

## Salivary gland application of botulinum toxin for the treatment of sialorrhea

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### ABSTRACT

Sialorrhea or excessive salivation, and drooling, are common and disabling manifestations in different neurological disorders. A review is made of the literature, based on a PubMed search, selecting those articles describing clinical trials involving the injection of botulinum toxin A in the salivary glands of patients with different diseases characterized by sialorrhea.

The most frequently treated diseases were infant cerebral palsy (30%), Parkinson's disease (20%) and amyotrophic lateral sclerosis (15%). Over half of the authors injected the product into the parotid glands, 9.5% into the submaxillary glands, and 38% into both. The total doses of toxin injected varied from 10-100 units of Botox® or 30-450 units of Dysport® according to the different authors. A reduction was observed in the production of saliva following these injections, and the duration of the therapeutic effect was 1.5-6 months. Six articles (30%) described the presence of adverse effects such as dysphagia, xerostomia and chewing difficulties.

Most of the clinical studies involved small patient samples, with no blinding or randomization, and no control group. Moreover, no data are available on the efficacy and adverse effects of treatment in the context of long-term prospective studies. The effective therapeutic dose and ideal form of application remain to be established, and require the conduction of further controlled clinical trials involving large sample sizes.

**Key words:** *Botulinum toxin, sialorrhea, salivary glands, neurological diseases.*

### INTRODUCTION

Sialorrhea or excessive salivation, and drooling, are common and disabling manifestations in different neurological disorders (1) such as amyotrophic lateral sclerosis (ALS) or Parkinson's disease, and often coincide with alterations in swallowing reflex (2).

Drug substances are an option (though not the only possibility) for the treatment of sialorrhea. Anticholinergic agents are the basic options in pharmacotherapy, and include glycopyrrolate, propantheline and scopolamine. These anticholinergic drugs reduce the volume of saliva as

a result of reversible muscarinic cholinergic receptor block (specifically the M3 receptors). However, undesirable adverse effects are often observed with such treatment, including constipation, urinary retention, tiredness, irritability and drowsiness (3-4).

Other therapeutic options include surgery, irradiation, "biofeedback" measures, positional techniques and oral motor or behavioral therapy (exercises to improve the oral musculature) (3).

## CONCEPT

Neurobotulinum toxin serotype A (TBA) has drastically changed the treatment of a broad range of autonomous hypersecretory alterations such as focal hyperhidrosis (axillary perspiration, sweating of the palms, or gustative perspiration), sialorrhea, pathological lacrimation, and rhinorrhea (5). Its application as treatment for sialorrhea was first proposed in 1997 by Bushara, in the form of an injection into the parotid glands of patients with amyotrophic lateral sclerosis and other neurological diseases (1). This toxin is produced by a gramnegative anaerobic bacterium, *Clostridium botulinum* (2). Its action is based on the inhibition of acetylcholine release at presynaptic level (1). The toxin acts upon the cholinergic nerve endings, causing proteolysis of SNAP-25 (synaptosomal associated protein, implicated in synaptic vesicle fusion with the presynaptic membrane)(1,5), thus resulting in local chemical denervation and the loss of neuronal activity in the target organ.

Two TBA formulations can be found on the market: Dysport® (Speywood Pharmaceuticals Ltd, Maidenhead, UK) and Botox® (Allergan Inc., Irvine, USA). It is estimated that one unit of Botox® is equivalent to 3 or 4 units of Dysport® (2).

The present study reviews the scientific literature on the injection of TBA into the human salivary glands, as palliative treatment for sialorrhea.

A Medline/PubMed search was conducted, covering the period between January to October 2005. The search was limited to articles published in English, French, German and Spanish. The key words used included sialorrhea, botulinum toxin, Botox® and hypersalivation. We selected those articles that involved the injection of botulinum toxin into the salivary glands as sole treatment in patients with sialorrhea.

A total of 21 articles were considered valid. The predominant treated pathologies characterized by sialorrhea were infant cerebral palsy (6 articles)(6-11), Parkinson's disease (4 articles)(12-15), and amyotrophic lateral sclerosis (2 articles)(16-18)(Table 1) - though such treatment has also been used in different ear, nose and throat problems (2 articles)(19-20), and in other pathologies (18,21-26)(Table 2). Of the total publications reviewed, only three corresponded to controlled clinical trials (11,14,26).

Over half of these studies were published in neurological journals (12-18,22,23,25,26), four in ear, nose and throat publications (10,19-21), three in neuropediatric journals (7-9), two in pediatric publications (6,11), and one in an oral and maxillofacial surgery journal (27).

Most of the authors describe injection into the parotid glands (50%)(1,8,12,13,15,17,22, 23,25,26), with a lesser percentage into the submaxillary glands (10%)(6,10,11). In turn, 40% inject the toxin into both gland locations (40%)(10,14,16,18-20,27).

In 11% of these studies (6,10,11,14,15,18,20,21,27), injection of the toxin was intraglandular under ultrasound guidance.

The total doses of toxin injected varied from 10-100 units

of Botox® or 30-450 units of Dysport®, and the duration of the therapeutic effect was 1.5-6 months.

On the other hand, different adverse effects were reported in 7 of the articles (30%), including dysphagia (22), dry mouth (15, 18, 22), chewing difficulty (22), and even a case of recurrent mandibular luxation (17).

## BOTULINUM TOXIN IN CEREBRAL PALSY PATIENTS

Jongerijs et al. (6) treated three children with the injection of TBA in both submaxillary glands, at two points in each gland, under ultrasound guidance with general anesthesia - delivering a total of 40 to 50 U of Botox® according to body weight. Salivation was assessed by quantitative sialometry based on the weight of cotton rolls, and applying a test to the parents. In two weeks a reduction in salivation weight of 51-63% was recorded for a variable time period of 4-7 months during which no adverse effects were recorded. Three years later, the same authors (11) conducted the first controlled clinical study comparing the efficacy of two different anticholinergic agents: bilateral TBA injections (a total of 30-50 U of Botox®) in the submaxillary glands, and the administration of transdermal patch scopolamine - using the salivation ratio (estimated percentage of the ratio between the observed drooling episodes and the total number of observations), severity scales and frequency of salivation, and a visual analog scale (VAS) as methods of measurement. The first treatment option yielded a maximum effect 2-8 weeks after injection, and fewer and less important adverse effects were recorded than with the administration of scopolamine.

Bothwell et al. (8) injected the toxin into the parotid glands (5 U in each gland), following the application of a local anesthetic cream (Emla®) one hour before. They recorded a lesser duration of the therapeutic effect, equivalent to 2-4 months in 55% of the sample, which was composed of 9 children aged between 14 and 17 years. Salivation was measured calculating the salivation ratio, the weight of the Kleenex® used to dry drooling, and the salivary frequency and severity scales. Unlike these authors, Ellies et al. (9) infiltrated both parotid glands (22.5 U of Botox® per gland) and the submaxillary glands (10 U per gland), under ultrasound guidance in five children, and measuring salivation via quantitative and qualitative sialometry. The resulting reduction in drooling lasted about three months. The duration in turn was from two weeks to six months in a larger sample (n=22) divided into two groups reported by Suskind and Tilton (10). One group (n=12) was injected with a total of 10-30 U of Botox® in the submaxillary glands only, while the other group (n=10) received infiltration of the submaxillary glands at a total dose of 30 U, and of the parotid glands at a total dose of 20-40 U.

## BOTULINUM TOXIN IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Giess et al. (16) confirmed the adequacy of the approach adopted by Bushara (1), since they infiltrated both parotids

**Table 1.** Different studies on the application of TBA for the treatment of sialorrhea on patients with cerebral palsy, amyotrophic lateral sclerosis and Parkinson's disease. TBA: botulinum toxin A. US: ultrasound. VAS: visual analog scale.

Authors	Year	Glands	Sample	Total dose (units)	US guide	Measurement system	Duration of effect (months)	Adverse effects observed
<b>Cerebral palsy</b>								
Jongerius et al. (6)	2001	Submaxillary	3	40-50 Botox®	Yes	Test and quantitative sialometry	4 minimum in n=2/3	No
Berweck et al. (7)	2002	Only in spasmodic muscle	300	2-29 Botox® or 5-40 Dysport®	Yes	-	Repeat after 3-6 months	-
Bothwell et al. (8)	2002	Parotid	9	10 Botox®	-	Test and Kleenex®	2 in 55%	No
Ellies et al. (9)	2002	Parotid and submaxillary	5	65 Botox®	Yes	Quantitative, qualitative sialometry	3	No
Suskind and Tilton (10)	2002	Submaxillary or both (P+S)	22	10-70 Botox®	Yes	quantitative sialometry and test	2 minimum (up to 6 months)	No
Jongerius et al. (11)	2004	Submaxillary	45	30-50 Botox®	Yes	Test and VAS	6 minimum	2 patients with dysphagia
<b>Amyotrophic lateral sclerosis</b>								
Giess et al. (16)	2000	Parotid (± submaxillary)	5	30-72 Botox®	-	Test, Kleenex®, gammagraphy	3 minimum	No
Porta et al. (18)	2001	Parotid + submaxillary	4	50-100 (according to body weight)	Yes	VAS	4.7	1 patient with dry mouth
Tan et al. (17)	2001	Parotid	1		No	-	-	Recurrent mandibular luxation
<b>Parkinson's disease</b>								
Pal et al. (12)	2000	Parotid	9	30-45 Botox®	-	Quantitative sialometry and VAS	-	Yes
Friedman and Potulska (13)	2001	Parotid	11	10 Botox®	No	Test and quantitative sialometry	1.5	No
Mancini et al. (14)	2003	Parotid + submaxillary	20	450 Dysport®	Yes	Test	3	No
Dogu et al. (15)	2004	Parotid	15	60 Botox®	Yes, in 8	Quantitative sialometry and VAS	4.4	Dry mouth in 2 patients

**Table 2.** Different studies on the application of TBA for the treatment of sialorrhea on patients with neurodegenerative diseases, idiopathic hypersalivation and head and neck carcinoma. TBA: botulinum toxin A. US: ultrasound. MCV: mean corpuscular volume. VAS: visual analog scale.

Authors	Year	Glands	Sample	Total dose (units)	US guide	Measurement system	Duration of effect (months)	Adverse effects observed
Bathia et al. (22)	1999	Parotid	4	20 Dysport®	-	Subjective	1.5-4	Dry mouth, dysphagia, chewing problems
Porta et al. (18)	2001	Parotid + submaxillary	10	50-100 Botox® (according to MCV)	Yes	VAS	4.7	Dry mouth (1 case)
Glickman and Deaney (23)	2001	Parotid	1	300 Dysport®	No	Subjective	6	No
Carod (25)	2003	Parotid	3	20-40 Botox® (50-60 again after 15 days)	No	Sialorrhea scale	3 minimum	No
Ellies et al. (19)	2001	Parotid + submaxillary	1	62 Botox®	No	Quantitative sialometry	3	No
Ellies et al. (21)	2002	Parotid + submaxillary	4	65 Botox®	Yes	Quantitative and qualitative sialometry, ultrasound	1-2 (6 months in 1 case)	No
Guntinas and Eckel (20)	2002	Parotid + submaxillary	3	260 Dysport®	No	Subjective	2	No
Ellies et al. (27)	2003	Parotid + submaxillary	13	50-65 Botox®	Yes	Quantitative sialometry and subjective	3 (7 months in 1 case)	No
Lipp et al. (26)	2003	Parotid	32	37.5-150 Dysport®	No	Quantitative sialometry and subjective	3-6	No

with a total of 30-72 U of Botox® (mean 46 U) in 5 patients - supplementing this amount with 5 U per submaxillary gland if the previous injection proved ineffective. No system was used for locating the glands, though the authors described three points of infiltration for the parotids: cranial, ventral and caudad. They observed a marked reduction in sialorrhea in three of the patients, with a minimum duration of three months, and stressed the improvement in quality of life and the absence of dry mouth or the aggravation of dysphagia in their patients.

In 10 patients with different chronic neurological pathologies, including four cases of ALS, Porta et al. (18) treated sialorrhea with simultaneous intraparotid and submandibular gland injections, under ultrasound guidance in all cases. The doses administered in each parotid gland ranged from 15-40 U of Botox® (mean 27.7 U) at points per gland. The doses injected into the submandibular glands corresponded to 10-

15 U of Botox® (mean 11.9 U). The total dose per patient ranged from 50-100 U (mean 76.6 U) according to body weight. The only patient that failed to improve significantly presented a bulbar form of ALS, and received the maximum dose corresponding to 40 U of Botox® per parotid gland and 10 U per submandibular gland. In the rest of cases a reduction of salivation was observed that persisted for 4-7 months (mean 4.7 months).

A case has been published (17) of recurrent mandibular luxation following bilateral injections of TBA into the parenchyma of both parotid glands (specifically, 5 U of Dysport® per gland in a first phase, and 10 U per gland in a second stage), with the purpose of treating sialorrhea in a 76-year-old woman diagnosed with ALS. The injection technique was based on manual palpation of the portion of the parotid gland located between the ascending mandibular ramus and the mastoid process. No side effects such as

mandibular weakness were observed after administration, though two months later the patient reported sudden inability to close the mouth, with associated mandibular pain. The patient had no antecedents of temporomandibular trauma or pathology. Clinical examination confirmed bilateral luxation of the mandible, which was manually reduced - though posteriorly the patient suffered spontaneous recurrences of luxation.

### **BOTULINUM TOXIN IN PATIENTS WITH PARKINSON'S DISEASE**

Pal et al. (12) described the injection of TBA in the parotid glands of 9 patients with Parkinson's disease. In coincidence with Bushara (1), ultrasound guidance was not used. Two points of injection were considered: lower, between the mastoid process and the lower part of the vertical ramus of the mandible (5 U of Botox®); and a second upper point with respect to the posterior margin of the masseter muscle (2.5 U of Botox®), corresponding to a total dose of 7.5-15 U of Botox® per gland. A positive effect was recorded in 6 of the patients, though its duration was not specified. More recently, 11 patients were treated with the same injection technique (1,13,28), administering 5 U of Botox® per parotid gland. A quantitative analysis of sialorrhea was made, and the duration of the effect was about 6 weeks.

Mancini et al. (14) conducted a double blind placebo-control study in a sample of 20 patients. One-half were injected with 450 U of Dysport®, while the other half received 2 ml of placebo in the parotid and submaxillary glands, under ultrasound guidance. Salivation was assessed by means of severity and frequency scales. The mean secretion of saliva in the toxin-treated group was significantly lower than in the placebo series, and this effect persisted for about three months. After injecting 30 U of Botox® per gland in 15 patients (15), quantitative sialometry showed that intraparotid injections under ultrasound guidance (n=8) improved sialorrhea to a greater degree than injections performed on a blind basis (n=7). Salivation was reduced during 2-6 months (mean  $4.4 \pm 1.2$ ), though two patients experienced slight xerostomia for one month.

### **BOTULINUM TOXIN IN PATIENTS WITH DIFFERENT NEUROLOGICAL DISORDERS**

Bhatia et al. (22) injected TBA via the subcutaneous route into the parotid glands of four patients, over the mandibular angle at the posterior margin of the masseter muscle, involving a dose of 20 U of Dysport®. The exception was a patient with motor neuron disease, who received half of the aforementioned dose, due to the risk of worsening the dysphagia. A beneficial effect was observed that persisted for a period of between 6 weeks and four months, though it must be stressed that salivation in these cases was subjectively assessed. Adverse effects such as chewing difficulty, dry mouth and worsening of the pre-existing dysphagia were reported. Using the same intraparotid technique, though without undesirable adverse effects, a dose of 150 U of Dysport® per gland was injected in a patient with central

degenerative neuropathy (23), resulting in subjective improvement that lasted 6 months. Likewise with intraparotid injections, though involving two sessions spaced two weeks apart, 20-40 U of Botox® were administered, followed by 50-60 U of the toxin in three patients with chronic neurological disease: motor neuron disease, Parkinson's disease and pontine infarction (25). The minimum duration of the effect was three months following assessment based on the sialorrhea intensity and severity scale (29). The efficacy of the intraparotid injection of three different doses of TBA versus the administration of placebo in patients with neurological disease has also been confirmed, resulting in a significant reduction in drooling among the patients injected with 75 U of Dysport® into each parotid gland - such administration being repeated three months later (26).

### **BOTULINUM TOXIN IN PATIENTS WITH OTHER PATHOLOGIES**

With the simultaneous infiltration of the parotid and submaxillary glands, involving total doses of 50-65 U of Botox®, different studies (9,19,21,27) in patients with a range of disorders (neurodegenerative diseases, idiopathic hypersalivation, head and neck carcinomas, etc.) have reported improvements in excessive salivation during an average period of about three months, without adverse effects. Likewise, a beneficial effect upon sialorrhea has been reported in three patients (20) with persistent pharyngo-cutaneous fistulas after total laryngectomy. A beneficial effect lasting about two months was observed, though assessment was subjective.

### **SALIVARY GLAND INJECTION OF TBA**

Primary sialorrhea is a relatively rare condition, while hypersalivation secondary to dysphagia or swallowing coordination problems is much more common in the context of neurological disease. This symptom has been treated by different authors based on TBA injection into the salivary glands.

Of the 21 articles found in the literature search involving TBA injection in humans, 15 corresponded to prospective case studies, while four were case-control studies (11,13,15,26), and two articles contributed a single clinical case each (17,23).

#### *- Type of anesthesia*

The type of anesthesia used ranged from topical local anesthetic cream (8,10) to general anesthesia (6,11), while some authors required no local anesthesia (9). The rest of studies did not specify the type of anesthesia used.

#### *- Needle caliber*

Regarding the needle caliber used for infiltration of the gland parenchyma, important variability has been observed - the caliber ranging from 21G (23) to 22G (18), 25G (6,11,22), 26G (14), 27G (16,25), 29G (13,17), and 30G (8,15,26).

#### *- Salivary glands injected*

Most authors injected the toxin into the parotid glands, possibly because the latter are superficial and thus are more

easily accessible for TBA injection, and because of the important contribution of these glands to total saliva output. Other investigators such as Jonguerius et al. (6,11) perform injection in the submaxillary glands, on the grounds that this avoids reduction of parotid output while the patient eats and drinks. Giess et al. (16) only injected TBA into the submaxillary glands in those cases where injection into the parotid glands proved scantily effective. Suskind and Tilton (10) in turn differentiated two groups of patients on deciding injection: one group was injected into the submaxillary glands, and the other into both the submaxillary and the parotid glands. No differences in the reduction of drooling were recorded between the two groups.

In the parotid gland, the number of injection points ranged from one (8,13,17) to two (10,12,15,18,26), three (cranial, medial and caudad)(16), and even 10 points (20). In the submaxillary gland, three (11,20), two (6) and one injection point have been used (10,18).

#### - TBA dose

A broad TBA dose range has been used, specifically from 10-100 U of Botox® or 20-300 U of Dysport® per patient. The safe maximum dose is not known, though it could be very low in some situations - particularly in patients with amyotrophic lateral sclerosis, who may be especially sensitive to the toxin. Likewise, the effect of repeated injections of TBA over time are not known, and it is not clear whether antibodies are produced as a result.

#### - Adverse effects

Adverse effects are not particularly frequent; however, some patients have experienced xerostomia, dysphagia and chewing difficulties. Recurrent mandibular luxation has even been reported in a patient with amyotrophic lateral sclerosis (17).

#### - Methods for the evaluation of treatment response

The sialorrhea intensity and frequency scale (29), used by authors such as Manzini et al. (14) and Carod (25), is an objective and inexpensive tool for assessing patient response to treatment. Other procedures used for the same purpose include the number of napkins used daily to contain excessive saliva production (8, 16), and even salivary gland gammagraphy (16). The importance of objective methods is that they seem to be more sensitive in detecting a reduction in sialorrhea or drooling than purely subjective assessments.

#### - Ultrasound guidance

One-half of the reviewed studies made use of ultrasound guidance for intraglandular injection. Blind puncture of the superficial lobe of the parotid gland allows the infiltration of TBA without too many technical complications, since the structure is relative superficial. Infiltration of the submaxillary gland is somewhat more difficult, since it is normally not palpable. This makes ultrasound advisable to identify the gland structure (21). In addition, ultrasound guidance makes it possible to avoid accidental damage to other anatomical structures - specifically the facial nerve in the case of injection into the parotid gland, or the facial vessels in the case of the submaxillary gland. Ultrasound allows safe application to the gland parenchyma even under unfavorable

anatomical conditions, as in patients with postoperative scar tissues. Moreover, it facilitates the detection of possible gland tissue alterations after injection.

#### - Duration of the effect therapeutic

As to the duration of the effect after the application of TBA, marked differences have been observed. In effect, the recorded duration ranged from one and a half months (13) to as long as 6 months (23).

## CONCLUSIONS

The injection of TBA into the salivary glands may be a valid treatment option in patients with sialorrhea, since it is able to improve quality of life. However, it is important to take into account that the duration of the therapeutic effect is limited in time, generally lasting a few months. Although TBA constitutes safe and effective treatment for secretory disorders such as focal axillary and palmar hyperhidrosis, the patient inclusion criteria differ among studies - many of which moreover involve samples that are too small to allow the obtainment of statistically significant results. In addition, most of these studies lack blinding, randomization or comparison versus placebo. Controlled studies are therefore needed to assess the maximum doses, location of the most effective and safe injection points, and definition of the number of TBA infiltrations required in neurological pathologies characterized by the presence of sialorrhea or drooling.

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