Efficacy of Botulinum Toxin in Treating Myofascial Pain in Bruxers: A Controlled Placebo Pilot Study

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ABSTRACT: The present investigation is a preliminary double-blind, controlled placebo, randomized clinical trial with a six month follow-up period. The study aimed to assess the efficacy of type A botulinum toxin (Botox, Allergan, Inc. Irvine, CA) to treat myofascial pain symptoms and to reduce muscle hyperactivity in bruxers. Twenty patients (ten males, ten females; age range 25-45) with a clinical diagnosis of bruxism and myofascial pain of the masticatory muscles were enrolled in a double-blind, controlled placebo, randomized clinical trial, with a treatment group (ten subjects treated with botulinum toxin injections- BTX-A) and a control group (ten subjects treated with saline placebo injections). A number of objective and subjective clinical parameters (pain at rest and during chewing; mastication efficiency; maximum nonassisted and assisted mouth opening, protrusive and laterotrusive movements; functional limitation during usual jaw movements; subjective efficacy of the treatment; tolerance of the treatment) were assessed at baseline time and at one week, one month, and six months follow-up appointments. Descriptive analysis showed that improvements in both objective (range of mandibular movements) and subjective (pain at rest; pain during chewing) clinical outcome variables were higher in the Botox treated group than in the placebo treated subjects. Patients treated with BTX-A had a higher subjective improvement in their perception of treatment efficacy than the placebo subjects. Differences were not significant in some cases due to the small sample size. Results from the present study supported the efficacy of BTX-A to reduce myofascial pain symptoms in bruxers, and provided pilot data which need to be confirmed by further research using larger samples.

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Myofascial pain of the masticatory muscles has a strong epidemiological relevance, affecting from 38-75% of patients with signs and symptoms of temporomandibular disorders (TMD) in Caucasian populations[1,2] and about 30% in Asian patients.[3] Therefore, despite the fluctuating and self-limiting nature of these disorders,[4] efficacious first-step symptomatic therapies are used to reduce their psychosocial impacts. Nevertheless, the syndrome has a complex pathogenesis which is often the expression of a multifactorial etiology with a number of systemic and local risk factors.[5]

Bruxism is an awake or sleep parafunctional activity which is strongly detrimental for all the stomatognathic structures, being responsible for tooth wear, periodontal tissue lesions, articular and/or muscular damage.[6] Despite the fact that a demonstration of a causal role for TMD has not yet been found[7] and doubts exist as to the etiology of both awake and sleep bruxism,[8-11] the clinical association between bruxism and myofascial pain is reported in other studies.[12,13] Many therapies have been proposed to treat

bruxism-related muscle hyperactivity, but the literature is inconclusive.[14-18]

Similarly, the uncertainty which characterizes knowledge on the etiopathogenesis of myofascial pain has led to the proposal of several treatment approaches for the condition, among which are: occlusal splints,[19,20] physiotherapy,[21] behavioral and physical treatments,[22] and drugs.[23-26] The common target of these therapies is muscle relaxation, and several alternative treatments have been introduced to achieve this goal.[27] Type A botulinum toxin is widely used to treat several pathologies associated with muscular hyperactivity,[28-31] and may represent a promising alternative to traditional therapies. This is suggested by some preliminary data from both case reports or case series studies[32] and clinical trials,[33,34] which seem to support its efficacy to treat myofascial pain patients as well. Given this premise, the present investigation is a preliminary double-blind, controlled placebo, randomized clinical trial with a six-month follow-up period. The current study aimed to assess the efficacy of type A botulinum toxin to treat myofascial pain symptoms in bruxers.

Material and Methods

Twenty patients (ten males, ten females; age range 25-45) with a clinical diagnosis of bruxism and myofascial pain of the masticatory muscles were enrolled at the Department of Maxillo-Facial Surgery, University of Padova, Padova, Italy. The presence of bruxism was diagnosed using a validated set of screening-oriented clinical diagnostic criteria, so that in the present work, bruxism is only approached in terms of its clinical impact on the masticatory apparatus and not as a more complex pathophysiological disorder affecting the central nervous system.[35] Diagnosis of bruxism was made when the patient exhibited, at least five nights a week, grinding/bruxing sounds during sleep for the past six months, as reported by his/her bed partner, and at least one of the following adjunctive criteria: observation of tooth wear or shiny spots on restorations; report of morning masticatory muscle fatigue or pain; masseteric hypertrophy upon digital palpation.

Myofascial pain of the masticatory muscles was diagnosed according to the Research Diagnostic Criteria (RDC) for TMD guidelines.[36] It is described as pain of muscular origin, including a complaint of pain, as well as pain associated with localized areas of tenderness to palpation in the muscle. The following criteria were needed: report of pain or ache in the jaw, temples, face, preauricular area, or inside the ear at rest or during function; pain reported by the subject in response to palpation of three or more of the following 20 muscle sites (right side and left side count as separate sites for each muscle: posterior temporalis, middle temporalis, anterior temporalis, origin of masseter, body of masseter, insertion of masseter, posterior mandibular region, submandibular region, lateral pterygoid area, and tendon of the temporalis. At least one of the sites must be on the same side as the pain complaint. No distinction between myofascial pain (RDC/TMD group Ia) and myofascial pain with limited opening (RDC/TMD group Ib) was made.

The design of the study provided a double-blind, controlled placebo, randomized clinical trial with treatment (ten subjects treated with botulinum toxin injections) and a control group (ten subjects treated with saline placebo injections).

Exclusion criteria for the the study were the following: a history of any treatment for bruxism and/or TMD during six months prior to the study; the presence of neuromuscular pathologies preventing the use of botulinum toxin (i.e., myasthenia gravis); a reported hypersensibility to clostridium botulinum type A neurotoxin. The treatment protocol provided four Type A botulinum toxin (BTX-A) (Botox, Allergan, Inc., Irivine, CA) intramuscular injections for each side (30 U) within the masseter muscles and three injections (20 U) within the anterior temporalis muscles, for a treatment total of 100 U. The injections were made during a single appointment under anatomo-topographic and/or ultrasonographic control. All injections were performed by the same maxillofacial surgeon.

The following clinical parameters were assessed at baseline and at three follow-up appointments at one week, one month, and six months respectively:

- pain at rest and at chewing, assessed by means of a Visual Analogue Scale (VAS) from 0 to 10, with the extremes being *no pain* and *pain as bad as the patient has ever experienced*;
- mastication efficiency, assessed using a VAS from 0 to 10, the extremes of which were *eating only semi-liquid* and *eating solid hard food*;
- maximum nonassisted and assisted mouth opening, protrusive and laterotrusive movements (in mm);
- functional limitation during usual jaw movements (0, absent; 1, slight; 2, moderate; 3, intense, 4, severe);
- subjective efficacy of the treatment (0, poor; 1, slight, 2, moderate; 3, good; 4, excellent); tolerability of the treatment (0, poor; 1, slight; 2, moderate; 3, good; 4, excellent).

Patients were informed of the possible side effects of botulinum toxin injections (tenderness after the injection and fatigue when chewing), and each patient gave informed consent prior to the start of the study.

Botulinum Toxin

Type-A botulinum toxin is one of the seven neurotoxic types (Btx A, B, C, D, E, F, G) of botulinum toxin, causing a prolonged inhibition of neurotransmitter release at peripheral cholinergic nerve terminals at both neuromuscular junctions and autonomic sympathetic and parasympathetic nerve terminals. Presynaptic blockade at neuromuscular junctions is the result of the following actions: binding to receptors on unmyelinated presynaptic membrane; uptake of toxin into nerve terminals by endocytosis; translocation across endosome membrane; and inhibition of transmitter exocytosis from presynaptic terminal.[37-41]

Despite their potential and dangerous toxicity, over the past two decades, botulinum neurotoxins have been used to treat muscle disorders associated with an excessive cholinergic activity,[42] such as blepharospasm,[43,44] spasmodic dysphonia,[45-47] and cervical dystonia.[31,48,49]

Botulinum-induced muscular relaxation is reversible and lasts for up to six months. The use of botulinum toxin for the treatment of myofascial pain in bruxers is not within the label indications for this product. Nevertheless, the choice of testing its efficacy in these pathologies was based upon encouraging findings of studies assessing its efficacy to treat pain in the orofacial region.[28-34] Off-label use of this agent is not prohibited, but it has to be approved by the Ethics Committee for the Protection of Human Subjects. The present investigation was designed under the approval of the Ethical Committee for Drugs Testing on Human Subjects at the University of Padova, Italy.

Statistical Analysis

Two groups of outcome variables were identified for statistical analysis:

- symptoms: pain at rest and at chewing (VAS values-from 0=*no pain* to 10=*pain as bad as the patient ever experienced*); mastication efficiency (VAS values from 0=*eating only semi-liquid* to 10=*eating solid hard food*); functional limitation during usual jaw movements (rating from 0=*absent* to 4=*severe*); subjective efficacy of the treatment (rating from 0=*poor* to 4=*excellent*); tolerability of the treatment (rating from 0=*poor* to 4=*excellent*);
- signs: maximum nonassisted and assisted mouth opening, protrusive and laterotrusive movements (mm).

To control for the differences between groups in baseline values, differences between the baseline and the three follow-up values for the outcome variables were considered for statistical analysis.

The new variables defined as differences were not created for the variables *subjective efficacy of the treatment* and *tolerability of the treatment*, which were not assessed at baseline.

Since the sample size is quite low, the authors preferred to perform a robust nonparametric approach, i.e. a two-sample permutation test in order to compare the two groups of patients (botulinum toxin group and control group) in the outcome variables with respect to time.[50] For the ordinal variables (functional limitation during usual jaw movements; subjective efficacy of the treatment; tolerability of the treatment) an Anderson-Darling permutation test was performed.[50]

For the variables defined as differences included in the statistical analysis, the alternative hypothesis was that patients treated with botulinum toxin had higher values than those treated with the placebo, except for the differences in pain at mastication, pain at rest and functional limitation, for which the placebo group was expected to have higher values than the botox group.

The Bonferroni-Holm method for multiple tests was also applied in order to control for multiplicity since several tests are applied to the same variables.[51,52] The cut-off significance level was set at $p<0.05$.

All statistical procedures were performed with the SAS, Ver. 8 (SAS Institute Inc., Cary, NC).

Results

Descriptive analysis performed on the original clinical outcome variables (jaw range of motion; mastication efficiency; pain at chewing; pain at rest) and on the variables defined as differences were reported in **Tables 1** and **2**. Boxplots showed the clinical outcome variable values (minimum, average and maximum values; first and third quartiles including 25% and 75% of values respectively; median) (**Figures 1-8**).

Descriptive analysis showed that values of maximum nonassisted and assisted mouth opening, protrusive and laterotrusive movements (mm) showed a slight increase in the botox group (differences between baseline and follow-up values tended to increase) and seemed to be unaltered in the placebo group (**Table 1**; **Figures 4-8**). As for symptoms, pain at rest and at chewing decreased in the botox group while remaining constant in the placebo group, even though mastication efficiency did not improve, either in the botox or in the placebo group (**Figures 1-3**). Similarly, changes in functional limitation with time did not differ between the two groups of patients. With regard to subjective parameters of efficacy and tolerability, the botox patients referred a greater improvement with time in their perception of treatment efficacy than placebo patients. Tolerance of the treatment was good for both groups of patients.

Table 1
Descriptive Analysis: Jaw Range of Motion at Different Times (Per Treatment)

Signs	Treatment	Mean value	Standard deviation	Minimum	Maximum
Maximum nonassisted opening (mm)					
Baseline	BTX-A	46.30	8.74	28.00	60.00
	Placebo	43.80	9.40	34.00	65.00
1 week	BTX-A	46.70	9.91	26.00	62.00
	Placebo	43.40	9.11	33.00	63.00
1 month	BTX-A	46.60	9.61	27.00	62.00
	Placebo	43.90	9.15	34.00	64.00
6 months	BTX-A	48.40	7.63	33.00	60.00
	Placebo	43.50	9.11	33.00	63.00
Maximum assisted opening (mm)					
Baseline	BTX-A	50.70	6.63	38.00	62.00
	Placebo	48.00	8.72	39.00	68.00
1 week	BTX-A	51.00	8.52	32.00	64.00
	Placebo	47.30	8.21	39.00	65.00
1 month	BTX-A	52.00	7.77	38.00	65.00
	Placebo	47.70	8.31	38.00	65.00
6 months	BTX-A	52.50	7.04	37.00	61.00
	Placebo	47.00	8.25	37.00	65.00
Protrusion (mm)					
Baseline	BTX-A	5.40	3.53	0.00	11.00
	Placebo	6.20	1.55	4.00	9.00
1 week	BTX-A	6.00	4.22	0.00	14.00
	Placebo	6.60	1.78	4.00	10.00
1 month	BTX-A	6.20	3.77	0.00	12.00
	Placebo	6.60	1.71	4.00	10.00
6 months	BTX-A	6.60	4.12	0.00	12.00
	Placebo	6.30	1.64	4.00	9.00
Right laterotrosion (mm)					
Baseline	BTX-A	10.90	2.03	9.00	15.00
	Placebo	8.80	1.14	7.00	11.00
1 week	BTX-A	11.70	2.41	9.00	15.00
	Placebo	9.00	1.49	6.00	11.00
1 month	BTX-A	11.60	2.46	8.00	15.00
	Placebo	9.20	1.23	7.00	11.00
6 months	BTX-A	11.40	1.71	9.00	15.00
	Placebo	8.90	1.60	6.00	11.00
Left laterotrusion (mm)					
Baseline	BTX-A	10.10	2.33	6.00	14.00
	Placebo	8.60	1.65	6.00	11.00
1 week	BTX-A	10.70	3.02	8.00	16.00
	Placebo	8.50	1.35	6.00	10.00
1 month	BTX-A	11.20	3.16	7.00	16.00
	Placebo	8.80	1.32	7.00	11.00
6 months	BTX-A	11.00	2.49	8.00	15.00
	Placebo	8.80	1.40	6.00	11.00

A permutation test performed on the outcome variables defined as differences showed significant differences between the two groups in the parameters *improvement in pain at chewing* and *patients' perception of treatment efficacy* at the six-month follow-up (**Table 3**). No significant differences between the two groups were shown in other outcome variables.

Table 2

Descriptive Analysis: Mastication Efficiency, Pain at Rest, and Pain at Clenching at Different Times

Symptoms	Treatment	Mean value	Standard deviation	Minimum	Maximum
Mastication efficiency (from 0 to 10)					
Baseline	BTX-A	7.70	2.26	5.00	10.00
	Placebo	8.00	1.63	6.00	10.00
1 week	BTX-A	7.10	2.38	4.00	10.00
	Placebo	7.70	1.77	5.00	10.00
1 month	BTX-A	6.40	2.17	3.00	10.00
	Placebo	8.20	1.32	6.00	10.00
6 months	BTX-A	7.40	1.90	4.00	10.00
	Placebo	7.50	1.96	5.00	10.00
Pain at chewing from 0 to 10					
Baseline	BTX-A	6.20	2.78	0.00	10.00
	Placebo	4.10	2.92	0.00	8.00
1 week	BTX-A	5.20	3.05	0.00	10.00
	Placebo	3.80	2.82	0.00	7.00
1 month	BTX-A	3.60	2.32	0.00	7.00
	Placebo	3.70	2.71	0.00	8.00
6 months	BTX-A	3.60	2.37	0.00	6.00
	Placebo	4.70	2.79	0.00	8.00
Pain at rest from 0 to 10					
Baseline	BTX-A	5.00	3.62	0.00	9.00
	Placebo	3.90	2.92	0.00	8.00
1 week	BTX-A	4.60	3.63	0.00	10.00
	Placebo	3.00	2.49	0.00	6.00
1 month	BTX-A	2.50	2.72	0.00	6.00
	Placebo	3.70	2.67	0.00	7.00
6 months	BTX-A	3.60	2.88	0.00	8.00
	Placebo	4.10	2.85	0.00	7.00

Discussion and Conclusions

The most common treatment approach to myofascial pain of masticatory muscles is based upon reversible and conservative symptomatic therapeutic modalities, such as occlusal splints,[19,20] physiotherapy,[21] behavioral and physical treatments,[22] and drugs.[23-26] The same treatment modalities, and in particular the adoption of occlusal splints, were proposed to treat bruxism, even though they are mainly directed to prevent bruxism-related damages (i.e., dental wear facets) rather than achieve a therapeutic effect.[14,19] The similarities in the approach to myofascial pain and bruxism patients are due to the absence of convincing etiological theories for both pathologies, which prevents the adoption of causal therapies. Furthermore, bruxism is one of the main risk factors for myofascial pain in the masticatory muscles[53,54] and the two disorders seem to be associated in the clinical setting.[12,13]

Considering these premises, the study hypothesis was that botulinum toxin may represent an alternative option to avoid prolonged treatment with occlusal splints and/or drugs.[29]

BTX-A was recently proposed for treatment of temporomandibular joint disk displacement using an injection within the lateral pterygoid muscle after intermaxillary fixation.[55,56] In general, the clinical data supports the efficacy of BTX-A to reduce joint noises related to disk displacement,[57] and indications for its use have been recently extended to patients with recurrent TMJ dislocation.[58]

Such positive effects on articular disorders are a consequence of the decrease in muscle tone, which improves jaw functioning. Botulinum toxin has proven effective in diseases characterized by increased painful muscle tone,

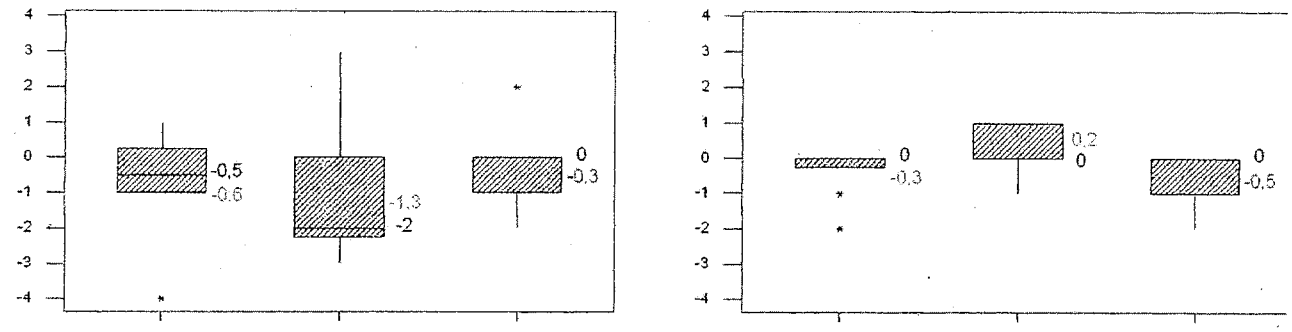

Figure 1
Mastication efficiency (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

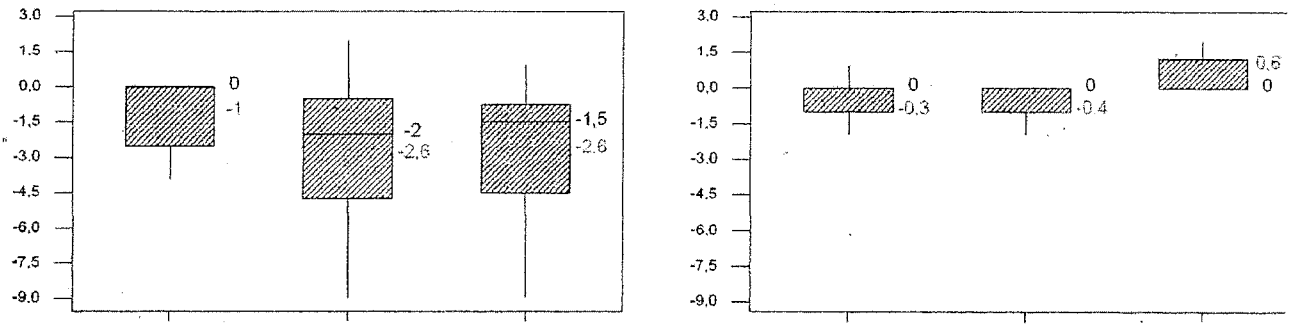

Figure 2
Pain at mastication (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

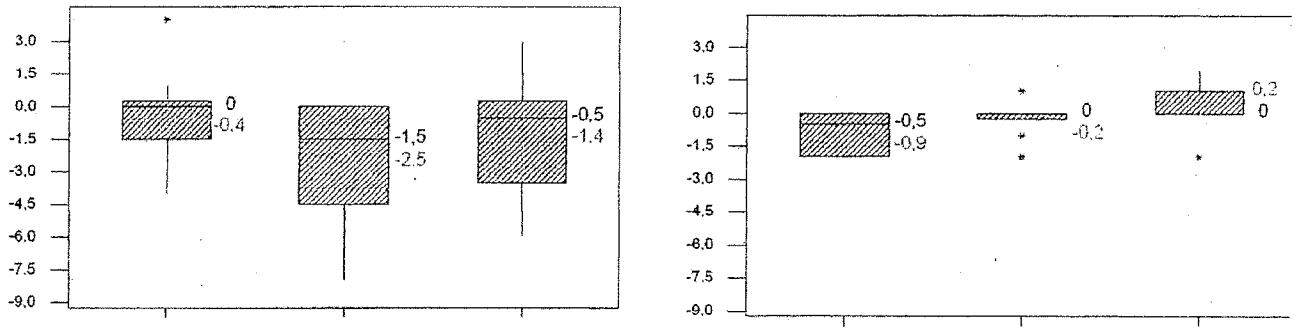

Figure 3
Pain at rest (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

and it might be indicated in bruxers and in patients with myofascial pain, as well.[59]

Results from the present investigation supported the efficacy of BTX-A to reduce myofascial pain symptoms, even though differences with the placebo were not significant in some cases. Descriptive analysis showed that improvements in both objective (range of mandibular movements) and subjective (pain at rest; pain at chewing) outcome variables were higher in the botox group than in the placebo patients. Patients treated with BTX-A referred

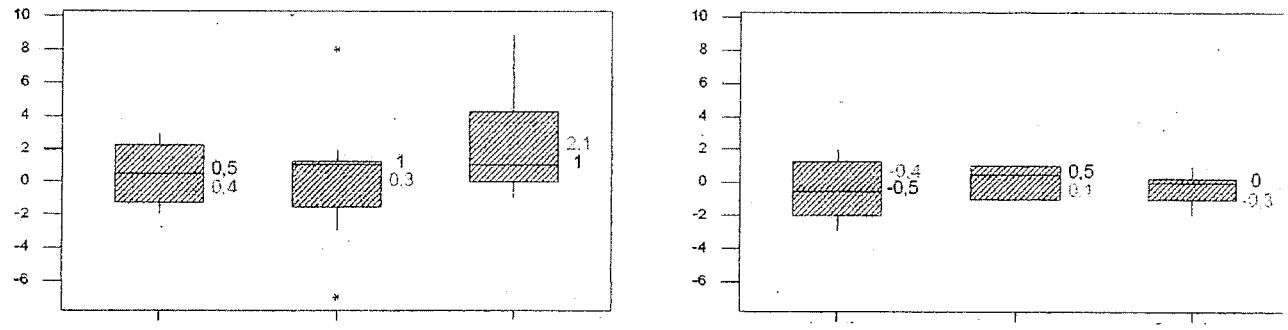

Figure 4
Maximum nonassisted mouth opening (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

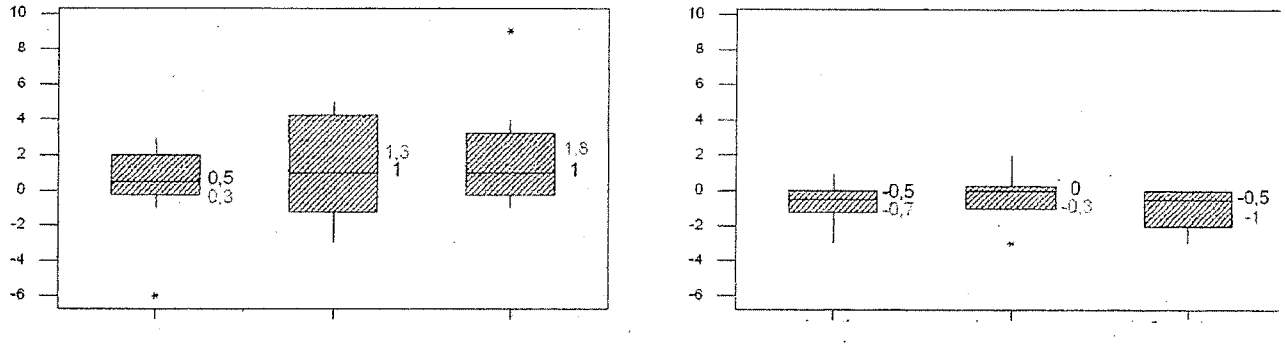

Figure 5
Maximum assisted mouth opening (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

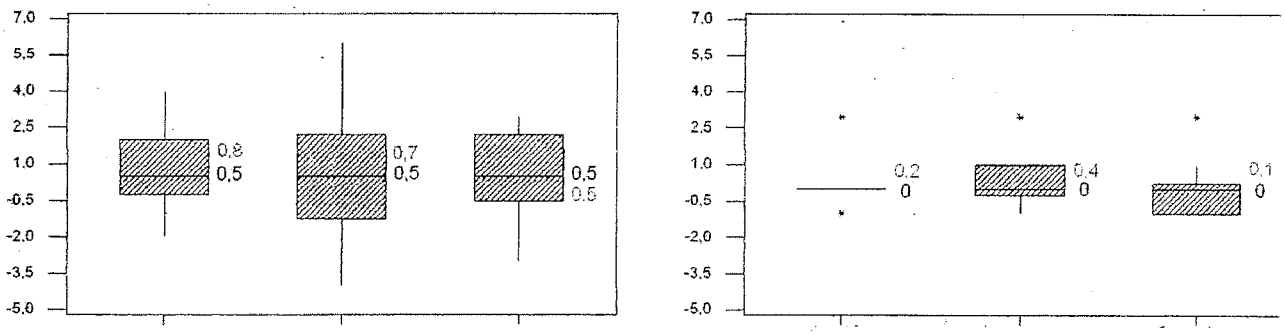

Figure 6
Right laterotrusive movement (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

a higher subjective improvement with time in their perception of treatment efficacy than the placebo patients.

The small sample size obviously limits generalization of results, even though one must be conscious that the same differences in efficacy between BTX-A and placebo might have been strongly significant for larger samples.

This study intended to provide pilot results on this particular issue, since sample size was small due to the difficulties in recruiting patients for a similar investigation, which was intended to test an off-label use of a poten-

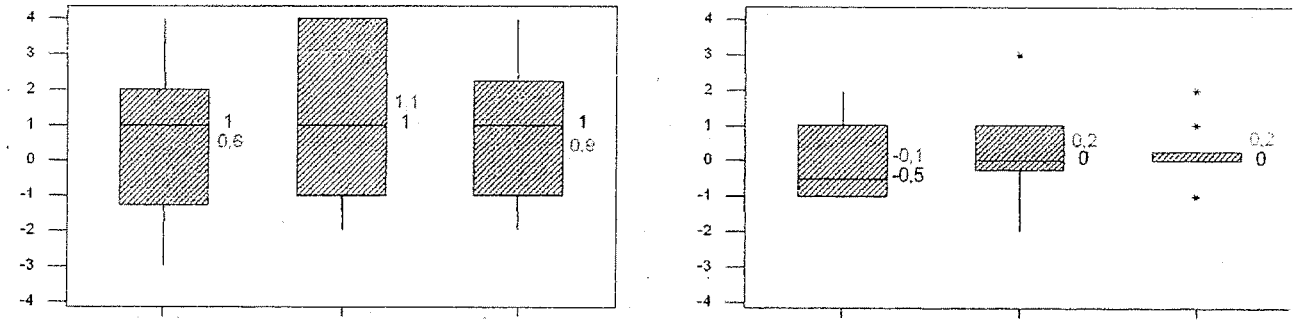

Figure 7
Left laterotrusive movement (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

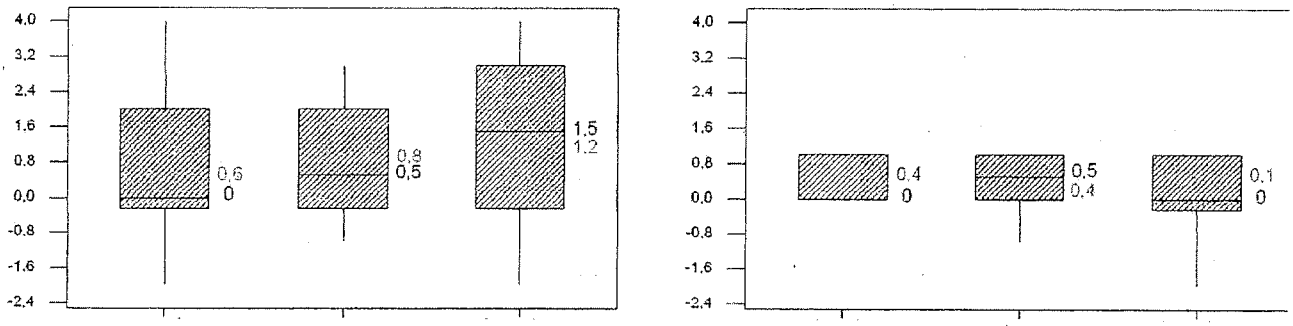

Figure 8
Protrusive movement (difference between baseline and one-week, one-month, and six-months values). BTX-A (left) vs. placebo (right).

Table 3
Permutation Test: Differences in Symptoms Between Baseline and One Week, One Month, and Six Months (BTX-A vs. Placebo)
Significance Level - $p<0.05$

Signs	Corrected p-values		
	Difference between baseline and 1-week values	Difference between baseline and 1-month values	Difference between baseline and 6-month values
Pain while chewing	NS	NS	0.023
Efficacy	NS	NS	0.01155

NS: not significant

tially dangerous drug. Nevertheless, a randomized clinical trial (RCT)-like design was adopted to start collecting evidence-based data on the use of BTX-A in bruxers. The present findings are in line with those from the current literature, which suggest an employment of botulinum toxin for additional minor neuromuscular conditions along with the number of neuromuscular disorders for which BTX-A represents a first choice option, such as blepharospasm, cervical dystonia, and several other focal dystonias.[60]

In the case of muscular TMD and bruxism, there is still a paucity of literature, even though encouraging premises for BTX-A employed in the treatment of these conditions exist.[32-34,61] Such observations are a cause for optimism and the authors suggest the need for a RCT conducted on an appropriate sample, whose size must be determined by an analysis that takes into account these present preliminary findings.

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