



**HAL**  
open science

## The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: A randomised double blind placebo controlled trial

Christopher Dowson, Arun Sahai, Jane Watkins, Prokar Dasgupta, Shamim Khan

► **To cite this version:**

Christopher Dowson, Arun Sahai, Jane Watkins, Prokar Dasgupta, Shamim Khan. The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: A randomised double blind placebo controlled trial. *International Journal of Clinical Practice*, 2011, 65 (6), pp.698. 10.1111/j.1742-1241.2011.02663.x . hal-00640463

**HAL Id: hal-00640463**

**<https://hal.science/hal-00640463>**

Submitted on 12 Nov 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**The safety and efficacy of botulinum toxin-A in the management of bladder oversensitivity: A randomised double blind placebo controlled trial**

Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-09-10-0494.R2
Wiley - Manuscript type:	Original Paper
Date Submitted by the Author:	18-Jan-2011
Complete List of Authors:	Dowson, Christopher; MRC Centre for Transplantation, Urology Department, Guy's and St Thomas NHS Foundation Trust & King's College London, Urology Sahai, Arun; MRC Centre for Transplantation, Urology Department, Guy's and St Thomas NHS Foundation Trust & King's College London, Urology Watkins, Jane; MRC Centre for Transplantation, Urology Department, Guy's and St Thomas NHS Foundation Trust & King's College London, Urology Dasgupta, Prokar; MRC Centre for Transplantation, Urology Department, Guy's and St Thomas NHS Foundation Trust & King's College London, Urology Khan, Shamim; MRC Centre for Transplantation, Urology Department, Guy's and St Thomas NHS Foundation Trust & King's College London, Urology
Specialty area:	

SCHOLARONE™  
Manuscripts

1  
2  
3 **The safety and efficacy of botulinum toxin-A in the management of bladder**  
4 **oversensitivity: A randomised double blind placebo controlled trial**  
5  
6  
7

8  
9 Christopher Dowson MBBS, Arun Sahai MBBS, Jane Watkins RGN, Prokar  
10  
11 Dasgupta MD, Mohammad S Khan MBBS.  
12

13  
14 Medical Research Council (MRC) Centre for Transplantation, King's College London,  
15  
16 King's Health Partners, Guy's Hospital, London SE1 9RT, UK  
17  
18

19  
20  
21  
22  
23 **Corresponding author:**  
24

25  
26 Prof. Prokar Dasgupta  
27

28  
29 Medical Research Council (MRC) Centre for Transplantation, King's College London,  
30  
31 King's Health Partners, Guy's Hospital, London SE1 9RT, UK  
32  
33

34  
35 Email: prokarurol@gmail.com  
36  
37  
38  
39  
40  
41  
42  
43  
44

45 **Keywords:** detrusor overactivity; bladder oversensitivity; botulinum toxin; overactive  
46  
47 bladder; sensory urgency  
48  
49  
50  
51  
52

53  
54 | Word count: 2882  
55  
56  
57  
58  
59  
60

## **Abstract**

### **Objective**

To assess the safety and efficacy of botulinum toxin-A (botn-A) in the management of patients with Bladder oversensitivity (BO).

### **Patients and Methods**

Twenty three consecutive patients with a diagnosis of BO refractory to anticholinergics were enrolled in this randomised, double blind, placebo controlled trial. Patients were randomly allocated to receive intra-detrusor injections of either botn-A (100U Botox®) or saline (placebo) via a flexible cystoscopic approach. The study was designed to have a 90% power to detect a change in the maximum cystometric capacity (MCC) of 30%. It was calculated that a total cohort of 58 patients would be required. Urodynamic assessment (UDS), voiding diaries (VD) and quality of life (QoL) were assessed at baseline and at 4 and 12 weeks following intervention.

### **Results**

An interim analysis was performed and the trial halted after recruitment of 23 patients due to poorly perceived patient benefit. Data were analysed for 21 patients (10 botn-A; 11 placebo). In the treatment arm there was a significant increase in MCC (mean rise 105ml;  $p=0.009$ ). However storage symptoms remained statistically unchanged following botn-A. Three patients in the treatment arm were required to perform clean intermittent self catheterisation with no clinical improvement. The limitations of this trial include the small samples size and the unplanned interim analysis.

1  
2  
3  
4 **Conclusions:** This is the first randomised, double blind, placebo controlled trial  
5  
6 examining the effects of botn-A exclusively in patients with BO. A significant increase  
7  
8 in MCC was observed but this did not translate to clinical benefit with no change  
9  
10 observed in the symptoms and quality of life for the majority of patients.  
11  
12

13  
14  
15  
16  
17 **Trial registration:** ISRCTN no. 57577615

18  
19  
20 (<http://www.controlled-trials.com/ISRCTN57577615/botulinum>)  
21  
22

23  
24  
25  
26 **What's known:** Numerous open label studies and several randomised controlled  
27  
28 trials have established that intra-detrusor injections of botulinum toxin A (botn-A) can  
29  
30 produce dramatic symptomatic and quality of life improvement in patients with  
31  
32 detrusor overactivity (DO). Patients with bladder oversensitivity (BO) present with a  
33  
34 similar symptom profile but are distinguished clinically by the absence of abnormal  
35  
36 detrusor contractions. There are currently no randomised studies examining the  
37  
38 effects of botn-A exclusively in patients with BO.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49

50 **What's new:** This study examines the efficacy and safety of botn-A in patients with  
51  
52 bladder oversensitivity. Although significant changes were observed in cystometric  
53  
54 parameters, such as an increase in maximum cystometric capacity, there was no  
55  
56 symptomatic improvement in 80% of patients.  
57  
58  
59  
60

## Introduction

Overactive Bladder Syndrome (OAB) is defined by the International Continence Society (ICS) 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]. First line management is usually undertaken in the primary care setting and consists initially of fluid management and bladder retraining followed by a trial of anticholinergic medication if required. If these efforts fail to control symptoms then a referral to secondary care usually follows where the patient will usually undergo further investigations including urodynamic assessment. At this stage a distinction can be made between patients with evidence of aberrant detrusor contractions during filling cystometry and those without. In the absence of any associated pathological abnormality the former condition is termed Idiopathic Detrusor Overactivity (IDO) and the latter as Bladder Oversensitivity (BO), previously termed motor urgency and sensory urgency respectively [2]. The most recent ICS terminology report defines bladder oversensitivity as “An increased perceived bladder sensation during filling with specific cystometric findings of i) early first desire to void ii) an early strong desire to void, which occurs at low bladder volumes iii) a low maximum cystometric capacity iv) no abnormal increases in detrusor pressure” [3]. In effect this divides patients with OAB into two distinct clinical groups. Both have the same symptomology i.e. frequency and urgency of micturition, but for one group this is correlated with an abnormal contraction of the bladder (IDO), whereas in the other it is not (BO).

Botulinum toxin-A (botn-A) has emerged as an effective second line therapy in the management of OAB and detrusor overactivity (DO) with a recent European consensus giving it a grade A recommendation for use in this condition [4].

1  
2  
3 Whist there is some experience of managing BO patients with botn-A reported in the  
4 literature they tend to form part of larger heterogeneous patient cohorts. To date  
5  
6 there have been no randomised, placebo controlled trials specifically examining the  
7  
8 effects of botn-A in this group of patients.  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For Peer Review Only

## Materials & Methods

This study was a randomised, double blind placebo controlled trial conducted at a single centre. The trial was performed in line with Good Clinical Practice and had local ethical approval (registration no. 06/Q0704; ISRCTN no. 57577615). Patients were randomised to either 100U Botox® (Allergan, Irvine, California) or normal saline (placebo). A list was prepared by an independent statistician and held in the trials office of the pharmacy department. Eligible patients were assigned a study number in sequence and the pharmacy dispensed either the placebo or active treatment according to the list. The trial injections were collected and prepared by a trained nurse who had no contact with the patient, such that the investigators received 10ml of clear solution without knowing whether it contained 100U of Botox or placebo.

Patients (18-79y) who fulfilled the criteria for a diagnosis of BO, as defined in the introduction, were invited to participate in the trial. All patients had failed conservative and pharmacological therapy with at least one anticholinergic medication. Exclusion criteria included current or planned pregnancy, breast feeding, painful bladder syndrome, pre-existing neurological condition, evidence of bladder outflow obstruction, indwelling catheter, previous bladder surgery, previous urological use of botn-A and continued anticoagulation with heparin or warfarin.

Urodynamic data were collected at weeks 0 and 12. These specifically included maximum cystometric capacity (MCC), first desire to void (FD), normal desire to void (ND), post void residual volume (PVR) and the presence/absence of DO. At week 0, 4 and 12, patients completed a three day voiding diary which recorded 24hr urinary frequency (UF), urinary urgency (UU) and urge urinary incontinence (UUI). They



1  
2  
3 were also asked to complete the short forms of the Urogenital Distress Inventory  
4 (UDI-6) and Incontinence Impact Questionnaire (IIQ-7) and the Patient Perception of  
5 Bladder Condition questionnaire (PPBC) to obtain a patient orientated assessment of  
6 the treatment.  
7  
8  
9  
10  
11

12  
13 The primary endpoint of the study was a change in MCC. A sample size of 58 was  
14 calculated to achieve a 90% power to detect a difference of 30%. Secondary  
15 endpoints included other urodynamic parameters [first desire to void (FD), normal  
16 desire to void (ND), post void residual volume (PVR)], OAB symptoms, assessment  
17 of QoL and PPBC.  
18  
19  
20  
21  
22  
23  
24  
25

26 The study procedures were performed in the out-patient setting by a single surgeon.  
27 Urodynamics were performed in accordance with the ICS guidelines [5]. Prior to any  
28 intervention all patients gave a urine sample to exclude infection (and pregnancy if  
29 appropriate) and all received a oral dose of ciprofloxacin 500mg. Lignocaine gel  
30 (Instillagel®, Clinimed, UK) was applied to the urethra prior to cystoscopy. Intra-  
31 detrusor, trigone sparing injections of either 100 U botn-A (Botox®, Allergan) or  
32 normal saline (placebo) were performed with a flexible cystoscopic technique using a  
33 4mm Olympus needle. Ten sites along the base, posterior and lateral walls of the  
34 bladder were injected with 1ml of solution containing either 10 U botn-A (Botox®,  
35 Allergan) in normal saline or normal saline alone (placebo). Three small bladder  
36 biopsies were taken, from 1cm above and lateral to the left ureteric orifice, baseline  
37 and at week 12 for use in a separate study. All patients were given a three day  
38 course of ciprofloxacin 500mg twice daily. Patients were individually unblinded after  
39 12 weeks once all study data had been collected. Those who had received placebo  
40 were offered 100U Botox in an open label fashion.  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 Independent statistical advice was sought with regards data. A repeated measures  
4 generalised linear model was used to compare the pre- and post intervention  
5 variable outcomes using SPSS® v17.0.  
6  
7  
8  
9

## 10 11 12 13 **Results**

14  
15  
16  
17 Between November 2007 and November 2009 a total of 28 patients were identified  
18 with a diagnosis of BO and invited to participate in this trial. Five patients declined  
19 with concerns regarding the risk of having to perform CISC. Of the 23 patients who  
20 were injected as per protocol – 1 failed to attend follow up and 1 was re-diagnosed  
21 as interstitial cystitis (Consort diagram – figure 1). Complete data for 21 patients was  
22 available (treatment arm = 10, placebo = 11. At this stage an unplanned interim  
23 analysis was undertaken with advice from the local research governance board, due  
24 to concern that the majority of patients had reported no clinical benefit. Following  
25 data analysis it was determined that there was likely to be little benefit in continued  
26 recruitment and the trial was terminated.  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40

41 Table 1 describes the baseline urodynamic parameters and OAB symptoms for the  
42 entire cohort and demonstrates a low MCC, FD and ND in addition to a high day time  
43 UF which is associated with UU on over 70% of occasions. The average age of the  
44 botn-A and placebo groups was not significantly different (49.6+/-19 and 46.7+/-17y,  
45 p=0.7). The ratio of males to females was 2:8 and 4:7 in the botn-A and placebo  
46 group respectively.  
47  
48  
49  
50  
51  
52  
53  
54

55  
56 *Urodynamic variables:* There was a significant rise in MCC, (the primary endpoint of  
57 the study), in patients receiving botn-A compared to placebo (p=0.009) (figure 2). In  
58 the botn-A arm there was an mean increase in FD (figure 3), ND and PVR although  
59  
60

1  
2  
3 they did not achieve statistical significance. One patient in the treatment arm and two  
4  
5 in the placebo arm demonstrated DO at week 12 which had not been observed at  
6  
7 baseline.  
8  
9

10  
11 *OAB Symptoms:* Overall there was no significant difference observed in UF, UU or  
12  
13 UUI at any time point in either group, and no trends were noted (figures 4–6).  
14  
15 Individually, only two patients felt their symptoms were improved by the injections,  
16  
17 whilst for the remainder their symptoms scores remained unchanged.  
18  
19

20  
21 *QoL measures:* There was significant improvement in IIQ-7 at 4 weeks which  
22  
23 became non-significant by week 12. There was no significant improvement in UDI-6  
24  
25 at any stage.  
26  
27

28  
29 *Patient perception of bladder condition:* No significant change was observed in  
30  
31 PPBC score throughout the study period.  
32  
33

34  
35 These results are summarised in Table 2.  
36  
37

38  
39 *Adverse events:* Three patients in the botn-A group were required to perform CISC  
40  
41 and none of them reported any symptomatic improvement. No one in the placebo  
42  
43 group required CISC. UTI was detected in 4 patients in the botn-A arm (2 associated  
44  
45 with performing CISC) and 1 in the placebo arm.  
46  
47

48  
49 A patient in the botn-A group reported a general malaise which lasted two months  
50  
51 following injections with no obvious cause identified. The patient did not require any  
52  
53 specific intervention.  
54  
55  
56  
57  
58  
59  
60

## **Discussion**

This study is the first randomised controlled trial examining the effects of botn-A exclusively in patients with BO. Despite enrolling only a third of the patients suggested by the power calculation the primary endpoint was achieved with the data demonstrating a significant increase in MCC and a trend towards improvement in FD and ND. This did not, however, translate into a meaningful clinical benefit as there was no overall difference detected in OAB symptoms, QoL (with the exception of IIQ-7 at week 4) or PPBC. Individually, only two (20%) patients in the treatment arm derived any benefit from the injections, whilst the remainder experienced no change in their symptoms.

Several studies include patients with BO in their cohorts. Schulte-Baukloh et al. reported a series of seven patients, who received 300U botn-A. At 12 weeks they observed a significant rise in MCC and FD with a decrease in UF, nocturia and pad usage[6]. Cohen et al reported a randomised controlled trial comparing 100u and 150U of botn-A in a cohort including patients with BO or IDO, although the authors do not distinguish between them in their analysis. Instead patients were sub-divided into those with UUI (“wet”) and those with no UUI (“dry”). They found a significant decrease in UF in the “dry” group and a significant decrease in UUI in the “wet” group. They found no significant change in MCC or PVR and they did not observe any significant difference between the two doses [7]. Flynn et al. also found no significant change in MCC and UF in a trial which compared either 200u or 300u botn-A with placebo in a group of patients with BO and IDO. They found significant improvement in UUI and QoL measures[8]. In an open label study Schmid et al described significant improvement in 100 patients with OAB (46 BO and 54 IDO)

1  
2  
3 who received 100u of botn-A. They observed an overall reduction in UF and UU.  
4  
5 They did not find a difference in treatment response between those with BO and  
6  
7 those with IDO [9]. A recent randomised, placebo controlled, dose response trial  
8  
9 involving 313 patients demonstrated an improvement in symptoms and QOL  
10  
11 measures overall. This study concluded that the presence of DO during filling  
12  
13 cystometry did not influence outcome, although the study was not specifically  
14  
15 designed to examine BO [10]. Overall these studies tend to demonstrate some  
16  
17 clinical improvement, although the data are inconsistent, particularly with regards to  
18  
19 changes in MCC and UF.  
20  
21  
22  
23  
24

25  
26 Two studies examining only patients with IDO demonstrate more consistent positive  
27  
28 results. Sahai et al found an improvement in almost all variables studied at 4 and 12  
29  
30 weeks after 200u botox with reductions in UF (15.4 to 9.2), UU (11.7 to 3.6) and UUI  
31  
32 (5.0 to 1.5) and an increase in MCC (181 to 313) at 12 weeks[11]. Khan et al found  
33  
34 UF, UU & UUI reduced significantly by 67%, 100% and 54% respectively at 4  
35  
36 weeks[12]. In these studies dramatic improvements are observed in the symptoms of  
37  
38 the majority of patients. In this study only 20% of patients demonstrated a  
39  
40 symptomatic improvement with no change (or trend towards change) in UF, UU and  
41  
42 UUI in the remaining 80%. We observed a significant increase in MCC (primary  
43  
44 endpoint) which did not correlate with a symptomatic improvement. On that basis we  
45  
46 sought statistical advice on re-powering the study to a symptomatic endpoint but  
47  
48 interim power calculations (Statmate™ Graphpad Software) suggested that even  
49  
50 with the small number of patients recruited we should have been able to detect a  
51  
52 significant difference of 4, 3 and 1.6 episodes per 24 hours for UF, UU and UUI.  
53  
54  
55  
56  
57  
58

59 Possible explanations for the observed lack of effect include insufficient dosage,  
60  
although many of the studies above utilised 100U of Botn-A with positive

1  
2  
3 symptomatic outcomes. A further possibility is injection technique. The goal in DO is  
4 to inject all areas of the bladder to “knock out” aberrant detrusor contractions. In true  
5  
6 BO no DO exists and it is therefore possible that localised injections into the bladder  
7  
8 base and trigone might be more appropriate, as this area contains the most dense  
9  
10 sensory innervation in the bladder and injections here have been shown to be  
11  
12 beneficial in non-neurogenic OAB [13]. Furthermore trigonal injections have now  
13  
14 been shown not to induce vesico-ureteric reflux, an early potential concern with this  
15  
16 technique [14;15]  
17  
18  
19  
20  
21

22  
23 In addition to an established motor effect botn-A has been shown in a number of  
24  
25 human studies to have a modulatory effect on the sensory apparatus of the bladder.  
26  
27 This includes inducing a decreased expression of the purinergic receptor P2X3, the  
28  
29 vanilloid receptor TRPV1, prostaglandins and nerve growth factor [16-18], all of  
30  
31 which have been implicated in the pathogenesis of IDO and BO [19-21]. These  
32  
33 observations, however, could be a secondary effect due to reduction in bladder  
34  
35 contraction/pressure rather than due to primary action of the toxin. More direct  
36  
37 evidence of sensory modulation has been derived from animal models in which  
38  
39 decreased release of the neurokinins, CGRP and SP, (which have also been  
40  
41 implicated in the pathogenesis of OAB), were observed following intra-vesical  
42  
43 instillation of botn-A [22-24]. Caution must be exercised when extrapolating these  
44  
45 results to IDO or BO as these laboratory models do not reproduce the specific  
46  
47 pathophysiology, which to date, remains unclear.  
48  
49  
50  
51  
52

53  
54 It remains to be seen whether BO and IDO represent distinct pathological entities.  
55  
56 Haylen et al. prospectively compared 77 patients with BO with 74 patients with IDO  
57  
58 and could find no significant clinical differences between the 2 groups except for a  
59  
60 significantly increased incidence of UUI in the IDO group [25]. A distinction has been

1  
2  
3 described at the molecular level, by Lui et al. who analysed bladder biopsies from  
4 patients diagnosed with IDO or BO. They found trigonal TRPV-1 in BO patients to be  
5 higher than that of the bladder body mucosa or that of control tissue. In contrast no  
6 differences were found in TRPV-1 levels from the trigone or bladder base in IDO  
7 patients [26].  
8  
9

10  
11  
12  
13  
14  
15  
16 Currently the diagnosis of BO depends on the absence of aberrant detrusor  
17 contractions during filling cystometry but this can be unreliable, lacking in  
18 reproducibility and there will undoubtedly be some overlap with IDO [27;28]. A  
19 cystometric distinction between the IDO and BO is unlikely to influence or provide  
20 any useful prediction of response to first line treatments [29;30]. In this study it's  
21 possible that these cystometric limitations have resulted in patients with IDO rather  
22 than BO being recruited, but given the positive outcomes for patients with IDO (as  
23 discussed above) we would have expected this to improve the overall symptomatic  
24 results. Despite these reservations the distinction between BO and IDO is important  
25 for future research and may be clinically relevant when counselling patients before  
26 botn-A as our data suggests the likelihood of a satisfactory outcome will not be as  
27 good for BO.  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44

45 Although the primary endpoint was achieved with a clear and significant increase in  
46 MCC, it did not correlate with an improvement in patient symptoms. This primary end  
47 point was chosen during the design phase as it was felt to be relatively objective and  
48 that previous experience with IDO patients had shown association between a rise in  
49 MCC and symptomatic improvement [11]. In retrospect, using a symptom as the  
50 primary endpoint, for example UU, would have been more appropriate.  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 The authors accept that this data is limited by the small numbers of patients and the  
4  
5 unplanned interim analysis. Nevertheless the lack of any symptomatic improvement  
6  
7 in most patients in this study, despite the changes in their urodynamic parameters is  
8  
9 significant and raises questions regarding the role of botn-A as a therapy for this  
10  
11 specific sub-group of OAB, particularly as we are used to observing far more  
12  
13 dramatic symptomatic improvements in the majority of patients in the IDO  
14  
15 population. In a wider sense this study also highlights the need for continued  
16  
17 research to attempt to understand and distinguish what distinct pathological entities  
18  
19 OAB represents and to describe their specific aetiologies so that future therapies can  
20  
21 be targeted more effectively.  
22  
23  
24  
25  
26  
27  
28  
29

### 30 **Conclusion**

31  
32  
33 The results of this double blind placebo controlled trial in the use of botn-A in BO are  
34  
35 disappointing. Despite demonstrating a significant increase in MCC there was no  
36  
37 overall improvement in OAB symptoms orl QoL. No clinical benefit was observed in  
38  
39 80% of patients reinforcing the need for continued research to identify and define the  
40  
41 different pathophysiological processes which present as the OAB syndrome.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



## Acknowledgements

PDG & AS acknowledge financial support from the Department of Health via the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London and King's College Hospital NHS Foundation Trust. They also acknowledges the support of the MRC Centre for Transplantation.

The authors are grateful for the statistical support and advice from Irene Rebollo Mesa PhD, Research Fellow in Biostatistics and Bioinformatics, MRC Centre for Transplantation, King's College London.

All authors are investigators for Allergan.

## Reference List

- (1) Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002; 21:167-178.
- (2) Abrams P, Blaivas JG, Stanton SL, Andersen JT. The standardisation of terminology of lower urinary tract function. The International Continence Society Committee on Standardisation of Terminology. *Scand J Urol Nephrol Suppl* 1988; 114:5-19.
- (3) Haylen BT, De Ridder D, Freeman RM et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn* 2010; 29:4-20.
- (4) Apostolidis A, Dasgupta P, Denys P et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus report. *Eur Urol* 2009; 55:100-119.
- (5) Schafer W, Abrams P, Liao L et al. Good urodynamic practices: uroflowmetry, filling cystometry, and pressure-flow studies. *Neurourol Urodyn* 2002; 21:261-274.
- (6) Schulte-Baukloh H, Weiss C, Stolze T, Sturzebecher B, Knispel HH. Botulinum-A toxin for treatment of overactive bladder without detrusor overactivity: urodynamic outcome and patient satisfaction. *Urology* 2005; 66:82-87.
- (7) Cohen BL, Barboglio P, Rodriguez D, Gousse AE. Preliminary results of a dose-finding study for botulinum toxin-A in patients with idiopathic overactive bladder: 100 versus 150 units. *Neurourol Urodyn* 2009; 28:205-208.
- (8) Flynn MK, Amundsen CL, Perevich M, Liu F, Webster GD. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. *J Urol* 2009; 181:2608-2615.
- (9) Schmid DM, Sauermann P, Werner M et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol* 2006; 176:177-185.
- (10) Chapple C.R, Dmochowski R, Nitti V et al. Dose ranging Phase 2 study of BOTOX (onabotulinumtoxinA) in idiopathic OAB: Benefit/risk assessment. Abstract. [uroweb.org](http://uroweb.org) . 2010.
- (11) Sahai A, Khan MS, Dasgupta 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.
- (12) Khan S, Panicker J, Roosen A et al. Complete Continence after Botulinum Neurotoxin Type A Injections for Refractory Idiopathic Detrusor Overactivity Incontinence: Patient-Reported Outcome at 4 Weeks. *Eur Urol* 2009.

- 1
- 2
- 3
- 4 (13) Smith CP, Chancellor MB. Simplified bladder botulinum-toxin delivery technique using
- 5 flexible cystoscope and 10 sites of injection. *J Endourol* 2005; 19:880-882.
- 6
- 7 (14) Kuo HC. Comparison of effectiveness of detrusor, suburothelial and bladder base injections
- 8 of botulinum toxin a for idiopathic detrusor overactivity. *J Urol* 2007; 178:1359-1363.
- 9
- 10 (15) Karsenty G, Elzayat E, Delapparent T, St-Denis B, Lemieux MC, Corcos J. Botulinum toxin type
- 11 a injections into the trigone to treat idiopathic overactive bladder do not induce
- 12 vesicoureteral reflux. *J Urol* 2007; 177:1011-1014.
- 13
- 14 (16) Apostolidis A, Popat R, Yiangou Y et al. Decreased sensory receptors P2X3 and TRPV1 in
- 15 suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human
- 16 detrusor overactivity. *J Urol* 2005; 174:977-982.
- 17
- 18 (17) Chuang YC, Yoshimura N, Huang CC, Wu M, Chiang PH, Chancellor MB. Intravesical
- 19 botulinum toxin A administration inhibits COX-2 and EP4 expression and suppresses bladder
- 20 hyperactivity in cyclophosphamide-induced cystitis in rats. *Eur Urol* 2009; 56:159-166.
- 21
- 22 (18) Liu HT, Chancellor MB, Kuo HC. Urinary nerve growth factor levels are elevated in patients
- 23 with detrusor overactivity and decreased in responders to detrusor botulinum toxin-A
- 24 injection. *Eur Urol* 2009; 56:700-706.
- 25
- 26 (19) Lowe EM, Anand P, Terenghi G et al. Increased nerve growth factor levels in the urinary
- 27 bladder of women with idiopathic sensory urgency and interstitial cystitis. *Br J Urol* 1997;
- 28 79:572-577.
- 29
- 30 (20) Ray FR, Moore KH, Hansen MA, Barden JA. Loss of purinergic P2X receptor innervation in
- 31 human detrusor and subepithelium from adults with sensory urgency. *Cell Tissue Res* 2003;
- 32 314:351-359.
- 33
- 34 (21) Kim JC, Park EY, Seo SI, Park YH, Hwang TK. Nerve growth factor and prostaglandins in the
- 35 urine of female patients with overactive bladder. *J Urol* 2006; 175:1773-1776.
- 36
- 37 (22) Andersson KE. Tachykinins: role in detrusor overactivity? *Eur Urol* 2006; 49:423-425.
- 38
- 39 (23) Chuang YC, Yoshimura N, Huang CC, Chiang PH, Chancellor MB. Intravesical botulinum toxin
- 40 a administration produces analgesia against acetic acid induced bladder pain responses in
- 41 rats. *J Urol* 2004; 172:1529-1532.
- 42
- 43 (24) Lucioni A, Bales GT, Lotan TL et al. Botulinum toxin type A inhibits sensory neuropeptide
- 44 release in rat bladder models of acute injury and chronic inflammation. *BJU Int* 2008;
- 45 101:366-370.
- 46
- 47 (25) Haylen BT, Chetty N, Logan V et al. Is sensory urgency part of the same spectrum of bladder
- 48 dysfunction as detrusor overactivity? *Int Urogynecol J Pelvic Floor Dysfunct* 2007; 18:123-
- 49 128.
- 50
- 51 (26) Liu L, Mansfield KJ, Kristiana I et al. The molecular basis of urgency: regional difference of
- 52 vanilloid receptor expression in the human urinary bladder. *Neurourol Urodyn* 2007; 26:433-
- 53 438.
- 54
- 55 (27) Homma Y, Kondo Y, Takahashi S, Kitamura T, Kawabe K. Reproducibility of cystometry in
- 56 overactive detrusor. *Eur Urol* 2000; 38:681-685.
- 57
- 58
- 59
- 60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- (28) Martin JL, Williams KS, Sutton AJ, Abrams KR, Assassa RP. Systematic review and meta-analysis of methods of diagnostic assessment for urinary incontinence. *Neurourol Urodyn* 2006; 25:674-683.
- (29) Majumdar A, Latthe P, Toozs-Hobson P. Urodynamics prior to treatment as an intervention: a pilot study. *Neurourol Urodyn* 2010; 29:522-526.
- (30) Malone-Lee JG, Al-Buheissi S. Does urodynamic verification of overactive bladder determine treatment success? Results from a randomized placebo-controlled study. *BJU Int* 2009; 103:931-937.

For Peer Review Only

1  
2  
3  
4  
5 Figure 1:- Consort Flowchart  
6  
7

8  
9 Figure 2: - Maximum cystometric capacity (MCC) at baseline and at 12 weeks following intra-  
10 detrusor injections. There is a significant rise in the MCC in the botn-A group ( $p=0.009$ ). No change is  
11 observed in the placebo arm.  
12  
13

14  
15 Figure 3: - First desire to void. An increase is observed in the botn-A arm although it does not reach  
16 statistical significance.  
17  
18

19  
20  
21 Figure 4: - Episodes of urinary frequency at weeks 0, 4 & 12. No significant differences were detected  
22 and no trends were evident.  
23  
24

25  
26  
27 Figure 5:-Episodes of urinary urge at weeks 0, 4 & 12. No significant differences were detected and  
28 no trends were evident.  
29  
30

31  
32  
33 Figure 6: - Episodes of urge urinary incontinence at weeks 0, 4 & 12. There is no significant difference  
34 detected and no trends observed.  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Table 1 – Baseline cystometric and symptom scores for entire study cohort

	Mean	SD
<b>MCC</b>	275.2 ml	70.6
<b>FD</b>	98.4 ml	64.6
<b>ND</b>	146.0 ml	56.8
<b>PVR</b>	22.1 ml	25.2
<b>UF</b>	14.2 voids/24hrs	4.4
<b>UU</b>	11.6 voids/24hrs	5.9
<b>UUI</b>	1.7 voids/24hrs	2.2

*MCC – maximum cystometric capacity; FD – first desire to void; ND – normal desire to void; PVR – post void residual volume; UF – urinary frequency; UU – urinary urgency; UUI – Urge urinary incontinence.*

Table 2 – Comparison of the botn-A and placebo arms at baseline (BL) and 4 and/or 12 weeks

		Botn-A	Placebo		Difference between mean change (95% CI)	p
<b>MCC</b>	BL	259	290			0.33
	12	365	290		105 (30 - 180)	0.009
<b>FD</b>	BL	86	110			0.40
	12	149	108		65 (-41 to 172)	0.22
<b>ND</b>	BL	119	171			0.03
	12	189	177		69 (-40 to 168)	0.22
<b>PVR</b>	BL	21	23			0.82
	4	62	29		35 (-24 to 95)	
	12	78	30		50 (-20 to 120)	0.22
<b>UF</b>	BL	15.6	12.8			0.17
	4	14.7	12.1		-0.1 (-3.9 to 3.7)	
	12	14.9	12.8		-0.9 (-4.9 to 3.1)	0.82
<b>UU</b>	BL	12.4	10.8			0.57
	4	12.8	11.0		-0.9 (-4.0 to 4.4)	
	12	12.5	11.8		-1.1 (-5.0 to 2.8)	0.78
<b>UUI</b>	BL	1.2	2			0.38
	4	1.4	2.4		-0.1 (-2.5 to 2.2)	
	12	1.1	2.9		-1.0 (-3.7 to 1.7)	0.52
<b>IIQ-7</b>	BL	19.2	12.9			0.04

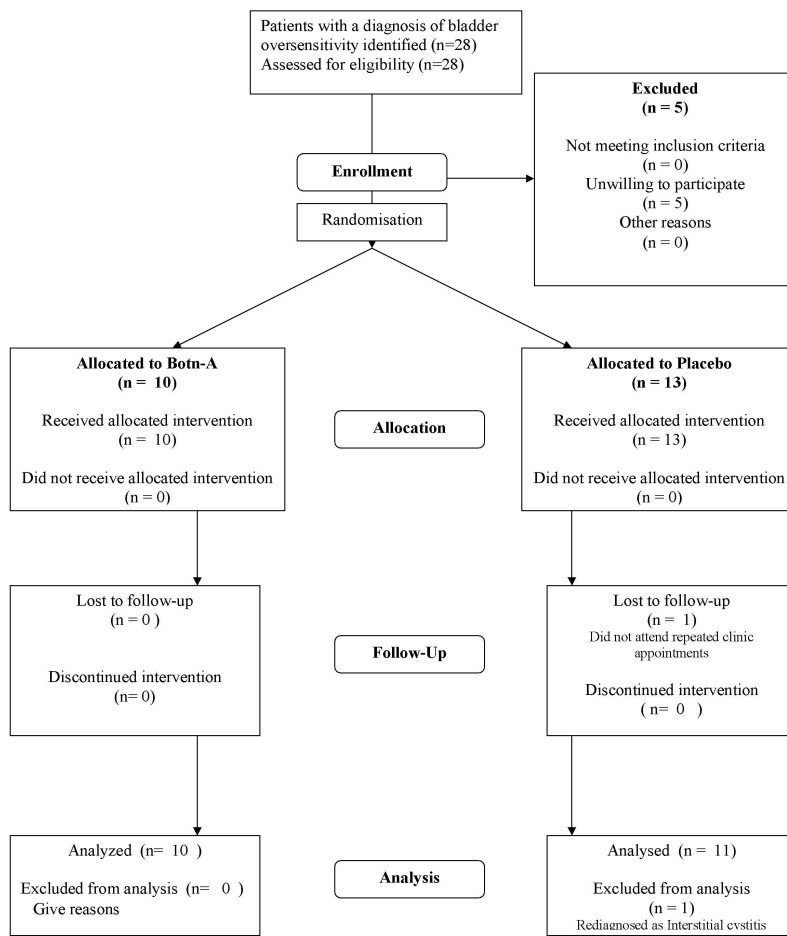
	4	12.7	13.9		-7.3 (-13 to -1.0)	
	12	14.2	15.2		-5.1 (-11 to 1.5)	0.06
<b>UDI-6</b>	BL	10.3	8.3			0.40
	4	9.2	8.9		-2.0 (-4.9 to 1.0)	
	12	8.2	8.6		-1.2 (-6.1 to 3.7)	0.50
<b>PPBC</b>	BL	3.6	3.9			0.33
	4	3.4	3.7		0 (-0.7 to 0.6)	
	12	3.7	3.8		0.2 (-0.6 to 1.0)	0.58

*Botn-A – botulinum toxin-A; MCC – maximum cystometric capacity; FD – first desire to void; ND – normal desire to void; PVR – post void residual volume; UF – urinary frequency; UU – urinary urgency; UUI – Urge urinary incontinence. IIQ-7 – Incontinence impact questionnaire short form; UDI-6 – Urogenital distress inventory short form; PPBC – Patient perception of bladder condition.*



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 1 - Consort Flowchart



209x297mm (300 x 300 DPI)

Figure 2

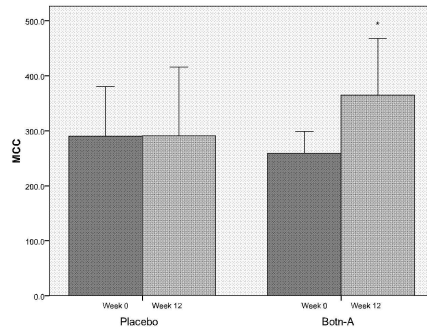


Figure 2: - Maximum cystometric capacity (MCC) at baseline and at 12 weeks following intra-detrusor injections. There is a significant rise in the MCC in the botn-A group ( $p=0.009$ ). No change is observed in the placebo arm.  
209x297mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 3

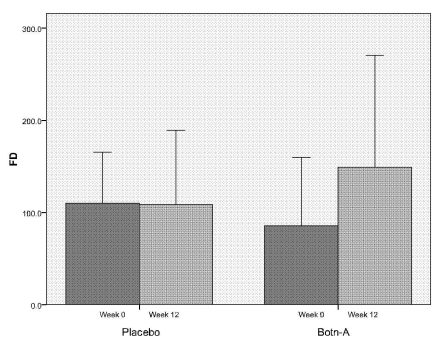


Figure 3: - First desire to void. An increase is observed in the botn-A arm although it does not reach statistical significance.  
209x297mm (300 x 300 DPI)

Figure 4

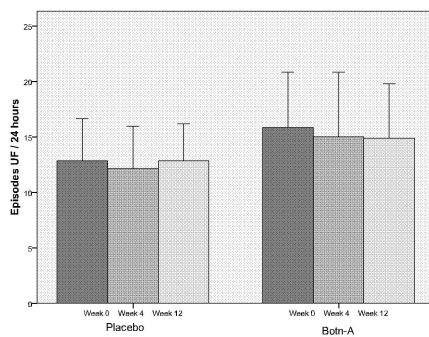


Figure 4: - Episodes of urinary frequency at weeks 0, 4 & 12. No significant differences were detected and no trends were evident.  
209x297mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 5

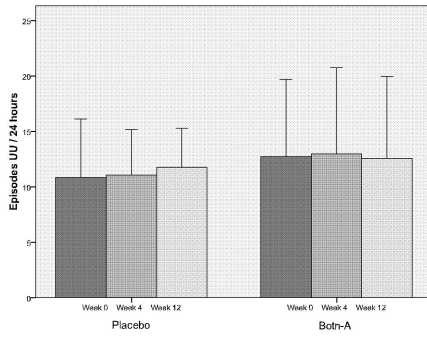


Figure 5:-Episodes of urinary urge at weeks 0, 4 & 12. No significant differences were detected and no trends were evident.  
209x297mm (300 x 300 DPI)

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Figure 6

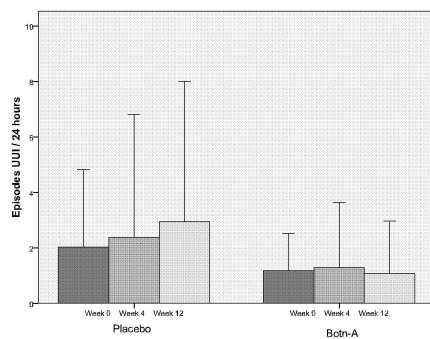


Figure 6: - Episodes of urge urinary incontinence at weeks 0, 4 & 12. There is no significant difference detected and no trends observed.  
209x297mm (300 x 300 DPI)