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Title: BOTULINUM-A TOXIN IN THE TREATMENT OF DETRUSOR HYPERREFLEXIA

Introduction and Aim of Study:

Botulinum A-toxin (BTX-A) is a potent neurotoxin isolated from Clostridium botulinum. BTX-A intramuscular injection induces a temporary, partial chemodenervation of the injected muscle and it causes relaxation in muscle tone and fibre atrophy and reduces motor unit potential size, thereby reduce the force of muscle contraction. BTX-A injection into the external urinary sphincter in spinal cord injured (SCI) men with detrusor-sphincter dyssynergia (DSD) has been reported. BTX-A is an inhibitor of acetylcholine release at the presynaptic neuromuscular junction BTX-A inhibits calcium mediated release of acetylcholine vesicles at neuromuscular junction, which results in reduced muscle contractility. BTX-A has catalytic zinc finger motif that may block activity of SNAP-25, protein important in synaptic vesicle fusion. Normally, calcium influx at neuromuscular junction drives fusion and release of neurotransmitter vesicles, process in which SNAP-25 usually participates Clinically, BTX-A injections have been used safely for treatment of focal dystonias and spasticity. The chemical denervation is a reversible process as axons re-sprout in about 3 to 6 months. BTX-A injections produce a reversible chemical sphincterotomy, which avoids external sphincterotomy with its attendant risks (bleeding, stricture). The aim of the study is to verify efficacy, side effects and to assess the best dosage of injection of BTX-A into detrusor muscle in patients suffering from detrusor hyperreflexia (DH) non-responsive to high doses of anticholinergic drugs .

Materials and Methods:

In the period from September 1999 to February 2001, we treated 71 patients with DH. 50 males (70.4%) and 21 Females (29.5%). Mean age 36 years (median 33.5$\pm$12.5; range 17-71). 65 out of 71 were SCI patients: 15.3% cervical lesion (ASIA A-D) and 84,6% dorsal lesion (ASIA A-D). 2 patients had multiple sclerosis, 2 iatrogen myelopathy, 2 myelomeningocele. All patients have a DH refractory to anticholinergic therapy and use intermittent catheterizzation (IC). Voiding diary was cecked pre-treatment and 6,24,36,48 weeks after treatment,videurodynamic pre and post-injection***.*** In 4 cases videourodynamic showed a vesico-ureteral reflux We administered oxybutynin 5 mg tablet 3 times/day, gradually reducing the dosage until total suspension in the third week post-injection. In the **first group** (high dosage group) of 61 patients we injected, with a 17 Ch cystoscope and a 23 G needle-tipped catheter (5 Fr), in 20-30 sites into detrusor muscle, trigone-sparing, 300 U.I. of american or 1000 U.I. of english BTX-A diluited in 10 ml of saline solution. Mean follow-up was of 10.1 months (median 11$\pm$4.7; range 0.5-18). In the **second group** (low dosage group) we used 500 U.I. of english toxin in 10 ml of saline solution. The follow-up was ranged from 1 to 4 months.

Results:

At 6 weeks follow-up we recorded an average improvement of bladder capacity of 240.5 ml (range 180-400). This data was confirmed by videourodynamic investigation that highlighted the disappearance of vesico-ureteral reflux in 3 out of 4 patients too. 28 out of 61 patients are currently in low-dose anticholinergic therapy.5 out of 61 patients referred hypostenia with reduced supralesional muscle force, but with regular daily activity. Hypostenia disappeared from 2 to 4 weeks after injection. 4 patients referred

vision disturbances that disappeared immediately after oral anticholinergic suspencion. Bladder overdistension may occurs sometimes. Only 1 treatment was perfomed in 38 patients with an efficacy period varying from 4 to 16 months. 2 treatments were perfomed in 22 patients with a mean interval from first injection of 8 months (median 8.5±3.3; range 1-13). 3 injectons only in 1 patient at 3 and 9 after first injection.In the second group (lower dose)1 patients out of 10 needed a second injection after 1 month. In 9 patients we obtained a pharmacoinduced bladder augmentation at 3 months follow-up.

Discussion and Conclusion:

Our study confirmed the efficacy of the BTX-A for patients with DH using IC. We obtained a significative increased bladder capacity with low detrusor pressure. An important side effect is hypostenia that was no severe and it had a temporary duration not more than 1 month. For this reason we tryed a lower dose and this short series showed to be effective avoiding side effects. Patients reported subjective improvement of continence and improved quality of life. After this full continence period, 3 patients asked for surgical rizothomy for a definitive continence status.

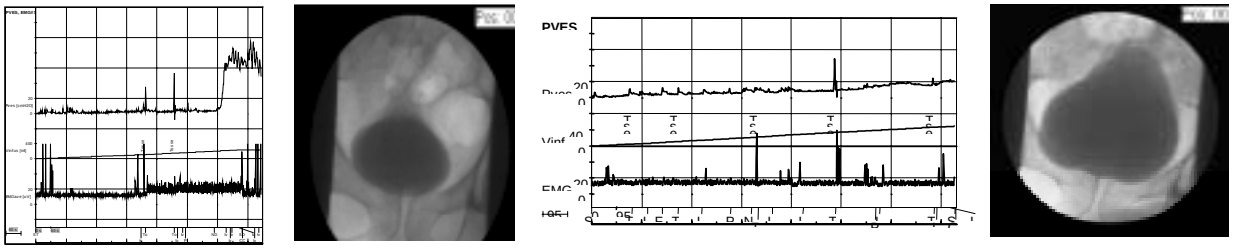

Fig.I – Videourodynamic before and 6 weeks after treatment: increased bladder capacity, lower bladder pressure