Acute Treatment of Trigeminal Neuralgia With Onabotulinum Toxin A

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Abstract: A double-blind, randomized, placebo-controlled study of patients with essential trigeminal neuralgia and treatment with a single injection of onabotulinum toxin A (BTX) was carried out. The efficacy, safety, and tolerability of either 1 mL 0.9% saline plus 50 U of BTX or only 1 mL of 0.9% saline injected subcutaneously in the affected area were evaluated. Cases with involvement of the third branch of the trigeminal nerve also received intramuscularly either 10 U of BTX or matching placebo in the masseter muscle, ipsilateral to the pain location. Pain was assessed with the visual analog scale (VAS). Twenty subjects were administered BTX, and 16 subjects received placebo. Two months after the intervention, a trend to statistical significance was observed for the VAS mean values in subjects treated with BTX and those who received placebo (VAS 4.9 vs 6.63, *t* test, $P = 0.07$). Three months after the injection, significant differences were observed in the average VAS score for subjects treated with BTX and those treated with placebo (VAS 4.75 vs 6.94, respectively; *t* test, $P = 0.01$). Onabotulinum toxin A was well tolerated and seems to be a safe and useful therapy for patients with essential trigeminal neuralgia.

Key Words: trigeminal neuralgia, onabotulinum toxin A, pain

(*Clin Neuropharm* 2013;36: 146–150)

Trigeminal neuralgia (TN), as defined by the International Association for the Study of Pain, features sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of 1 or more branches of the trigeminal nerve.[1] It is one of the most frequent causes of paroxysmal recurrent facial pain with an annual incidence ranging from 4 to 5 per 100,000 population.[2] Trigeminal neuralgia has a significant impact on quality of life and the socioeconomic performance of the patients. Cases without an established etiology as well as those with presumed or confirmed vascular compression of the fifth cranial nerve are denominated classic or essential TN (ETN). The clinical diagnosis of such cases must necessarily include a normal neurological examination showing no neurological deficits. On the other hand, the diagnosis of symptomatic TN is made when investigations identify a structural abnormality other than a vascular compression affecting the trigeminal nerve. Such abnormalities include multiple sclerosis in young subjects, tumors, and abnormalities of the base of the skull. Essential TN typically affects elderly patients and is most commonly related to neurovascular compression. It is uncommon in people younger than 30 years and most likely related to venous compression.[3] The pathophysiologic mechanisms of trigeminal neuralgia are not fully understood, but fortunately valuable pharmacological and surgical treatments have been developed. Most patients improve with oral medications including carbamazepine,[4] but in some cases, invasive procedures including neurovascular decompression,[5] gamma knife stereotactic radiosurgery,[6] percutaneous radiofrequency thermocoagulation, and partial sensory rhizotomy[7] may be required. Unfortunately, some patients continue to have persistent or recurrent painful attacks even despite multiple operations.[8] Based on previous results,[9] we conducted a double-blind, randomized, controlled trial of onabotulinum toxin type A versus placebo in the management of pain due to ETN.

PATIENTS AND METHODS

A double-blind, randomized, placebo-controlled study was performed. Both men and women, older than 18 years, with a clinical diagnosis or ETN based on established clinical criteria[1] were included. All of them underwent a brain magnetic resonance imaging to rule out secondary cases. The main objective of the study was to assess the efficacy and safety of a single injection of onabotulinum toxin A (BOTOX [BTX]) in the management of pain in ETN. The subjects included regularly come to the Neurology Department of the Hospital de Clínicas for care because of a diagnosis of idiopathic trigeminal neuralgia. Subjects who had not responded satisfactorily to the usual treatment approaches were included in the study. They were randomly selected from the Neurology Department database. Candidates interested in the study signed an informed consent of agreement to participate in the latter and were randomized by central allocation concealment, to receive either 50 U of BTX subcutaneously or placebo (0.9% saline) via the same route. This dosage was used since our previous study[9] found significant benefit from it without the presence of troublesome collateral effects. The department staff contacted the central office when the subjects came for the intervention to decide which treatment to administer. Neither the investigators nor the individual making the call had any relationship with the patient or the attending physician. Once the intervention was decided, the assistant prepared a 1-mL syringe: 0.9% saline plus 50 U of BTX or only 1 mL of 0.9% saline. The injections were always administered by the same physician, who used an identical technique with all the subjects, that is, a subcutaneous injection in various sites, 1 cm apart from one another in the path of the branch/branches involved (Fig. 1). The same type syringes and needles were used in both groups. Subjects with involvement of the third branch of the trigeminal nerve also received intramuscularly either 10 U of BTX or matching placebo, according to randomization, in the masseter muscle, ipsilateral to the pain location. Subjects with a history of trigeminal neuralgia secondary to other processes, subjects who responded to the usual medical therapy, and those with changes in their habitual medical management 2 months before the study were excluded. Women of childbearing potential underwent a pregnancy test before the study, and if the test was negative, a contraceptive method was indicated so that they could be included in the study. Subjects with known hypersensitivity to botulinum toxin and subjects with a concomitant condition where invasive procedures are contraindicated were also excluded from the study. All subjects

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Conflicts of Interest and Source of Funding: Dr Federico Micheli has received honoraria for consultancy and conferences from Allergan, Ipsen, Merz, Biotoscana, Schering Plough, Glaxo and Novartis. The remaining authors have no conflicts of interest to declare.

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DOI: 10.1097/WNF.0b013e31829cb60e

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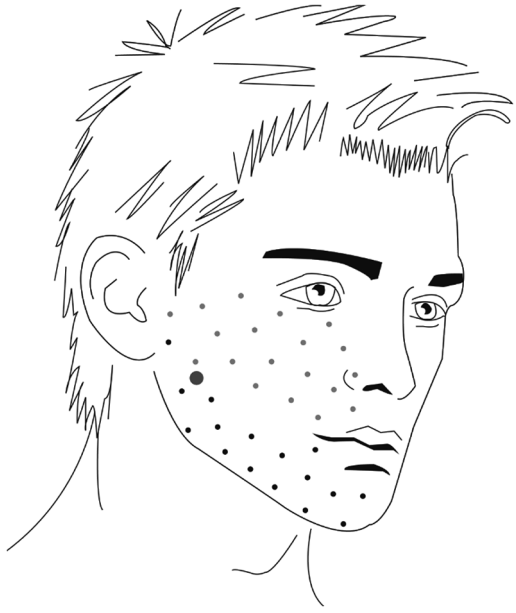

FIGURE 1. Injection sites of BTX. Gray dots correspond to V_2 territory; black dots are for V_3 territory. Large spot indicates the masseter muscle injection site.

were assessed at baseline and at 1, 2, and 3 months after the administration of either botulinum toxin or placebo. Pain was evaluated with the visual analog scale (VAS), including the impact on function by the presence or absence of mild, moderate, severe, or disabling pain when performing activities of daily living, such as talking, eating, drinking, or brushing one's teeth (scale from 0 to 4 points for each activity: 0 = absent, 4 = disabling; maximum score: 16 points). In addition, the effects of treatment on the patient's quality of pain were evaluated according to Short Form (36) (SF36) at baseline and at the end of follow-up. Secondary effects were also recorded. The results were evaluated according to the intent-to-treat analysis. The primary end points were pain severity and frequency of the attacks per day, whereas the secondary end point was the quality of life.

Statistical Analysis

Basic frequency measures were used as well as proportions to evaluate the differences between the subjects treated with BTX and those treated with placebo. Normality of data was analyzed using the Wilk-Shapiro test. Parametric tests were used in cases when data distribution included normality; nonparametrical tests were used when data distribution did not show evidence of normality. The effects of BTX in time were evaluated by using the Kaplan-Meier curve; also the hazard ratios (HRs) were assessed by means of the Cox proportional risk model. The STATA package, version 8 (College Station, Tex), was used for the analysis.

RESULTS

Thirty-six subjects (19 men and 17 women) were included in this study. Their main characteristics are shown in Table 1. Twenty subjects were administered BTX, and the remaining 16 subjects received placebo. Thirty-one subjects were on carbamazepine (19 in the BTX group and 12 in the placebo group), at an average dose of 867.74 mg/d, with an SD of 289.12 mg and a 400- to 1.400-mg range. Four subjects were on gabapentin (1 in the BTX and 3 in the placebo group), at an average dose of 1.050 mg/d, with an SD of 173.21 mg and a 900- to 1.200-mg range. Only 1 subject in the placebo group was on amitriptyline at a dose of 75 mg/d. All patients remained on their medications during the study. Average duration of the use of these medications for the management of pain was 4.75 years, with an SD of 3.74 years and a range of use of 1 to 20 years. All the subjects included in the study complained of pain at examination. One subject in the BTX group and 5 more in the placebo group complained of hiccups or anesthesia in the region involved. Three subjects in the BTX group and another 3 patients in the placebo group showed diminished corneal reflex. Nine subjects in the BTX group and 3 subjects in the placebo group complained of allodynia in the region involved. Finally, 18 subjects in the BTX

TABLE 1. General Features of the Included Patients

Feature	BOTOX (n = 20)	Placebo (n = 16)	Test	*P*
Age, y			*t* Test	NS
Mean/median (SD)	64.5/63.5 (12.94)	66.06/62 (14.16)		
Age range	42–90	44–93		
Sex, male:female, n	9:11	10:6	Fisher exact	NS
Affected branch				
V_2	7	6	Fisher exact	NS
V_3	5	3		
V_2 and V_3	8	7		
Side				
Left	7	11	Fisher exact	NS
Right	13	5		
Years with neuralgia			*t* Test	NS
Mean/median (SD)	6.2/6 (5.01)	5.2/5 (3.1)		
Range	1–20	1–10		
Surgical procedure			Fisher exact	NS
Yes/no	3/17	5/11		

NS indicates not statistically significant.

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group and 14 in the placebo group had trigger points. The VAS reported for the subjects randomized to BTX averaged 8.85 points versus 8.19 points for those who were randomized to placebo. No statistically significant differences were observed for the mean values (*t* test, −0.66 points; $P = 0.29$). Furthermore, VAS score was stratified in patients using carbamazepine to look for any differences among treatment groups, showing no significant differences between placebo and BTX groups at the initial assessment (n = 31; VAS 8.33 vs 8.79, respectively; *t* test, −0.46 points; $P = 0.45$). The baseline functional impact recorded for the subjects treated with BTX averaged 10.5 points, with an SD of 3.05 points, and a 4- to 15-point range; for those treated with placebo, the above record reached 6.25, with an SD of 3.13 points, and a 2- to 13-point range. This 4.25-point difference was statistically significant (*t* test, $P < 0.001$). The SF36 averaged 90.7 (SD, 22.21) points in subjects treated with BTX, and for those treated with placebo, the average score was 95.75 (SD, 16.78) points; this 5.05-point difference was not statistically significant (*t* test, $P = 0.46$). The average number of paroxysms per day reported by the subjects in the BTX group was 29.1, with an SD of 31.36 and a range from 0 to 100 paroxysms per day. Moreover, the average number of paroxysms in the placebo group was 31.06 (SD, 31.62) with range from 0 to 100 paroxysms per day. The assessment 1 month after the intervention showed a nonsignificant difference for the VAS average for the subjects treated with BTX and those treated with placebo (VAS 5.05 vs 6.06, respectively; *t* test, $P = 0.29$). When dividing subjects using carbamazepine (n = 31), a trend for statistical significance was found among BTX users (VAS 6.75 vs 4.79, placebo vs BTX; *t* test, 1.96 points; $P = 0.06$). No significant difference was observed for the mean functional impact scores obtained through this evaluation (5.15 vs 4.06, respectively; *t* test, $P = 0.45$). However, a significant decrease was observed for the number of paroxysms among the subjects treated with BTX as compared with those who received placebo. (Mann-Whitney *U* test, $P = 0.036$). Two months after the intervention, a trend to statistical significance was observed for the VAS mean values in subjects treated with BTX and those who received placebo (VAS 4.9 vs 6.63, *t* test; $P = 0.07$). At this time, subjects on carbamazepine who received BTX showed a significant decrease in pain as measured by VAS (6.91 vs 4.63, placebo vs BTX, respectively; *t* test, 2.29 points; $P = 0.02$). The differences as to the functional impact scale were not statistically significant (3.8 vs 4.63, respectively; *t* test, $P = 0.55$). The ranking obtained for the number of paroxysms in subjects treated with BTX was lower than that obtained for subjects treated with placebo; this difference was statistically significant. (Mann-Whitney *U* test, $P = 0.01$). Three months after the intervention, significant differences were observed in the average VAS score for subjects treated with BTX and those treated with placebo (VAS 4.75 vs 6.94, respectively; *t* test, $P = 0.01$). Again, subjects treated with carbamazepine in which BTX was injected showed a significant decrease in VAS score (7.08 vs 4.58 placebo vs BTX, respectively; *t* test, 2.5 points; $P = 0.007$). Also, significant differences were observed in the rankings obtained for the number of paroxysms of the subjects treated with BTX and those treated with placebo (Mann-Whitney *U* test, $P = 0.006$). Despite this, the average score in functional impact did not show significant differences (3.15 vs 4.81, respectively; *t* test, $P = 0.16$). The SF36 administered during the last evaluation did not show significant differences between the subjects treated with BTX or placebo (99.45 vs 95.63, respectively; *t* test, $P = 0.26$) and did not show a statistical difference when comparing the mean value of the score obtained between the initial and the final SF36 (paired *t* test: 92.94 vs 97.75, respectively $P = 0.18$). Comparing the score related to the initial VAS and the VAS at the end of follow-up, subjects treated with BTX evidenced a significant difference as to the mean score (initial vs final VAS 8.85 vs 4.75, respectively, paired *t* test; $P < 0.001$). Subjects treated with placebo did not show evidence of statistically significant difference for said score (VAS 8.19 basal vs 6.94 final, paired *t* test; $P = 0.12$). Subjects on carbamazepine depicted a significant difference in the initial versus final VAS score when BTX was the intervention added to their treatment (8.79 vs 4.59, initial vs final, respectively, paired *t* test, 4.21 points; $P < 0.0001$). The same was observed when comparing the functional impact scale at baseline and at the end of follow-up for the subjects treated with BTX (10.5 basal vs 3.15 final, paired *t* test; $P < 0.001$) and those treated with placebo (6.25 basal vs 4.81 final, paired *t* test; $P = 0.17$). After evaluating the number of paroxysms per day reported by the subjects at baseline and at the end of follow-up, the following was observed: the average number of paroxysms per day in subjects treated with BTX was 29.1, whereas at the end of the third month, they decreased to only 7.1; this difference was statistically significant (paired *t* test, $P < 0.001$). The mean number of paroxysms per day reported by the subjects on placebo was 31.06, whereas at the end of the third month, they reported 21.25 paroxysms per day. This reduced frequency of the number of paroxysms was not statistically significant (paired *t* test, $P = 0.19$). The adverse events reported were hematoma at the site of administration (2 subjects treated with BTX) and slight facial asymmetry due to weakness (2 subjects treated with BTX). No severe adverse events were reported in this study. The subjects under evaluation were followed up for an average of 88.64 days (median, 90.5 days; SD, 13.97 days; range, 48–119 days; with a total of 1616 days/patients). Twenty-four (11 in the BTX group and 13 in the placebo group) of the 36 subjects evaluated experienced a relapse, and symptoms became as disturbing as at baseline (before the intervention). After a 90-day follow-up, the probability of nonrelapse in the placebo group was 19%; this percentage was the same after 111 days of follow-up (95% confidence interval [CI], 5%–40%). Conversely, the probability of nonrelapse in the BTX group after a 91-day follow-up was 50% (95% CI, 27%–69%). After a 110-day follow-up, such probability decreased to 38% (95% CI, 13%–62%) (Fig. 2). The relapse rate for every 100 patients per month in the placebo group was 71.04, whereas the relapse rate for the subjects treated with BTX was 30.93 for 100 patients per month. The difference between the 2 groups showed a trend for statistical significance (log-rank test,

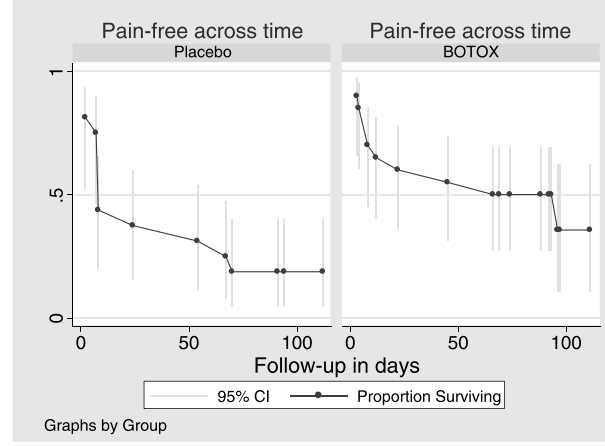

FIGURE 2. Proportion of patients remaining pain-free across time treated with placebo or botulinum toxin (BOTOX).

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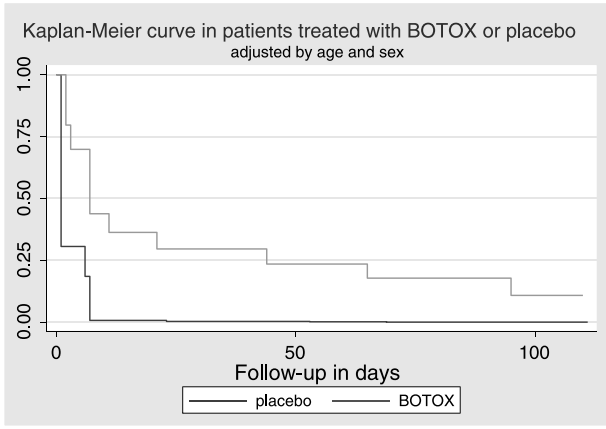

FIGURE 3. Kaplan-Meier curve in patients treated with either botulinum toxin (BOTOX) or placebo.

$P = 0.09$), which became statistically significant when adjusting for sex (stratified log-rank test, $P = 0.02$). Finally, a Cox proportional risk model was used, with the Efron correction method; the HR for a relapse in subjects treated with BTX was 0.35 (95% CI, 0.15–0.83; $P = 0.017$), adjusted for age and sex. The HR for relapse in male subjects was lower (HR, 0.28; 95% CI, 0.18–0.67; $P = 0.004$), adjusted for the rest of the variables. Age did not show any significant effect when adjusted for the rest of the variables (HR, 0.99; 95% CI, 0.99–1.01; $P = 0.33$). This effect is illustrated in Figure 3. The proportionality of risk was verified by means of a test based on Schoenfeld residues, preserving this assumption (Schoenfeld χ^2 test, $P = 0.71$).

DISCUSSION

Despite not devoid of adverse effects, systemic pharmacological therapy is the core treatment for ETN and carries less risk than surgical procedures. Drugs useful for this condition include carbamazepine, amitriptyline, baclofen, lamotrigine, gabapentin, sodium valproate, and phenytoin. Most patients with ETN have a positive response to drug therapy; however, long-term studies have shown a gradual decrease in their efficacy over time. As some cases are refractory to such therapeutic approaches, diverse invasive procedures are used to diminish pain. Nonetheless, ETN is most common among elderly patients, and some of them are not good candidates for surgical procedures. In addition, surgical treatments are on occasion unsuccessful or poorly tolerated and dangerous, showing that there are many refractory patients for whom existing treatments are inadequate. Complications and adverse effects include cardiovascular stress during the procedures, local hemorrhages, and postoperative sensory disturbances including painful anesthesia, masseter weakness, infections, and transitory diplopia after surgery.[10] We first described the beneficial effects of BTX in a patient with both TN and hemifacial spasm. She received BTX to control the involuntary movements, but it proved to be effective also in the control of pain.[11] We subsequently reported 12 patients with ETN treated with BTX injections in an open-label trial, 10 of whom had a good response, suggesting that BTX could be an interesting tool in the management of such patients.[9] Since then, several case reports[12–16] and clinical trials with small number of patients[17–20] have shown similar results, with most patients responding to BTX (Table 2). Recently, Wu et al[21] reported a randomized, double-blind, placebo-controlled study of 42 subjects with ETN treated with BTX concluding that this therapy has beneficial effects among these patients. Our study

TABLE 2. Comparison of the Different Trials of BTX in TN

Study	Type of Study	Patients	Intervention	Comparator	Measure	Outcome	Benefit Duration
Borodic et al,[17] 2002	Open-label	11	BTX 30–50 U	None	Perception of the patient	8/11 have at least 50% reduction in pain	5–10 wk
Türk et al,[18] 2005	Randomized, open-ended	8	BTX 50 U	None	VAS, pain frequency	Mean rank frequency reduction from 4 to 1.25, mean rank VAS reduction from 4 to 1.19	6 mo
Zúñiga et al,[9] 2008	Open-label	12	BTX 20–50 U	None	VAS, no. paroxysms	Mean VAS reduction from 8.83 to 4.08 at week 8, mean no. paroxysms reduction from 23.42 to 8.67 at wk 8	60 d
Bohluli et al,[17] 2011	Open-ended	15	BTX 50 U	None	VAS, frequency of attacks, global assessment	Reduction of pain frequency and severity	6 mo
Wu et al,[21] 2012	Randomized, double-blind, controlled trial	42 (BTX 22, placebo 20)	BTX 75 U	Placebo	VAS, pain frequency, PGIC	Improvement in all scales used	12 wk
This study	Randomized, double-blind, controlled trial	36 (BTX 20, placebo 16)	BTX 50 U	Placebo	VAS, SF36, functional scale, attacks frequency	Mean VAS reduction from 8.85 to 4.75 in BTX patients, mean attacks frequency reduction from 29.1 to 7.1 attacks	3 mo

PGIC, Patients Global Impression of Change.

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is one of the largest reported to date, demonstrating that BTX injections are a minimally invasive procedure that can play a role in the treatment of TN before considering other more invasive therapies or even systemic pharmacological options. One month after the injection, pain intensity was not modified, but the number of paroxysms had significantly decreased. At 2 months, BTX did not perform better than the placebo arm regarding pain severity, but the number of pain attacks continued to be lower, and at the third month, significant differences were observed as the number of paroxysms and pain severity had considerably diminished in the active arm. Our study also showed that, when adding BTX to their current treatment, a significant decrease in pain expression was felt by most of the subjects, synergizing the antinociceptive effects of other medications. The mechanism of action by which BTX controls pain is poorly understood, and several hypothesis have been advanced including direct blockade of the release of nonacetylcholine transmitters.[22] It has also been reported that botulinum toxin targets C fibers and probably TRPV1 (transient receptor potential cation channel, subfamily V, member 1) receptors, blocks neurotransmitter release, and subsequently reduces pain, neurogenic inflammation, and cutaneous heat pain threshold.[23] It has been known that botulinum toxin can block the exocytosis of synaptic vesicles and prevents the release of several neurotransmitters.[24] In addition, they attenuate a slow phase of KCl-evoked glutamate and other neurotransmitter release, which may be associated with synaptic vesicle mobilization.[25] Our patients showed a relief of more than 50% in crisis frequency in the medium term. The progressive pain improvement suggests that BTX could have a preventive rather than analgesic effect. However, in some individual cases, pain almost remitted at the time of the injection (unpublished observation). Whether this is a placebo effect cannot be ruled out. We used an empirical dose 50 U of BTX based on our experience and injected on the trigger points as well as in the masseter muscles to reach the required dose without causing significant facial paresis, but different doses and injection sites need to be explored. This study shows that the acute treatment of ENT with BTX is useful and, in the doses used, almost devoid of adverse effects. It does not show how long the effect lasts, thus, how frequent it has to be administered. Previous cases have shown benefits ranging from 3 to 5 months.[12] Our study also shows that there is a significant risk reduction of presenting reemerging pain even after 110 days of BTX injection. For some reason, this effect seems to be higher among males. Based on our results, BTX seems to be an effective alternative for the treatment of ETN; further long-term studies need to be carried out to validate our findings.

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