RESEARCH ARTICLE

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

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ABSTRACT: Background: Either botulinum toxins (BoNTs) A and B have been used for improving drooling in different neurological conditions.

Methods: Consecutive patients affected by Amyotrophic Lateral Sclerosis (ALS) or Parkinson's Disease (PD) accompanied by severe drooling were randomized to receive botulinum neurotoxin type A (BoNT-A) or B (BoNT-B) injections into the salivary glands. Following the first treatment, when sialorrhea returned to baseline (at least three months after the first injection), subjects were re-treated with the other serotype. Ultrasound-guided injections into parotid and submandibular glands were bilaterally performed: total doses were 250 U BoNT-A (Dysport) and 2500 U BoNT-B (Neurobloc). Objective (cotton roll weight) and subjective (*ad hoc* clinical scales) evaluations were performed at baseline, after 1 and 4 weeks, and every 4 weeks until drooling returned to baseline.

Results: Twenty-seven patients (15 ALS and 12 PD) were enrolled, fourteen completed the study. BoNT-A and BoNT-B treatments gave both subjective and objective improvements in all patients. The latency was significantly shorter after BoNT-B treatments (3.2 ± 3.7 days) compared to BoNT-A (6.6 ± 4.1 days; $P = 0.002$). The mean benefit duration was similar at 75 and 90 days for BoNT-A and BoNT-B, respectively (P = NS). The only toxin-related side effect was a change to saliva thickness.

Conclusions: Either 250 U Dysport or 2500 U Neurobloc have similar effectiveness and safety in controlling sialorrhea. BoNT-B has a shorter latency and comparable duration. Cost analysis, considering the doses used in this study protocol favored BoNT-B treatment.

Key Words: amyotrophic lateral sclerosis; botulinum toxin A; botulinum toxin B; Parkinson's disease; sialorrhea; ultrasound guidance

Sialorrhea (or "drooling") is defined as the overflow of saliva from the mouth caused by excessive production of saliva, the inability to retain saliva within the mouth, or swallowing impairment[1] and is a common and disabling symptom of two neurodegenerative diseases: amyotrophic lateral sclerosis (ALS) and advanced Parkinson's disease (PD).[1,2]

In recent years, botulinum neurotoxin (BoNT) has emerged as an alternative and effective treatment for drooling with a good tolerability profile. Two serotypes of BoNT, A and B, have been reported to be both efficacious and safe in a range of diseases, but notably in ALS and PD.[2–7]

Clinical studies on patients with myofascial pain syndrome and cervical dystonia have compared botulinum neurotoxin type A (BoNT-A) and B and have shown a higher incidence of dry mouth (a side effect of the toxin treatment but the desirable effect for treatment of sialorrhea) with the use of BoNT-B.[8–10] Therefore, BoNT-B may have a preferential action on autonomic terminals and hence could be particularly effective in the treatment of secretory disorders.[11–13] Conceivably, BoNT-B could be more effective than

Additional Supporting Information may be found in the online version of this article.

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Relevant conflict of interest/financial disclosure: ARB received research grants by Ipsen, the manufacturer of Dysport. Other authors have no conflict of interest. Full financial disclosure and author roles can be found in the online version of this article.

Received: 29 September 2010; **Revised:** 11 March 2010; **Accepted:** 13 September 2010

Published online 21 January 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.23473

serotype A in the management of sialorrhea because of the dry mouth effects. However, to the best of our knowledge, no study has directly addressed the comparative issue of the two toxin serotypes in this condition. Therefore, the present pilot study was designed to initially evaluate BoNT-A versus BoNT-B in terms of effectiveness and tolerability for the treatment of sialorrhea.

Patients and Methods

The study was designed as a prospective, randomized, crossover, pilot-scale, double-blind trial comparing ultrasound-guided injections performed with both BoNT-A and BoNT-B consecutively for the treatment of sialorrhea.

Patients

We included consecutive ALS or PD patients who presented with significant sialorrhea. The two toxin serotypes were not matched against placebo for ethical reasons, as the effects of the products were already clearly known from the literature. The study was approved by the Local Ethical Committee, and the patients signed informed consent.

Exclusion criteria included: previous BoNT injections in salivary glands within the last 6 months; intermittent use of drugs interfering with salivary glands' function (anticholinergics); use of aminoglycosides or spectinomycin; intolerance or allergy to BoNT or human serum albumin; and systemic or facial diseases making the subject unsuitable for the study.

Randomization and Enrolment

Subjects were randomly allocated to one of the treatment groups using a computer-generated randomization list. The respective toxins were prepared by an independent investigator; all other study personnel and patients were blinded to the treatments. After the first treatment with one serotype, when sialorrhea returned to baseline (but in any case not before 3 months), subjects received a second treatment with the other BoNT serotype. To maintain study blinding, the products were prepared according to the same procedure and reconstituted with the same volume of sterile 0.9% saline.

Treatment

Ultrasound (US)-guided BoNT injections into each parotid gland (two sites per gland) and each submandibular gland (one site per gland) were performed bilaterally by the same physician (M.P.), skilled in US-guided procedures and according to previously published methods.[7,14–16] After a B-mode and color Doppler US study of the glands with a 7.5-MHz superficial probe, the injections were performed under continuous US guidance using a scan oriented along each gland major axis with free-hand technique.

The treatments were as follows:

1. BoNT-A (trade name: Dysport; Ipsen, Slough, Berkshire, UK)—a total of 250 U was injected: 100 U (in 0.4 mL of saline) was injected into two sites of each parotid and 25 U (in 0.1 mL of saline) into a single site of each submandibular gland (1 mL total volume injected).
2. BoNT-B (trade name: Neurobloc; Eisai, Tokyo, Japan)—a total of 2,500 U was injected: 1,000 U (in 0.4 mL of saline) into two sites in each parotid and 250 U (in 0.1 mL of saline) into a single site in each submandibular gland (1 mL total volume injected).

We used 2,500 U of BoNT-B based on previous reports.[7,17,18] Assuming that the conversion factor between the other available BoNT-A brand (Botox; Allergan, Irvine, CA) and BoNT-B is 1:50[19,20] and that a Botox:Dysport dose ratio ranges from 1:3 to 1:6,[21,22] we chose a conversion factor for Dysport:Neurobloc as 1:10. Both 250 BoNT-A units and 2,500 BoNT-B were therefore diluted in 1 mL to inject the same volume of each product and preserve the study blinding.

Clinical Evaluations

Standardized evaluations were performed at baseline, 1 and 4 weeks after injection, and every 4 weeks thereafter until drooling returned to baseline in all patients, as assessed by the same investigator (A.G.) who was blinded to the treatment.

Latency and duration of the effect were assessed by telephone calls to the patients and self-report by the caregivers. Effectiveness was determined by means of objective (cotton roll weight) and subjective (dedicated clinical scales) evaluations.

In keeping with previous work,[7,18,23] saliva production was quantitatively determined by weighing five cotton rolls after retaining for 5 minutes in the mouth. All the assessments were performed in standardized conditions: at the same time of the day, with the patient seated, fasting for 1 hour, and after a swallow of saliva. The magnitude of change to the weight of the cotton rolls was considered the primary endpoint of the study. Other secondary endpoints were aimed at the impact evaluation of drooling on daily life, as assessed by means of: drooling severity scale (DSS; range: 0–4), drooling frequency scale (DFS; 0–3),[24] an adapted version of drool rating scale (DRS; 0–45),[25] a visual analogic scale (VAS; 0–10),[26] and a clinical global impression (CGI; 2–13). The safety assessment was based on reports of side effects.

Economic Impact of Treatment

The cost of each toxin treatment was calculated; the differences in terms of cost and cost/effectiveness ratio of the two treatments could therefore be compared.

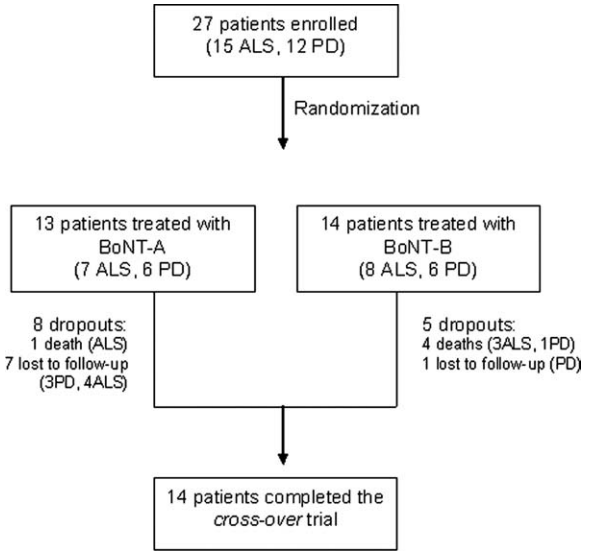

FIG. 1. Flow diagram of the study.

Statistical Analysis

Because of the pilot nature of this study, only limited statistical analyses could usefully be performed. The statistical analysis was also further impeded by the high dropout rate experienced (discussed below). Therefore, only limited analyses were performed on this small data set.

Data normality was tested by means of the Shapiro–Wilk *W* test. As the majority of variables were not normally distributed, we used nonparametric statistics. In-line with the methods of previous crossover studies,[27–29] the effects of different BoNT serotypes on the outcome measures (latency, duration of benefit, drooling scales, VAS, CGI, and roll weight) were compared using a Wilcoxon matched pair test. The effect of the order of treatment and serotype on the outcome was assessed by means of Mann–Whitney *U* test. Fisher's exact test was used to compare the category variables (occurrence of side effects).

Values were expressed as mean ± standard deviation (range). *Statistica 7.0* (StatSoft, Tulsa, OK) software was used for all statistical analyses. All tests were two-sided with a level of significance set at $P < 0.05$.

Results

Twenty-seven subjects (15 ALS and 12 PD patients) were randomized to receive BoNT injections (Fig. 1). Thirteen patients (mean age 71.5 ± 7.4) were lost at follow-up after the first treatment. Five patients died before the retreatment date for causes not related to BoNT treatment: 4 patients with ALS died from the worsening of their underlying respiratory insufficiency (1 after 1 week, the others after about 3 months) and 1 PD patient died from myocardial infarction 3 months after the first treatment. Four ALS and 4 PD patients could not respect the follow-up visits schedule due to the advanced stage of disease but continued to be treated with BoNT every 3 months (except for 3 ALS patients). No patient abandoned the study because of side effects.

Therefore, 14 patients completed the study and were included in the per-protocol analysis: 7 with ALS (5 women) and 7 with PD (2 women). Table 1 summarizes the demographic and clinical characteristics of these patients.

Compared with baseline, either BoNT-A or BoNT-B treatments gave a clear-cut benefit in all patients, both subjective and objective. After the second treatment, all patients wanted to be retreated, except for 2: 1 patient with ALS (severe dry mouth) and 1 with PD (poor benefit). When the data were unblinded, both subjects were found to have been treated with BoNT-A.

BoNT-A Versus BoNT-B

The toxin treatment order (first or second) did not influence the occurrence of side effects or any of the parameters used to assess the outcome (Supporting Information Table A). Accordingly, baseline evaluations were not statistically different (Supporting Information Table A).

The latency was significantly shorter after BoNT-B (3.2 ± 3.7 days) than that after BoNT-A (6.6 ± 4.1 days; $P = 0.002$; Fig. 2). The mean duration of benefit was similar in the two groups: 2.5 months (75 days) for BoNT-A and 3.1 months (93 days) for BoNT-B (P = NS; Fig. 2). At 1 week, BoNT-B treatments reduced the cotton roll weights more than that of BoNT-A ($P = 0.024$; Fig. 2). At 1 week and at the first month, BoNT-B treatments resulted in slightly better subjective clinical scales (Fig. 2). From the second month, there were no significant differences between BoNT serotypes in both objectively and subjectively measured drooling (Fig. 2).

TABLE 1. Baseline demographic and clinical characteristics of the patients who completed the study and were included in the per-protocol analysis

	Total (n = 14)	ALS (n = 7)	PD (n = 7)
Sex ratio (M/F)	7/7	2/5	5/2
Age at treatment (yr)	66.3 ± 9.8 (45–83)	64.1 ± 10.7 (45–77)	68.4 ± 9.2 (56–83)
Disease duration (yr)	8 ± 9.7 (1–35)	2.1 ± 1.1 (1–4)	13.9 ± 11 (3–35)
Drooling duration (mo)	8. 9 ± 4.2 (4–20)	6.9 ± 2.5 (4–10)	8.4 ± 4.2 (5–20)

Values are mean ± SD (range).
ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease; M, males; F, females.

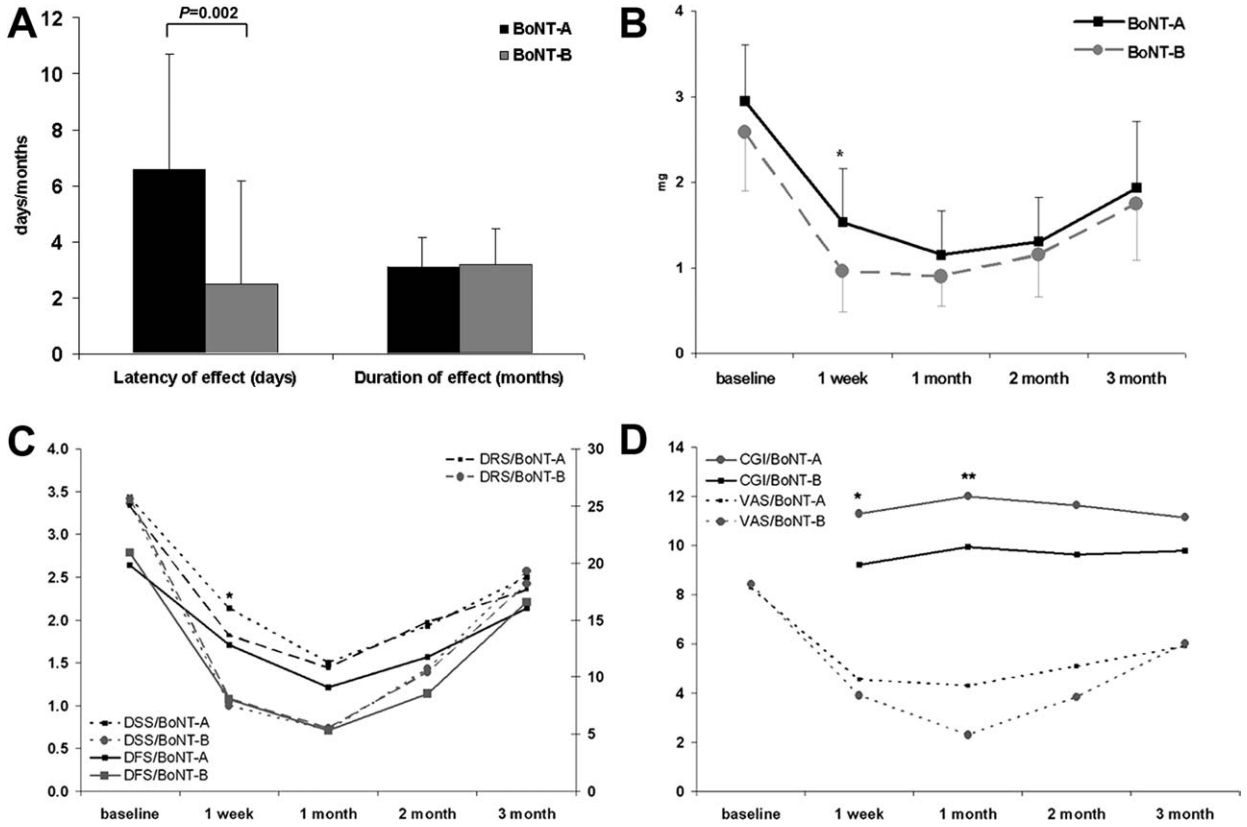

FIG. 2. (**A**) Latency of effect (days) and duration of effect (months) in the two treatment groups. (**B**) Saliva weight (mg) as assessed by means of the cotton roll method at baseline and during periodic assessments. Values are mean (±SD). *P = 0.024. (**C**) Efficacy comparison between BoNT-A and BoNT-B according to the subjective scales. Values are mean. *P = 0.024 (DSS). (**D**) Efficacy comparison between BoNT-A and BoNT-B according to the subjective scales. Values are mean. *P = 0.024 (CGI); **P = 0.021 (CGI).

Costs Analysis

At present, in our country (Italy), 250 Dysport U costs about 192 € (0.77 € for unit) whereas the price of 2,500 Neurobloc U is 100 € (0.04 € for unit). Therefore, BoNT-A (Dysport) treatment is more expensive per patient in this standardized clinical setting than BoNT-B (Neurobloc).

Intention to Treat Analysis

Although the study was designed as a crossover trial, there were two active treatments in the first part. As the analysis included only patients completing the study and hence could be biased towards favorable outcomes, a post hoc parallel comparison was also carried out.

In the first part of the study, 13 patients received BoNT-A and 14 BoNT-B (Fig. 1). The latency was significantly shorter after BoNT-B (2.4 ± 1.4 days) than that after BoNT-A (5.9 ± 3.3 days; P = 0.001). The mean benefit duration was similar in the two groups: 2.3 months (69 days) for BoNT-A and 3.2 months (96 days) for BoNT-B (P = NS). At baseline, the two treatment groups were not significantly different using any scale. At 1 week BoNT-B gave improved results over BoNT-A in all objective or subjective scales (Table 2). At the first month, BoNT-B treatments were slightly better than BoNT-A in some of the subjective clinical scales whereas, there were no significant differences in the objective evaluation (Table 2).

Safety

Side effect data were gathered from the total number of treatments (41, including patients who dropped out). The only reported toxin-related side effect was the modification of saliva thickness. This led to dry mouth in 11 treatments (26.8%) and viscous saliva in six (14.6%; Table 3). Injection-related adverse events were negligible and did not differ between toxin serotype or disease diagnosis. Significantly no patient reported the typical burning sensation often found after BoNT-B injection in other applications.[30,31]

All side effects were transient and rated mild or moderate by the patients with the exception of 1 case of severe dry mouth and 1 of troublesome viscous saliva, both reported by ALS patients. None of the treated patients reported dysphagia or facial weakness occurring or exacerbating after BoNT injection.

Discussion

In-line with previous studies,[32] our data confirmed the effectiveness of both serotypes of BoNT in the treatment of sialorrhea in both ALS and PD patients.

TABLE 2. Efficacy measures of all the patients treated with BoNT in the first part of the study (intention to treat analysis)

Weeks after treatment	BoNT-A		BoNT-B		*P* level
	No.	Mean ± SD	No.	Mean ± SD	
Saliva weight					
0	13	3.0 ± 0.8	14	2.4 ± 0.6	0.10
1	11	1.5 ± 0.7	14	1.0 ± 0.5	0.03
4	9	1.1 ± 0.6	12	0.9 ± 0.2	0.97
8	8	1.3 ± 0.6	12	1.2 ± 0.6	0.94
12	6	1.5 ± 0.8	11	1.9 ± 0.6	0.23
DSS					
0	13	3.6 ± 0.7	14	3.5 ± 0.5	0.50
1	11	2.2 ± 1.1	14	0.9 ± 1.0	0.01
4	9	1.6 ± 0.9	12	0.6 ± 0.7	0.02
8	8	2.0 ± 1.4	12	1.5 ± 1.4	0.42
12	6	2.5 ± 1.6	11	2.5 ± 1.1	0.80
DFS					
0	13	2.7 ± 0.5	14	2.8 ± 0.4	0.68
1	11	2.0 ± 0.8	14	1.1 ± 1.1	0.04
4	9	1.6 ± 0.5	12	0.8 ± 0.8	0.03
8	8	1.8 ± 1.0	12	1.3 ± 1.0	0.30
12	6	2.2 ± 1.2	11	2.2 ± 0.8	0.76
DRS					
0	13	26.4 ± 7.2	14	24.3 ± 4.0	0.26
1	11	16.9 ± 8.9	14	6.4 ± 5.9	0.01
4	9	11.0 ± 7.7	12	5.4 ± 4.4	0.04
8	8	18.0 ± 12.9	12	9.5 ± 7.5	0.11
12	6	21.2 ± 12.8	11	16.9 ± 9.3	0.42
VAS					
0	13	8.5 ± 1.2	14	8.4 ± 1.5	0.98
1	11	5.7 ± 2.1	14	3.5 ± 2.9	0.04
4	9	4.5 ± 2.9	12	2.3 ± 1.7	0.10
8	8	5.4 ± 3.4	12	3.8 ± 2.9	0.30
12	5	4.6 ± 4.3	9	5.7 ± 3.4	0.55
CGI					
1	11	9.3 ± 2.1	14	11.4 ± 1.4	0.01
4	9	10.1 ± 2.4	12	11.8 ± 1.7	0.06
8	8	9.4 ± 2.9	12	11.5 ± 2.2	0.04
12	6	9.5 ± 3.7	11	11.0 ± 2.4	0.51

Statistically significant differences are underlined.

Subtle differences emerged between BoNT-A and BoNT-B treatments.

Comparison Between BoNT-A and BoNT-B

This is the first crossover, prospective, randomized, pilot study addressing the differences of efficacy and safety of BoNT type A versus type B in the treatment of sialorrhea. Minimal previous data from controlled[17] and open[6,7,18] studies showed a significant saliva reduction and favorable safety and tolerability profiles in either ALS or PD patients treated with BoNT-B. All previous studies reported on the effect of a single brand[2,3,5–7,15,17,18,23,33,34] (there is only one BoNT-B available commercially, in any event), and the outcome measures are difficult to compare due to differences in the study protocols. Only recently, Wilken et al.[35] have compared the efficacy of BoNT-A versus BoNT-B in a parallel open study, enrolling 30 children with sialorrhea and finding no significant differences after the first injection.

In our series, up to the first month, BoNT-B treatments gave slightly improved results over BoNT-A for some of the clinical scales. The most relevant finding was that BoNT-B had a significantly shorter latency than BoNT-A (3 vs. 6 days). This is the first study showing this difference in patients with sialorrhea: similar findings have been reported in other studies on dysphonia,[20] facial wrinkles,[36,37] and axillary hyperhidrosis.[38] The different latencies might be due to various characteristics of the two serotypes, perhaps diffusion and/or affinity for autonomic fibers.

BoNT-B may diffuse more than BoNT-A, thus potentially explaining the rapid onset observed in motor disorders[20,36,37] and the higher incidence of autonomic side effects after injection.[8–10] Conversely,

TABLE 3. Summary of adverse events reported after all the performed treatments (intention to treat analysis)

Adverse events	BoNT-A (22 treatments)	BoNT-B (19 treatments)	*P*
Treatment related			
Pain at injection sites	1	1	NS
Subcutaneous hematoma	0	1	NS
Bleeding in the mouth	1	1	NS
Related to toxin effect			
Viscous saliva	3	3	NS
Dry mouth	4	7	NS

Values are the number of treatments characterized by the side effect.

one study in animals has revealed that BoNT-B spreads less than the equivalent doses of BoNT-A.[39] Autonomic side effects are sometimes observed far from the injection site (such as dry mouth after treatment for axillary hyperhidrosis[38]). Remarkably, a case of botulism due to BoNT-B presenting with pure autonomic dysfunction has been reported.[40] In addition, BoNT-B is particularly effective even at very low doses (when compared with the doses used for motor disorders) for the treatment of axillary hyperhidrosis.[41] Taken together, these data could indicate a possible superiority of BoNT-B in the management of secretory disorders, mainly due to the hypothesized affinity for postganglionic neurons containing M3 receptors (such as those responsible for salivation).[39]

Injection Technique

Injection methods (number of injected glands, anatomic or US-guided targeting) widely varied in previous reported trials. As in several previous studies,[7,15,18] we injected the BoNTs under US guidance. Although more expensive and time consuming, there is limited evidence that US guidance for BoNT injection into the parotid glands may lead to a better dose–response relationship than blind injections.[16] We observed no severe side effects of 41 treatments, supporting the injection technique we used for highly targeted injections.

Injections were performed into both parotids and submandibular glands because previous experiences have already shown the superiority of the combined treatment.[5,7,17,25,34] The parotid glands produce thin saliva in contrast to the more viscous saliva produced by submandibular and sublingual glands.[41] According to our protocol, a higher dose was injected in the parotid glands, which probably unbalanced the overall combined saliva composition. This might explain the side effects observed which related to the composition of saliva (thickness, viscosity) reported by some patients. A higher dosage into the submandibular glands or, conversely, lower doses into the parotids may reduce this side effect. In keeping with two previous double-blind controlled studies in cervical dystonia,[9,42] we found no significant differences between BoNT-A and BoNT-B with respect to injection site pain.

Finally, all the published studies comparing BoNT-A versus BoNT-B have used Botox. To date, no report has compared the efficacy of Dysport, an alternative and widely available BoNT-A product, versus Neurobloc in the treatment of muscular or glandular disorders.

Study Limitations

Our pilot study had a number of potential limitations that are important to record.

Sialorrhea typically complicates diseases such as ALS and PD in their late and severe stages. Consequently, many patients could not attend the frequent follow-up visits and did not complete the study. The majority (6 of 8 still alive) are still being treated with BoNT. A higher death rate is expected when enrolling ALS patients.

We did not attempt sample size calculations for this work as this was designed as a pilot study only with an expected high rate of drop-outs due to the disease conditions we examined. However, a study powered to detect a 30% difference in our primary outcome measure (cotton roll weight) with 80% sensitivity at a $P < 0.05$ should have enrolled 24 patients, taking into account a drop-out rate of 40%. The intention to treat analysis with the comparisons of parallel arms in this first pilot study has nevertheless confirmed the efficacy and relative superiority of BoNT-B (Table 2). This result overcomes a potential bias of a crossover design, such as any residual effect of the first treatment influencing the outcome of the second treatment. We also did not attempt further detailed statistical analyses on the data set obtained, due to the issues with trial size and patient drop-out. However, the pilot data we obtained still demonstrates useful findings in the comparisons of these BoNT products for the treatment of the target indication.

Finally, even though we adopted the doses more commonly reported for both serotypes in the treatment of sialorrhea, a reliable conversion rate (i.e., a dose equivalence) is still lacking and probably not achievable due to the quantity of clinical data that would be required to establish such a ratio with any reliability. Of note, the study where the highest dose of Dysport used to date for sialorrhea (450 U) was injected, reported the same latency observed in the present trial (1 week) and a shorter duration (1 month).[15]

Conclusion

In conclusion, from our pilot study, 250 U of Dysport or 2,500 U of Neurobloc into both parotid and submandibular glands are effective and safe for the treatment of sialorrhea. BoNT-B has shorter latency and comparable duration when compared with BoNT-A. The economical aspects of the treatment are

different: at the doses used in this study, the cost of BoNT-B is approximately half of that of BoNT-A. Further studies with an adequate sample size are needed to confirm the results of these preliminary observations and to address the optimal doses to be used in routine clinical practice.

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