THE OUTCOMES OF INTRAVESICAL BOTOX A INJECTIONS IN PATIENTS WITH REFRACTORY OVERACTIVE BLADDER SYNDROME TREATED IN GSH FROM 1 JANUARY 2016 TO 31 DECEMBER 2018

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DECLARATION

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Abstract

Over the last 50 years botulinum toxin has become an effective medical therapy, used in a variety of specialities for different indications. A growing body of evidence indicates its beneficial effects in treating medication refractory detrusor over activity. This modality of treatment has been offered at Groote Schuur Hospital (GSH) in South Africa since 2012. Therefore, a review of our outcomes is necessary.

Objective:

Primary:

1. Determine the subjective success following intravesical Botox injections for the treatment of OABS.

Secondary:

1. Describe the population of patients receiving intravesical Botox injections for the treatment of refractory OABS

2. Determine the rate and type of complications associated with intravesical Botox injection and the duration of treatment success.

3. Determine any patient factors associated with shorter duration of treatment success following the treatment of refractory OABS with intravesical Botox injections

Methods:

We conducted a quantitative, descriptive, retrospective study. The data collection sheet included the following details from the participants: demographic details, pre-existing medical conditions, method of diagnosis, and any previous treatment, the reason for stopping previous treatment, intra operative details and early complications at 1-6 weeks. Also included were details of any symptoms at follow up visits at 6- and 12-months post procedure. Subjective success was defined as the patients reporting improvement of symptoms at the first follow up visit. Duration of treatment success was defined as the time that lapsed between the date of Intravesical Botox injections and when the patient requested repeat treatment.

Inclusion and exclusion criteria:

We included patients who received intravesical Botox injections for OABS from 1 January 2016 - 31 December 2018. We excluded those who received intravesical Botox treatment for reasons other than OABS.

Statistical analysis:

A sample of 50 subjects was used. Summary statistics for age were reported as mean and standard deviation. Categorical variables were reported as simple frequencies and percentages. Associations between categorical variables were evaluated using the Fisher's exact test. Groups were compared in terms of age using the Tow-sample Mann-Whitney test. Analyses were performed using Stata Version 16.

Results:

The age of our participants ranged from 25 to 85 years (m = 54.72, ds = 14.74). 36% were post- menopausal, 92% were para 1 or more, 52% had a BMI of more than 30 kg/m^2, 30% were smokers, 40% were hypertensive and 10% had diabetes mellitus.

All the patients reported improvement of symptoms at the 2-6 weeks' follow-up review. At the 6 months follow up visit less than a third of the participants complained of overactive bladder symptoms with only four (8%) patients requesting repeat intravesical Botox treatment. At the 12 months follow up visit just over half of the patients were experiencing overactive bladder symptoms with 21 (42%) requesting repeat intravesical Botox injections. There were few complications related to the intravesical Botox injection procedure. All the procedures were performed under local anaesthesia none of which needed to be abandoned due to pain of bleeding. Seven (14%) patients required temporary clean intermittent catheterisation (CIC). Eight (16%) patients had experienced a UTI (urinary tract infection) by the six weeks follow up visit.

We found that hypertensive patients were significantly more likely to request repeat Botox at six months compared to non-hypertensive patients. Fisher's exact of 0,020. No other patient related factors showed any significant association in relation with repeat Botox injections at 6 months and 12 months.

Conclusion: Our findings confirmed the benefit of intravesical Botox injection treatment in patients with OABS with minimal complications.

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Abbreviations

BMI:	Body mass index
Botox:	Botulinum toxin
CIC:	Clean intermittent catheterization
DO:	Detrusor over activity
Epilus:	Epidemiology of lower urinary symptoms survey
GSH:	Groote Schuur hospital
HREC:	Human Research Ethics Committee
LUTS:	Lower urinary tract symptoms
MCC:	Maximum cytometry capacity
NOBEL:	National overactive bladder evaluation
NK:	Natural killer
OABS:	Overactive bladder syndrome
PVR:	Post void residual
SPSS:	Statistical package for the social sciences
SUI:	Stress urinary incontinence
UCT:	University of Cape Town
UI:	Urinary incontinence
UK:	United Kingdom
USA:	United States of America
UTI:	Urinary tract infection
UUI:	Urge urinary incontinence

Chapter 1: Introduction and Literature review:

1.1 Introduction

Overactive bladder syndrome (OABS) is a syndrome consisting of urinary frequency, urinary urgency, and nocturia with or without incontinence. We will adopt the definition of OABS as per The Nobel and Milson studies. They specified the definition of OABS as being urinary urgency with or without urge incontinence, in the absence of pathologic or metabolic factors that would otherwise explain the symptoms.[1] This will exclude medical conditions such as diabetes, heart failure, multiple sclerosis, Parkinson's disease, spinal cord injury, cancer, interstitial cystitis, pregnancy. The overactive bladder is classified as wet when occurring with urge urinary incontinence. Overactive bladder dry occurs without urgency incontinence.

The symptoms of OABS significantly decrease socio-economic and quality of life and can lead to depression and anxiety.

Patients with overactive bladder can be treated with combination of conservative measures, which include lifestyle changes, caffeine intake reduction, pelvic floor exercises and bladder drill. Once this fails to address symptoms, one of a range of the available medical treatment options such as anticholinergic medication (e.g. oxybutynin, tolterodine, solifenacin, tropium) and b3 receptors agonists such mirabegron are considered. The majority of clinicians may try two or more oral medications first, before moving onto a second-line treatment, which currently include implantable sacral nerve stimulators (which is not available in Groote Schuur Hospital) or intravesical botulinum toxin A. Botulinum toxin (BoNT-A) has rapidly became established as a treatment option for refractory overactive bladder (OAB) Onabotulinumtoxin A (Botox) has been available at Groote Schuur Hospital since 2012.

Many recent randomized trials together with physician survey of Onabotulinumtoxin A (Botox) in patients suffering symptoms of OABS have demonstrated that injection of the toxin into the detrusor of adults with OABS who have failed conservative and anti-cholinergic therapy has beneficial effects both in clinical and urodynamic parameters. The duration of effect of Botox may range from six to 12 months, with symptom improvement seen as early as 2 weeks post injection of the Botox.[2]

1.2 Epidemiology and symptoms of overactive bladder

Overactive bladder (OAB) affects both men and women. It may have a significant impact on overall quality of life, sexual function, sleep, and mental health. Many randomised controlled trials (RCTs) have studied the prevalence of OAB in developed countries and assessed the impact it has on quality of life. The Epic study studied the prevalence of lower urinary tract symptoms (LUTS) and OAB. It was conducted in five countries; Canada, Germany, Italy, Sweden, and the UK with a high number of participants (64238). Results showed an overall OAB prevalence of 11.8%, with no significant difference in terms of prevalence among men and women.[3, 4]

The findings of the Epilus (the epidemiology of lower urinary tract symptoms survey) study, a population –based, cross-sectional survey conducted in the US, UK, and Sweden to assess the prevalence and bother of OAB opposes the commonly held misconception that OAB symptoms affect mostly older individuals. However, there is clear evidence that the symptoms of overactive bladder increased with age in both sexes. [5]

Most of the patients with OAB have a combination of symptoms. Urgency with or without urinary incontinence in the absence of frequency or nocturia is present in 23% of women. Estimated half of patients with OAB have a combination of at least two symptoms, and approximately one-third of patients reported a combination of more than two OAB symptoms. It is also common to see patients who suffer all four symptoms of overactive bladder (about 7%). It is rare to see the symptom of frequency in the absence of nocturia (this occurs in only about 4% with OAB).[6]

In addition to the Epilus study, The National Overactive Bladder Evaluation (NOBEL) program was developed to estimate the prevalence of OAB and its burden in the United States. Izalco assessed the influence of gender on OAB and its symptoms. Similar to this study the NOBEL study had shown an overall OAB prevalence of 16% .[7] this study revealed that specific overactive bladder symptoms are more frequent in women with increasing age, especially after the age of 60 years. The association with age in overactive bladder is much stronger in females. Concurrently there is a steady increase with age of OAB in women throughout their lifetime.[7,]

There is good evidence of a relationship between body mass index (BMI) and the presence of urge urinary incontinence. Women with an increased BMI above 30 (unit of measure) were two times more likely to develop detrusor over activity with urge UI than those with BMI less than 24. [9]

In addition, the Epilus study, a population –based, cross-sectional survey conducted in the US, UK, and Sweden to assess the prevalence and bother of OAB therefore to update the results NOBEL. This RCT concludes that, the prevalence of OAB is directly proportional to the age.

Moreover, Milson et al conducted a population-based prevalence study to determine the prevalence and symptoms of OAB. This was also a multinational survey including France, Germany, Italy, Spain, Sweden, and the UK with many participants, 16.776 men and women aged more than 40 years. This study used very specific definition of OAB as well as stress incontinence and found an overall prevalence of OAB symptoms to be 16.6%, similar to the Nobel study. [10] The Milson study also examines the frequency at which overactive bladder patients sought medical consultation and treatment. It revealed that about 17.4% of women were likely to report their symptoms.[11] When individual symptoms were assessed, it was revealed that frequency was reported in 85% of participants, urgency in 54% and urge continence in 36%. Frequency was therefore the most predominant symptom. These symptoms increased with increasing age as established in previous studies. The prevalence of OABS in women also a gradually increases up to the age of 60 years, with levelling off seen between 60years and 70 years of age then there is again a progressive increase after 75 years of age. [12]

With regards to quality of life for patients with OAB symptoms, several studies have shown the significant negative impact that OAB has on daily activities, including mental health and sexual Function. The Milson study showed that 65% of participants reported that OAB symptoms adversely affect their quality of life. Medical consultation in this population was high in this study (approximately about 61%) however, less than one-third of patients who sought medical consultation received treatment. The patients sought medical attention as often for frequency and urgency symptoms as they did for urge incontinence. About two –third of participants with OAB had tried a number of conservative management options to reduce their symptoms such as reducing fluid intake, exercise and the use of absorbent products in addition to medical management of OAB.[13, 14] about age, the older patients are more likely to seek medical help than younger patients with overactive bladder. Lack of awareness of effective treatment for overactive bladder was among the reasons for younger patients not seeking medical help.

In addition, the review by Irwin et al of the Epic study demonstrated that the degree of bother among OAB suffers increased as the number of lower urinary tract symptoms increased. The

study concluded that in patients suffering urgency alone, only approximately 8% were bothered by their symptoms. In the women that presented with symptoms of urgency in addition to any other lower urinary tract symptoms, approximately 33% of expressed discomfort from their symptoms. The prevalence of bother increased remarkably in those who presented with at least two lower urinary tract symptoms together with urgency. Indeed, the trial concluded that the likelihood of bother increases proportionally with the increasing number of urinary tract symptoms 90% with all four OAB symptoms reported bothering at some time .[15, 16, 17]

The effect of nocturia on quality of life is controversial as some experts believe that nocturia is part of normal urination pattern.

Several RCT have evaluated the prevalence of overactive bladder and looked at establishing the impact that it has on quality of life. The significant and variable findings of these studies have been presented above. Some of these findings are contradictory and confusing. Nevertheless, there are some common threads, which include; overactive bladder is common in men and women, the prevalence of OAB and its symptoms increase with age. Furthermore, it is important to note that isolated symptoms are quite rare. It is much more common to have a combination of symptoms with frequency being the most commonly reported symptom. There is evidence that overactive bladder has significant impact on the quality of life, quality of sleep, and mental health. In addition, the level of bother increases with relatively with the number of symptoms experiencing by the individual.

1.3 Diagnosis of OABS

Making the diagnosis of overactive bladder involves taking a good history, including a bladder diary, which can provide detailed information concerning behaviour and urinary habits. In addition, symptom questionnaires assist in detecting specific symptoms and its impact on quality of life. It is important to exclude any other medical conditions that can cause the symptom complex of urgency, urge incontinence, frequency and nocturia. A urine dipstick evaluation and a post void residual measurement would be standard investigations. Urodynamic studies and cystoscopy may be necessary if the diagnosis is in question or in refractory cases.

1.4 Treatment of OABS

Patients with overactive bladder symptoms are initially treated with conservative measures including lifestyle modifications such as reduction in caffeine intake, pelvic floor exercises and bladder drill before considering medical therapy such as anticholinergic medication (e.g.oxybutynin, tolterodine, solifenacine, tropium). Despite the variety of drugs available, patients usually abandon their use for multiple reasons such as refractory symptoms or the side effect such as dry mouth, dry, eyes, constipation or urinary retention. Mirabegron is a novel b3adrenoreceptor agonist, recently introduced and approved by USA food and drug administration for the treatment of OAB symptoms. Multinational randomized controlled trials have supported the efficacy and tolerability of the latter drug in the clinical setting of patients with OAB for up to twelve weeks of therapy. A phase III trial showed the safety and tolerability of 12-month treatment of mirabegron. Discontinuation due to adverse events was low both using 50mg and 100mg dose of mirabegron. Recently published phase II and phase III RTC have shown that the b-3 adrenoceptor selective agonist, mirabegron represents a valid medical option both for patients with OABS who are anti-muscarinic naïve, as well those where anti-muscarinic are ineffective or not tolerated. [19, 20, 21] Serious adverse effects incidence are threefold less than compare to tolterodine (anticholinergic). Many clinicians will consider oral agents before considering another option of treatment. The other options include implantable sacral nerve stimulators and botulinum toxin.

Botulinum toxin is a potent neurotoxin produced by the Gram–negative anaerobic bacteria clostridium botulinum. Toxin was first described in 1895 by Emile van Ermengem. [19, 20] in 1989 the Food and Drug Administration (FDA) approved Botox (onabotulinumtoxinA,) for the treatment of strabismus, blepharospasm and cervical dystocia in patients older than 12 years. In 2002 Botox was approved for cosmetic uses and in 2004 for the treatment of axillary hyperhidrosis. In 1988 Hallam et al.[21] use botulinum A toxin in a patient with intractable constipation caused mainly by anismus. Their promising results opened new possibilities of using botulinum toxin in patients with detrusor sphincter dyssynergia and eventually with overactive bladder syndrome.[22,23] In August 2011 the FDA approved Botox for the treatment of neurologic detrusor over activity, laryngeal dystonia, occupational cramps, tension headaches, and vaginismus[24,]

Today, seven antigenically distinct forms of botulinum toxin exist, including serotypes A, B, C, D, E, F and G [26,27] Only serotypes A and B are commercially available currently with serotype A, marketed as Botox or Dysport, or Xeomin, and serotype B as Myobloc. A Botulin

works by blocking the presynaptic release of acetylcholine causing complete or partial paralysis and weakening of the overactive detrusor muscle. Historically, intramuscular botulin injection was first approved in 1989 to treat strabismus and subsequently noticed to be effective in treatment of different disorders characterized by focal skeletal muscle hyperactivity. In addition, botulinum toxin was found to be effective first when injected into the detrusor of the patients with neurologic detrusor over activity as a result of spinal cord injury. [25] Since then multiple randomized controlled trials have demonstrated significant efficacy in ameliorating neurologic overactive bladder by reducing detrusor pressure and increasing bladder capacity therefore reducing episodes of incontinence and improving quality of life in-patient with neurologic incontinence. However, these improvements depend of the degree of impaired bladder emptying. A number of RCTs have shown that the mechanism of action is more complicated than a simple paralysis of detrusor or a simple returning of neuronal sensory receptors expression of the bladder to normal level.[26]

Furthermore, biopsies taken from patients after Botox injection demonstrated effective resolution of detrusor over activity. Another mechanism of action of botulin includes a complex inhibition of effect on vesicular release excitatory neurotransmitters and the axonal expression of other proteins thought to be important in, mediating the intrinsic or spinal reflexes, believing to cause neurologic detrusor over activity [26]

Sahai et al. reported the first randomized, double blind, placebo-controlled trial comparing the efficacy of BoNT/A versus placebo in the treatment of patients with idiopathic detrusor over activity IDO (when there is no defined cause) in males and females [27]. BoNT/A of 200 U (10 U/ml) was injected at 20 sites with trigone sparing. Significant increases in maximum cytometry capacity (MCC) from 182ml to 313ml was observed at 4 weeks. BoNT/A also reduced the episodes of frequency (mean change from 15.44 to 7, 93 per day).

Some trials have been designed to evaluate the outcome of the lower dose BoNT/A 100mgU in the treatment of refractory idiopathic detrusor overactivity (IDO). In a small scaled study (10 Botox versus 11 placebo), Dowson et al. reported that Botox could significantly increase the mean MCC by 105ml, but storage symptoms and quality of life remained statistically unchanged following Botox injection.[28,29]

Chappelle et al. conducted a study on Botox injection 100 U versus placebo in 558 patients of either sex and showed different results. Botox injection not only decreased urinary incontinence

(UI) episodes (mean change from 5.5 to 2, 55 / day versus5, 7 to 4,67 /day for placebo at 12 weeks) but also improved other symptoms such as urge urinary incontinence and quality of life. [29, 30]

To assess the dose response relationship of intra detrusor BoNT/A, Dmochowski et al. conducted a trial using Botox doses, ranging from 50U to 300U administered as 20 intra detrusor injections for patients with OAB. They found durable efficacy for all BoNT/A dose groups of 100U and above. Similarly, Fowler et al. confirmed that by 2 weeks BoNT/A at doses of 100 U or more produced significantly greater improvements than placebo in health related quality of life questionnaires. This was sustained for up to 36 weeks. Denys et al. performed a trial to evaluate the efficacy and tolerability of low doses of BoNT/A of 50U, 100 U and 150U compared to placebo in patients with idiopathic OAB. They reported more than 50% improvement from baseline in urgency and UUI at 3 months in 65% and 56% patients receiving 100 U and 150 U respectively. Complete continence was also achieved in 55% and 50% after 100 U AND 150U respectively.[29]

The injection method of all the above studies was intradetrusor injection with trigone sparing in order to reduce the major adverse effect of vesicoureteral reflux. Nonetheless, 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. [31, 32,]

With regards to adverse events of BoNT/A injection, according to a meta-analysis of BoNT/A there was a significant increase in post void residual (PVR) (32,77ml versus 2.01 ml placebo), as well as increased incidence of urinary tract infection (19, 69% vs 5.94% placebo) and incidence of clean intermittent catheterization (8.41% vs 0.46% placebo).

When treating patients with neurogenic detrusor over activity NDO (when there is relevant neurologic condition), BoNT/A led to increased risk of haematuria and urinary retention. The risk of increased PVR was dose dependent, doses of more than 150 U were found to be associated with an increased risk of PVR above 200ml. In addition, age above 60 years with low flow rate on Urodynamic studies was associated with increased PVR after Botox injections. [34]

Over the last 50 years' botulinum toxin has become an effective medical therapy. It is used in a variety of specialities for different indications. A growing body of evidence indicates its

beneficial effects in treating medication refractory detrusor over activity, with minimal invasive intervention. This modality of treatment has been practised at Groote Schuur Hospital (GSH) in South Africa since 2012, with a recent increase in demand. Therefore, a review of our outcomes is necessary.

Chapter 2: Methods

2.1 Study hypothesis: Botulinum Toxin A (Botox) injections for refractory Overactive Bladder Syndrome is associated with good treatment outcomes and minimal side-effects.

2.2 Study setting and Population

Groote Schuur Hospital is a tertiary level hospital in the city of Cape Town, South Africa. Patients with refractory overactive bladder syndrome are referred to our Female Continence Clinic, which is a combined Urology and Urogynaecology clinic. At this clinic, patients with refractory OAB are assessed for the need for treatment with intravesical Botox. Patients qualifying for Intravesical Botox treatment at Groote Schuur Hospital have usually failed treatment with anticholinergic drugs or have intractable side effects on that treatment. A small number of patients have medical conditions for which anticholinergics are contra-indicated. Up until the writing of this document the only anticholinergic that is available at Groote Schuur Hospital for the treatment of OABS is Oxybutanin. Those who qualify for intravesical Botox treatment have the procedure performed in C6 Day Theatre under local anesthesia or general anesthesia. The patients are discharged on the same day after successfully emptying their bladder. Our study participants were derived from these patients.

Following the treatment with intravesical Botox injections, the patients are reviewed at 1-6 weeks at the Female continence clinic. After this they are seen at 6 monthly intervals to re-assess their symptoms and determine if or when repeat therapy is necessary.

2.3 Aims and Objectives

Aims: The aim of this study was to determine the success rate of intravesical Botox for the treatment of refractory OABS. In addition, we aimed to determine the complication rate and the duration of treatment success following a single treatment episode.

Study objectives:

Primary:

1. Determine the subjective success following intravesical Botox injections for Overactive bladder syndrome (OABS).

Secondary:

1. Describe the population of patients receiving intravesical Botox injection
2. Determine the rate and type of complications associated with intravesical Botox injection and the duration of treatment success.

3. Determine if there are any patient factors associated with shorter duration of treatment success.

For the purpose of this study subjective treatment success was defined as the patient reporting cure or an improvement in her symptoms of overactive bladder at the 2-6-week follow-up visit. The duration of treatment success was defined as the period from the time of initial Botox injection until the patient requested a repeat dose of Botox.

2.4 Inclusion criteria and exclusion criteria

We included all patients who received their first intravesical Botox injections from 01 January 2016 – 31 December 2018. We excluded those who received intravesical Botox for reasons other than OABS or had an abnormal cystoscopy.

2.5 Study design

We conducted a quantitative, descriptive, retrospective study. Participants were identified using the C6 theatre register. We used convenience sampling and included all the patients that had intravesical Botox therapy in the study period and met the inclusion and exclusion criteria. Folders of all the patient were retrieved and examined in order to extract demographic, clinical and outcome data. No standardised questionnaire was used during the study period, clinical notes were used as a substitute. A purpose designed data collection sheet was used to collect the necessary data (see appendix one). This data was entered into an excel spreadsheet for data analysis.

2.6 Statistical analysis

A sample of 50 subjects was used. Summary statistics for age were reported as mean and standard deviation. Categorical variables were reported as simple frequencies and percentages. Associations between variables were evaluated using the Fisher's exact test and cases that requested repeat Botox were compared to those that did not in terms of age using the Tow-sample Mann-Whitney test. Analyses were performed using Stata Version 16.

Chapter 3: Results

An initial search yielded 61 patients from the C6 theatre registrar that received intravesical Botox injection treatment during the inclusion period from 01 January 2016 to 31 December 2018. One patient was excluded because of an abnormal cystoscopy finding. Ten patient files were missing and could not be included in the study. Fifty patients were included in the study with n=50.

3.1 Participants Demographic details

The mean age of the participants was 55.22 years with a median of 54.5 and maximum age of 85 years old. The youngest patient was 25 years old.

Table: 1A variable age

age	N	Min	Mean	P^{50}	Max	ad	iqr
	50	25	54,22	54.5	85	14.74413	18

Table: 1B Patient demographic details (n=50)

Demography & Risk factors	N = 50	%
Black	5	10
Mixed race	22	44
White	23	46
Post- menopausal	18	36
Parous women	46	92
Nulliparous	4	8
BMI more than 30 kg/m^2	26	52
BMI not documented	19	38
Smokers	15	30
Smoking status not documented	9	18
Hypertensive	20	40
Diabetic	5	10

In terms of the demography of the patients, 18(36%) were post-menopausal and 32(64%) premenopausal. Five (10%) participants were black, 22(44%) mixed race, and 23(46%) white.

Four patients (8%) were nulliparous, 6 (12%) were para 1 and 40 (80) were multiparous women. Five (10%) participants had a BMI of less than 30kg/m^2, and 26 (52%) had a BMI of more than 30 kg/m^2, unfortunately in 19 (38%) the BMI was not documented. Fifteen (30%) were smokers while 26 (52%) were non-smokers, in nine participants (18%) the smoking status was not documented. Five participants (10%) were diabetic and 20 (40%) were hypertensive.

3.2 Diagnosis and previous treatment of OABS

This study showed that only two (4%) of patients had their diagnosis of OABS made by clinical findings alone (history, examination and urine dipstick) whereas in 48 (96%) patients the diagnosis was made by a combination of history, examination and urodynamic studies.

When assessing previous treatment for OABS and reasons for abandoning previous treatments, this study revealed that 43 patients (86%) had bladder training with a pelvic floor physiotherapist prior to Botox treatment, while 49 (98%) had prior treatment with oral anticholinergics. More than half (58%) of the patients abandoned the previous oral anticholinergic treatment due to intolerable adverse side effects, while 42% stopped treatment because of refractory symptoms.

3.3 Intravesical Botox injection procedure

When looking at the technique, dose and sites of intravesical Botox injection, this study shows that all the patients included in the study had the procedure performed under local anaesthesia. Local anaesthesia included topical Remicaine gel. No intravesical anaesthetic instillation or conscious sedation was given for any of the patients in the study.

In 92% (46) of patients a dose of 100IU Botox was used; while in only four patients (8%) a Botox dose of 200 IU was used. The reason for this was not clearly documented in the folders. In all patients included in the study, the 100 or 200 IU of Botox was diluted into 20 ml of saline and injected into 20 injection sites across the dome of the bladder.

With regards to cystoscopy findings prior to the injection of Botox, in 40 (80%) patients the cystoscopy was documented as normal, however in 10 patients (20%) the findings were not documented.

When looking at the intra operative complications of the intravesical Botox injections, our study found that five (10%) patients had some degree of bleeding during the procedure. Pain during the procedure was documented in only 8% of patients. Neither the pain nor the bleeding was severe enough to require that the procedure be abandoned.

Table 2: Intraoperative complications of intravesical Botox injection. (n=50)

Intra and post -operative complications	N=50	Percentage
Bleeding	5	10
Patient feeling pain during procedure	4	8
Procedure abandoned for pain of bleeding	0	0

3.4 Treatment outcomes

All fifty (100%) patients reported subjective cure or improvement in their symptoms of OABS at the two to six week follow up clinic visit.

Table 3: Symptoms and complications at 2 to 6 weeks following intravesical injection (n=50)

Symptoms & Complications assessment	Number	Percentage
Subjective improvement	50	100
Urgency	4	8
Nocturia	3	6
Urge urinary incontinence	4	8
Voiding dysfunction	6	12
SUI (stress urinary incontinence)	1	2
UTI	8	16

In terms of OABS symptom specific assessment at the initial (2 to 6 weeks) follow up, our findings were that: urgency was present in 4 (8%) and nocturia was present in 3 (6 %) of participants. Urge urinary incontinence was present in four (8%) patients. Symptoms of incomplete voiding were present in six (12%), all of which had a PVR of more than 150 ml, 7 (14%) required CIC (clean intermittent self-catheterisation). The duration of CIC was poorly documented in the folders. SUI was present only in one (2%), while 8 (16%) had a suspected urinary tract infection (UTI) on urine dipstick.

Table 4 Symptoms at 6 months following intra vesical Botox injection (n=50)

Symptoms & Complications assessment	Number	Percentage
Urgency	14	28
Nocturia	11	22
Urge urinary incontinence	14	28
Voiding dysfunction	13	26
SUI (stress urinary incontinence)	2	4
UTI	1	2
Requested repeat intra vesical Botox injection	4	8

At the 6-month follow-up visit, urgency was present in 14 (28%). Nocturia was present in 11 (22%). Urge urinary incontinence was present in 14 (28%). Voiding dysfunction was present in 13 (26%). SUI was present in two patients (4%); whereas suspected UTI on urine dipstick was present in only one (2%). At this visit only four (8%) patients requested to repeat intravesical Botox injection treatment for recurrence of overactive bladder symptoms. In another two patients (4%) the ongoing management plan was not documented.

Table 5: Symptoms and complications at 12 months following intra vesical Botox injection (n=50)

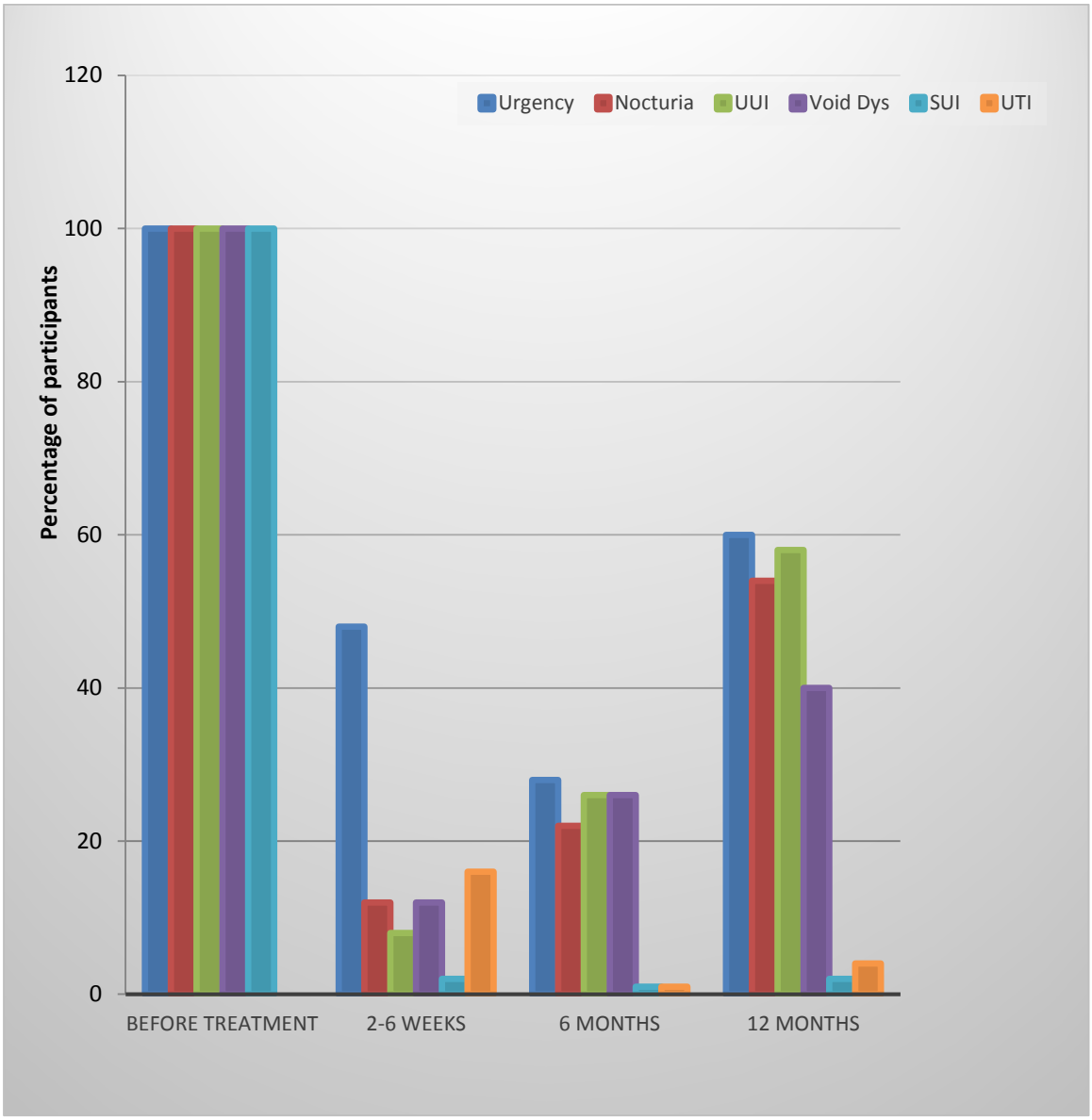
Symptoms & Complications assessment	Number	Percentage
Urgency	30	60
Nocturia	27	54
Urge urinary incontinence	29	58
Voiding dysfunction	20	40
SUI (stress urinary incontinence)	1	2
UTI	4	8
Requested repeat intra vesical Botox injection	21	42

The OABS symptom specific assessment at 12 months follow up showed a recurrence of symptoms as follows: urgency was present in 30 (60%) participants, nocturia in 27 (54%), urge urinary incontinence in 29 (58%) and symptoms of incomplete voiding in 20 (40%). Whereas SUI was present in only 1(2%) patient, and suspected UTI in 4 (8%). Twenty-one (42%)

patients requested a repeat dose of intravesical Botox for recurrence of symptoms of OABS at 12 months.

Below is a summary of the OAB symptoms experienced by the participants from the time of initial injection until the 12 month follow up visit. It shows a marked improvement of symptoms, followed by a return of symptoms at 6 and 12 months as depicted.

Figure 1: Summary of OAB symptoms over the duration of the study period



3.5 Patient factors associated with shorter duration of treatment success

Furthermore, we attempted to assess whether there were any patient specific factors which effected the duration of efficacy of the intravesical Botox treatment. We used the request for repeat Botox treatment at 6 months as an indication of poor efficacy. We compared the group of women who requested repeat Botox at 6 months (n=4) with those who did not request repeat treatment at 6 months (n=46). We looked at several variables, including age, BMI, menopausal status, co-morbid medical conditions (diabetes and hypertension) and smoking status. Unfortunately, due to the retrospective nature of the study, some of the information regarding these variables was missing from participant folders.

3.5.1 Hypertension

We considered the association between Hypertension and repeat Botox at 6 months. There were no cases in the non-HPT group that required repeat Botox at 6 months, while there were 4 (21.05%) cases in the Hypertension group that required repeat Botox at 6 months. Our hypothesis was that the odds of repeat Botox at 6 months is associated with hypertension status. We applied the two-sided Fisher's exact probability test which gave us a p value of 0, 020. The p-value is less than 0.05 and thus we concluded that repeat Botox at 6 months is associated with HPT.

3.5.2 BMI

We assessed the impact of BMI (body mass index) in relation to repeat Botox injection treatment at 6 months. The findings reveal that none of the five patients with a BMI of less than 30 required repeated Botox at 6 months. However, three (11.54%) out of 26 women with a BMI of more than 30 requested a repeat Botox treatment at 6 months. This is not statistically significant.

3.5.3 Menopausal status

Our results show that a slightly larger proportion of post menopause cases (10%) required repeat Botox at 6 months compared to the pre-menopausal cases (5%), however this did not reach statistical significance.

3.5.4 Smoking

We only had information with regards to smoking status from 39 of the 50 participants. Given the data available, no association was found between smoking status and the request for repeat Botox at 6 months.

3.5.5 Diabetes mellitus

When looking at the impact of diabetes mellitus in relation to repeated Botox injection treatment at 6 months, the study did not show any significant impact. Among 40 non-diabetic patients only 3 (7%) required repeat Botox at 6 months, whilst one patient among non-diabetic required repeat Botox injection at 6 months. This was not statistically significant.

3.5.6 Patient risk factors associated with repeat Botox at 6 months and 12 months

The number of women requesting repeat Botox at 6 months was low (n=4), we therefore decided to compare the group of women that requested repeat Botox at 12 months (n=21) to the group that did not request repeat Botox at 12 months (n=25). Although the number of patients requesting repeat Botox injection at 12 months was increased to 42% compared to the 8% at 6 months, statistical analysis at 12 months did not reveal any patient related risk factors (Menopausal status, BMI, DM, Parity, Smoking or hypertension) that were associated with the need for repeat Botox at 12 months.

This table summarizes the number of patients with each specific risk factor that required Botox at 6 months and 12 months.

Table 6: Summary of patient risk factors in relation to repeat Botox at 6 months and 12 months

Demography & Risk factors	6 months N (%)	12 months N (%)
Post- menopausal Patients	3/30 (10)1/30(3)	1/30(3)
Pre-menopausal Patients	1/18 (5.5) 0/18(0)	0/18(0)
Parous women	4/46 (8)2/46(4)	2/46(4)
Nulliparous	0/4 (0)0/4(0)	0/4(0)
BMI > 30(more than 30)	3/26 (11.5)4/26(15)	4/26(15)
BMI <30(less than 30)	0/5 (0)	0/5 (0)
Smokers	1/14 (7)2/14(14)	2/14(14)
Non-smokers	2/25(8)	3/25(12)
Non –Hypertensive	0/28(0)	1/28(3)
Hypertensive	4/19*(21)	5/19(26)
Diabetic	3/40(7)	4/40(1)
Non diabetic	1/5(20)	1/5(20)

*statistically, significant Fisher exact of 0, 020

Chapter 4: Discussion and Conclusion

4.1 Discussion

4.1.1 Summary of key findings

This study assessed the outcome of intravesical Botox injections in 50 patients with refractory OABS by investigating subjective improvement, post-operative complications, the duration of efficacy of intravesical Botox as well as the impact of patient individual risk factors in relation to Botox efficacy was explored. We found that the intra-operative complications were minimal, none of which required the procedure to be abandoned. All our participants reported subjective cure at the initial follow up visit with a significant improvement in the symptoms of OAB. There was a gradual return of OAS symptoms over the next 12 months, however only approximately half of the participants were complaining of OAB symptoms at 12 months and were requesting repeat treatment. The only risk factor identified to be related to a shorter duration of treatment was hypertension.

4.1.2 Previous treatment of OABS

Our study agrees with what has been shown in the literature about poor continuation rates of anticholinergic treatment due to intolerable side effects or inefficacy. A UK study looking at prescription data from a longitudinal patient database retrospectively assessed persistence to several anticholinergic drugs. After 12 months, on average only one third of patients were still taking their anticholinergic medication [36]

Almost all the patients in our study had been previously treated with anticholinergic drugs for their OABS. Our study revealed the 58% of our patients had abandoned anticholinergic treatment due to adverse side effects, while 42% stopped because of refractory symptoms. This high light the importance of an alternative treatment option being readily available for the treatment of OABS.

4.1.3 Intravesical Botox treatment outcomes

Our findings reveal excellent subjective response to intravesical Botox injection treatment at the initial follow-up visits. All patients reported improvement of their symptoms at the 2-6 weeks' review.

These findings are in keeping with several previous studies that have demonstrated the efficacy of intravesical Botox injection treatment of OABS patients. Deffontaines-Ruffin et al in 2011

looked at 71 patients with an intravesical Botox dose of 300 IU; 46% of patients were continent and 31% improved at three months after the injections. [36]

Giannantoni et al in 2011 looked at the efficacy of intravesical Botox injection treatment for OABS in eight patients using 100 IU Botox. They found that 100% of patients had decreased urinary frequency and urinary incontinence episodes, improved quality of life and urodynamic findings. Similarly, Khan, et al conducted a retrospective study on 46 patients with OABS using 100 IU intravesical Botox and found a 78% improvement of symptoms for up to nine months. [37]

Furthermore, our findings reveal improvement of symptoms beyond 12 months in more than half of the participants. Only 4 (8%) patients required repeat Botox at 6 months and 21 (42%) at 12 months. This is in keeping with report of Apostolidis et al in 2009 that reported that intravesical Botox injection has a mean duration of efficacy of approximatively seven to nine months.[38]

This study shows few complications related to Botox injections. Seven (14%) patients only required CIC (clean intermittent catheterisation), and urinary tract infections were documented in eight (16%) patients at initial review, then one (2%) at 6 months and four (8%) at 12 months. This is in keeping with the results of a meta-analysis, of BoNT/A showing significant increase in post void residual (PVR) (32, 77ml versus 2.01 ml placebo), as well as increased incidence of urinary tract infection (19, 69% vs 5.94% placebo) and incidence of clean intermittent catheterization (8.41% vs 0.46% placebo).

4.1.3 Patient factors associated with shorter duration of treatment success

Our findings reveal that hypertensive patients were more likely to request repeat Botox treatment at six months than non-hypertensive patients.

This may be linked to the fact that hypertensive patients are being treated with diuretics, which may increase the volume of urine voided. This will in turn worsen frequency and urgency and could result in the recurrence of bothersome OABS symptoms occurring earlier. Other individual risk factors such as DM, menopausal status, and parity did not show any significant difference in relation to the need to repeat Botox injection treatment at 6 months and 12 months.

4.2 Conclusion

This is the first South African study evaluating the efficacy of intravesical Botox for the treatment of refractory overactive bladder syndrome. Our findings confirm the study

hypothesis that intravesical Botulinum Toxin A (Botox) injections for refractory Overactive Bladder Syndrome is associated with good treatment outcomes and minimal side-effects. All of our patients reported a subjective cure or improvement in their OABS symptoms two to six weeks following treatment. These symptoms improved for at least 12 months in half of the participants. Very few complications were reported.

In view of all above, Botox injection treatment, should be an option for all patients in our setting with overactive bladder symptoms refractory to medical treatment unless contra-indicated.

4.3 Study limitations

We cannot draw an inference for all South African patients as this study was performed in a specific region of the Western Cape where the population may not be representative of the rest of the South African population. In addition, as with any retrospective study, we were limited in getting certain necessary detailed information due to not having a structured patient questionnaire. A prospective study is recommended in the future.

4.4 Study strengths

Our sample size is comparable to many of the previous studies investigating outcomes in patients treated with intravesical Botox.

This is the first study to assess the effectiveness of intravesical Botox injection in Africa in general and particularly in a South African population.

This study may be of relevant value in helping the urogynaecology services to elaborate a protocol to be used for patients seeking intravesical Botox injection treatment and their follow up.

Conflict of interest

There is no conflict of interest for this study

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APPENDICES

Appendix 1: Data collection sheet

PATIENT FOLDER NUMBER: _____

Date of Birth

STUDY NO.: _____

DATE OF BOTOX INJECTION:

_____

Demographics:

1. Age:	
2. Menopausal STATUS 1) pre 2) post	
3. Population Group 1) Black South African 2) Colored 3) White 4) Asian	
4. Smoker 1) Yes 2) No 3) Not documented	
5. BMI 1) <30 2) >30 3)Not documented	

6. Parity 1) Nulliparous 2) Parous 1 3) 2 or above	
6 DM (Diabetic mellitus) 1) No DM 2) well controlled DM 3) uncontrolled DM 4) Not documented	
7 HPT (Hypertensive) 1) No HPT 2) well controlled HPT 3) uncontrolled HPT 4) Control not documented 5) Diabetic status not documented	

OAB METHOD OF DIAGNOSIS

8 How was the diagnostic of OAB made 1)By clinical assessment only (history, examination and urinalysis) 2)BY clinical assessment together with Urodynamic study	
9 PREVIOUS TREATMENT previous treatment with bladder retraining 1. Yes 2. no Previous Anticholinergics 1 Yes < 6 months 2 Yes > 6 months 3 No	

Vaginal oestrogen 1.Yes 2. No 3. Not documented Other (specify)	

Reasons for abandoning previous treatment and seeking Botox injection, Botox administration

Type of anesthesia, dosage, site and number of injections

10 Reason of stopping Anticholinergics 1) Sides effects 2) Refractory symptoms 3) Side effects and refractory symptoms 4) No supply and/or unable to afford the cost 5) Other reasons (Specify)	
11 Type of anesthesia used 1) Local – remicaine jelly 2) GA 3) Other (specify) ----------	
12 What dose of Botox was used 1) 100 mg 2) 200mg 3) Not documented 4) Other (specify) _____	
13 Number of injection sites 1) 10 2) 20 3) Other	

Botox Dilution

14 How many mls of N/Saline were used to dilute Botox for injection 1) In 10 ml 2) In 20 ml 3) Not documented	

Cystoscopy finding prior to Botox INJECTION

15 what was the Cystoscopy finding before Botox injection 1 Cystoscopy findings in keeping with OABS 2 Cystoscopy finding were abnormal 3 3. Not specified	

Intraoperative events:

16 was there intra operative difficulty Bleeding 1 Yes 2 No Patient feeling pain – requiring procedure to be aborted 1) Yes 2) no Poor visualization 1.Yes 2.No 3.No any adverse events documented	

Follow up Period

17. What was the initial follow period 1) 1-2 weeks 2) 6 weeks	

18. Post void residual at initial follow-up 1) Less than 150 ml 2) More than 150 ml	
19 Required CIC 1) Yes 2) no	
20 History or documentation of UTI since the procedure 1) Yes 2) no	

Symptoms assessment at initial follow up, (2 to 6 weeks follow up after botulinum injection)

21 Subjective impression of improvement 1) Yes 2) No Not documented	
22 Urgency 1) Improved 2) Unchanged 3) Worse 4) absent 5) Absent 6) Not documented	
23 Nocturia -more than 2x 1) Present 2) Absent 3) Not documented	
24 Urge 1) Present 2) Absent 3. Not documented	
25 Symptoms of voiding dysfunction	

1) Yes 2) No 3) Not documented	
26 SUI 1) Yes 2) No 3) Not documented	

Symptoms assessment in 6 moths follow up after Botulinum injection

27 Urgency 1) Present 2) Absent 3) Not documented	
28 Nocturia – more than 2x 1) Present 2) Absent 3) Not documented	
29 Voiding dysfunction 1) Yes 2) No 3) Not documented	
30 SUI 1) Yes 2) No 3) Not documented	
31 URGENCY 1) Present 2) Absent 3) Not documented	
32 Patient requesting repeat Botox	

1) Yes 2) no	

Follow up in 12 months after Botulinum –A injection

33 Urgency 1) Present 2) Absent 3) Not documented	
34 Nocturia – more than 2x 1) Present 2) Absent 3) Not documented	
35 Voiding dysfunction 1) Yes 2) No 3) Not documented	
36 UTI 1) Present 2) Absent 3) Not documented	
37 Patient required Repeat Botox 1) Yes 2) Not 3) Not documented	

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12 March 2019

HREC REF: 725\2019

Dr K Bronsard
Obstetrics & Gynaecology
H-Floor, OMB

Dear Dr Bronsard

PROJECT TITLE: THE OUT COME OF INTRAVESICAL BOTOX INJECTION FOR PATIENTS WITH REFRACTORY OVERACTIVE BLADDER SYNDROM TREATED AT GROOTE SCHUUR HOSPITAL
FROM 01 JAN 2015 TO 31 Dec 2018 (MMED Candidate - Dr K Aoloko)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanresearchethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledges that the student, Dr Kibedi Aoloko will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON: EHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001833.
International Review Board (IRB) number: IRB00001838

HREC 725\2019