

SAFETY AND FEASIBILITY OF INTRAVESICAL INSTILLATION OF BOTULINUM TOXIN IN HYDROGEL-BASED SLOW RELEASE DELIVERY SYSTEM IN PBS/IC PATIENTS: A PILOT STUDY

Hypothesis / aims of study

Painful bladder syndrome/interstitial cystitis (PBS/IC) persists as a challenging syndrome in urology with prevailing symptom of bladder pain. In the case of other treatment failure, intradetrusor injection of botulinum toxin A (BTX) may be administered; however, due to the seriousness and duration of adverse events (AE), BTX injections are only considered as a fifth line therapy (1). Common drug AEs include dysuria, the need for abdominal straining to void, large post-void residuals, and the need for intermittent self-catheterization that persists for one to three months.

Intravesical instillation is an appealing alternative to injection of BTX. The efficacy of intravesical BTX instillation was only tested in a few open label trials for overactive bladder patients whereby the clinical improvement observed was short-lasting with a mean duration of 6.8 weeks (2,3). The short exposure duration of the urothelium to BTX could be one of the factors responsible for the lack of a sustained effect. Therefore, an extended release formulation or a mechanism through which the contact time between BTX and the bladder's urothelium is extended, may address this shortcoming.

TCGel (TheraCoat Ltd., Raanana, Israel) is a novel hydrogel with reverse thermal gelation properties: It has a high viscosity at body temperature and it is fluid-like at low temperatures. This allows for a simple instillation of the cooled liquid TCGel pre-mixed with BTX into the bladder where it solidifies and serves as a drug reservoir allowing for gradual release of the drug for 6-8 hours and thereby for its extended contact with bladder urothelium. Here we report the results of a pilot clinical trial in which for the first time, the feasibility, tolerability, and safety of intravesical instillation of BTX mixed with TCGel was evaluated in patients with PBS/IC.

Study design, materials and methods

This was an open label single arm pilot trial in which the feasibility, tolerability and safety of intravesical instillation of BTX mixed with TCGel was evaluated. Patients were considered eligible if they were diagnosed with severe PBS/IC [IC Symptom Index (ICSI) and IC Problem Index (ICPI) score of more than 12 each] and were not previously treated with intradetrusor BTX injection. Subjects practicing Clean Intermittent Catheterization, subjects implanted with permanent neuro-stimulation device, subjects with prior anti-incontinence surgery and interventions (mid-urethral slings, Burch bladder suspension, sacral neuromodulation, or tibial nerve stimulation), pregnant or lactating females were excluded.

Enrolled patients underwent a single intravesical instillation of 200 units of onabotulinumtoxin A (BOTOX®) premixed with chilled 40 ml of TCGel (TCGel+BTX). The TCGel+BTX mixture was instilled through a 12 Fr Nelaton/Tieman urethral catheter lubricated with anesthetic gel. The catheter was removed immediately after the instillation. Patients had follow-up (FU) visits at 2, 6 and 12 weeks post instillation. The main safety endpoints included AEs, urine analysis and culture. The efficacy outcome measures, taken at baseline and each FU, included 3-day bladder diary prior to visit, ICSI, ICPI and the 10-point Visual Analogue Scale (VAS) for pain assessment.

Results

Fifteen patients (male: n=6 and female: n=9, age range 24-76) were enrolled in the trial and received a single TCGel+BTX instillation. No patient discontinued the trial. At baseline, patients complained of increased urinary frequency, urgency and bladder pain (median VAS score 7) and were severely symptomatic (ICSI range 12-19 and ICPI range 12-16). VAS score at the instillation was comparable to the baseline, i.e., did not indicate increase in pain. There was a single severe AE of the pre-existing submandibular lymphadenopathy excised; non-malignancy pathology reported. Three patients experienced mild self-resolved constipation which appeared from 24 hours to 3 weeks post instillation and was considered possibly related to the investigational product (IP) or instillation. The following AEs were reported as not related to IP or instillation: 1) Two patients had mild urinary tract infection 2-5 weeks post instillation, 2) one patient had mild flu, 3) one patient had worsening of bladder pain and depression symptoms at Week 12, 4) one patient reported gingivitis post dental cleaning, and 5) one patient had fungal vaginitis.

A reduction from baseline in the ICSI and ICPI scores as well as the VAS score was observed at the first follow up visit (Week 2); this reduction was also apparent at Week 12. Likewise, a reduction from baseline was observed in the daytime urinary frequency and urge episodes, while the nocturnal frequency remained unchanged.

Interpretation of results

This is the first clinical trial in which the effect of intravesical instillation of TCGel+BTX, allowing for a slow release of BTX, was evaluated in patients with PBS/IC. The results of this trial suggest that intravesical instillation of TCGel+BTX is generally safe and well tolerated. The instillation procedure did not require any general or spinal anesthesia in contrast to the intradetrusor injection procedure. No serious drug-related AEs were reported. In contrast to intravesical injections, no discomfort or pain associated with the procedure was observed and no lasting adverse effects associated with the treatment were reported. Considering the high sensitivity of IC patients to invasive treatments, simple intravesical instillation of BTX appears to be well tolerated. The apparent sustained reduction of PBS/IC symptoms is difficult to interpret due to the small number of subjects;

however, the results are encouraging and provide the basis for further exploration of the safety and efficacy of TCGel+BTX in a randomized placebo controlled trial.

Concluding message

As this form of treatment has the potential for being a viable treatment option, further exploration of the efficacy and safety of BTX mixed with TCGel is warranted.

References

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Disclosures

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