

## **BOTULINUM A TOXIN INTRAVESICAL INJECTIONS IN THE TREATMENT OF BLADDER HYPERSENSITIVE DISORDERS: A PILOT STUDY**

### Hypothesis / aims of study

Botulinum A Toxin (BTX-A), a pre-synaptic neuromuscular blocking agent, has been traditionally used to treat muscle spasticity. Recent evidence in a rat chemical cystitis model and in patients with interstitial cystitis, also showed an antinociceptive effects, indicating the neurotoxin modulates the activity of bladder afferent nerves (1). This pilot study evaluated the efficacy and tolerability of BTX-A intravesical treatment in patients affected by pelvic-perineal pain associated with the urgency-frequency syndrome, and no evidence of detrusor overactivity.

### Study design, materials and methods

Eleven patients (9 females and 2 males), affected by urgency-frequency syndrome and bladder pain refractory to conventional therapy for more than 6 months, were included in this prospective study. They all received in-depth information about the procedure and provided written, informed consent to treatment. Patients underwent a complete urological work-up including urine analysis and culture, micturitional diary, urodynamics and Visual Analogic Scale (VAS, scores 1-10) for pain quantification. 200 units of commercially available BTX-A diluted in 20 ml of normal saline were injected into the detrusor muscle (20 sites, sparing the trigone) under cystoscopic control. The procedure was performed under intravenous general anaesthesia. After treatment, a 16 Ch Foley indwelling catheter was routinely inserted for 24 hours. Patients were discharged after overnight observation and were followed up for voiding conditions. Uroflowmetry was performed after catheter removal. VAS scale and urodynamics were repeated after 1 and 3 months.

### Results

Before treatment, the mean VAS score was  $9.3 \pm 0.9$ ; on urodynamics mean cystometric capacity was  $267.2 \pm 85.4$  ml, 1 patient showed detrusor hypocontractility, none had detrusor overactivity. Twenty-four hours after BTX-A treatment, 2 patients needed complementary intermittent catheterisation. The other 9 patients completely emptied their bladders using abdominal straining without significant post-void residual urine. One month after therapy the mean VAS score was  $5.8 \pm 2.4$  ( $p < 0.05$ ); all patients reported different grades of dysuria even though post-void residual urine was not significant. Three months after treatment the mean VAS score was  $6.1 \pm 2.8$  ( $p < 0.05$ ); in 4 cases dysuria persisted and 2 patients continued with intermittent self-catheterisation. Overall bladder pain was improved in 9 patients at 1 and 3 months follow up. Mean bladder capacity increased to  $302.5 \pm 60.7$  ml and  $335.7 \pm 89.8$  ml respectively. Two patients underwent further intravesical BTX-A injections 6 months after the first session. Apart from incomplete emptying, no other complications or systemic side effects were reported.

### Interpretation of results

In recent years there has been increasing evidence that BTX-A may have analgesic properties in animals and in humans. A recent multi-centre case series examined the effect of intravesical BTX-A on patients with refractory interstitial cystitis. Overall, about 69% of patients referred a subjective improvement lasting a mean of 3.72 months (1). Exactly, how BTX works in the bladder is as yet unclear. Cholinergic blockade at the neuromuscular junction does not account for such sensory effects. Other mechanisms may be involved, possibly the neurotoxin acts directly at the level of bladder sensitive nerves. Laboratory studies have shown BTX-A blocks release of many neurotransmitters from afferent C-fibers. These include ATP, Substance P, Neurokinin A and CGRP, which have direct vasoactive effects with subsequent leukocyte adhesion and tissue oedema, and can modulate the micturition reflex causing detrusor overactivity (2).

Under the conditions imposed in this study, BTX-A intravesical treatment is safe, effectively

reduces pelvic-perineal pain and increases bladder capacity in the majority of patients, even though its effects last for a short time. No systemic side effects were recorded. Incomplete bladder emptying in 2 cases is a serious complication, especially for non-neurogenic patients who are not used to performing self-catheterisation. Dysuria, although reported by the majority of patients 1 month after treatment, was not considered as an intolerable side effect.

#### Concluding message

BTX-A intravesical treatment is a safe and effective alternative option for patients with pelvic-perineal pain who are refractory to conventional therapy. Pelvic pain is relieved in the majority of patients for a few months. Incomplete bladder emptying is the only unwanted complication. As the effects of botulinum-A toxin are transient, repeated doses are needed for effective control of bladder pain and urgency and the dose with the longest duration and lowest risk of urinary retention needs to be identified.

#### References

- (1) Emerging role of Botulinum toxin in the management of voiding dysfunction. J Urol, 171:2128-2137, 2004
- (2) A focused review on the use of botulinum toxins for neuropathic pain. Clin K Pain, 18:S177, 2002