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ORIGINAL COMMUNICATION

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# Long-lasting benefits of botulinum toxin type B in Parkinson's disease-related drooling

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**Abstract** *Purpose* To investigate the safety, efficacy and effectiveness of botulinum toxin type-B (BTX-B) injections into the parotid glands to reduce drooling in Parkinson's disease (PD) subjects. *Methods* A double-blind, randomised, placebo-controlled study enrolled 36 advanced phase PD subjects who complained of disabling drooling. Patients received either 4000U BTX-B or placebo. Anatomically guided injections were performed. Outcome measures were chosen to assess both the subjective feeling of improvement (i.e. the Drooling Severity and Frequency Scale, DSFS, visuo-analogic ratings of familial distress, VAS-FD, and social distress, VAS-SD) and objective saliva reduction (saliva production over five minutes was checked by weighing dental rolls). The Global Impression Score (GIS) was also applied, rating improvement from 0 to 3. *Results* One month after injections, BTX-B patients showed a meaningful improvement in almost all subjective outcomes. Two-way analysis of variance gave a significant time × treatment effect, F-value being 52.5 ($p < 0.0001$) for DS-FS, 23.2 ($p < 0.0001$) for VAS-FD, 29 ($p < 0.0001$) for VAS-SD, and 28.9 ($p < 0.0001$) for UPDRSADL drooling item score. All BTX-B subjects declared sialorrhea reduction of any kind (moderate for 44.4 % cases, and dramatic for 33.3 % subjects), at variance with 61.1 % controls who denied any benefit from treatment. (Chi-square = 22.9; $p < 0.0001$). When present, benefits lasted on average 19.2 ± 6.3 weeks in the BTX-B group compared to 6.7 ± 1.4 weeks in controls (T-value: 26.4; $p < 0.0001$). *Conclusions* BTX-B represents a safe and efficacious tool for the management of PD-related drooling, ensuring a long-lasting waning of this disabling symptom.

**Key words** botulinum toxin type-B · drooling · Parkinson's disease

## Introduction

In Parkinson's disease (PD) advanced phase, drooling is a noteworthy symptom which negatively affects patient's quality of life both interfering with social participation and increasing care burden [1]. To date, treatment options have been aimed at reducing the unfavourable impact of drooling on social interaction and subsequently decreasing the risk of aspiration-related lung infections. Anti-cholinergic drugs are effective for this option, though poorly tolerated. Invasive procedures, such as parotid gland irradiation, salivary gland ligation or excision are recommended in strictly selected cases [2, 3].

It has been shown that botulinum toxin (BTX) effective action is not restricted to neuromuscular junction,

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but may be extended to acetylcholine release inhibition at autonomic nerve terminals. In parotid glands saliva outflow may be thus modulated. Few double-blind, placebo-controlled studies have so far confirmed the positive risk/benefit ratio of BTX type A (BTX-A) in reducing PD-related sialorrhea [4–6].

The recent introduction of botulinum toxin type B (BTX-B, Neurobloc® by Elan Pharmaceuticals) as a new botulinum toxin serotype in clinical practice initially arised concerns about the higher incidence of autonomic collateral effects [7]. Hence, BTX-B is supposed to provide some advantages in the treatment of autonomic dysfunction when compared to BTX-A, owing to a more selective impact on vegetative symptoms [7]. A previous randomised controlled trial (RCT) already showed the efficacy of anatomically guided injections of BTX-B into the parotid and submandibular glands in improving sialorrhea in 16 PD patients.

However, the observed benefits using BTX-B were counterbalanced by several adverse effects, including mouth dryness and neck pain so that the ultimate judgment on BTX-B cost-effectiveness has not yet been devised [8].

The present study was designed to ascertain the effectiveness of BTX-B treatment on PD-related drooling and the duration of perceived benefit.

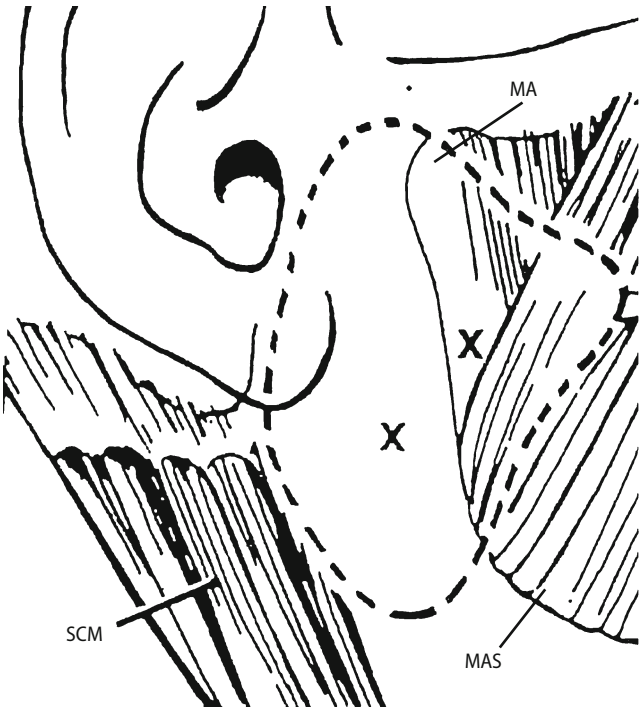


**Fig. 1** Anatomical landmarks driving the injection procedure. The parotid gland is outlined by the dashed line. Injection sites are marked by X. *SCM* sternocleidomastoid; *MAS* masseter; *MA* mandible

## Methods

### Study design

Double-blind, randomized, placebo-controlled trial of PD outpatients complaining of moderate to severe drooling.

### Subjects

PD outpatients consecutively referred to the Movement Disorder Centre for advice were enrolled if the following inclusion criteria were fulfilled: a) probable PD, as diagnosed according to the Gelb criteria [9], b) complaint of moderate to severe drooling causing meaningful social restrictions and having a score ≥2 on the drooling item of the Unified Parkinson's Disease Rating Scale (UPDRS, ADL section).

Patients were excluded if they showed contraindications to BTX, had undergone surgery for sialorrhea and/or had been previously exposed to BTX. No changes in the scheduled anti-parkinsonian therapy were allowed throughout the study.

Eligible patients were randomly assigned to receive either 4000U BTX-B (0.8 ml of injectable solution, Neurobloc® 5000 U/ml) or 0.8 mL 0.9 % saline solution (placebo) into each pre-auricular portion of the parotid gland.

The injections were performed using a 1 mL syringe with 27 gauge needle penetrating to a depth of 1–1.5 cm into two sites, behind the angle of the ascending mandibular ramus and into the infero-posterior portion of the gland, just before the mastoid process (Fig. 1). In order to avoid chewing difficulties, no injection was carried out in the portion of the gland lying over the masseter muscle, as identified by asking the patient to clench his teeth.

Randomisation was performed by matching consecutive eligible patients to a list of random numbers, which corresponded to numbered sealed envelopes containing the treatment group allocation. The investigator assessing patient eligibility was not involved in the randomisation process and both the assessor, examining all the patients, and the treating physician were blinded to treatment allocation. The study was approved by the local ethic committee.

### Assessment

A comprehensive clinical assessment was performed at baseline (T0) and one month after treatment (T1) at the same time of day. Subsequently, on a monthly schedule, telephone calls were performed to ask patients about the persistence of benefit. Should the patient complain of drooling recurrence, the examiner would invite him to the Centre in order to repeat the assessment. Subjects were also instructed to call the Centre when the perception of benefit decreased. In any case, treatment benefit was declared as waned when objective measures of saliva production showed a return to baseline values.

### Subjective measures of outcome

The impact of drooling on daily life was checked using the Drooling Severity and Frequency Scale (DS-FS), as well as a measure of patient embarrassment within the familial (VAS-FD) and social (VAS-SD) context. All the quoted measures ask subjects to rate symptom severity from 0 (no disability/distress) to 100 (maximum disability/distress ever experienced). The UPDRS-ADL item scores were also recorded for drooling and swallowing (dysphagia). All these measures were applied at both T0 and T1.

Furthermore, at T1, patients were requested to declare their satisfaction with the treatment by filling the Global Impression Score (GIS), which rated outcome on a –3 (dramatic worsening) to +3 (dramatic improvement) scale with 0 being "no change at all". They were also asked: "Would you feel like undergoing repeated BTX treatment for drooling?"

### Objective measures of outcome

The amount of saliva production was quantified in fasting upright seated patients by evaluating the weight of five dental rolls (size: 3.5 cm × 0.5 cm) retained in the mouth for five minutes. The wet rolls were weighed using an electronic device provided with 10 mg sensitivity. The average of two repeated measurement, obtained 30 minutes apart, was taken as an index of salivary outflow. The potential diffusion of BTX-B into the masseter muscle was ruled out by assessing the muscle strength and resistance: patients were asked to chew gum up to the fatigue threshold while the number of chewing movements performed over five minutes were counted.

This test was preferred to the simple manual assessment of masseter strength as routinely applied in the neurologist clinical practice, since it approximated a quantitative measurement of muscle function.

### Data analysis

The distribution and level of different independent variables (age, sex, disease duration, drooling duration, drooling severity) were compared at baseline in the two groups using the Chi-square for categorical data, the unpaired t-test for parametric continuous data and the U-Mann Whitney test for non-parametric continuous data.

The two-way analysis of variance for repeated measures was applied to test both intra- and inter-group changes in outcome measures after treatment. Patients scoring 2 to 3 on the GIS were assumed to be disability-free. The probability of achieving such outcome after BTX-B treatment, with respect to placebo, was expressed in terms of odds ratio ±95 % confidence limits.

## Results

Thirty-six subjects (M/F: 26/10; age: 71.9 ± 5.9 years, disease duration: 12.0 + 6.8 years; Hoehn & Yahr stage: II to IV) were randomly assigned to receive BTX-B treatment or placebo, 18 per group. They complained of distressing drooling since a mean of 3.4 ± 2.4 years Patients' demographic and clinical characteristics were similarly distributed in the two treatment groups (Table 1). No significant differences were found between groups with respect to the several measures of drooling severity.

One month after the injections, BTX-B group showed a significant improvement in almost all outcome measures, whereas most controls did not declare any clinical change (Table 2). A significant *time x treatment* effect, favouring BTX-B, was confirmed by the application of the two-way analysis of variance for DS-FS ($F = 52.5$ $p < 0.0001$), VAS-FD ($F = 23.2$, $p < 0.0001$), VAS-SD ($F = 29$, $p < 0.0001$) and UPDRS-ADL drooling score ($F = 28.9$, $p < 0.0001$), as well as for saliva production measured by dental roll weight ($F = 33$, $p < 0.0001$).

Furthermore, the GIS was rated 2 (moderate improvement) by 44.4 % of BTX-B subjects and 3 (dramatic improvement) by 33.3 % of patients, against a report of 0 (no changes) by 61.1 % and 1 (mild improvement) by 33.3 % controls (Chi-square = 22.9; $p < 0.0001$). No subject complained that drooling worsened. All BTX-B patients, compared to only 7 controls, declared that they were satisfied with their treatment and would be willing to receive repeated injections. The odds ratio of achieving a moderate to dramatic drooling improvement after BTX-B treatment, with respect to placebo (or no treatment) was 59.5 (95 % confidence limits: 5.9–595).

Three BTX-B patients complained of mild, transient swallowing difficulties starting ten days after the injec-

**Table 1** Demographic and clinical baseline data by treatment group

| | Neurobloc® (N = 18) | Placebo (N = 18) | Between-group comparison at baseline |
|---|---|---|---|
| Women/Men | 4/14 | 6/12 | Not significant (Fisher's exact test) |
| Age (years) | 73.1 ± 5.8 | 70.8 ± 6 | Not significant (unpaired T-test) |
| Hoehn & Yahr stage: | | | |
| II | 1 | 4 | |
| III | 10 | 10 | Not significant |
| IV | 7 | 4 | (test of proportions) |
| Disease duration (years) | 11.7 ± 6.1 | 12.5 ± 7.7 | Not significant (unpaired T-test) |
| Drooling duration (years) | 3.9 ± 7.2 | 2.8 ± 4.6 | Not significant (unpaired T-test) |

**Table 2** Drooling severity change in the two groups after treatment

| Outcome variable | BTX-B (N=18) | | Placebo (N=18) | | Two-way analysis of variance: time x treatment effect |
|---|---|---|---|---|---|
| | T0 | T1 | T0 | T1 | |
| DS-FS | 77.0 ± 12.2 | 40.4 ± 18.1 | 72.9 ± 10.3 | 69.3 ± 11.8 | F: 52.5 ($p < 0.0001$) |
| VAS-FD score | 68.6 ± 25.2 | 26.1 ± 24.5 | 65.3 ± 25.9 | 60.5 ± 27.7 | F:23.2 ($p < 0.0001$) |
| VAS-SD score | 78.3 ± 18.4 | 32.7 ± 28.8 | 71.7 ± 26.6 | 69.4 ± 26.6 | F: 29 ($p < 0.0001$) |
| UPDRS-ADL Drooling Item | 2.9 ± 0.7 | 1.5 ± 1.0 | 3.1 ± 0.7 | 3.0 ± 0.9 | F: 28.9 ($p < 0.0001$) |
| UPDRS-ADL Dysphagia Item | 1.1 ± 0.9 | 1.0 ± 0.7 | 0.9 ± 0.9 | 0.9 ± 0.9 | NS |
| Dental roll weight change (T0-T1) g | 2.1 ± 1.1 | 1.4 ± 0.9 | 1.7 ± 0.8 | 1.9 ± 0.8 | F: 33 ($p < 0.0001$) |

*NS* not significant (using U-Mann-Whitney test); *DS-FS* Drooling Severity and Frequency Scale; *FD* Familial Distress; *SD* Social Distress

tions and recovering within 2 weeks. The UPDRS-ADL dysphagia item did not change at T1 in any group. No patients exhibited cervical haematoma, facial palsy or any other relevant adverse events. No variations in the masseter muscle fatigue threshold were observed in the placebo group while one BTX-B patient showed a transient mild weakness of chewing.

The effect duration was 19.2 ± 6.3 weeks in BTX-B subjects, as compared to 6.7 ± 1.4 weeks in the 7 controls who declared drooling improvement ($F = 26.4$; $p < 0.0001$).

## Discussion

The effects of botulinum toxin type-B in treating acetylcholine-mediated autonomic disorders were reported by Racette [10] in an open-label study and confirmed by Ondo [8]; the latter performed the first double-blind, placebo-controlled study of BTX-B efficacy in reducing sialorrhea in 16 PD patients. Since then, there has been limited data reporting a significant reduction of sialorrhea in patients suffering from neurodegenerative disorders, including PD patients, following injections of BTX-B into the parotid glands, both with and without ultrasound guidance [11]. Transient mild side effects, like mouth dryness and dysphagia worsening, were reported at a similar rate as following botulinum toxin type A treatment [12–14].

Results from this study confirm the long-term effectiveness of BTX-B treatment in reducing drooling-related disability suggesting a positive impact on social interaction in advanced phase PD patients. The striking impact and safety of BTX-B was supported by both subjective and objective measures of salivary outflow. This double blind, RCT methodology allowing random allocation to either active treatment or placebo, produced results that concur with earlier, less well-designed observational studies or with randomised, controlled studies applying less comprehensive outcome evaluations.

The only previous RCT on this topics studied a smaller sample and was not designed to determine duration of effect, as in the present study [8].

In agreement with Ondo et al., we injected the BTX-B using anatomical references rendering the procedure easy to apply and relatively inexpensive [8].

The injection procedure described in this study used small needles to inject the superficial portion of the parotid glands in order to minimise the risk of injury to either the external carotid artery or the facial nerve. We decided to restrict the treatment to the parotid glands since they are large, near the skin and easily accessible for injection. An extensive approach, including the treatment of submandibular glands, might have induced an excessive saliva reduction, thus interfering with the already impaired swallow mechanisms and leading to dysphagia worsening [15, 16]. Furthermore, the sparing of sub-lingual and submandibular salivary outflow allowed to preserve an adequate production of amylase, kallicrein and IgA that are thought to prevent dental caries [17].

This decision increased patient compliance towards the procedure and allowed easy anatomical target outlining, without the need for ultrasound guidance, which is often recommended in previous studies using BTX-A, in cases of submandibular gland treatment or where there is difficulty in parotid gland location due to the presence of adipose tissue or scarring [5, 17, 18].

Our procedure enabled us to demonstrate the positive effects of BTX-B treatment in the management of PD-related drooling. The subjective judgments of patients (i.e. the reported decrease in levels of distress encountered within the personal familial and social context) concurred with our objective findings of salivary flow reduction, as measured by weighing saliva-soaked dental rolls.

The comprehensive set of outcome assessments allowed us to measure the overall effect of BTX-B treatment and showed that active treatment resulted in a 60-fold increased chance of being disability-free, with respect to placebo.

The choice of adding subjective perception of improvement to objective measures of saliva production is in agreement with the rationale of matching treatment efficacy with effectiveness. In this sense, the multiple scales adopted (VAS-FD, VAS-SD, Drooling severity and frequency scale, UPDRS-ADL item score for drooling, Global Impression score) aim at assessing the impact of drooling reduction after treatment on patient's health perception as well as on his social behaviours.

Finally, follow-up data described an enduring effect, after BTX-B treatment, lasting up to six months, thus ensuring an optimum cost-benefit ratio.

The longer effect duration observed after BTX-B injection as compared to BTX-A [4–6] could prompt further trials aimed at comparing the clinical effectiveness provided by the two different serotypes. Its effectiveness encourages to enlarge the experience by testing its clinical potential in the palliative care of Parkinson-plus syndromes, like multiple system atrophy.

In conclusion, BTX-B injections into the parotid glands without ultrasound guidance can be regarded as the treatment of choice in the management of distressing PD-related drooling. Future studies should also include a cost-benefit analysis to estimate the usefulness of BTX-B as a long-term treatment in this indication.

**Conflict of interest** The authors declare no conflict of interest.

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