Use of botulinum toxin A for drug-refractory trigeminal neuralgia: preliminary report

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Objective. Botulinum toxin type A (BTX-A) has been used to treat migraine and occipital neuralgia. We report preliminary results of an ongoing study that assesses the efficacy of BTX-A on trigeminal neuralgia (TN) patients refractory to medical treatment.
Study design. We treated 15 patients (8 men and 7 women) between 28 and 67 years of age who were suffering from drug-refractory TN from February 2008 to January 2010. Symptoms, including pain duration, provoking factors, affected nerve branch, frequency of TN attacks, and severity of pain just before injections, were evaluated 1 week, 1 month, and 6 months after injection. We injected 50 U reconstituted BTX-A solution at the trigger zones. The overall response to treatment was assessed via a 9-point patient global assessment scale and compared with values at baseline. Statistical analysis was performed by the analysis of variance (ANOVA) test for frequency of TN attacks, the Friedman test for severity of pain, and the Wilcoxon signed-rank test for PGA, and all with the use of SPSS software.
Results. Eight men and 7 women aged 28-67 years (mean 48.9 y) suffering from TN from 6 months to 24 years all improved regarding frequency and severity of pain attacks; in 7 patients, pain was completely eradicated and there was no need for further medication. In 5 patients, nonsteroidal antiinflammatory drugs were enough to alleviate pain attacks, and 3 patients again responded to anticonvulsive drugs after injection. All patients developed higher pain thresholds after injections. The ANOVA test showed a significant difference in frequency of attacks before injection and at 1 week, 1 month, and 6 months after injection ($P < .001$). Friedman test and pair comparison of pain severity scores with Bonferroni correction adjustment showed a significant difference ($P < .001$) between severity of pain before and after injection. Wilcoxon signed-rank test showed significant improvement in all patients up to 6 months after injection ($P < .001$). Complications included transient paresis of the buccal branch of the facial nerve in 3 patients.
Conclusion. This study supports other similar studies and shows that BTX-A is a minimally invasive method that can play a role in treating TN before other more invasive therapies, i.e., radiofrequency and surgery. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:47-50)**

Trigeminal neuralgia (TN) is a unilateral disorder that is characterized by brief pains, abrupt in onset, and limited to the distribution of ≥1 divisions innervated by the trigeminal nerve. The prevalence of this pain is about 1 in 25,000 people, and occurs slightly more in women than men. Patients are usually middle-aged or older.[1] Many modalities have been used to alleviate the pain or reduce the intensity and frequency of this disorder. Pharmacotherapy with anticonvulsive drugs still seems to be the first choice. However, surgical procedures, such as microvascular decompression, stereotactic rhizotomy, percutaneous balloon compression, and many other methods, are sometimes indicated.[2] The wide variety of treatment modalities, possibility of severe complications in some techniques, and presence of some refractory cases show that much exists for further research.[3] Botulinum toxin type A (BTX-A) has been used to treat pains such as migraine and occipital neuralgia.[4] We report preliminary results of an ongoing

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study that assesses the efficacy of BTX-A on TN patients.

PATIENTS AND METHODS

The study was an open-end study to assess the efficacy of BTX-A on TN. We treated 15 patients (8 men and 7 women) between 28 and 67 years of age who were suffering from TN from 2008 to 2010. Fifteen patients treated for clinically documented TN according to the Winn criteria (the presence of unilateral paroxysmal stabbing pain limited to the branches of the trigeminal nerve, tender trigger zones, frequent pain free intervals between pain sessions, response to anticonvulsants, and absence of neurologic defect) as well as the criteria defined for TN by the International Headache Society.[5] Patients with a history of surgery or pathologic conditions (e.g., tumors) were excluded, as were those with a musculoskeletal disorder (which was considered to be a relative contraindication for BTX-A injection) or with a history of previous surgical procedure on the cranial base for TN. All 15 patients had previously undergone pharmacologic treatment protocols (carbamazepine, antiepileptic drugs such as gabapentin, cannabinoids, etc. for several months to a year), that were or had become ineffective. All patients had been injected with 1.8 mL lidocaine at the trigger zone, which alleviated the pain while the anesthetic lasted. Trigger zones were stated by the patients and confirmed by clinical examination. Their pain recurred after anesthesia wore off.

The study was approved by our Ethics Committee. The details were explained to each of the patients, and they were informed of the possibility of transient paresis of the facial nerve at the injection. Informed consent was included in the documents of each patient.

Data included patient demographics, gender, age, presence of trigger zone, side of involvement, nerve branch involved, total/partial success (after treatment), and complications. Symptoms of pain, including duration, provoking factors, involved nerve branch, frequency of TN attacks (number per day), and severity of pain (11-point visual analog scale), just before injections and after 1 week and 1 month were evaluated and documented. The patient overall response to treatment were assessed via a 9-point patient global assessment scale and compared with that before injection (baseline). On that scale, −4 meant marked worsening, 0 meant no change, and +4 meant marked improvement or complete painlessness.

Preparation of the injection solution

Three milliliters of normal saline solution was mixed in a vial of BTX-A, and a fresh solution was prepared according to manufacturer's guidelines; 50 U reconstituted material was injected at the trigger zones. The effects were documented at each visit.

Analysis

The statistical analysis was performed by the analysis of variance (ANOVA) test for frequency of TN attacks, the Friedman test for severity of pain, and the Wilcoxon signed-rank test for patient global assessment scale. SPSS software (v. 16) was used.

RESULTS

Eight men and 7 women aged 28-67 years (mean 48.9 years) suffering from TN for 6 months to 24 years were studied. Demographic data and pain characteristics of patients are presented in Table I. In 5 patients, the mandibular nerve alone was the origin of pain and in 4, the maxilla. More than 1 branch of trigeminal nerve was involved in 5 patients (both maxilla and mandible in 4, both maxilla and ophthalmic nerves in 1). The ophthalmic nerve alone was involved in 1 patient (Table I). All of the patients improved regarding frequency and severity of pain attacks up to 6 months after injection (Table II). In 7 patients, pain was completely eradicated and there was no need for further medication. In 5 patients, nonsteroidal antiinflammatory drugs were enough to alleviate pain attacks, and 3 patients again became responsive to anticonvulsive drugs after injection. The ANOVA test used to compare frequency of attacks showed a significant difference between frequency of attacks before injection (F_0) and 1 week (F_1) or 1 month (F_2) after injection ($P < .001$). The Friedman test and pair comparison of pain severity scores with Bonferroni correction adjustment showed a significant difference ($P < 0.001$) between severity of pain before injection (S_0) and after injection (S_1 and S_2). Wilcoxon signed-rank test showed significant improvement in all patients in the patient global assessment scale 6 months after injection ($P < .001$). Complications included transient paresis of the buccal branch of the facial nerve in 3 patients; in 2 of them it was not significant and resolved in 2 weeks; in the third patient the paresis was severe, requiring physiotherapy, and took about 3 months to disappear. We did not have any cases of eyelid ptosis or dysphagia or any systemic side effects.

DISCUSSION

TN pain

Trigeminal neuralgia is an excruciatingly painful neuropathic facial disorder typically presenting as paroxysmal or abrupt pain lasting from several seconds to minutes and rarely up to several hours. The pain is said to feel like stabbing electric shocks occurring spontaneously or after stimulation of a trigger zone. Idiopathic

Table I. Demographic data and pain characteristic of TN patients

Patient	*Gender*	*Age (y)*	*Provoking factors*	*Duration (mo)*	*Affected branch*			*Complications*
					Mandible	*Maxilla*	*Ophthalmic*	
1	M	67	Spontaneous	36			×	Temporary partial paralysis
2	M	28	Spontaneous	6	×	×		—
3	F	55	Spontaneous	24	×			Temporary partial paralysis
4	M	62	Spontaneous	60		×		—
5	M	32	Spontaneous	12	×			—
6	M	48	Cold-spontaneous-speaking	288		×	×	
7	F	45	Touch-cold-stress	24	×	×		—
8	M	53	Speaking	48	×			—
9	M	65	Spontaneous	8		×		—
10	F	60	Spontaneous	60		×		—
11	F	29	Spontaneous-stress	18	×	×		—
12	M	34	Spontaneous	24	×			—
13	F	46	Spontaneous	6	×			—
14	F	51	Spontaneous	96		×		—
15	F	58	Spontaneous	24	×	×		Temporary partial paralysis

Table II. Pain severity and frequency over treatment course

Patient	*Severity of pain (VAS)*			*Frequency of attacks (per d)*			*Global assessment (after 6 mo)*
	S_0	S_1	S_2	F_0	F_1	F_2	
1	10	3	2	60	5	3	3
2	8	0	0	10	0	0	4
3	7	2	2	25	2	3	4
4	10	4	2	40	5	5	3
5	9	0	0	20	0	0	4
6	6	0	0	30	0	0	3
7	7	0	0	15	0	0	4
8	5	0	0	45	0	0	4
9	10	5	5	50	10	10	1
10	9	2	2	60	5	8	3
11	5	0	0	5	0	0	4
12	8	2	1	10	2	2	4
13	10	3	2	50	20	20	2
14	6	0	0	25	0	0	4
15	10	2	2	50	5	10	3

VAS, Visual analog scale; S_0, F_0, before injection; S_1, F_1, 1 week after injection; S_2, F_2, 1 month after injection.

trigeminal neuralgia occurs in 1 out of 100,000 people and is found more frequently in patients >50 years old. It may be typical (i.e., with paroxysmal pain only) or atypical (i.e., with association of a permanent background of pain). The skin of the face is painful upon TN attacks in the area innervated by V1, V2, or V3 of the trigeminal nerve. An etiology often cannot be found. The pain is severe and may ensue by talking or swallowing. Analgesics are usually ineffective. There may be a trigger point in the oral cavity that sparks the attack.[6] Treatment of TN is possible via both surgery and medication.

Medical approach

The medical approach is usually used first in an attempt to treat TN noninvasively. This is usually accomplished using anticonvulsants. Carbamazepine is the classic medication of choice for this purpose. Long-term studies, however, have shown a gradual decrease in its efficacy over time. Initial response to this medication is ~80%. After 10 years, however, its effectiveness decreases to 50%.[6] Other antiepileptic drugs, such as gabapentin, as well as cannabinoids have also been used.

Other methods

Another method by which to manage TN is neurectomy. It has been reported to be successful in 88.2% of patients. Balloon compression is another method used to treat TN patients, for which initial pain relief prevalence has been reported in 93%. But unilateral facial sensory loss has been reported in 61% of the patients.[6] Use of microvascular decompression (MVD) for TN caused by venous pressure is another effective method of treatment in which the pain recurrence ranges from 31.0% to 75%, within 1-3 years after the initial operation, owing to development of new veins around the nerve root in 87.5% of the cases. Lee et al.[7] did an electronic search of patient records from 1988 to 1998 and found that 393 patients were treated with MVD for TN caused by veins. The pain recurred in 122 patients (31.0%). MVD is a major neurosurgical operation that may have serious complications as well as prolonged convalescence.[6]

Several studies have documented the beneficial effects of BTX-A on reducing the frequency and severity of facial pains. The actual mechanism of this relief is not well understood. Some authors believe that injection of botulinum toxin inhibits secretion of acetylcholine in nerve endings, causing relaxation of muscles and finally relief of pain, whereas others think that the injection stops secretion of some nociceptive neuropeptides in addition to acetylcholine, which may help to prevent pain sensation.[8-10]

In the present series, all 15 patients who were suffering from refractory TN received 50-100 U BTX-A solution at each trigger zone. All of them experienced considerable relief of pain and some complete cure up to the time of writing. These findings were in accord with the studies by Türk et al.[11] and Zúñiga et al.[12] In both studies, the pain attacks were considerably alleviated. Türk et al. conducted a relatively similar study, considering 8 patients who were suffering from TN and injected with 100 U of botulinum solution below and under the zygomatic arch at the involved site.[11] Zúñiga et al. injected BTX into the subcutaneous tissue in 12 TN patients with good results in 10 of them.[12] In our study, partial paresis occurred in 3 of the 15 patients, which resolved spontaneously in 2 cases and disappeared in the third patient after physiotherapy and 3 months of time. In Türk et al.'s series no paresis was reported, and complications were dysesthesia in one patient and difficulty in chewing in another.[11] In Zúñiga et al.'s study, paresis was reported in 1 patient that recovered spontaneously. In our study, complete cure was seen in 7 patients (1 of them had a 24-year history of severe pain attacks). In the other 8 patients, the severity and frequency of pain were both considerably reduced. In all of these patients, pain threshold was improved and a stronger stimuli was necessary to provoke the pain, and pain attacks weakened and duration decreased (up to 6 months later in 15 of the present patients).

In conclusion, this study supports other similar studies and shows that BTX-A is a safe minimally invasive method that can play a role in treating TN before other more invasive therapies, i.e., radiofrequency and surgery. However, long-term assessment is still under way.

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