholinergic therapy was used as inclusion criteria in two studies [34,36].

Sahai et al. reported the first randomized, double-blind, placebo-controlled trial to compare the efficacy of BoNT/A versus placebo in treating patients with refractory IDO of either sex [33]. BoNT/A of 200 U (10 U/mL) was injected at 20 sites with trigone sparing. Significant increases in maximum cystometric capacity (MCC) from 182 mL to 313 mL were observed at 4 weeks. BoNT/A also reduced episodes of frequency (mean change from 15.44 to 7.93 times per day), urgency (mean change from 11.69 to 9.21 times per day) as well as UUI (mean change from 4.98 to 1.9 times per day) at 4 weeks, and a significantly better improvement in QOL as compared with placebo was noted. The beneficial effects persisted for at least 24 weeks. Brubaker et al. also compared 200 U intradetrusor BoNT/A injection at 15 to 20 sites versus placebo in women with refractory idiopathic UUI [34]. Based on the Patient Global Impression of Improvement, they found a greater clinical response rate and a greater reduction in mean incontinence episodes in those who received BoNT/A compared to those who received placebo. The median duration of responses was 373 days, significantly longer than 62 days for placebo. Later Tincello et al. conducted a larger study to evaluate the efficacy of BoNT/A 200 U for the treatment of refractory IDO [35]. In this study, 122 women received BoNT/A injection at 20 sites and 118 women received placebo. In the treatment group, patients experienced greater reduction of median voiding frequency, urgency episodes, and leakage episodes compared with placebo (difference 1.34, 2.50, and 4.33 respectively). Continence was more common after BoNT/A injection. Flynn et al. used 200 U and 300 U BoNT/A of higher concentration (66–100 U/mL in 10–12 sites) versus placebo to treat 22 female patients with refractory OAB [36]. The combined results of the two different doses showed that there were significant improvements in daily incontinence episodes (mean change from 7.9 to 3.4 times), pads changed per day (mean change from 4.4 to 2.2) and QOL questionnaires in the treatment group.

On the other hand, some trials were designed to evaluate the benefit of BoNT/A 100 U in the treatment of refractory IDO. In a small-scaled study (10 BoNT/A versus 11 placebo), Dowson et al. reported that BoNT/A could significantly increase the mean MCC by 105 mL, but the storage symptoms and QOL remained statistically unchanged following BoNT/A 100 U injection [37]. However, Chapple et al. conducted a study of BoNT/A 100 U versus placebo in 558 patients of either sex and showed different results [43]. BoNT/A 100 U not only decreased urinary incontinence (UI) episodes (mean change from 5.5 to 2.55 times per day for BoNT/A versus mean change from 5.7 to 4.67 times per day for placebo) at 12 weeks but also improved the treatment benefit scale, other OAB symptoms (episodes of UUI, micturition, urgency, and nocturia) and health-related quality of life (HRQOL). Nitti et al. also tested BoNT/A 100 U versus placebo in 557 patients of either sex with idiopathic OAB and confirmed the benefit of BoNT/A in decreasing daily frequency of UI episodes vs placebo (mean change from 5.5 to 2.85 times per day for BoNT/A versus mean change from 5.1 to 4.23 times per day for placebo) [38]. All other OAB symptoms including frequency, urgency, and nocturia episodes as well as HRQOL were also improved greater by BoNT/A 100 U compared with placebo.
Table 1. Randomized controlled trials of botulinum toxin A for idiopathic detrusor overactivity.

| Authors/Year          | No. Patients | Injection Method          | UI Episode (%Change) | Frequency (%Change) | MCC (%Change) | Pdetmax (%Change) | Urinary Retention Requiring CIC (%) | Duration of Benefit |
|-----------------------|--------------|----------------------------|----------------------|--------------------|--------------|-------------------|-------------------------------------|---------------------|
| Sahai et al. /2006 [33] | 18           | Intravesical injection (trigone sparing) | −18                  | −7                 | −15          | −4                | None                                | NA                  |
| Botox 200 U           | 16           | Intravesical injection (trigone sparing) | −70                  | −49                | +72          | −59               | 37.5%                               | >24 weeks           |
| Brubaker et al. /2008 [34] | 15           | Intravesical injection (trigone sparing) | −5                   | NA                 | NA           | NA                | None                                | 62 days             |
| Botox 200 U           | 28           | Intravesical injection (trigone sparing) | −75                  | NA                 | NA           | NA                | 43%                                 | 373 days            |
| Flynn et al. /2009 [36] | 7            | Intravesical injection (trigone sparing) | 9.3                  | −6.8               | NA           | NA                | None                                | NA                  |
| Botox 200 U or 300 U  | 15           | Intravesical injection (trigone sparing) | −57.5                | −12.2              | NA           | NA                | 7                                   | >6 weeks            |
| Dmochowski et al. /2010 [39] | 44           | Intravesical injection (trigone sparing) | −17.4                | NA                 | NA           | NA                | 0                                   | NA                  |
| Botox 50 U            | 56           | Intravesical injection (trigone sparing) | −20.7                | NA                 | NA           | NA                | 5.4                                 | 18 weeks            |
| Botox 100 U           | 55           | Intravesical injection (trigone sparing) | −18.4                | NA                 | NA           | NA                | 10.9                                | 24 weeks            |
| Botox 150 U           | 50           | Intravesical injection (trigone sparing) | −23                  | NA                 | NA           | NA                | 20                                  | 36 weeks            |
| Botox 200 U           | 52           | Intravesical injection (trigone sparing) | −19.6                | NA                 | NA           | NA                | 21.2                                | 36 weeks            |
| Botox 300 U           | 55           | Intravesical injection (trigone sparing) | −19.4                | NA                 | NA           | NA                | 16.4                                | 36 weeks            |
| Dowson et al. /2010 [37] | 13           | Intravesical injection (trigone sparing) | 45                   | 0                  | 0            | NA                | 0                                   | 12 weeks            |
| Botox 100 U           | 10           | Intravesical injection (trigone sparing) | −8.3                 | −4.5               | +40.9        | NA                | 30                                  | 12 weeks            |
| Rovner et al. /2011 [40] | 44           | Intravesical injection (trigone sparing) | −51.7                | −15.6              | +4.7         | −10.7             | 0                                   | NA                  |
| Botox 50 U            | 57           | Intravesical injection (trigone sparing) | −69.9                | −23.9              | +8           | 0                 | 3.6                                 | 12 weeks            |
| Botox 100 U           | 54           | Intravesical injection (trigone sparing) | −64.6                | −26.4              | +15.1        | +24               | 9.1                                 | 12 weeks            |
| Botox 150 U           | 49           | Intravesical injection (trigone sparing) | −89.6                | −14.4              | +19.3        | +3.4              | 12.7                                | 36 weeks            |
| Botox 200 U           | 53           | Intravesical injection (trigone sparing) | −80                  | −24.8              | +17.2        | +5.5              | 18.2                                | 36 weeks            |
| Botox 300 U           | 56           | Intravesical injection (trigone sparing) | −77.6                | −27.1              | +21.8        | +23.1             | 16.4                                | 36 weeks            |
| Fowler et al. /2012 [41] | 44           | Intravesical injection (trigone sparing) | −53.5                | NA                 | NA           | NA                | 0                                   | NA                  |
| Botox 50 U            | 57           | Intravesical injection (trigone sparing) | −68.3                | NA                 | NA           | NA                | 14.6                                | 12 weeks            |
| Botox 100 U           | 54           | Intravesical injection (trigone sparing) | −66.2                | NA                 | NA           | NA                | −                                   | 24–36 weeks         |
| Botox 150 U           | 49           | Intravesical injection (trigone sparing) | −81.3                | NA                 | NA           | NA                | −                                   | 24–36 weeks         |
| Botox 200 U           | 53           | Intravesical injection (trigone sparing) | −73                  | NA                 | NA           | NA                | −                                   | 24–36 weeks         |
| Botox 300 U           | 56           | Intravesical injection (trigone sparing) | −72.3                | NA                 | NA           | NA                | −                                   | 24–36 weeks         |
Table 1. Cont.

| Authors/Year | No. Patients | Injection Method | UI Episode (%Change) | Frequency (%Change) | MCC (%Change) | Pdetmax (%Change) | Urinary Retention Requiring CIC (%) | Duration of Benefit |
|--------------|--------------|------------------|----------------------|---------------------|--------------|------------------|-------------------------------------|-------------------|
| Denys et al. / 2012 [42] | 31 | Intravesical injection (trigone sparing) | 29% had UII reduction > 50% | +10.5 | -49.3 | 3.2 | NA |
|   | 23 | Placebo | 37% had UII reduction > 50% | NA | +8 | -51.2 | 13 | 6 months |
|   | 23 | Botox 50 U | 65% had UII reduction > 50% | NA | +8 | -36.5 | 4.3 | 6 months |
|   | 23 | Botox 100 U | 56% had UII reduction > 50% | NA | +9.5 | -49.5 | 13.3 | 6 months |
|   | 30 | Botox 150 U | 56% had UII reduction > 50% | NA | +9.5 | -49.5 | 13.3 | 6 months |
| Tincello et al. / 2012 [35] | 118 | Intravesical injection (trigone sparing) | -3.2 | -9.6 | NA | NA | 4 | NA |
|   | 122 | Placebo | -73.1 | -19.1 | NA | NA | 16 | 6 months |
| Chapple et al. / 2013 [43] | 271 | Intravesical injection (trigone sparing) | -13.9 | -6 | NA | NA | 0.7 | NA |
|   | 277 | Placebo | -53.2 | -19.7 | NA | NA | 6.9 | 12 weeks |
|   | 277 | Botox 100 U | -17.1 | 4.1 | NA | NA | 0.4 | NA |
| Nitti et al. / 2013 [38] | 277 | Intravesical injection (trigone sparing) | -48.2 | -16.9 | NA | NA | 5.4 | 12 weeks |
To assess the dose response relationship of intradetrusor BoNT/A, Dmochowski et al. conducted a trial using BoNT/A of doses ranging from 50 U to 300 U administered as 20 intradetrusor injections for male and female patients with idiopathic OAB and UUI [39]. They found durable efficacy for all BoNT/A dose groups of 100 U or greater. However, doses greater than 150 U contributed minimal additional or clinically relevant improvement in symptoms and HRQOL. On the other hand, use of clean intermittent catheterization (CIC) was dose dependent. Therefore, 100 U of BoNT/A may be the appropriate dose balancing the benefits and safety profiles. Rovner et al. tested the same dose range and also found that dose of 100 U or more led to significant improvements in OAB symptoms [40]. Dose-response relationship was observed in the changes of mean MCC and the volume at first involuntary detrusor contraction. Fowler et al. confirmed that BoNT/A at doses of 100 U or more produced significantly greater improvements than placebo in HRQOL by week 2, and the effect could sustain for up to 36 weeks [41]. Denys et al. performed a trial to evaluate the efficacy and tolerability of low doses of BoNT/A (50 U, 100 U and 150 U) compared to placebo in patients with idiopathic OAB [42]. They reported more than 50% improvement versus baseline in urgency and UUI at month 3 in 65% and 56% patients receiving 100 U and 150 U BoNT/A injections. Complete continence was achieved in 55% and 50% patients after 100 U and 150 U BoNT/A, respectively. These benefits persisted up to 6 months.

Recently, a meta-analysis including eight publications to evaluate the safety and efficacy of BoNT/A in treating idiopathic OAB was published [12]. It was reported that BoNT/A significantly decreased the mean number of UI per day (−2.77 versus −1.01, the standard mean difference [SMD] = −1.68) and the mean number of mic uritons per day (−1.61 versus −0.87, SMD = −1.82); increased MCC (91.39 versus 32.32, SMD = 63.82) and volume voided (44.29 versus 7.36, SMD = 33.05) compared with placebo. Besides, 29.20% of patient treated with BoNT/A became incontinence-free versus 7.95% of patients with placebo (odds ratio [OR] = 4.89). In addition, the injection method of all the above studies was intradetrusor injection with trigone sparing in order to reduce the potential complication of vesicoureteral reflux. However, two RCTs by Kuo et al. and Manecksha et al. revealed that bladder base/trigone injection of BoNT/A was as safe and effective as bladder body injections with or without trigone involvement [44,45].

### 3.2. Neurogenic Detrusor Overactivity

In 2000, Schurch et al. reported a preliminary study of BoNT/A in treating NDO patients. In their initial experience, BoNT/A of 200 U to 300 U significantly increased MCC and decreased detrusor voiding pressure, and complete continence was restored in 17 of 19 cases by 6 weeks [46]. On searching with “Botulinum toxin A” and “detrusor overactivity” on Pubmed in November 2015 and reviewing relevant articles in the reference lists, we identified that at present there are four randomized, placebo-controlled trials which examined the efficacy of BoNT/A for NDO (Table 2) [47–50].

Schurch et al. conducted the first randomized trial to determine the efficacy of two doses of BoNT/A (200 U and 300 U administered as 30 intradetrusor injections) in patients with urinary incontinence caused by NDO [47]. Both BoNT/A treatment groups had significantly decreased UI episodes (mean change −58% and −54% for 200 U and 300 U respectively), increased MCC (mean change 174.2 mL and 92.9 mL for 200 U and 300 U respectively), and improved QOL. There was no clinically relevant difference between the two doses of BoNT/A. The other two clinical trial by Cruz et al. and Ginsberg et al. also tested 200 U and 300 U BoNT/A in patients with NDO [48,49]. Significantly greater improvements in UI episodes, QOL, and urodynamic parameters including MCC and maximum detrusor pressure during the first involuntary detrusor contraction compared with placebo were noted in both doses of BoNT/A in both studies. Again, both 200 U and 300 U of BoNT/A yielded similar efficacy and duration of benefits.

Consistent with above findings, Herschorn et al. performed a trial using BoNT/A 300 U with intradetrusor injection at 30 sites for NDO patients [50]. After injection of BoNT/A, there was a lower frequency of UI episodes, greater improvements in urodynamic and QOL parameters compared with placebo. Interestingly, the clinical benefits lasted for up to 9 months.
Table 2. Randomized controlled trials of botulinum toxin A for neurogenic detrusor overactivity.

| Authors/Year          | No. of Patients | Patients Type | Injection Method | Continence (%)/ UI Episode (%Change) | MCC (%Change) | Pdetmax (%Change) | Urinary Retention Requiring CIC (%) | Duration of Benefit |
|-----------------------|-----------------|---------------|------------------|--------------------------------------|---------------|-------------------|-------------------------------------|---------------------|
| Schurch et al. /2005 [46] |                 |               |                  |                                      |               |                   |                                     |                     |
|                       | Placebo         | 21            | 53 SCI, 6 MS     | Intravesical injection (trigone sparing) | 24/-10        | +18               | -13                   | -                   | NA                  |
|                       | Botox 200 U     | 19            |                  |                                       | 71/-58        | +85               | -59                   | -                   | >24 weeks           |
|                       | Botox 300 U     | 19            |                  |                                       | 53/-54        | +63               | -56                   | -                   | >24 weeks           |
| Cruz et al. /2011 [47] |                 |               |                  |                                      |               |                   |                                     |                     |
|                       | Placebo         | 92            | 121 SCI, 154 MS  | Intravesical injection (trigone sparing) | 7.6/-36       | +3                | +15                   | 12                  | 13.1 week           |
|                       | Botox 200 U     | 92            |                  |                                       | 38.0/-67      | +64               | -55                   | 30                  | 42.1 week           |
|                       | Botox 300 U     | 91            |                  |                                       | 39.6/-62      | +64               | -64                   | 42                  | 42.1 week           |
| Herschorn et al. /2011 [49] |                 |               |                  |                                      |               |                   |                                     |                     |
|                       | Placebo         | 29            | 38 SCI, 19 MS    | Intravesical injection (trigone sparing) | NA/0          | -21.9             | +4                    | -                   | NA                  |
|                       | Botox 300 U     | 29            |                  |                                       | NA/-25        | +21.5             | +49.1                 | -                   | 9 months            |
| Ginsberg et al. /2012 [48] |                 |               |                  |                                      |               |                   |                                     |                     |
|                       | Placebo         | 149           | 189 SCI, 227 MS  | Intravesical injection (trigone sparing) | NA/-31.1      | +6.3              | -4.7                  | 10                  | 92 days             |
|                       | Botox 200 U     | 135           |                  |                                       | NA/-65        | +59.9             | -68.4                 | 35                  | 256 days            |
|                       | Botox 300 U     | 132           |                  |                                       | NA/-73        | +65.6             | -70.7                 | 42                  | 254 days            |
Recently, a meta-analysis including the four RCTs was published [13]. It was revealed that BoNT/A resulted in changes of the mean number of UI per week (SMD = −10.91), MCC (SMD = 146.09), and maximum detrusor pressure (SMD = −32.65). Regardless of the doses of 200 U or 300 U, BoNT/A was more effective than placebo in treating patients with NDO.

4. Adverse Events

According the meta-analysis of BoNT/A in treating IDO patients, BoNT/A significantly increased PVR (32.77 vs. 2.01, SMD = 31.73), proportions of urinary tract infection (UTI) (19.69% and 5.94%, OR = 3.89), and proportions of CIC (8.41% and 0.46%, OR = 13.39) versus placebo [12]. In treating NDO patients, BoNT/A also led to a higher risk of UTI (relative risk [RR] = 1.48), hematuria (RR = 1.81), and urinary retention (RR = 5.87) requiring catheterization [13]. The effect of increased post-void residual volume (PVR) was dose dependent, and doses >150U was found to be more commonly associated with PVR > 200 mL [39,40]. It was reported that age >61 years, low maximum flow rate, low voiding efficiency (a percentage of the voided volume compared to the prevoid bladder volume <90%), and large PVR at baseline were risk factors for these adverse events [51]. The effect of increased PVR peaked by 2 weeks following BoNT/A injection, with a gradual decrease thereafter [39,49]. For urinary retention requiring catheterization, the duration was 6 weeks or less in more than half of the patients [12]. On the other hand, a meta-analysis showed there was no significant difference between trigonal and extratrigonal BoNT/A injection in terms of adverse events [52]. Kuo et al. demonstrated in a pilot study that intravesical instillation of liposome-encapsulated BoNT/A could effectively reduce the episodes of frequency and urgency in OAB patients without any increase in PVR or risk of UTI [53]. The promising role of liposome as vehicles delivering BoNT/A should be further validated. Finally, these results indicated that the adverse events of BoNT/A were primarily localized to the urinary tract, in contrast to the systemic effects of anticholinergic agents. Although muscle weakness or hyposthenia has been reported after BoNT/A injection, the incidence of systemic adverse events was rare and the duration was transient [54,55].

5. Conclusions

By blockade of neurotransmitter release and suburothelial sensory receptors expression, BoNT/A could cause chemical denervation of detrusor muscle. For patients with refractory OAB, BoNT/A offers an effective treatment option and the adverse events were primarily localized to the lower urinary tract.

Acknowledgments: This research received grant sponsor from China Medical University Hospital. Grant number was DMR-101-052.

Author Contributions: Po-Fan Hsieh drafted the manuscript. Hung-Chieh Chiu, Kuan-Chieh Chen, and Chao-Hsiang Chang revised the manuscript. Eric Chieh-Lung Chou supervised the drafting and revision.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

- OAB: overactive bladder
- QOL: quality of life
- DO: detrusor overactivity
- BONT/A: botulinum toxin A
- UUI: urgency urinary incontinence
- IDO: idiopathic detrusor overactivity
- NDO: neurogenic detrusor overactivity
- Ach: acetylcholine
MCC maximum cystometric capacity
UI urinary incontinence
HRQOL health-related quality of life
CIC clean intermittent catheterization
PVR post-void residual volume
UTI urinary tract infection

References
1. Abrams, P.; Cardozo, L.; Fall, M.; Griffiths, D.; Rosier, P.; Ulmsten, U.; van Kerrebroeck, P.; Victor, A.; Wein, A. The standardisation of terminology of lower urinary tract function: report for the Standardisation Sub-committee of the International Continence Society. Neurourol. Urodyn. 2002, 21, 167–178. [CrossRef] [PubMed]
2. Stewart, W.F.; van Rooyen, J.B.; Cundiff, G.W.; Abrams, P.; Herzog, A.R.; Corey, R.; Hunt, T.L.; Wein, A.J. Prevalence and burden of overactive bladder in the United States. World J. Urol. 2003, 20, 327–336. [PubMed]
3. Irwin, D.E.; Milsom, I.; Hunskaar, S.; Reilly, K.; Kopp, Z.; Herschorn, S.; Coyne, K.; Kelleher, C.; Hampel, C.; Artibani, W.; et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur. Urol. 2006, 50, 1306–1314. [CrossRef] [PubMed]
4. Lawrence, J.M.; Lukacz, E.S.; Nager, C.W.; Hsu, J.W.; Luber, K.M. Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. Obstet. Gynecol. 2008, 111, 678–685. [CrossRef] [PubMed]
5. Nitti, V.W. Clinical Impact of Overactive Bladder. Rev. Urol. 2002, 4, S2–S6. [PubMed]
6. Al-Ghazo, M.A.; Ghalayini, I.F.; Al-Azab, R.; Hani, O.B.; Matani, Y.S.; Haddad, Y. Urodynamic Detrusor Overactivity in Patients with Overactive Bladder Symptoms. Int. Neurourol. J. 2011, 15, 48–54. [CrossRef] [PubMed]
7. Gormley, E.A.; Lightner, D.J.; Faraday, M.; Vasavada, S.P.; American Urological Association; Society of Urodynamics, Female Pelvic Medicine. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J. Urol. 2015, 193, 1572–1580. [CrossRef] [PubMed]
8. Chapple, C.R.; Khullar, V.; Gabriel, Z.; Muston, D.; Bitoun, C.E.; Weinstein, D. The Effects of Antimuscarinic Treatments in Overactive Bladder: An Update of a Systematic Review and Meta-Analysis. Eur. Urol. 2008, 54, 543–562. [CrossRef] [PubMed]
9. Veenboer, P.W.; Bosch, J.L. Long-term adherence to antimuscarinic therapy in everyday practice: A systematic review. J. Urol. 2014, 191, 1003–1008. [CrossRef] [PubMed]
10. van Ermengem, E. Classics in infectious diseases. A new anaerobic bacillus and its relation to botulism. Rev. Infect. Dis. 1979, 1, 701–719. [CrossRef] [PubMed]
11. Ellsworth, P.; Travis, M. Onabotulinum toxin A: A therapeutic option for refractory neurogenic detrusor overactivity and idiopathic overactive bladder. Urol. Nurs. 2014, 34, 165–171. [PubMed]
12. Cui, Y.; Zhou, X.; Zong, H.; Yan, H.; Zhang, Y. The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: A systematic review and meta-analysis. Neurolour. Urodyn. 2015, 34, 413–419. [CrossRef] [PubMed]
13. Zhou, X.; Yan, H.L.; Cui, Y.S.; Zong, H.T.; Zhang, Y. Efficacy and safety of onabotulinumtoxinA in treating neurogenic detrusor overactivity: A systematic review and meta-analysis. Chin. Med. J. (Engl.) 2015, 128, 963–968. [PubMed]
14. Lucas, M.G.; Bosch, R.J.; Burkhard, F.C.; Cruz, F.; Madden, T.B.; Nambari, A.K.; Neisius, A.; de Ridder, D.J.; Tubaro, A.; Turner, W.H.; et al. EAU guidelines on surgical treatment of urinary incontinence. Eur. Urol. 2012, 62, 1118–1129. [CrossRef] [PubMed]
15. Li, B.; Peet, N.P.; Butler, M.M.; Burnett, J.C.; Moir, D.T.; Bowlin, T.L. Small molecule inhibitors as countermeasures for botulinum neurotoxin intoxication. Molecules 2010, 16, 202–220. [CrossRef] [PubMed]
16. Dong, M.; Yeh, F.; Tepp, W.H.; Dean, C.; Johnson, E.A.; Janz, R.; Chapman, E.R. SV2 is the protein receptor for botulinum neurotoxin A. Science 2006, 28, 592–596. [CrossRef] [PubMed]
17. Dolly, O. Synaptic transmission: inhibition of neurotransmitter release by Botulinum toxins. Headache 2003, 43 (Suppl. 1), S16–S24. [CrossRef] [PubMed]
18. Yoshida, M.; Miyamae, K.; Iwashita, H.; Otani, M.; Inadome, A. Management of detrusor dysfunction in the elderly: Changes in acetylcholine and adenosine triphosphate release during aging. *Urology* 2004, 63, 17–23. [CrossRef] [PubMed]

19. Karsenty, G.; Denys, P.; Amarenco, G.; De Seze, M.; Gamé, X.; Haab, F.; Kerdraon, J.; Perrouin-Verbe, B.; Ruffion, A.; Saussine, C.; *et al.* Botulinum toxin A (Botox®) intradetrusor injections in adults with neurogenic detrusor overactivity/urodynamic overactive bladder: A systematic literature review. *Eur. Urol.* 2008, 53, 275–287. [CrossRef] [PubMed]

20. Atiemo, H.; Wynes, J.; Chuo, J.; Nipkow, L.; Sklar, G.N.; Chai, T.C. Effect of Botulinum toxin on detrusor overactivity induced by intravesical adenosine triphosphate and capsaicin in a rat model. *Urology* 2005, 65, 622–626. [CrossRef] [PubMed]

21. Brady, C.M.; Apostolidis, A.N.; Harper, M.; Yiangou, Y.; Beckett, A.; Jacques, T.S.; Scaravilli, F.; Fowler, C.J.; Anand, P. Parallel changes in bladder suburothelial vanilloid receptor TRPV1 (VR1) and pan-neuronal marker PGP9.5 immunoreactivity in patients with neurogenic detrusor overactivity (NDO) following intravesical resiniferatoxin treatment. *BJU Int.* 2004, 93, 37–49. [CrossRef] [PubMed]

22. Brady, C.; Apostolidis, A.; Yu, G.; Baecker, P.A.; Ford, A.P.; Freeman, A.; Jacques, T.S.; Fowler, C.J.; Anand, P. P2X3-immunoreactive nerve fibres in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin (RTX). *Eur. Urol.* 2004, 46, 247–253. [CrossRef] [PubMed]

23. Apostolidis, A.; Popat, R.; Yu, G.; Cockayne, D.; Ford, A.P.; Davis, J.B.; Dassault, P.; Fowler, C.J.; Anand, P. Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of Botulinum toxin for human detrusor overactivity. *J. Urol.* 2005, 174, 1529–1532. [CrossRef] [PubMed]

24. Smet, P.J.; Moore, K.H.; Jonavicius, J. Distribution and colocalization of calcitonin gene-related peptide, tachykinins, and vasoactive intestinal peptide in normal and idiopathic unstable human urinary bladder. *Lab. Invest.* 1997, 77, 37–49. [PubMed]

25. Chuang, Y.C.; Yoshimura, N.; Huang, C.C.; Chiang, P.H.; Chancellor, M.B. Intravesical Botulinum toxin A administration produces analgesia against acetic acid induced bladder pain responses in rats. *J. Urol.* 2004, 172, 1529–1532. [CrossRef] [PubMed]

26. Lavin, S.T.; Southwell, B.R.; Murphy, R.; Jenkinson, K.M.; Furness, J.B. Activation of neurokinin 1 receptors on interstitial cells of Cajal of the guinea-pig small intestine by substance P. *Histochem. Cell Biol.* 1998, 110, 263–271. [CrossRef] [PubMed]

27. Giannantoni, A.; Di Stasi, S.M.; Nardicchi, V.; Zucchi, A.; Macchioni, L.; Bini, V.; Goracci, G.; Corea, M. Botulinum-A toxin injection into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. *J. Urol.* 2006, 175, 2341–2344. [CrossRef]

28. Liu, H.T.; Chancellor, M.B.; Kuoh, H.C. Urinary nerve growth factor levels are elevated in patients with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A injection. *Eur. Urol.* 2009, 56, 700–706. [CrossRef]

29. Papagiannopoulou, D.; Vardoulis, L.; Dimitriadis, F.; Apostolidis, A. Retrograde transport of radiolabelled botulinum neurotoxin type A to the CNS after intradetrusor injection in rats. *BJU Int.* 2015, 24. [CrossRef] [PubMed]

30. Wiseman, O.J.; Fowler, C.J.; Landon, D.N. The role of the human bladder lamina propria myofibroblast. *BJU Int.* 2003, 91, 89–93. [CrossRef] [PubMed]

31. Khullar, V.; Nadler, R.; Chalita, C.; Yeo, L.; Underwood, J. Muscarinic type 2 receptors on bladder sensory nerves: A new site of drug action for detrusor overactivity? In Proceedings of the Abstracts of the 33rd Annual Meeting of the International Continence Society, Florence, Italy, 5–9 October 2003.

32. Radziszewski, P.; Dobronski, P. Treatment of the non-neurogenic storage and voiding disorders with the chemical denervation caused by botulinum toxin type A: A pilot study. *Neurourol. Urodyn.* 2001, 20, 410–412.

33. Sahai, A.; Khan, M.S.; Dassault, P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: Results from a single center, randomized, double-blind, placebo controlled trial. *J. Urol.* 2007, 177, 2231–2236. [CrossRef] [PubMed]

34. Brubaker, L.; Richter, H.E.; Visco, A.; Mahajan, S.; Nygaard, I.; Braun, T.M.; Barber, M.D.; Menefee, S.; Schaffer, J.; Weber, A.M.; *et al.* Pelvic Floor Disorders Network. Refractory idiopathic urge urinary incontinence and botulinum A injection. *J. Urol.* 2008, 180, 217–222. [CrossRef] [PubMed]
35. Tincello, D.G.; Kenyon, S.; Abrams, K.R.; Mayne, C.; Toozs-Hobson, P.; Taylor, D.; Slack, M. Botulinum toxin a versus placebo for refractory detrusor overactivity in women: A randomised blinded placebo-controlled trial of 240 women (the RELAX study). *Eur. Urol.* 2012, 62, 507–514. [CrossRef] [PubMed]

36. Flynn, M.K.; Amundsen, C.L.; Perevich, M.; Liu, F.; Webster, G.D. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. *J. Urol.* 2009, 181, 2608–2615. [CrossRef] [PubMed]

37. Dowson, C.; Sahai, A.; Watkins, J.; Dasgupta, P.; Khan, M.S. The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: A randomised double-blind placebo-controlled trial. *Int. J. Clin. Pract.* 2011, 65, 698–704. [CrossRef] [PubMed]

38. Nitti, V.W.; Dmochowski, R.; Herschorn, S.; Sand, P.; Thompson, C.; Nardo, C.; Yan, X.; Haag-Molkenteller, C.; EMBARK Study Group. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: Results of a phase 3, randomized, placebo controlled trial. *J. Urol.* 2013, 189, 2186–2193. [PubMed]

39. Dmochowski, R.; Chapple, C.; Nitti, V.W.; Chancellor, M.; Everaert, K.; Thompson, C.; Daniell, G.; Zhou, J.; Haag-Molkenteller, C. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: A double-blind, placebo controlled, randomized, dose ranging trial. *J. Urol.* 2010, 184, 2416–2422. [CrossRef] [PubMed]

40. Rovner, E.; Kennelly, M.; Schulte-Baukloh, H.; Zhou, J.; Haag-Molkenteller, C.; Dasgupta, P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurolour. Urodyn.* 2011, 30, 556–562. [CrossRef] [PubMed]

41. Fowler, C.J.; Auerbach, S.; Ginsberg, D.; Hale, D.; Radziszewski, P.; Rechberger, T.; Patel, V.D.; Zhou, J.; Thompson, C.; Kowalski, J.W. OnabotulinumtoxinA improves health-related quality of life in patients with urinary incontinence due to idiopathic overactive bladder: A 36-week, double-blind, placebo-controlled, randomized, dose-ranging trial. *Eur. Urol.* 2012, 62, 148–157. [CrossRef] [PubMed]

42. Denys, P.; Le Normand, L.; Ghout, I.; Costa, P.; Chartier-Kastler, E.; Grise, P.; Hermieu, J.F.; Amarenco, G.; Karsenty, G.; Saussine, C.; et al. Efficacy and safety of low doses of onabotulinumtoxinA for the treatment of refractory idiopathic overactive bladder: A multicentre, double-blind, randomised, placebo-controlled dose-ranging study. *Eur. Urol.* 2012, 61, 520–529. [CrossRef] [PubMed]

43. Chapple, C.; Sievert, K.D.; MacDiarmid, S.; Khullar, V.; Radziszewski, P.; Nardo, C.; Thompson, C.; Zhou, J.; Haag-Molkenteller, C. OnabotulinumtoxinA 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: A randomized double-blind placebo-controlled trial. *Eur. Urol.* 2013, 64, 249–256. [CrossRef] [PubMed]

44. Kuo, H.C. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics. *Neurolour. Urodyn.* 2011, 30, 1242–1248. [CrossRef] [PubMed]

45. Manecksha, R.P.; Cullen, I.M.; Ahmad, S.; McNeill, G.; Flynn, R.; McDermott, T.E.; Grainger, R.; Thornhill, J.A. Prospective randomised controlled trial comparing Trigone-sparing versus trigone-including intradetrusor injection of abobotulinumtoxinA for refractory idiopathic detrusor overactivity. *Eur. Urol.* 2012, 61, 928–935. [CrossRef] [PubMed]

46. Schurch, B.; Stöhrer, M.; Kramer, G.; Schmid, D.M.; Gaul, G.; Hauri, D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: A new alternative to anticholinergic drugs? Preliminary results. *J. Urol.* 2000, 164, 692–697. [CrossRef]

47. Schurch, B.; de Sèze, M.; Denys, P.; Chartier-Kastler, E.; Haab, F.; Everaert, K.; Plante, P.; Perrouin-Verbe, B.; Kumar, C.; Fraczek, S.; et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. *J. Urol.* 2005, 174, 196–200. [CrossRef] [PubMed]

48. Cruz, F.; Herschorn, S.; Aliotta, P.; Brin, M.; Thompson, C.; Lam, W.; Daniell, G.; Heesakkers, J.; Haag-Molkenteller, C. Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: A randomised, double-blind, placebo-controlled trial. *Eur. Urol.* 2011, 60, 742–750. [CrossRef] [PubMed]
49. Ginsberg, D.; Gousse, A.; Keppenne, V.; Sievert, K.D.; Thompson, C.; Lam, W.; Brin, M.F.; Jenkins, B.; Haag-Molkenteller, C. Phase 3 efficacy and tolerability study of onabotulinumtoxinA for urinary incontinence from neurogenic detrusor overactivity. *J. Urol.* **2012**, *187*, 2131–2139. [CrossRef] [PubMed]

50. Herschorn, S.; Gajewski, J.; Ethics, K.; Corcos, J.; Carlson, K.; Bailly, G.; Bard, R.; Valiquette, L.; Baverstock, R.; Carr, L.; *et al.* Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: A randomized, double-blind trial. *J. Urol.* **2011**, *185*, 2229–2235. [CrossRef] [PubMed]

51. Jiang, Y.H.; Ong, H.L.; Kuo, H.C. Predictive factors of adverse events after intravesical suburothelial onabotulinumtoxina injections for overactive bladder syndrome-A real-life practice of 290 cases in a single center. *Neurourol. Urodyn.* **2015**, *28*. [CrossRef] [PubMed]

52. Davis, N.F.; Burke, J.P.; Redmond, E.J.; Elamin, S.; Brady, C.M.; Flood, HD. Trigonal versus extratrigonal botulinum toxin-A: A systematic review and meta-analysis of efficacy and adverse events. *Int. Urogynecol. J.* **2015**, *26*, 313–389. [CrossRef] [PubMed]

53. Kuo, H.C.; Liu, H.T.; Chuang, Y.C.; Birder, L.A.; Chancellor, M.B. Pilot study of liposome-encapsulated onabotulinumtoxina for patients with overactive bladder: A single-center study. *Eur. Urol.* **2014**, *65*, 1117–1124. [CrossRef] [PubMed]

54. Grosse, J.; Kramer, G.; Stöhrer, M. Success of repeat detrusor injections of botulinum a toxin in patients with severe neurogenic detrusor overactivity and incontinence. *Eur. Urol.* **2005**, *47*, 653–659. [CrossRef] [PubMed]

55. Del Popolo, G.; Filocamo, M.T.; Li Marzi, V.; Macchiarella, A.; Cecconi, F.; Lombardi, G.; Nicita, G. Neurogenic detrusor overactivity treated with English botulinum toxin A: 8-year experience of one single centre. *Eur. Urol.* **2008**, *53*, 1013–1019. [CrossRef] [PubMed]

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons by Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).