

Intraoral Botulinum Toxin Injection in Mental Foramen Site in the Treatment of Trigeminal Neuralgia

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ABSTRACT

BACKGROUND

Botulinum toxin type-A (BTX-A), has been used successfully in trigeminal neuralgia treatment. In this research, a novel method is proposed to assess the effectiveness of the BTX-A injection to the mental nerve. The present study aimed to evaluate BTX-A injection effectiveness in the mental nerve of trigeminal neuralgia (TN) patients who had a trigger zone in the mental nerve distribution.

METHODS

In this quasi-experimental, pre-and post-test design without control group research, 50 units of BTX-A was injected into the mental foramen site in 20 patients. Pain frequency and Visual Analog Scale (VAS) was evaluated prior to the treatment and in the first week, the second month, the sixth month, and the first year after treatment. Responders were those patients with a decrease of 50 percent in the score of mean pain in the second and sixth month.

RESULTS

The study included 20 patients. Pain intensity and attack frequency was decreased significantly by BTX-A. Ninety-five percent of patients reacted to therapy in the first year. After an average period of 165 ± 31.6 (44 - 235) days, 50 percent of patients encountered recurrence and, for a second time, received treatment.

CONCLUSIONS

Injection appears to be a very successful technique in the mental foramen site; the attack frequency and pain severity are reduced after each injection. Based on the present research, intraoral injection of BTX-A to the mental foramen site is an efficient and safe treatment. In TN and possibly other similar disorders, BTX-A can be a beneficial treatment technique. A fast and long-term advantage is provided by BTX-A, without systemic effects.

KEY WORDS

Botulinum Toxin, Trigeminal Neuralgia Treatment

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BACKGROUND

According to the International Association for the Study of Pain (IASP), trigeminal neuralgia is a unilateral facial pain syndrome defined by sharp, brief, paroxysmal lancinating pains recurrent and limited to the distribution of trigeminal nerve divisions.¹ Its prevalence is around 1 in 25000.² Idiopathic cases, besides ones with the fifth cranial nerve's vascular compression are considered as classical TN (CTN); symptomatic TN (STN) is observed in secondary cases of tumours, multiple sclerosis, and structural abnormalities in the skull base.³ At first, pharmacological agents typically are used for treating TN patients.⁴ In almost 80 % of patients, the medicine may help to handle the pain.

Carbamazepine is the first line of treatment that relieves most of the symptoms detected. In most TN patients, other medicines, such as phenytoin, baclofen, oxcarbazepine, lamotrigine, sodium valproate, and gabapentin, effectively decrease the symptoms as well. Medicines in the TN treatment have some side effects, including lethargy, dizziness, fatigue, vomiting, nausea, reversible thrombocytopenia, occasional granulocyte reduction, or hepatitis associated aplastic anaemia. With inadequate effects or undesirable side effects of pharmacological therapy, surgery is a choice. Since TN involves percutaneous radiofrequency thermal rhizotomy, neurectomy of the trigeminal nerve branches outside the skull, percutaneous ablation using heat to generate the trigeminal nerve or trigeminal ganglion lesions, glycerol injection into the trigeminal cistern, percutaneous retrogasserian glycerol rhizotomy, physical compression, cryotherapy, alcohol injections, trigeminal ganglion balloon micro compression, botulinum toxin injection, and gamma knife radiosurgery (GKRS), a number of surgical methods are applied for relieving the pain. Many surgical processes can result in certain complications,⁵ including facial paraesthesia, hearing loss, hypoesthesia, keratitis, masseter weakness and paralysis, transient paralysis of cranial nerves III and VI, such as dysesthesia, diminished corneal reflex, and anaesthesia Dolorosa, or immediate complete vision loss in one eye after trigeminal radiofrequency rhizotomy because of acute traumatic optic neuropathy.⁶

TN may be relieved by the injection of BTX-A in trigger zones.⁷⁻¹⁰ In TN treatment, hematoma / oedema and facial asymmetry, including the commissure distortion, muscle relaxation, and the eyelid ptosis at the injection site, are the frequent side effects caused by botulinum toxin. All such side effects have been mild and vanished automatically with no more treatment. There have been no systemic side effects.¹¹ BTX-A has been administered intradermally and subcutaneously in all the research. The present study aimed to evaluate BTX-A injection effectiveness in the mental nerve of TN patients who had a trigger zone in the mental nerve distribution.

METHODS

In this quasi-experimental, pre-and post-test design without control group research, according to the Börü et al study and the calculation of standard deviation of VAS before and after the intervention were 0.6 and 2.4, respectively, and the

minimum difference between the means of 1.5 and a 95 % confidence level and the power of 80 %, 20 samples were examined.¹²

Before the treatment, the objective, process, and safety aspects of this study were clarified to all patients. From April 2017 to September 2018, all patients referred to the Maxillofacial Surgery Polyclinic and diagnosed with classical TN were included in the study. In order to avoid the existence of structural pathology, each patient went through magnetic resonance imaging. They were diagnosed with classical TN, based on the International Classification of Headache Disorders (ICHD-2),¹³ Further, patients' demographic characteristics, trigger factors, involvement side, disease duration, and medicines were recorded before treatment. Medicines, including gabapentin, carbamazepine, amitriptyline, and pregabalin, were used by most patients at the baseline. In the study period, these medicines were stopped, and no new ones were taken. In this study, the inclusion criteria were the failure in the present treatment, baseline pain intensity of ≥ 4 , and attack frequency of ≥ 4 per day.

Further, exclusion criteria were any systemic illness or any agent use potential to interfere with BTX-A. Moreover, all patients referred to the Maxillofacial Surgery Polyclinic and not diagnosed with classical TN were excluded, finally pregnant women or those with a plan of pregnancy during the treatment period were excluded. Enrolment continued until twenty patients of classical TN were found .0.5 mg of human albumin, 0.9 mg of sodium chloride, and 300 Units (U) of *Clostridium botulinum* type A neurotoxin complex form the content of each Dysport vial (botulinum toxin A); this content first was diluted in 3 mL saline solution (0.9 %). Then, 50 U (0.5 mL) was injected at every site. To administer toxin in all patients, a 28-gauge insulin needle was applied, and all injections to the patients was done by one professional maxillofacial surgeon.

The patients were seated with heads supported by a headrest. Their mouths were open to some extent, and the needle was pointed to the mandibular bone for the injection to the mental nerve, through the mandibular buccal vestibule between lower premolars at a depth of 5 mm around the mental foramen; the solution was administered around the mental nerve. Throughout the process, the echo graphic or radioscopic guide was not applied. Even though most patients have been followed-up up until now, the study consisted of the patients' one-year follow-up after treating with BTX-A. Before starting the study, baseline examinations were carried out. In the first week, the second month, the sixth month, and one year, the patients were examined.

Then, the details of adverse effects and pain severity were requested. On the basis of the Visual Analog Scale, pain severity related to chewing, tooth brushing, and cold weather was documented. Patients were requested to contact the hospital when they experienced the pain in this period. Patients were examined once more when the pain recurred, and if necessary, injections were given again. The pain severity was assessed using the VAS (the 11-point visual analog score). From baseline to endpoint, ≥ 50 % decrease in mean pain score was considered a reaction to treatment. At each visit, the negative effects were documented.

Percentages and distributions of frequency were computed. We used the Wilcoxon signed-rank test to compare

the VAS and the frequency before and after the intervention. At the level of $P < .05$, results were statistically significant. The SPSS software version 21 was used to carry out tests.

The research ethics committee of the Shahid Saduqi University of Medical Science reviewed and approved the study protocol and procedures with No IR.IUMS.REC.1397.478.

RESULTS

The study included 20 patients with the age range of 37 - 77 years (the mean age: 54.8 ± 4.5). Of them, ten were females (50 %) and ten were males (50 %). The mean disease period was 5.3 ± 2.8 years. Before the intervention, the mean score of baseline pain (VAS) was 9.8 ± 0.5 ($p = .06$). At the first week, the second month, the sixth month, and the first year, this score was 3.8 ± 1.2 , 2.2 ± 0.8 , 1.9 ± 0.9 , and 1.2 ± 0.8 , respectively. Significant differences was observed between the score of baseline VAS and those of the first week, the second month, the sixth month, and the first year ($P = .001$, $P = .001$, $P = .001$, and $P = .001$). The number of attacks per day was used to calculate attack frequency.

Before the intervention, the mean baseline attack frequency was 311.6 ± 81.5 ; further, it was 83.5 ± 28.2 , 64.4 ± 23.5 , 42.1 ± 19.2 , and 24.3 ± 10.7 at the first week, the second month, the sixth month, and the first year, respectively. A statistically significant difference was observed between the frequency at baseline and that in the first week, the second month, and the sixth month ($P = .001$, $P = .001$, $P = .001$, and $P = .001$) (Table 1). Reaction to the treatment was considered to be a ≥ 50 % reduction in pain score from baseline to endpoint. Patients response to the treatment, on the basis of this criteria, was 15 (75 %), 17 (85 %), 18 (90 %), and 19 (95 %) at the first week, the second month, the sixth month, and the first year, respectively. At the end of the first year, 12 (60 %) patients were pain-free.

After the mean period of 165 ± 31.6 (44 - 235) days, 10 (50 %) patients encountered recurrence; thus, for a second time, they were treated. 1 patient did encounter no change in pain severity and frequency, although he received a third injection throughout the one-year period. Negative effects: 1 patient encountered short-term inferior labial weakness on the side of injection; this effect vanished in 2 months.

Variables	Baseline	First Week	P	Second Month	P	Sixth Month	P	First Year	P
VAS	9.8 ± 0.5	3.8 ± 1.2	.001*	2.2 ± 0.8	.001*	1.9 ± 0.9	.001*	1.2 ± 0.8	.001*
Frequency	311.6 ± 81.5	83.5 ± 28.2	.001	64.4 ± 23.5	.001	42.1 ± 19.2	.001	24.3 ± 10.7	.001

Table 1. Visual Analogue Score (VAS) and Frequency Changes
*the Wilcoxon signed-rank test

DISCUSSION

Based on the results, at each follow-up, attack frequency and pain intensity in patients who received BTX-A improved clinically and statistically. A recurrence was not seen in the sixth month in about half of the patients; however, it developed in the remaining half. The patients' follow-up is continuing. There is also an attempt to publish long-term research results. The attack frequency and pain severity were reduced increasingly. In the present work, a similar technique to other authors was not used. In the first year, pain severity was reduced by about 95 %, according to this technique. In the last decade, BTX-A has been used in TN; in nearly all research, BTX-A injected intracutaneously, subcutaneously, and into the trigger zone in the painful area of the face.^{9,14-16} In the present research, 50 U of BTX-A was injected in the mental foramen site. According to Wu et al., BTX-A was safe and efficient in the TN treatment; it was injected by them in the painful area intradermally and submucosally; their reaction rate was as high as 70 %.¹⁴ 86 TN patients were treated by Jian-Huo Xia et al.; they also injected it intracutaneously in the painful area of the face, reaching the effectiveness rate at week 8 by 80 %. Based on other research, BTX-A injection in the painful area of the face relieves pain significantly in TN.^{15,16} According to a recent study by Batifol et al., a low dose of injection is needed into the trigger zone.

Also, they showed a high response rate to BTX-A.¹⁷ In a single-blinded randomised placebo-controlled research, Sheta et al. reported a significant pain decrease in the BTX-A group as compared with the placebo group. They further showed a significant rise in quality of life and a reduction in the number of acute medicine.¹⁸ In a double-blinded randomised placebo-controlled trial, Zhang et al. used 25U for one group and 75 U for the other; then, they compared the results with a placebo group. Based on the results, in BTXA groups, compared to the placebo group, the reaction rates were higher significantly; however, no statistically significant difference was observed between 25U and 75U groups. Just 4 randomised controlled investigations have been conducted up to 2016, according to systematic review. One hundred seventy-six patients with TN were in total treated. Based on their results, BTX-A is a highly efficient and useful substance compared to the placebo in the TN treatment. Their injection method was intradermal and / or subcutaneous.¹⁹ The injection in the present research method was administered nearby mental nerve. A substantial success was observed in this technique. Compared to other methods, it was slightly more effective. Further, in this work, no substantial safety concerns were observed.

CONCLUSIONS

Based on the present research, the intraoral injection of BTX-A to the mental foramen site is an efficient and safe treatment. In TN and possibly other similar disorders, BTX-A can be a beneficial treatment technique. It is fast acting and provides long-term relief without systemic effects. Further double-blind trials with the right number of patients would confirm our results and investigate if higher doses have a longer-term impact and to optimise injection sites. Also, more studies can help to explain optimal schedules and methods for injection.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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