Intermittent catheterisation after Botulinum toxin injections: the time to reassess our practice

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Abstract

Introduction

Botulinum toxin has become a widely adopted treatment for patients with recalcitrant overactive bladder (OAB) symptoms. Some recommend the institution of clean intermittent self- catheterisation (CISC) if a post void residual exceeds 200 mls post treatment but there is no evidence for this recommendation. The aim of this study was to identify whether abstinence from CISC as a routine strategy for patients with a post void residual (PVR), post intra-detrusor botulinum toxin injections, is associated with any measureable adversity.

Methods

This was a cohort observation study. Patients with lower urinary tract symptoms (LUTS) attending a medical urology centre were observed pre and post botulinum toxin treatment. Intra-detrusal botulinum toxin injections were administered in the day treatment centre at a medical urology centre in London, United Kingdom. Patients were reviewed at follow up consultations to measure PVR.

Results

240 patients were studied; there were 215 women and 25 males. 196 patients (82%) received botulinum toxin injections and were not managed with CISC. 18% were using CISC prior to injections and continued. None of the 196 developed acute retention or significant voiding symptoms.

Conclusions

Our study indicates that routine administration of CISC based on an arbitrary PVR volume is unlikely to confer benefit. In order to avoid patients being deterred from botulinum treatment we recommend that CISC be reserved for those who have troublesome voiding symptoms as well as a raised PVR. It is unlikely that CISC, initiated on the basis of an arbitrary PVR volume would benefit the patient.

Key words

Botulinum, Intermittent, Catheterisation, CISC, PVR, UTI

Brief summary

CISC should not be initiated post botulinum toxin injections on the basis of an arbitrary post void residual, patients will not be harmed.

Introduction

Intra-detrusal injection of botulinum toxin has become a widely adopted practice in the treatment of patients with recalcitrant overactive bladder (OAB) symptoms. There is good evidence of efficacy with improved quality of life (1). The literature recommends that post-injection, patients found to have a post-void residual (PVR) urine ≥ 150 ml or ≥ 200 ml, should be started on clean, intermittent self-catheterisation (CISC) (2), but this discourages patients from undergoing treatment (3, 4) and some refuse repeat injections because they disliked or could not perform CISC (2). Given this barrier, it is surprising that there is no published evidence that justify the prescription of CISC on the indication of a PVR threshold. Why then should we be recommending an invasive treatment in the absence of evidence to justify it?

Complete urine retention and unpleasant voiding symptoms relieved by CISC would seem strong indications for CISC. There is a number of consensus statements which define PVR volumes beyond which CISC should be initiated, but they do not reference evidence of validation (5). Some might argue that CISC be used to protect against hydronephrosis, as is the

case after spinal cord injury, but botulinum toxin reduces detrusor contractility (6) obviating the risk unless complete retention occurs. Thus, there has to be legitimate doubt over whether CISC confers benefit, or avoids harm to those who have a PVR over a pre-determined threshold, but we do know that it does cause substantial patient inconvenience (7).

There have been a number of randomised controlled trials of botulinum toxin injections for overactive bladder or bladder hyperreflexia. In every case there has been an emphasis on measuring voiding function post-injection by assessing PVR and in these trials CISC was initiated for PVR of ≥ 200 ml, and in one case ≥ 150 ml (3, 8-12). In none of these studies was a justification or explanation offered for the choice of threshold for initiating CISC.
We observed a number of patients who declined CISC, despite an increased PVR, after botulinum toxin injection, and noted that they came to no harm. Given the absence of evidence, we ceased to recommend CISC based on an arbitrary PVR. We reserved the method for patients who developed acute retention or symptoms of retention reversed by CISC and for patients already using CISC prior to botulinum toxin treatment.

If clinicians wish to recommend CISC based on a PVR, then data from an RCT should justify this. Prior to embarking on an RCT it is necessary to know whether an effect is likely to be detected and if so, what is the likely size. No such data exists, so before considering an RCT the first task must be an observational study to discover *a priori* whether there is a problem for CISC to remedy anyway. We set out to ascertain whether patients, post-botulinum toxin injection, experience any measurable harm when not using CISC regardless of the PVR. The aim of this

study was to identify whether abstinence from CISC as a treatment, post intra-detrusor botulinum toxin injections, in patients with a post void residual, was associated with any measureable adversity.

Materials and Methods

The study was approved by Noclor Research London – St Pancras Reference-168107. This was a cohort observation which began in June 2011 lasted until January 2013. Patients with lower urinary tract symptoms (LUTS) attending a medical urology centre in London were observed pre and post botulinum toxin treatment. Male and female patients diagnosed with refractory overactive bladder (OAB), unresponsive to antimuscarinic agents with bladder retraining and who were offered botulinum toxin injections as treatment were observed. OAB symptoms were diagnosed using a validated hybrid international consultation on incontinence questionnaire (ICIQ) and female lower urinary tract symptoms questionnaire (FLUTS), with sections of the questionnaire focusing on urinary frequency and urgency symptoms. Patients were given an information sheet about the botulinum toxin treatment and were provided with a counselling session, and an opportunity to ask questions and address any concerns about the treatment. Patients were informed about the risks associated with the intervention and were given a choice over local or general anaesthetic. A written informed consent was obtained. Consented patients were later put on the surgical list for botulinum toxin injections.

Intra-detrusal botulinum toxin injections were administered in the day-treatment centre at a north London hospital by two different Consultant Gynaecologists on various days. Patients

were administered Allergan (Botox A) 200 IU, injected in 20x 1ml aliquots, in an array pattern and sparing the trigone. 200 IU was the standard dose administered according to local clinical guidelines and authorised by the chief pharmacist and medicines management committee at the hospital trust. A dose less than 200 IU had been audited as ineffective with patients requiring frequent subsequent injections. The injections were placed in the detrusor muscle rather than just under the urothelium and mainly in the base and sidewalls of the bladder (avoiding the trigone) as this is where the bladder afferents are clustered. Two weeks later the patients were reviewed and during the interim they continued with prior antimuscarinic therapy. They had the option of earlier contact with the medical urology centre if necessary. At follow-up consultations patients were asked about specific side effects; voiding dysfunction and symptoms of infection. The ICIQ-FLUTS questionnaire, which focuses on urinary frequency, urgency symptoms; stress symptoms, voiding symptoms, pain symptoms and quality of life was used to analyse patient symptoms. The symptom set is described in Figure 1 which demonstrates the distribution of the symptoms. Patients provided a midstream urine specimen for dipstick analysis, light microscopy for pyuria and routine culture; a bladder scan was conducted to measure post-void residual. This was the assessment protocol carried out during each follow up consultation and patients were treated for a urinary tract infection, if it was diagnosed.

Patients with a post void residual of ≥ 150mls had a blood sample obtained to measure creatinine and monitor kidney function. A creatinine of between 70- 120 mcmol/L was accepted according to local clinical guidelines, patients not within those parameters were required to

have a renal tract scan to detect the probability of hydronephrosis. Patients who were unable to void, or had used CISC preoperatively were managed with CISC. In all other cases this technique was not advocated unless a patient described clear, troublesome voiding symptoms that were relieved by removal of residual urine. In such cases, CISC was taught in a private consultation room. Patients were given an information sheet on how to perform CISC and were also given verbal instructions on the principles and technique of catheter insertion and informed about infection control management. Patients were routinely followed up in the outpatients department two weeks after the first botulinum treatment, followed by four weeks, then six weeks and lastly eight weeks. The same assessments and checks were repeated at each visit. Patients had the opportunity to attend the department earlier if they were concerned or had LUTS. The sample size was calculated using G*Power© version 3.1.9.2 using the Wilcoxon-Mann-Whitney- test method. The smallest, clinically significant effect size, that would justify changing practice, was estimated as 3 symptoms from a score that measured 39 symptoms, where normal persons described zero symptoms. The estimate drew on data obtained from an observational study of treatment of patients with OAB (13). This gave a Cohen's d ($d = \frac{\overline{x}_1 - \overline{x}_2}{s}$) d = 0.65; $\alpha = 0.05$; Power $(1 - \beta) = 0.8$ or 80%. We required a minimum of 40 patients. Recruitment had continued until this was achieved.

Results

240 patients were studied; there were 215 women and 25 males. The mean age of the women was 57.6 years sd=14.7; the mean age of the males was 49.1 sd=14.4 the difference being insignificant. The distribution of the LUTS symptoms measured after the botulinum treatment

and their overlap are shown in the Venn diagram of Figure 1. 43 of the 240 patients (18%) used CISC prior to treatment and continued to use it afterwards. 12 patients (5%) had medical histories of autonomic neuropathy, spina bifida, cerebrovascular disease or multiple sclerosis. 31 patients (13%) who were using CISC prior to treatment sustained voiding symptoms after receiving botulinum toxin injections. These symptoms were reported as troublesome and relieved by continued use of CISC. 196 patients (82%) that were not managed with CISC were reviewed serially and saw their residual urine gradually subside over time. They did not develop voiding symptoms or urinary retention after botulinum toxin injections and were not managed with CISC. There were many similarities in the baseline data between patients in the CISC group and the non-CISC group (Table 1). Thus the mean duration of symptoms for groups was 7.35 years (sd=3.8). They also described similar numbers of 24-hour incontinence episodes (Mean = 2.8; sd = 2); a similar number of pain symptoms (mean= 0.57; sd= 0.976) and similar numbers of urgency symptoms (mean=5.5; sd=3). The number of voiding symptoms was higher in patients from the non-CISC group (average number of symptoms = 7.3, sd= 4.8), compared to the CISC group (average number of symptoms = 7.0, sd= 5.5). The CISC group appeared to have more stress incontinence symptoms (average number of symptoms = 3, sd= 2.6. median = 4.0) compared with the non-CISC group (average number of symptoms = 0.75, sd= 1.0, median = 0.5) but this was not statistically significant (Mann Whitney U = 1986, p = .74). The comparison has been shown in table 2 and 3.

After the botulinum toxin injection there was no significant difference in residual urine between patients who used CISC (mean = 2.2 ml, sd= 8.8, median = 0) and those who did not (mean = 20,

sd= 55, median = 0) (Mann Whitney U = 1222, p = .29). The combined residual urine amount in patients using CISC was 111 ml (95% CI= 68 to 1544; Max = 1400 ml, Range= 20 ml). This is illustrated in Figure 2. For those not using CISC the combined residual urine amount was 82 ml (95% CI= 73 to 90 ml; Max = 1100, Range= 10 ml) again the difference was not statistically significant (Mann Whitney U = 70786, p=.77). Those not using CISC manifested a wide variance which is seen by comparing Figure 3.

Figure 4 plots the symptoms scores of the 240 patients within the observation and the average total. The ICIQ-FLUTS questionnaire was used as an assessment tool at each follow up visit. There was a significant fall of symptoms at the first visit post botulinum injection which was maintained at the second review visit. There was a return of symptoms at the third and fourth visit after the injection. There were no between-group differences in urgency, the patients' assessment of treatment response, frequency, incontinence, voiding, or pain symptoms. There were no differences in pyuria or positive urine culture, and no evidence of differences in renal biochemistry at any stage during follow-up. At the third and fourth clinic review, symptoms of urinary urgency became dominant. Figure 5 illustrates the urgency symptoms indicating a need for another botulinum toxin treatment. Patients who had an elevated PVR (>150 ml) and did not commence on CISC saw the residual decrease with each visit (Figure 3) in contrast to those using CISC (Figure 2). The patients who did not use CISC, including all those with a PVR ≥ 150 ml failed to demonstrate any symptoms, sign or pathology that would be amenable to CISC.

Discussion

Current clinical practice advocates the use of CISC based on a PVR of 150 ml or more. This is an arbitrary criterion which is not based on evidence. We used CISC but only in patients who had appropriate symptoms that were demonstrably relieved by CISC. Thus, a number of our patients lived with significant urine residuals volumes, well over 150 ml, during the weeks after the botulinum toxin injection. They appeared to come to no harm such a hydronephrosis or urinary retention. This is important because many are denied the option of botulinum injection because of fears of these conditions after the injections. These data imply that these fears may be exaggerated. This study has its limitations. We were not blinded; we did not measure the quality of life, nor was this a randomised controlled trial. To some extent we should be reassured over bias arising from the lack of blinding because we used and objective measure (PVR) that behaved in an appropriate manner by falling during the weeks after injection. These data render an RCT extremely difficult to justify because we failed to detect significant adversity in the group who did not use CISC. Thus we are not able to propose a plausible outcome measure, nor are we able to offer a variable that could be used in a sample size estimate. If observational data cannot detect a significant outcome, an RCT would be less likely to achieve this.

The study was motivated by patient preference, following experiences with patient coming to no harm despite refusing CISC after a significant PVR was detected. CISC is avoidable by ensuring that patients are frequently monitored and assessed for retention symptoms post treatment. Many patients are alarmed at the prospect of CISC and state that they would be

reluctant to take this on with the result that they do not receive botulinum toxin treatment. This study has led us to a different approach to consent. We explain that we shall do our utmost to avoid using CISC, despite degrees of retention, and should only use it for limited periods if a symptomatic retention occurred. This seems to be a palatable risk for our patients and more therefore consent to the treatment. Introducing CISC should be based on individual symptom assessments following treatment. A patient reporting troublesome voiding symptoms such as hesitancy, reduced stream, intermittent stream and straining to void should be considered for CISC but this study indicates that patients without such symptoms are unlikely to benefit.

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