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BOTULINUM A TOXIN INTRAVESICAL PASSIVE ADMINISTRATION IN THE TREATMENT OF PAINFUL BLADDER SYNDROME: PRELIMINARY RESULTS

Hypothesis / aims of study

Painful bladder syndrome (PBS) is characterized by suprapubic pain related to bladder filling, increased day- and night- time urinary frequency, and no urinary infection or other evident pathology.
Botulin toxin A (BoNT/A) might have antinociceptive effects as it is reported to modulate bladder afferent nerve activity. To date, BoNT/A has been injected intravesically to treat neurogenic and idiopathic detrusor overactivity and few data are available on intravesical passive diffusion of BoNT/A as therapy for voiding dysfunction and PBS.
In the present study we investigated the efficacy and safety of intravesical BTX-A passive administration in patients affected by painful bladder syndrome, frequency and urgency who were refractory to conventional treatment modalities.

Study design, materials and methods

Five female patients (mean age 57 years, range: 41-75) with refractory PBS, were included in the study. Exclusion criterion was detrusor overactivity as determined by urodynamics. Three of the 5 patients had already undergone BoNT/A intravesical injections with excellent results. Clinical and urodynamic improvements had lasted about 3 months. All 5 subjects signed an informed consent form before undergoing BoNT/A therapy. Baseline evaluation included a complete urological work-up, with urine analysis and culture, micturitional diary, urodynamics and Visual Analogue Scale (VAS, score 1-10) for pain assessment. Patients received a single intravesical instillation of BoNT/A 200U, (Botox) diluted in 100 ml of normal saline, without any form of local or systemic anesthesia. The BoNT/A solution was instilled through a 12 Fr Foley indwelling catheter and retained in the bladder for 40 minutes. VAS and micturitional diary were repeated one week, 1 and 3 months after instillation.

Results

At baseline all patients complained of severe day- and night- time urinary frequency. (mean frequency : 9 ± 3 and 4.4 ± 3.1, respectively) The mean VAS score was 6.4 ± 2.5. On urodynamics, mean bladder capacity was 261.6 ± 34.8. No patients showed any impairment of bladder emptying.
One week after treatment, micturitional diaries showed mean daytime urinary frequency fell from 9 ± 3 to 7.6 ± 2.8, and mean night-time urinary frequency dropped from 4.4 ± 3.1 to 3.4 ± 3.7. The mean VAS score dropped significantly from 6.4 ± 2.5 to 3.6 ± 2.07. The improvement in the VAS score was particularly marked in 3 patients, 2 of whom also presented reductions in day- and night- time urinary frequency and urgency, as shown by the micturitional charts. On urodynamics mean value of maximum cystometric capacity was 309.7 ± 48.4. We did not detect any increase in post-void residual volume.
The improvement in symptoms and in bladder capacity persisted at the 3 month check-up only in 1 case. Two of the three responders had previously received BoNT/A intravesical injections. Symptoms and urodynamic parameters did not change in 2/5 patients.
No severe systemic or local side effects were reported during instillation, after catheter removal or bladder emptying. One of the three responders referred bladder pain during treatment and had to empty her bladder after 30 minutes. Another responder presented with weakness for some hours after treatment.

Interpretation of results

In recent years there has been increasing evidence that BoNT/A has analgesic properties in animals and humans. As BoNT/A intravesical instillation is easy to perform and repeat on an outpatient basis, and does not require any anesthesia or special equipment, it would appear an ideal candidate for therapy for patients with PBS. Unfortunately, the preliminary results of this study, which need to be confirmed in a larger cohort of patients, show bladder pain was reduced in only 3/5 patients; the benefit persisted for 3 months in only one. Inadequate dose, insufficient instillation time and/or no pre-instillation administration of substances to increase urothelial permeability, could account for lack of efficacy.
As the molecular weight of BoNT/A is 150 KD, the drug cannot penetrate intact epithelium to reach the sub-urothelial sensitive nervous plexus and the interstitial cells projecting deep into the sub-urothelium space, both of which are involved in bladder pain transmission .

Concluding message

BoNT/A intravesical passive diffusion has the potential to be effective treatment of the PBS syndrome. Trials on more patients need to be conducted to optimise results.

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HUMAN SUBJECTS: This study was approved by the regional ethics committee and followed the Declaration of Helsinki Informed consent was obtained from the patients.