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Karsenty G[1], Boy S[2], Reitz A [2], Knapp P A[3], Bardot P[1], Tournebise H[1], Fortanier C[1], Loundou A[1], Bladou F[1], Serment G[1], Schurch B[2]

1. Hôpital Salvator-Université de la méditérrannée., 2. Neuro-Urology, Swiss Paraplegic Center, Balgrist University Hospital, 3. Neurourology. Swiss paraplegic centre. Balgrist University Hospital

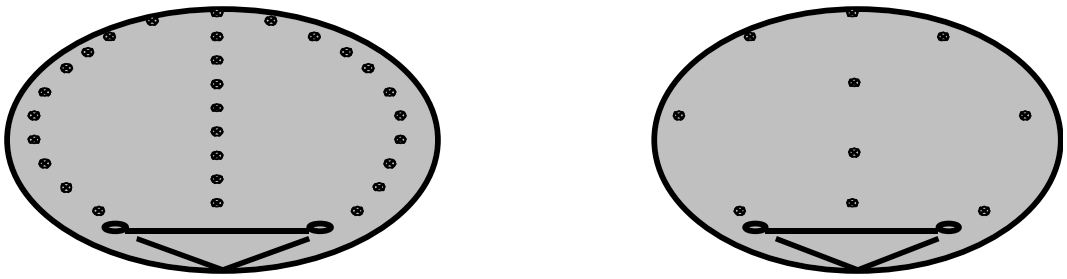
BOTULINUM TOXIN-A (BTA) IN THE TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY INCONTINENCE (NDOI) - A PROSPECTIVE RANDOMIZED STUDY TO COMPARE 30 VS. 10 INJECTION SITES

Hypothesis / aims of study

Injection of 300 units of BTA (Botox®) into the detrusor muscle is a safe, reversible and effective treatment of NDOI. The initial injection technique consists of 30 injection spots disseminated over the detrusor muscle sparing the trigone. Each spot receives 10 units of BTA diluted in 1 ml of saline. This technique was designed to ensure that the BTA effect covers a maximal part of the bladder smooth muscle by diffusion spreading from each injection spot. Spreading of biologic activity of BTA from a point injection has been shown to be dose dependent in the animal striated muscle [1], but has never been studied in the smooth muscle. The aim of this study was to estimate the diffusion of the biologic effect of BTA's injections into human bladder smooth muscle. Our hypothesis was no difference between 30 and 10 injections in terms of improvement of cystomanometric bladder capacity (CBC) (primary endpoint), decrease of the mean number of incontinence episodes/3 days (NID) and improvement of quality of life measured with a self administrated questionnaire validated in this specific population: the Qualiveen™ (quality of life index QoLI and Specific Urinary Problem Impact SUPI) (secondary endpoints). Additionally pain or discomfort of the procedure was evaluated with visual analogue scale.

Study design, materials and methods

This study was approved by the ethical committee, an informed consent was obtained from all the patients. A prospective, randomized, single blinded study was conducted in adult patients with chronic spinal cord lesion, that performed intermittent self catheterization and suffered from NDOI resistant to anticholinergics. Efficacy of two protocols of intradetrusor injections of 300 units of BTA (Botox®) was compared. Injections were done under local anesthesia (40 ml lidocaïne 2% diluted in 60 ml saline, 30 min instillation), in one session, using a rigid cystoscope (20 CH) and a flexible disposable needle (16G). In Protocol 1 (P1) 300 units were distributed over 30 injection points (10 units diluted in1ml of saline/point). In protocol 2 (P2) the same total dose was distributed over 10 points (30 units diluted in 1ml of saline/point) Trigone was not injected.



P1 P2

Patients were evaluated before the procedure then 6, 12 and 24 weeks after. Comparison of change in parameters after BTA between P1 and P2 was analyzed with generalized estimating equation.

Results

24 patients, 15 women and 9 men suffering from NDOI related to a traumatic chronic spinal lesion (15), multiple sclerosis (8), or myelomeningocele (1) were included.

Initial CBC was 256 ml+/-126 (overall), 242ml+/-126 (P1) and 256ml+/-128 (P2) (overall vs P1 vs P2 ns). CBC increased significantly ($p<0.05$ except P2 24 weeks) up to 426ml+/-117 (P1) vs 537ml+/-116 (P2); 449+/-126 (P1) vs 468ml+/-161(P2); and 455+/-73 (P1) vs 346+/-43 (P2) respectively 6, 12 and 24 weeks after BTA.

Initial NID was 4.7+/-3.3 (overall), 4.7+/-4.2 (P1), 3.7+/-2.2 (P2) (overall vs P1 vs P2 ns). NID decreased significantly ($p<0.05$ except at 24 weeks) to 1.4+/-1.5 (P1) vs 0.7+/-1.3 (P2); 0.7+/-1.2 (P1) vs 1.1+/-1.8 (P2) and 1.1+/-1.8 (P1) vs 1.8+/-2.4 (P2) respectively 6, 12 and 24 weeks after BTA.

SUPI was significantly improved after BTA in both arms at 6 and 12 weeks and also at 24 weeks in P1. QOLI was significantly improved after BTA only in P2 arm. There was no significant difference in the improvement of CBC, the decrease of NDI or the improvement of Qol scores after BTA between P1 and P2 arms at any time (generalized estimating equation).
Pain during the procedure among patients with preserved sensibility was significantly less in P2 arm: mean EVA (P1) 7.1+/-2.3 vs mean EVA (P2) 3.4+/-4.4 ($p=0.004$, Mann Whitney).
There was no severe side effect reported. 4 patients experienced transient grade 1 hematuria, no longer than 24 hours, and 3 patients had a symptomatic UTI at day 7.

Interpretation of results

Efficacy, safety and effect on QoL of intradetrusor injection of 300 units of BTA to treat NDOI was not affected by a threefold increase in dose per injection point and subsequent threefold decrease in total number of injections. This observation provides an indirect evidence of a dose dependant diffusion of BTA biologic activity within human bladder wall. In a practical standpoint this observation allows us to shorten and simplify the procedure of BTA intradetrusor injection to treat NDOI decreasing the pain for patients with preserved sensation as well as the risk of technical error or bleeding. A complete follow-up at 36 weeks will be completed to study a possible change in duration of the BTA effect.

Concluding message

Dose dependent diffusion of BTA within human bladder wall allows us to decrease the total number of injection points needed to deliver the same total curative dose.

References

1 Histologic assessment of dose-related diffusion and muscle fiber response after therapeutic botulinum A toxin injections. Mov Disord. Jan;9(1):31-9 (1994)

FUNDING: A.DE.RE.M and GENULF