

Efficacy of Incobotulinumtoxin Type A (Xeomin®) in the Management of Sialorrhea in Neurodegenerative Diseases

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Abstract

Introduction: One of the symptoms of two very common and serious neurodegenerative diseases such as Amyotrophic Lateral Sclerosis and Parkinson's disease is sialorrhea. 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). Botulinum toxin A is a non invasive and poor side effects alternative. Aim of this study is to examine therapeutic resources for sialorrhea in Amyotrophic Lateral Sclerosis and Parkinson's disease, by objective and subjective evaluation.

Materials and methods: 20 patients with sialorrhea caused by Parkinson's disease (10 patients) and ALS (10 patients). Incobotulinum toxin A (XEOMIN®, Merz Pharma), was injected under ultrasound guide in the submandibular and parotid glands. At t0 (pre-injection), t1 (30 days later), t2 (90 days later), t3 (120 days later), t4 (150 days later) and t5 (180 days later, only in PD group) 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.

Results: In Parkinson's and ALS group gauze's test, sugar lump's test and VAS improved until 6 months (PD group) and 5 months (ALS group), with $p < 0,05$.

Conclusion: This study concludes that therapeutic resource with Botulinum toxin A is an efficient treatment option for sialorrhea in patients with ALS and PD.

Keywords: Parkinson's disease; Amyotrophic lateral sclerosis; Sialorrhea; Botulinum toxin A; Dysphagia

Introduction

Sialorrhea, a clinical state characterized by an abnormal and an 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 [1]. There are three greater salivary glands (parotid, submandibular and sublingual) and a lot of lesser glands. In the unstimulated state, 70% of saliva is secreted by submandibular and sublingual glands [2]. Conversely, in the stimulated state the parotids glands provide most of the saliva [3].

Sialorrhea is one of the symptoms of two very common and serious neurodegenerative diseases: Amyotrophic Lateral Sclerosis (ALS), around 50-80% of patients and Parkinson's disease (PD), around 70-80% of patients [4-6].

ALS is characterized by a progressive degeneration of motor neurons in the spinal cord, brain stem and motor cerebral cortex, evolved to a muscular paralysis in bulbar, cervical, thoracic and lumbosacral regions [7]. Parkinson's disease has a progressive course and a shorter lifespan; there are three most important clinical signs: shaking, slow movement and muscle stiffness [8,9]. In these patients, the central process of drooling is the abnormal saliva's clearance. The abnormal co-ordination of buccal, facial and lingual musculature results in the over sediment of saliva in the oral cavity and in the inhibition of swallowing reflex; saliva get through the margin of the lips and the throat. Therefore the dysphagia caused by neuromuscular disorder and normal saliva's flow cause sialorrhea in neurodegenerative diseases [10]. Clinically it can cause macerations and fissures in perioral region (so infections), halitosis, dysarthria, aspiration pneumonia, asphyxiation [11]. Psychologically, patients feel uneasy, awkwardness and they tend to cut themselves off, worsening mood.

Sialorrhea is known to be difficult to treat. Management can be conservative or more invasive. Medical therapy makes use of anticholinergic drugs [12]. Glycopyrrrolate and transdermal scopolamine are very available in the treatment of sialorrhea but have also a lot of side effects (tachycardia, urinary retention, confused view, instability, daze).

Surgically it can be made the excision of salivary glands, duct's ligation and transposition; this solution is final but dangerous [13]. Radiation is not used because the side effects and the carcinogenic potential [14].

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 telodendron 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 [15-17].

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Aim of this study is to examine, by objective and subjective evaluation, safety and efficacy of IncobotulinumtoxinA (Xeomin®, Merz Pharma) in 20 patients with sialorrhea due to Amyotrophic Lateral Sclerosis (ALS) and Parkinson's disease.

Materials and Methods

The study was performed in a term of six months (November 2016-April 2017); we have recruited 20 patients with sialorrhea, of which 10 suffering from Parkinson's disease and 10 diagnosed with ALS.

In the first group (PD) patients average age was 76,5 +/- 6,7 years; in the second group (ALS) was 55,3 +/- 3,6 years.

Inclusion criteria

- Confirmed diagnosis of ALS and PD diagnosis.
- Diagnostic imaging of dysphagia by FLS (nobody had PEG) [18];
- No effect to the previous medical therapy with Amitriptyline (LAROXYL® 7 drops/die) [19].

Exclusion criteria

- No confirmed diagnosis of ALS and PD diagnosis;
- 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. For the group of patients with Parkinson's disease the average drug's dosage given bilaterally in the parotid gland was 12,5 +/- 3,9 U, in the submandibular gland was 12,2 +/- 4,5 U. Patients with ALS were treated with 14,25 +/- 4,3 U in the parotid gland and 13,3 +/- 4,1 U in the submandibular gland.

Evaluation

The evaluation criteria were three, one subjective and two objectives:

- Visual Analogue Scale (VAS): patients had to estimate the level of salivation (1 was the best state and 10 the worst state);

- 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 (only in PD group because in ALS group efficacy finished at t4).

We used TWO WAY ANOVA statistical analysis.

All patients were submitted to accurate anamnesis and medical exam, with attention to the swallowing; all patients signed informed consent in written form.

Results

Parkinson's group

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 t0=1,7 ± 0,2, t1=0,9 ± 0,19; sugar lump's test t0=29,7 ± 7,2, t1=65,5 ± 14,07). Since t1, there is a slow and gradual reduction of the effect, that results halved at t4 (150 days, gauze's test t4=1,3 ± 0,2, sugar lump's test t4=50,3 ± 11,3) and finished 30 days later (180 days, gauze's test t5=1,65 ± 0,2, sugar lump's test t5=35,1 ± 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 (t0=9, 2 ± 0,7, t1=3 ± 0,8, t4=5,2 ± 0,63 and t5=8,3 ± 0,6), with p<0,05. So the effect lasts 6 months, then the treatment should be repeated.

	t0 (pre-injection)	t1 (30 days)	t2 (90 days)	t3 (120 days)	t4 (150 days)	t5 (180 days)
pz1	2,02	0,99	1,1	1,1	1,2	1,99
pz2	2	1,1	1,1	1,1	1,5	1,8
pz3	2,1	1,01	1,01	1,3	1,5	1,8
pz4	1,78	0,9	1,1	1,4	1,55	1,7
pz5	1,4	0,5	0,9	1,1	1,1	1,3
pz6	1,9	1,2	1,1	1,4	1,7	1,76
pz7	1,6	1,1	1,23	1,32	1,45	1,55
pz8	1,5	0,99	0,99	0,87	1,1	1,5
pz9	1,34	0,98	0,98	0,98	0,98	1,23
pz10	1,98	1,1	1,01	1,23	1,45	1,87
Average	1,762	0,987*	1,052*	1,18*	1,353*	1,65
DS	0,280547085	0,191197978	0,092231593	0,17907168	0,238469658	0,24832774

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

	t0 (pre injection)	t1 (30 days)	t2 (90 days)	t3 (120 days)	t4 (150 days)	t5 (180 days)
pz1	30	68	65	55	53	38
pz2	25	56	56	43	32	29
p3	33	78	65	61	58	40
pz4	20	50	51	53	42	32
pz5	27	44	44	42	39	27
pz6	35	70	64	63	53	38
pz7	45	93	85	76	67	49
pz8	33	70	70	65	66	43
pz9	27	66	54	53	45	29
pz10	22	60	52	45	48	26
Average	29,7	65,5*	60,6*	55,6*	50,3*	35,1
DS	7,257945837	14,07322122	11,73977096	10,84435337	11,3729699	7,665941995

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

	t0 (pre injection)	t1 (30 days)	t2 (90 days)	t3 (120 days)	t4 (150 days)	t5 (180 days)
pz1	10	2	4	5	5	8
pz2	9	4	4	5	6	7
p3	8	4	4	5	4	8
pz4	9	3	4	6	6	9
pz5	10	3	4	4	5	8
pz6	10	3	5	5	5	9
pz7	8	2	4	4	5	8
pz8	9	3	3	5	5	9
pz9	10	4	4	5	5	9
pz10	9	2	3	5	6	8
Average	9,2	3*	3,9*	4,9*	5,2*	8,3
DS	0,788810638	0,816496581	0,567646212	0,567646212	0,632455532	0,674948558

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

	t0 (pre injection)	t1 (30 days)	t2 (90 days)	t3 (120 days)	t4 (150 days)
pz1	2,1	0,99	0,9	1	2,1
pz2	1,9	1	0,8	1,2	1,8
pz3	2,01	1,01	0,8	1,2	2
pz4	2,09	1	1	1,2	2
pz5	2,1	0,8	1	1,2	2,2
pz6	2,2	1	1,1	1,3	2,1
pz7	2,5	1	1,1	1,3	2,5
pz8	2,1	0,98	0,8	1,2	2,1
pz9	2,6	0,98	0,8	1,2	2,6
pz10	2,1	1	0,76	1,2	2,6
Average	2,17	0,976*	0,906*	1,2*	2,2
DS	0,215819	0,062574	0,133016	0,08165	0,274874

Table 4: Gauze's test in ALS group: Statistical improvement until 120 days after infiltration (p<0,05).

ALS group

In the group of patients with ALS, data obtained by two objective tests are similar for the effect and the evolution of treatment (Tables 4-6).

The best of efficacy is evident at t1 (30 days), when the flow is halved (gauze's test t0=2,17 ± 0,2, t1=0,97 ± 0,06; sugar lump's test t0=16 ± 1,3, t1=30,6 ± 2,2, p<0,05); in the following 60 days the reaction is constant. At 120 days (t3) the effect is reduced (gauze's test t3=1,2 ± 0,08; sugar lump's test t3=27,1 ± 2,8, p<0,05), 30 days later the decrease is more statistically sudden, so at t4 (150 days) in the oral cavity we observed a quantity of saliva similar than at t0 (gauze's test t4=2,2 ± 0,2; sugar lump's test t4=17,1 ± 1,1, p<0,05). VAS test was congruent with objective evaluations (t0=8,7 ± 0,9, t1=2,2 ± 0,4, t3=3,4 ± 0,5 and t4=8,6 ± 1,07, p<0,05).

In this case the effect lasts 5 months.

Discussion

Botulinumtoxin A treatment reduces saliva's flow to 50% both in patients with Parkinson's disease and with diagnosis of ALS [20]. This significant efficacy was obtained by a non-invasive treatment and a method of administration that thanks to ultra-sound guidance minimizes the risk of iatrogenic injuries, as the loss of the facial nerve [21].

Patients perceived and reported clinical benefit until 6 months in Parkinson's group and 5 months in ALS one. 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 months in

	t0 (pre injection)	t1 (30 days)	t2 (90 days)	t3 (120 days)	t4 (150 days)
pz1	15	32	32	31	17
pz2	16	33	32	31	18
p3	16	34	33	31	18
pz4	17	29	29	24	18
pz5	18	28	27	24	18
pz6	15	27	27	25	16
pz7	15	30	30	27	15
pz8	16	31	30	26	17
pz9	14	32	31	27	16
pz10	18	30	28	25	18
Average	16	30,6*	29,9*	27,1*	17,1
DS	1,333333	2,221111	2,13177	2,884826	1,100505

Table 5: Sugar lump's test in ALS group: Statistical improvement until 120 days after infiltration (p<0,05).

pz1	8	2	2	3	8
pz2	8	2	2	3	7
p3	7	3	3	3	7
pz4	9	2	3	4	10
pz5	8	2	2	3	8
pz6	10	2	2	4	9
pz7	9	2	2	4	9
pz8	9	2	2	3	9
pz9	9	3	3	3	9
pz10	10	2	2	4	10
Average	8,7	2,2*	2,3*	3,4*	8,6
DS	0,948683	0,421637	0,483046	0,516398	1,074968

Table 6: VAS test in ALS group: Patients refer objective improvement until 120 days after infiltration (p<0,05).

patients with Parkinson's disease and every five months in patients with ALS. Maybe in this last group the effect lasts less for faster evolution of the disease and decline of deglutition [22].

Recruited patients did not showed collateral effects. In fact, no patients referred an important worsening of dysphagia caused by treatment. Some minimal worsening in Parkinson's group (1/10 patient) and in ALS group (2/10 patients) might be attributable to evolution of core disease; this did not caused PEG's use [23,24]. 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.

In both groups, 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) [25,26]. 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) [27,28].

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 [29].

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 [30].

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 [31,32].

Conclusion

According to international literature, in spite of the small number of patients, our study concludes that therapeutic resource with Botulinum toxin A is an efficient treatment option for sialorrhea in patients with ALS and PD [33-35].

References

- McGeachan AJ, Mcdermott CJ (2017) Management of oral secretions in neurological disease. *Pract Neurol* 17: 96-103.
- Gonzalez-L MD, Martinez C, Bori Y Fortuny I, Suso-Vergara S (2017) Factors in the efficacy, safety, and impact on quality of life for treatment of drooling with botulinum toxin type a in patients with cerebral palsy. *Am J Phys Med Rehabil* 96: 68-76.
- Sant' Anna AE, Hazarbassanov RM, de Freitas D, Gomes JÁ (2012) Minor salivary glands and labial mucous membrane graft in the treatment of severe symblepharon and dry eye in patients with Stevens-Johnson syndrome. *Br J Ophthalmol* 96: 234-239.
- Sufit R, Miller R, Mitsumoto H (1999) Prevalence and treatment outcomes of sialorrhea in Amyotrophic Lateral Sclerosis patients as assessed by the ALS Patient Care Database. *Ann Neurol* 46: 506
- Jackson CE, McVey AL, Rudnicki S, Dimachkie MM, Barohn RJ (2015) Symptom management and end-of-life care in amyotrophic lateral sclerosis. *Neurol Clin* 33: 889-908.
- Harriman M, Morrison M, Hay J, Revonta M, Eisen A, et al. (2001) Use of radiotherapy for control of sialorrhea in patients with amyotrophic lateral sclerosis. *J Otolaryngol* 30: 242-245.
- Andersen PM, Abrahams S, Borasio GD, de Carvalho M, Chio A, et al. (2012) EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)—revised report of an EFNS task force. EFNS Task Force on Diagnosis and Management of Amyotrophic Lateral Sclerosis. *Eur J Neurol* 360-375.
- Kalia LV, Lang AE (2015) Parkinson's disease. *Lancet* 29: 896-912.
- Mukherjee A, Biswas A, Das SK (2016) Gut dysfunction in Parkinson's disease. *World J Gastroenterol* 22: 5742-52.
- McGeachan AJ, Hobson EV, Al-Chalabi A, Stephenson J, Chandran S, et al. (2017) A multicentre evaluation of oropharyngeal secretion management practices in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 18:1-9.
- Costa CC, Ferreira JB (2008) Injections of botulinum toxin into the salivary glands to the treatment of cronic sialorrhoea. *Rev Bras Cir Cabeça Pescoço*: 28-31.
- Banfi P, Ticozzi N, Lax A, Guidugli GA, Nicolini A, et al. (2015) A review of options for treating sialorrhea in amyotrophic lateral sclerosis. *Respir Care* 446-454.
- Stamatiki S, Behar P, Brodsky L (2008) Surgical management of drooling: Clinical and caregiver satisfaction outcomes. *Int J Pediatr Otorhinolaryngol*: 1801-1805.
- Karakoc M, Yon MI, Cakmakli GY, Ulusoy EK, Gulunay A, et al. (2016) Pathophysiology underlying drooling in Parkinson's disease: Oropharyngeal bradykinesia. *Neurol Sci*: 1987-1991.
- Jost WH (2016) The option of sonographic guidance in Botulinum toxin injection for drooling in Parkinson's disease. *J Neural Transm* 123: 51-55.
- Guidubaldi A, Fasano A, Ialongo T, Piano C, Pompili M, et al. (2011) Botulinum toxin A versus B in sialorrhea: A prospective, randomized, double-blind, crossover pilot study in patients with amyotrophic lateral sclerosis or Parkinson's disease. *Mov Disord* 26: 313-319.
- Olivera AF Filho, Silva GA, Almeida DM (2016) Application of botulinum toxin to treat sialorrhea in amyotrophic lateral sclerosis patients: A literature review. *Einstein* 14: 431-434.

18. Hammer MJ, Murphy CA, Abrams TM J (2013) Airway somatosensory deficits and dysphagia in Parkinson's disease. *J Parkinsons Dis*: 39-44.
19. Sinha S, Simlai J, Praharaj SK (2016) Very Low Dose Amitriptyline for Clozapine-Associated Sialorrhea. *Curr Drug Saf*: 262-263.
20. Barbero P, Busso M, Artusi CA, De Mercanti S, Tinivella M, et al. (2016) Ultrasound-guided botulinum toxin-A injections: A method of treating sialorrhea. *J Vis Exp*: 117.
21. Young CA, Ellis C, Johnson J, Sathasivam S, Pih N (2011) Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. *Cochrane Database Syst Rev* CD006981.
22. Narayanaswami P, Geisbush T, Tarulli A, Raynor E, Gautam S, et al. (2016) Drooling in Parkinson's disease: A randomized controlled trial of incobotulinum toxin A and meta-analysis of Botulinum toxins. *Parkinsonism Relat Disord* 30: 73-77.
23. Tiigimäe-Saar J, Taba P, Tamme T (2017) Does Botulinum neurotoxin type A treatment for sialorrhea change oral health? *Clin Oral Investig* 21:795-800.
24. Breidenbach MA, Brunger AT (2004) Substrate recognition strategy for botulinum neurotoxin serotype A. *Nature* 432: 925-929.
25. Meningaud JP, Pitak-Arnop P, Chikhani L, Bertrand JC (2006) Drooling of saliva: A review of the etiology and management options. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 101: 48-57.
26. Mancini F, Zangaglia R, Cristina S, Sommaruga MG, Martignoni E, et al. (2003) Double-blind, placebo-controlled study to evaluate the efficacy and safety of botulinum toxin type A in the treatment of drooling in parkinsonism. *Mov Disord* 18: 685-688.
27. Dogu O, Apaydin D, Sevim S, Talas DU, Aral M (2004) Ultrasound-guided versus 'blind' intraparotid injections of botulinum toxin-A for the treatment of sialorrhoea in patients with Parkinson's disease. *Clin Neurol Neurosurg* 106: 93-96.
28. Andy W, Revan Kumar J, Jörgen E, Doron A, Anne Marie Lynge P, et al. (2017) A guide to medications inducing salivary gland dysfunction, xerostomia and subjective sialorrhea: A systematic review sponsored by the world workshop on oral medicine VI. *Drugs RD*: 1-28.
29. Jaume Miranda R, Lluís Brunet L, Eduard Lahor S, Magí F (2015) Salivary secretory disorders, inducing drugs and clinical management. *Int J Med Sci* 12: 811-824.
30. Salat-Foix D, Suchowersky O (2012) The management of gastrointestinal symptoms in Parkinson's disease. *Expert Rev Neurother* 12: 239-248.
31. Blackhall LJ (2012) Amyotrophic lateral sclerosis and palliative care: Where we are and the road ahead. *Muscle Nerve* 45: 311-318.
32. Ng L, Khan F, Young CA, Galea M (2017) Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 10: CD011776.
33. Weikamp JG, Schinagl DA, Verstappen CC, Schelhaas HJ, de Swart BJ, et al. (2016) Botulinum toxin-A injections vs. radiotherapy for drooling in ALS. *Acta Neurol Scand* 134: 224-231.
34. Petracca M, Guidubaldi A, Ricciardi L, Ialongo T, Del Grande A, et al. (2015) Botulinum toxin A and B in sialorrhea: Long-term data and literature overview. *Toxicol* 107: 129-140.
35. Srivaniachapoom P, Pandey S, Hallett M (2014) Drooling in Parkinson's disease: A review. *Parkinsonism Relat Disord* 20: 1109-1118.