97

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RECOMMENDATIONS ON THE USE OF BOTULINUM TOXIN IN THE TREATMENT OF LOWER URINARY TRACT (LUT) DISORDERS AND PELVIC FLOOR DYSFUNCTIONS: A EUROPEAN CONSENSUS PANEL REPORT

Hypothesis / aims of study

Due to the increasing number of potential indications for the use of Botulinum neurotoxins in urological and pelvic floor disorders, the wide variety of injected doses, injection techniques, treatment and follow-up protocols a European expert panel consensus conference was convened, with the following aims: (1) to evaluate the evidence for, and clinical considerations in the use of botulinum toxins in treating urological and pelvic floor disorders; (2) to consider possible roles for future research of botulinum toxins in treating other urological conditions; and (3) to propose evidence-based recommendations for the use of botulinum toxins in the clinical areas of interest.

Study design, materials and methods

A consensus panel of the European researchers with high volume of key publications on the topic was developed and a consensus conference on the use of botulinum toxin in urological and pelvic floor disorders was convened. A systematic review of the PubMed database for English language fully published literature was performed by the working panel, and existing recommendations were considered. The consensus panel met in a closed session; relevant data were presented, and the quality of evidence and strength of recommendation were graded using the Levels of evidence (LoE) and recommendation grades applied by the European Association of Urology. The final recommendations were approved by a unanimous consensus of the panel.

Results

Neurogenic detrusor overactivity (NDO): Most data come from the use of Botox® 300 U. There is LoE 1b that Botulinum neurotoxin type A (BoNT/A) improves incontinence episodes, urodynamics key parameters such as bladder capacity and maximum detrusor pressure, as well as quality of life. Grade A recommendation was given for the use of BoNT/A to treat NDO refractory to oral anticholinergics in patients willing and able to use clean intermittent catheterisations (CISC). Patients should be told the mean duration of efficacy does not exceed 8 months. Repeat injections are recommended as they have been shown to be efficacious (LoE 3). No systematic analysis is yet available on the efficacy of different doses.

Idiopathic OAB/DO: Most results were obtained with 200 U of Botox®. Efficacy was usually examined for up to 6 months after treatment. There is LoE 1b that intradetrusor BoNT/A injections improve OAB symptoms, urodynamic parameters and quality of life in patients with idiopathic DO refractory to oral pharmacotherapy. There is LoE 1b that Botulinum toxin B is also effective but of short duration. No systematic analysis is yet available on the efficacy of different doses. Reinjections have not been investigated yet. Urinary tract infections (UTIs) were symptomatic following treatment. Grade A recommendation with caution was given for the use of BoNT/A to treat intractable IDO in patients willing and able to use CISC, as the risk of voiding difficulty is not accurately evaluated to date as well as the actual duration of effect. Future studies should address the benefit risk ratio for the best minimal dose. Residual volumes should be measured regularly. *Injection techniques*: No direct comparative efficacy studies exist on the number of injection sites, trigonal versus non-trigonal injections or the use of rigid versus flexible cystoscope. Most of the data come from detrusor injections of Botox®. The level of evidence of data relating to the advantages of detrusor versus suburothelial injections is between 2b to 4. Intradetrusor and suburothelial injections increased cystometric capacity as opposed to bladder base injections (LoE 2b). It is recommended that the dilution of Botox® should be 10mu/ml per site (Grade B). Thus the number of injection sites depends on the total dose being administered. The optimum dose for dilution of Dysport® has yet to be established. The choice of flexible or rigid cystoscope should be left to local expertise. The depth and location for injections should be within the detrusor muscle outside the trigone (Grade C). *Children OAB/DO*: Few studies exist, the majority using Botox®. They showed considerable improvements in bladder capacity, detrusor pressure, bladder compliance, urinary continence, incidence of UTIs, as well as a reduction of vesicoureteral reflux, but LoE is only 3. It is recommended that dosage range is determined by body weight; 5-10 mu/kg body weight up to a maximum of 300 U Botox® has been shown to be effective and safe, although caution should apply for the maximum dose. A minimum age of 3 years is suggested as there is little data for younger ages. Other recommendations stand as in adult NDO indications. *Sphincter injections*: Most of the experience comes from patients with neurogenic detrusor sphincter dyssynergia (DSD). Improvements have been reported in the urine flow, PVR, maximal urethral closure pressure, maximal detrusor pressure during voiding, functional bladder capacity, frequency and hesitancy, and QoL (LoE 1b). Despite the high LoE, the clinical value of this has to be studied further before a recommendation can be made. If injection is done, 100U Botox® in 4 mls of normal saline should be used. Sphincter injections in children are reported almost exclusively in non-neurogenic dysfunctional voiding with improvements in Qmax, pelvic floor EMG, post-void residual, detrusor leak point pressure, incidence of UTIs, hydronephrosis, and incontinence, but the LoE is only 3. Before its use in children is recommended the longer term clinical value needs to be assessed. *Bladder pain syndrome*: Evidence for the efficacy of Botox® in BPS is at level 3 and duration of action is less than 5 months. Submucosal injections of the trigone were involved in most studies. In the absence of placebo controlled data, it is impossible to recommend the use of BoNT-A in BPS. Patients should be warned of the possible need to perform CISC or worsening pain. *Prostate injections*: Although all studies showed improvements in symptom scores, peak flow rates, post-void residuals, PSA, quality of life, and decreases in prostate size, most evidence is at level 3. There is currently insufficient data to recommend this promising treatment for bladder outlet obstruction due to BPH. Further placebo-controlled studies are urgently needed. *Pelvic floor disorders*: The LoE for a positive effect of BoNT/A in patients suffering from pelvic floor muscle 'spasms' presenting as dyspareunia, dysmenorrhoea or vestibulodynia, as well as chronic perineal pain and anorectal

disorders is at best 2a, the vast majority of studies being level 3. Insufficient evidence exists on which to base clinical advice. There is need for robust clinical trials to prove that BoNT/A is truly efficacious in this disparate group of patients. *Adverse events*: Botulinum toxin can be used in the LUT with the current doses and techniques as the clinical results show that it is overall safe. Side effects have been reported mostly in low incidence (Grade A). Further follow up of safety is necessary as botulinum toxin in other applications has shown histological, autonomic and other secondary effects. Similar studies are also needed in urological treatment (Grade A). Patients treated for DO should accept beforehand to perform CISC as increase of residual/ retention is the most frequent complication (Grade A).

Interpretation of results

Despite the increasing number of studies on the use of botulinum toxins in urogenital and pelvic floor disorders, heterogeneous study designs using a variety of primary and secondary outcomes and lack of large well-designed, placebo-controlled and comparative trials compromise the LoE and do not allow for robust recommendations of use in non-bladder indications.

Concluding message

Botulinum toxin can be used in the LUT with the current doses and techniques as the clinical results show that it is overall safe. As the drug is still unlicensed for urological indications, appropriate local permissions should be in place and patients should give written informed consent. There is Grade A recommendation for the use of BoNT/A to treat intractable symptoms of NDO and - with caution - IDO in patients willing to use CISC. Larger placebo-controlled and comparative trials are needed before robust recommendations can be given for the use of a single and repeat injections in other indications, the duration of effect, the long-term safety, the optimal dose and injection technique, the time for repeat injection.

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What were the subjects in the study?	**None**