



Treatment Response of Botulinum-A Toxin Intradetrusor Injections for Overactive Bladder (OAB) and Neurological Detrusor Overactivity (NDO) Refractory to Anticholinergics and Beta₃-Adrenoceptor Agonists

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Authors' contributions

This work was carried out in collaboration among all authors. Author FRM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors MAS, AAJ, MM, SAS, SR, UFM and AA managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Overactive bladder (OAB), defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology.

Methods: A retrospective review of patients getting intradetrusor onabotulinumA injections for OAB and NDO over a 6-year time frame was conducted. The principal outcome measures involved patient's subjective improvements in OAB and NDO symptoms and the duration of symptomatic relief following every treatment. The secondary results measured relation of patient's age and duration of each effective treatment cycle.

Results: One hundred and thirty-Eight (138) consecutive patients who met the inclusion criteria were included in the study. The average age of women was 59.43 years. Eighty four (61%) of participants were still receiving botox injections while 54 women stopped treatment. The average time period between botulinum A injection and its efficacy in controlling OAB symptoms varied from 3 -8.5 months. There was no decrease in efficacy of the treatment with more cycles of treatment. The average age of women who received one, two, three and four or more cycles were 61.7, 53.87, 63.03, and 56.75 years respectively, which showed with advanced age efficacy of botulinum toxin does not decrease.

Conclusions: Our results suggest that in patients who respond to intradetrusor botulinumA treatment, the duration of response does not decline with more treatment cycles, suggesting it as a safe long term treatment option for controlling OAB symptoms. Also there is no relation between advanced age and subsequent efficacy of botulinum A intradetrusor injections.

Keywords: Neurogenic detrusor overactivity; overactive bladder syndrome; Botulinum toxin A; efficacy; age.

1. INTRODUCTION

Overactive bladder (OAB) syndrome is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology [1]. There are various treatment options for idiopathic detrusor overactivity (IDO) for patients with symptoms of overactive bladder (OAB). International Consultation on Incontinence (ICI 2013) [2], European Urology Association (EAU 2014) [3] and National Institute for Health and Care Excellence (NICE 2013) recommend the use of botulinum toxin type A for the management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics: overactive bladder and neurogenic detrusor overactivity (NDO) [4]. 16.6% of the population in Europe aged 40 years and over suffer from OAB symptoms [5]. Most sufferers in Europe do not seek medical attention or remain undiagnosed [6]. In Europe, only 27% of those with OAB who consult a doctor receive treatment. OAB symptoms increases with age, 30-40% of those aged 75 years and over in Europe suffer from OAB [5]. Its prevalence increases with age and its attendant consequences, including diminished social interaction, increased fall-related injury and

reduced quality of life, profoundly affects older women [7-9].

Even though various basic and clinical studies have been done, the reason of OAB remains to be established [10]. Three key causes have been proposed regarding the basis of OAB: myogenic, neurogenic and urotheliogenic. Sacral nerve roots S2, S3 and S4 supply the detrusor muscle and provoke contraction via the parasympathetic nervous system [11]. Acetylcholine (ACh) mediates this response and acts on muscarinic receptors (M2 and M3 subtypes), with the M3 subtype being principally accountable for bladder contraction. Increasing evidence has suggested that the urothelium is not just a passive barrier, but is also is a responsive structure that is capable of detecting thermal, mechanical and chemical stimuli. Transmitters released from the urothelium may alter the excitability of afferent nerves and affect detrusor muscle contractility [12,13]. Absence of the urothelium may cause an increase in the spontaneous activity of detrusor [14]. Thus the urothelium is an important participant in the pathophysiology of OAB. According to the National Institute for Health and Care Excellence (NICE) in the UK [4], The International Consultation on Incontinence (ICI) [2] guidelines and the European Association of Urology (EAU) [3] Botulinum toxin A is licensed

for the management of bladder dysfunctions in adult patients who are not adequately managed with anticholinergics in overactive bladder and neurogenic detrusor over activity. Although not fully elucidated, botulinum A which is derived from the gram positive bacterium *Clostridium botulinum* has a recognized targeted, sensorimotor action. In its motor mechanism it blocks peripheral acetylcholine release at presynaptic cholinergic nerve terminals. It affects the efferent pathways of detrusor activity via inhibition of acetylcholine release. Its sensory action blocks the release of neurotransmitters associated with the genesis of pain, and preclinical and clinical pharmacodynamics studies suggest that botulinum suppresses peripheral sensitisation, thereby possibly also inhibiting central sensitisation. Botulinum may alter afferent (peripheral sensory) nerve activity by inhibiting the release of glutamate, substance P and calcitonin gene-related peptide from afferent nerves, reducing autocrine stimulation and afferent activity [15-17]. It also inhibits ATP release and increasing NO release from urothelial cells, leading to reduced signaling to the suburothelium and afferent nerves [18]. Downregulation of the ATP-gated purinergic P2X3 receptor and the transient receptor potential vanilloid type-1 receptor in suburothelial nerve fibers, leading to reduced afferent signaling is also a mechanism of action of botulinum toxin A. Inhibiting release of acetylcholine or prostaglandin from interstitial cells, in turn reducing afferent activity.

In United Kingdom Botulinum Toxin-A is currently recommended for injection into the detrusor for treating OAB symptoms. Treatment with botulinum toxin A [6] should only be offered if women have been trained in clean intermittent catheterization and have performed the technique successfully, and are able and willing to perform clean intermittent catheterization on a regular basis for as long as needed. (NICE) [4].

In the UK, NICE, currently recommends 200 units onabotulinumA, with consideration of a lower dose of 100 units in women who prefer a dose with which they would be less likely to need catheterization but who accept a reduced chance of success [4]. However, the AUA and, EAU currently recommend 100 units onabotulinum A as a starting dose [19,20]. Onabotulinum A may be injected into the bladder wall via a rigid or flexible cystoscope under either local or general anaesthesia. It is injected

systematically at 10 – 30 sites around the bladder wall, depending on the dose employed (10 units per site), avoiding the trigone [21]. Intradetrusor injection of onabotulinum A is a relatively minor procedure when compared to alternative surgical treatments and is usually undertaken as a day-case procedure. It therefore provides a viable minimally invasive alternative to major surgical intervention for OAB. However, the effects of an individual onabotulinum A treatment are of limited duration, and patients usually require repeated treatments. Although national guidance in the UK [4] suggests that patients should receive no more than three treatments per year, there is little evidence available regarding the duration of response to inform clinical practice. The objective of this study was to investigate the efficacy and duration of response to intradetrusoronabotulinumA injections for the treatment of DO in women and relation between age and repetitive treatment success.

2. METHODOLOGY

A retrospective review of patients receiving intradetrusoronabotulinumA injection (100 units) for OAB and NDO between 2010 and 2017 was conducted. Data were collected manually from both operation records and follow-up clinic notes, using a data collection proforma. The principal outcome measures involved patient's subjective improvements in OAB and NDO symptoms and the duration of symptomatic relief following every treatment. Main treatment failure was defined as less than 3 months of symptom relief. The secondary results measured relation of patient's age and duration of each effective treatment cycle. Statistics were evaluated using Microsoft Excel Mac: 2011 and IBM SPSS 16.

2.1 Inclusion Criteria

- Confirmed diagnosis of NDO or OAB
- Inadequately controlled on anti muscarinic therapy
- No recent (within 12-weeks) botulinum toxin injections for any indication
- Patient who were able and willing to learn clean intermittent catheterization (with the help of a carer).

2.2 Exclusion Criteria

Patients who were unable to speak, listen properly were excluded from study.

3. RESULTS

A total of 138 patients were included during the 6-year period.

Before surgery urodynamic investigation was conducted on all patients selected for intradetrusor on a botulinum A injections. The indications for the treatment were OAB, NBO, mixed symptoms of urinary urgency and stress urinary incontinence with predominantly OAB symptoms and OAB symptoms with no evidence of DO on urodynamic investigation in 72 %, 4%, 20% and 4% respectively. Ninety one (91%) patients had received supervised bladder retraining, 92% used anticholinergic medications, and 23% tried beta₃-adrenoceptor agonists. During the study period 54 women dropped treatment; however 84 women still continue to have open access for treatment with botulinum in future when required. Of those who discontinued treatment, 67% had only one treatment cycle treatment. The reasons for withdrawing treatment were patient's wish in 23%, a further invasive surgical procedure in the form of either augmentation cystoplasty or urinary diversion in 31%, recurrent urinary tract infections secondary to high urinary residuals in 15%, patient declined the use of intermittent self-catheterization in spite of agreeing before starting treatment in 5%, and 26% women did not contact hospital after 12 months of the treatment.

The average time period between botulinum A injection and its efficacy (the average duration of efficacy) in controlling OAB symptoms varied from 3 - 8.5 months. The number of women

received one treatment with intradetrusor botulinum toxin A was 62 (45%), 29 women received two injections, 25 had 3 injections and 22 patients were given four or more injections. There was no decrease in efficacy of the treatment with more cycles of treatment (Fig. 2). The average efficacy of intradetrusor botulinum toxin A injection was 3 months in one cycle, 5.7 months in women having two injections, 8 months of OAB symptom control in women who had 3 injections and 8.5 months of good control of OAB symptoms in patients who had undergone four or more than four injections (Fig. 1).

The average age of women was 59.43 ± SD 14.62 years. The average age of women who received one, two, three and four or more cycles were 61.7, 53.9, 63, and 56.8 years respectively, which showed with advanced age efficacy of botulinum toxin does not decrease (Fig. 2).

The key postoperative problems recorded were high urinary residuals, urinary tract infections and voiding difficulties within 3 months after botulinum A treatment. Subsequent to onabotulinum A treatment, 29% of women developed high urinary residual (>200mls), 28 % of patients had a UTI and 29 % required intermittent self-catheterization (ISC). Results showed risk of high residuals of urine in women who were >60 year old (18%) in comparison with women who were under the age of 60 (10%). Also the percentage of women developed UTI were more in older age group (20% out of total 28% of women who suffered from UTI).

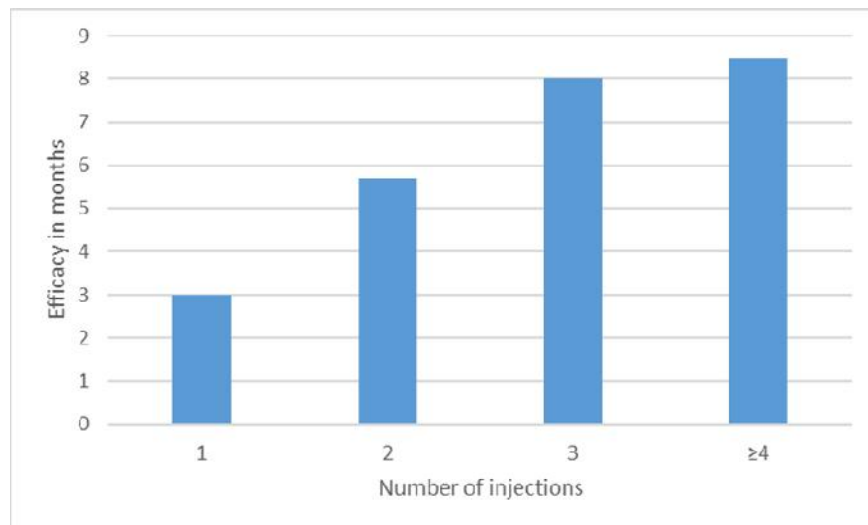


Fig. 1. Botulinum A injection and its efficacy

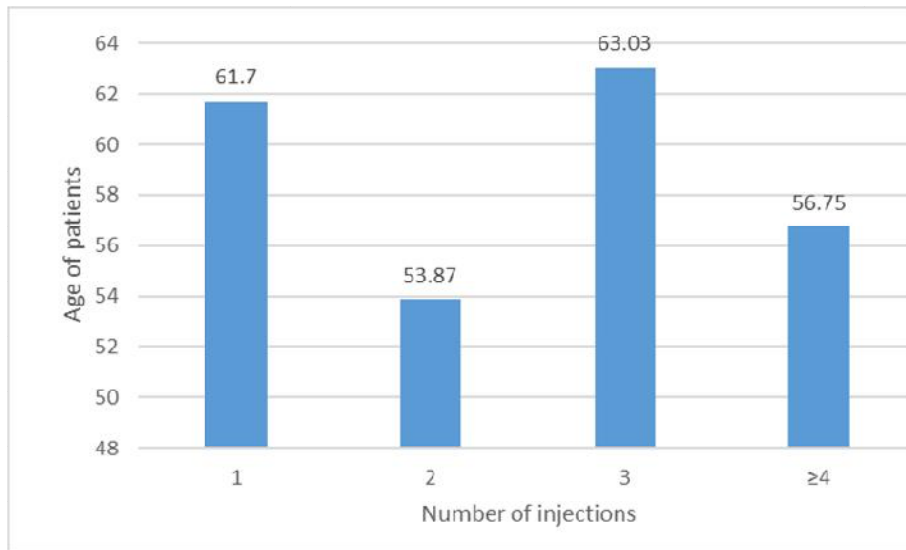


Fig. 2. Frequency of botulinum A injection according to age

4. DISCUSSION

This study examined patient response to treatment for refractory OAB treatments in months and relation of patient's age with botulinum intradetrusor A injection response. The results from this study are mainly timely given the NICE 2013 guidelines on management of urinary incontinence, which highlight the importance of appropriate measures in defining the optimal treatment pathway [22]. The guidelines note, for example, that before treatment with botulinum toxin A, patients should be able and willing to perform clean intermittent catheterization on a regular basis for as long as needed. Our current clinical practice which follows the national guideline (NICE) was adopted before recruiting patients before the study, that is, all patients selected for intradetrusor injection of onabotulinumA had urodynamic investigation and all undertook at least one modality of conservative treatment such as anticholinergic medication, bladder retraining or α or beta receptor agonist, preceding to treatment.

The mean interval between patients receiving on a botulinum A treatment and patient's contact to urology secretary for repeat injections was used as an estimate of the length of treatment response. Treatment failure was regarded as no benefit from OAB symptoms of less than 3 months and none of the patient received repeat injection at less than 6 month interval. The average time period between botulinum A injection and its efficacy (the average duration of

efficacy) in controlling OAB symptoms varied from 3 -8.5 months. There was no decrease in efficacy of the treatment with more cycles of treatment.

Few studies have investigated the duration of response to on a botulinum A (100 units) after repeat injections; those that have often included relatively small numbers of participants, included both men and women, and investigated the effects of on a botulinum A on neurogenic DO only. It is therefore difficult to directly compare the results of these studies with the data from this study. Although, Nitti et al. [23], reported data for a relatively large population with total of 438 patients who received 100U only throughout the study and who had complete treatment cycles over the 3.5-year study, showed the median duration of effect was 7.6 months.

The data from the current study suggest a range of 3 to 8.5 months between the first and fourth treatments. Chohan et al. [24] suggest that in patients who respond to onabotulinum A treatment, the duration of response declines after the fifth treatment, suggesting a possible tolerance effect and a subsequent decline in efficacy., but distinctively, in our study no decrease in efficacy of treatments seen with repeated treatment cycles. Our data concluded the average efficacy of intradetrusor botulinum toxin A injection was 3 months in one cycle, 5.7 months in women having two injections, 8 months of OAB symptom control in women who had 3 injections and 8.5 months of good control

of OAB symptoms in patients who had undergone four or more than four injections.

There are important limitations to this study. It analyzed patients from a single center, and inevitably included a small number of patients. At the 4 week follow-up appointments, subjective assessment was made for symptomatic relief and patients were requested to call the unit when symptoms recurred with a minimum interval of 3 months since the previous injection and were offered subsequent injections at ≥ 6 month interval.

Increasing age was independent risk factor for poorer treatment response to each treatment. The age is associated with lower urinary tract changes which develop with aging, including decreased urethral closure pressure and detrusor contractility, and increased detrusor over activity, may predispose older women to an OAB that may be more refractory to treatment [25-27].

In literature limited data is available regarding the effect of age on onabotulinumtoxin A treatment response and satisfaction. Holi et al. [28], found a differential treatment effect with respect to age and the 50% or greater OAB reduction treatment outcome, however, our findings showed no difference in success of symptom control with 100 units of botulinum toxin A intradetrusor injections.

One of the limitations of this study was discontinuation of treatment with intravesical botulinum injections. Fifteen (39%) women stopped treatment. The main reasons for withdrawing treatment were further invasive surgical procedure in the form of either augmentation cystoplasty or urinary diversion in 05/15 (31%) followed by patient's wish in 3/15 (23%) and recurrent urinary tract infections secondary to high urinary residuals in 2/15 (15%). One patient (5%) declined the use of intermittent self-catheterization in spite of agreeing before starting treatment.

The common complications postoperatively were high urinary residuals (29%), urinary tract infections (28%) and voiding difficulties (29%) within 3 months after botulinum A treatment. These figures are almost similar to the data already published in the literature. Urinary retention has been seen from 5.4% to 43% of patients, in published studies [29-36]. Due to the risk of urinary retention and voiding difficulty

onabotulinum A therapy should only be offered to women who are able and willing to self-catheterize [4,21].

Urinary tract infection is a well-known post-operative complication of botulinum toxin injection as seen in some studies [37] which have shown strong link between urinary retention and UTI. Patients who have high post void residuals are predisposed to UTIs, and yet UTIs are known to precipitate high residual urine volumes in patients.

Limitations to this study are relatively small patient numbers and as with any retrospective study, the findings are reliant on the retrospective review of data. The mean follow-up duration of minimum 12 months is adequate to establish short and medium term durability of effect, though we are not able to answer the question of long-term success from this cohort of patients at this time. In spite of limitation of this study the results are promising and age is not a restrictive factor for offering repetitive injections of botulinum toxin A for OAB symptoms.

5. CONCLUSION

Among women with refractory urgency urinary incontinence, treatment with onabotulinum toxin A resulted in a daily improvement in episodes and the duration of response does not decline with more treatment cycles. In addition, increasing age is not associated with a decreased response to repetitive treatment cycles.

CONSENT AND ETHICAL APPROVAL

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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