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Prospective Randomised Controlled Trial Comparing Trigone-Sparing versus Trigone-Including Intradetrusor Injection of AbobotulinumtoxinA for Refractory Idiopathic Detrusor Overactivity

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Abstract

Background: Botulinum toxin A is effective for treatment of idiopathic detrusor overactivity (IDO). The trigone is generally spared because of the theoretical risk of vesicoureteric reflux (VUR), although studies assessing injection sites are lacking.
Objective: Evaluate efficacy and safety of trigone-including versus trigone-sparing intradetrusor injections of abobotulinumtoxinA in patients with IDO.
Design, setting, and participants: Twenty-two patients from one centre were randomised to trigone-including or trigone-sparing injections.
Intervention: Injection of 500 U abobotulinumtoxinA diluted to 20 ml into 20 trigone-including or trigone-sparing sites.
Measurements: The primary outcome measure was total overactive bladder symptom score (OABSS) at 6 wk. The OABSS questionnaire was completed at 0, 6, 12, and 26 wk. Baseline and postinjection urodynamic studies and micturating cystourethrograms were performed. Baseline values and subsequent time points were compared by *t* test. A mixed-effect model was used for repeated measures in time.
Results and limitations: For symptom scores at baseline compared with scores at 6 wk postinjection, the mean total OABSS improved from 22.4 to 8.7 ($p < 0.001$) in the trigone-including group compared with 22.7 to 13.4 ($p < 0.03$) in the trigone-sparing group. The difference in mean change from baseline was 4.4 points in favour of the trigone-including group ($p = 0.03$). The total OABSS at 12 and 26 wk and the urgency subscale scores at 6, 12, and 26 wk showed significant improvement in favour of the trigone-including group. Mean postvoid residual volumes and clean intermittent self-catheterisation rates between the two groups were similar. No patients developed VUR. Performing injections under general anaesthetic was a limitation, as tolerability under local anaesthetic was not assessed. A further limitation is the lack of a trigone-only arm.
Conclusions: Trigone-including injections are superior to trigone-sparing injections for the treatment of refractory IDO and did not cause VUR in this study.
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1. Introduction

Intradetrusor injection of botulinum toxin A (BoNT-A) is effective for patients with pharmacologically refractory idiopathic detrusor overactivity (IDO) [1–4]. BoNT-A is a potent neurotoxin produced by *Clostridium botulinum*. BoNT-A cleaves the synaptosomal-associated protein 25 (SNAP-25) protein, preventing the formation of the soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) complex. This prevents fusion of the synaptic vesicles containing acetylcholine to the neuronal membrane and prevents the consequential release of neurotransmitter [5]. In urology, the two most widely used brands of BoNT-A are Botox (Allergan Pharmaceuticals, Irvine, CA, USA), now referred to as onabotulinumtoxinA, and Dysport (Ipsen Biopharm Ltd., Wrexham, UK), referred to as abobotulinumtoxinA, as enforced by the US Food and Drug Administration. The trigone is generally spared because of the theoretical risk of inducing vesicoureteric reflux (VUR). However, sensory nerve endings are particularly dense within the trigone and bladder base [6]; therefore, including this area may improve efficacy. In a nonrandomised study, Mascarenhas et al. showed trigone-including injections of onabotulinumtoxinA did not cause VUR in neurogenic patients and Karsenty et al. demonstrated similar safety in patients with IDO [7,8]. The first randomised controlled trial of onabotulinumtoxinA in neurogenic overactive bladders showed superiority of including, rather than excluding, the trigone [9]. Lucioni et al. conducted a nonrandomised study using onabotulinumtoxinA comparing trigone inclusion versus trigone-sparing and showed no difference [10]. Two further studies, also using onabotulinumtoxinA, showed that bladder base/trigone injections were as effective as bladder body/trigone [11,12]. A European consensus report recommends that BoNT-A be injected within the detrusor muscle outside the trigone (grade C recommendation), as the data assessing injections sites were considered inadequate [13]. A recent review revealed most data for studies on IDO in adults involved onabotulinumtoxinA with very little data on abobotulinumtoxinA [14].

2. Materials and methods

2.1. Objectives

The purpose of our study was to evaluate the efficacy and safety of trigone-including versus trigone-sparing intradetrusor injections of BoNT-A in patients with IDO. To our knowledge, this is the first study to evaluate injection sites using abobotulinumtoxinA (Dysport).

2.2. Study design

From September 2010 to November 2010, patients with urodynamic-proven IDO refractory to anticholinergic therapy were recruited. This study received approval from the Hospital Research/Ethics Committee (REC reference 2008/08/13) and was registered with Current Controlled Trials (ISRCTN12589059).

Male and female patients ≥17 yr with urodynamic-confirmed detrusor overactivity, who had failed ≥6 wk anticholinergic therapy or discontinued therapy due to intolerability were eligible. All patients gave written consent and were given an information leaflet. At recruitment and prior to surgery, urine was tested for infection, and for pregnancy in women of childbearing age; infection and pregnancy excluded participation. Patients previously injected with BoNT-A were excluded. Patients with any neurologic condition or coagulopathies were excluded, as were men with clinical or urodynamic evidence of bladder outflow obstruction. All patients discontinued anticholinergic medication at least 2 wk prior to injection and remained off anticholinergic medication for the study duration.

Patients were randomised using a random digit table to receive trigone-including or trigone-sparing BoNT-A injections and were blinded throughout the study.

2.3. Assessment

All patients were assessed at baseline, 6, 12, and 26 wk after injection. Baseline and 6-wk assessment comprised history, physical examination, the overactive bladder symptom score (OABSS) questionnaire [15], uroflowmetry, postvoid residual (PVR) volume, cystometrography (CMG), and micturating cystourethrography (MCUG). Twelve and 26-wk assessment comprised history, physical examination, PVR volume measurement, and the OABSS questionnaire. PVR volume measurement was performed using an ultrasound bladder scanner (Verathon BVI 3000, Verathon Medical, UK, Ltd., Aylesbury, Buckinghamshire, UK). Patients who had not already discontinued anticholinergic medication were instructed to do so 2 wk prior to baseline assessment. CMG was performed according the International Continence Society recommendations [16]. Symptoms were evaluated using the validated seven-question OABSS questionnaire (Appendix A) (score range: 0–28). The urgency subscale (questions 3–6) was used to assess severity of urgency (score range: 0–16) [15].

2.4. Injection technique

AbobotulinumtoxinA (500 U) was reconstituted with 20 ml 0.9% saline. Patients received general anaesthesia and 400 mg intravenous ciprofloxacin at induction. Intradetrusor injections were performed with a rigid 21F ACMI cystoscope, a flexible injector sheath, and disposable inner sheath/needle with a 27G tip (Olympus, reference numbers NM-101C-0427, MAJ-656; Olympus KeyMed, Southend, UK) with bladder volume at about 150 ml. Patients randomised to trigone-sparing injections had 1-ml injections at 20 sites into the bladder wall, sparing the trigone. Patients randomised to trigone-including injections had 5 1-ml injections into the trigone and 15 1-ml injections into the bladder wall, for a total of 20 injections (Fig. 1). The depth of injection was approximately 2 mm (half the length of the 4-mm injection needle), without raising a bleb, as described by Kuo [11]. All procedures were performed as day cases, with no inpatient stay required.

2.5. Follow-up, data collection, primary and secondary outcomes

Patients had follow-up at 6, 12, and 26 wk. All patients had MCUG and urodynamic studies 6 wk after injection, and clinical review including PVR measurement and the OABSS questionnaire at weeks 6, 12, and 26. The primary outcome was change in total OABSS at 6 wk. Secondary outcomes were changes in total OABSS at weeks 12 and 26, OABSS urgency subscale at 6, 12, and 26 wk, changes at 6 wk of maximum cystometric capacity (MCC), maximum detrusor pressure in filling phase (MDP), volume at first desire to void (VFDV), volume at urgent desire to void (VUDV), PVR, and incidence of VUR. MDP during the filling phase (including phasic or terminal detrusor overactivity) was reported as a measure of the amplitude of involuntary detrusor contractions.

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