

LONG-TERM EFFICACY OF INCOBOTULINUMTOXINA IN THE MANAGEMENT OF SIALORRHEA IN PARKINSON'S DISEASE

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INTRODUCTION

One of the symptoms of a common and serious neurodegenerative diseases such as Parkinson's disease is sialorrhea (around 70-80% of patients). Sialorrhea (abnormal and over sediment of saliva in the oral cavity) is caused by a deglutition difficulty or an increased production of saliva, that flows out of the mouth. It can cause macerations and fissures in perioral region, halitosis, dysarthria, aspiration pneumonia, asphyxiation and patient's awkwardness. Management can be conservative (medical therapy using anticholinergic drugs) or more invasive (surgery with excision of salivary glands, duct's ligation and transposition).

Surgical solution is final but dangerous. Radiation is not used because the side effects and the carcinogenic potential.

A non invasive and efficacy treatment is botulinum toxin A (BTX-A) injection in salivary glands. Botulinum toxin A temporarily blocks the release of acetylcholine and a number of other neurotransmitters from synaptic vesicles. The glands flow is controlled by autonomic nervous system: both parasympathetic and sympathetic have a role, but the latter is less important. The parasympathetic system uses acetylcholine to stimulate saliva's production, through glands receptor. BTX-A goes through cholinergic telodendrion and blocks neurotransmitter, so the gland's activity. Different study demonstrated efficacy (until 4-6 months) and safety of BTX-A injection in sialorrhea caused by Parkinson's disease and Amyotrophic Lateral Sclerosis with ultrasound guide.

MATERIALS AND METHODS

The study was performed in a term of six months (November 2016-April 2017); we have recruited 18 patients with sialorrhea caused by Parkinson's Disease (9 male and 9 female).

Patients average age was 76,5 +/- 6,7 years.

Inclusion criteria :Confirmed diagnosis of PD. Diagnostic imaging of dysphagia by FLS (nobody had PEG); No effect to the previous medical therapy with Amitriptyline (LAROXYL® 7 drops/die).

Exclusion criteria :No confirmed diagnosis of PD; No or severe (with PEG) dysphagia by FLS (nobody had PEG); Efficacy of medical therapy with Amitriptyline (LAROXYL® 7 drops/die).

Incobotulinum toxin A (XEOMIN®), reconstituted with saline water, was injected under ultrasound guide, so we had a great vision of submandibular and parotid glands, and of all surrounding structures including the facial nerve, that is very close to the parotid gland. We injected using two points for the parotid gland and one point for the submandibular gland. The patients were treated with the average drug's dosage given bilaterally in the parotid gland (12,5 +/- 3,9 U), in the submandibular gland (12,2 +/- 4,5 U).

All patients were submitted to accurate anamnesis and medical exam, with attention to the swallowing; all patients signed informed consent in written form. At t0 (pre-injection) and every month we submitted Visual Analogue Scale (VAS) to estimated the level of salivation (1 was the best state and 10 the worst state), Gauze's test to perform the weighed of the gauze after 1 minute and Sugar lump's test to evaluate time necessary for melting.

Gauze's test: patient shallows sitting; then we have put a piece of gauze, previously weighed, under the tongue, asking them to keep head tilted forward without swallowing. One minute later we have pulled off and weighed the gauze. Generally the gauze absorbs 0,12 g/min of saliva.

Sugar lump's test: Patient shallows and then we put a sugar lump under the tongue, evaluating the necessity time for melting.

Data were noticed in these times: t0=pre-injection;t1=30 days later;t2=90 days later;t3=120 days later;t4=150 days later;t5=180 days later

STATISTICAL ANALYSIS. We used TWO WAY ANOVA

RESULTS

Data analysis demonstrated gauze's test, sugar lump's test and VAS test improved until 6 months so we reinjected every 6 months ($p < 0,05$). The two diagrams of gauze's test and sugar lump's test (Tables 1 and 2) show the clear reduction of the flow of saliva and the variations of the effect during the time.

After the analysis of both objective tests, it's evident that efficacy of treatment is best after 30 days (t1), when we obtain a reduction over 50% of drooling (gauze's test $t_0=1,7 \pm 0,2$, $t_1=0,9 \pm 0,19$; sugar lump's test $t_0=29,7 \pm 7,2$, $t_1=65,5 \pm 14,07$).

Since t1, there is a slow and gradual reduction of the effect, that results halved at t4 (150 days, gauze's test $t_4=1,3 \pm 0,2$, sugar lump's test $t_4=50,3 \pm 11,3$) and finished 30 days later (180 days, gauze's test $t_5=1,65 \pm 0,2$, sugar lump's test $t_5=35,1 \pm 7,66$), with $p < 0,05$.

Comparing these two diagrams with the diagram of VAS, we demonstrated objective benefit coherently with tests' results (Table 3); in fact data statistically decreased until t4 ($t_0=9,2 \pm 0,7$, $t_1=3 \pm 0,8$, $t_4=5,2 \pm 0,63$ and $t_5=8,3 \pm 0,6$), with $p < 0,05$. So the effect lasts 6 months, then the treatment should be repeated.

DISCUSSION

Botulinumtoxin A treatment reduces saliva's in patients with Parkinson's. This significant efficacy was obtained by a non-invasive treatment and a method of administration that thanks to ultrasound guidance minimizes the risk of iatrogenic injuries, as the loss of the facial nerve.

Patients perceived and reported clinical benefit until 6 months. Efficacy was limited in time, for the event of sprouting. In this study, the transient effect makes necessary to repeat the treatment on average every six. Recruited patients did not showed collateral effects. In fact, no patients referred an important worsening of dysphagia caused by treatment. No patients referred paralysis of facial nerve due to sonographic guide that reduce incidence of nerve's lesion or others side effects, such as xerostomia. Around 30% of patients reported a different pattern of saliva; after treatment they reported presence of most slimy saliva. Mainly this events due to transient interruption of parotids activity (watery secretion) and predominance of submandibular and sublingual (slimy secretion). The change of pattern did not cause any clinical problem to these patients; in some of them the different pattern was useful because reduced a lot the events of choking sensation (especially night-time). Advantages for patient subjected to these therapeutic treatment are important for lower incidence of aspiration pneumonia, macerations, rhagades and fissures in perioral region (so infections) and because decrease emargination and awkwardness in these patients that minimize relationship for embarrassment of drooling. The objective of the treatment is to provide always a minimum flow of saliva in patients; indeed the dryness of oral cavity may cause the onset of other complications (fissures, dental decay, etc.) that are not easy to improve in these patients. Also the caregivers benefit from treatment because the sialorrhea may require a continuous health care, so a distress for patient and for those who takes care of him.

CONCLUSION

According to international literature, in spite of the small number of patients, our study concludes that Botulinum toxin A is an efficacy treatment option for sialorrhea in patients with PD in two years; for six months patients reduced an annoying symptom with no side effects

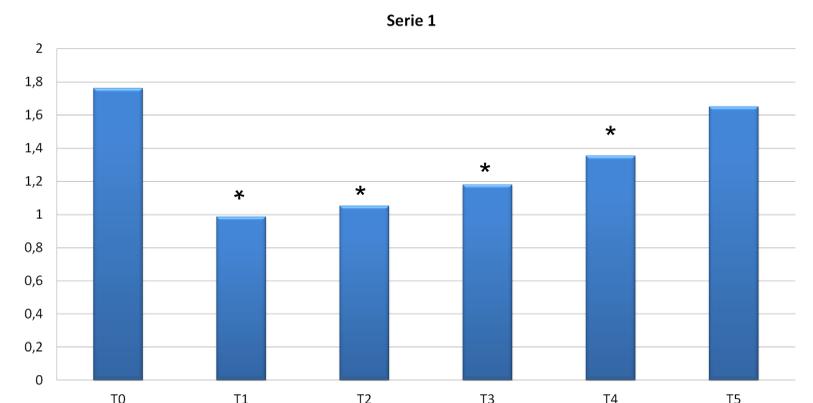


Table 1: Gauze's test: Statistical improvement until 150 days after infiltration ($p < 0,05$)

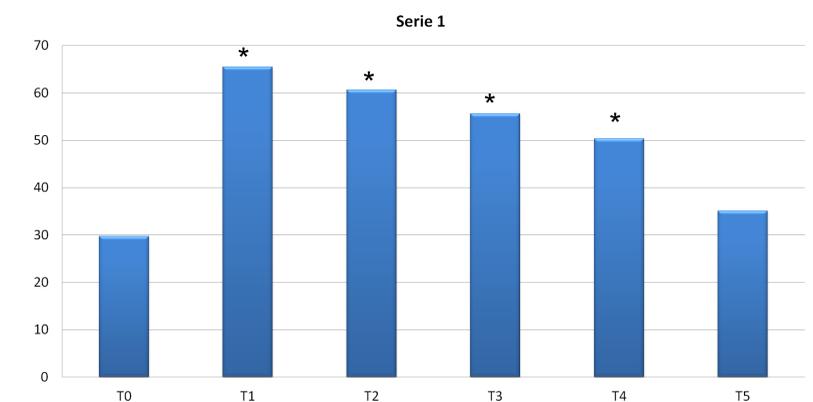


Table 2: Sugar lump's test : Statistical improvement until 150 days after infiltration ($p < 0,05$)

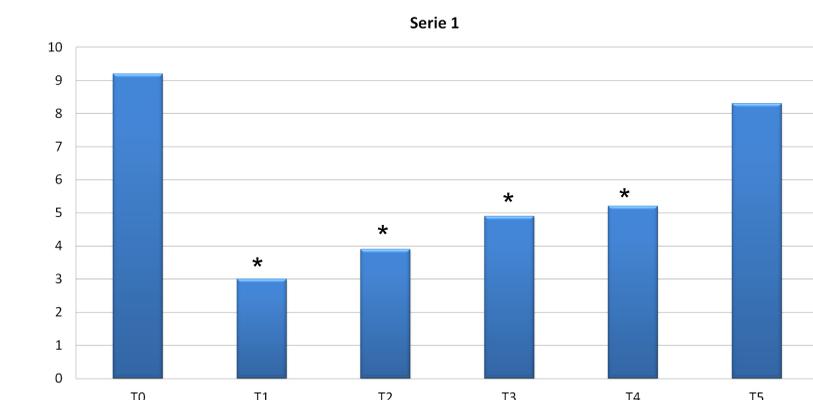


Table 3: VAS test : Patients refer objective improvement until 150 days after infiltration ($p < 0,05$)