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Chapter 7

Drug-Refractory Trigeminal Neuralgia: Treatment via Botulinum Toxin Type A

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Additional information is available at the end of the chapter

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Abstract

Trigeminal neuralgia (TN) is a disorder characterized by severe abrupt lancinating pains, limited to areas of distribution of the fifth cranial nerve—the trigeminal nerve. Numerous modals have been used to reduce or alleviate the intensity and frequency of pain. Drug therapy with anticonvulsive drugs is still the first choice. Migraine and occipital neuralgia have been treated via botulinum toxin type A (BTX-A). Symptoms of TN (pain duration, initiating factors, affected nerve branch, frequency of attacks, and severity of pain) are assessed before injections, and evaluated 1 week, 1 month, and 6 months after injection of 50 U reconstituted BTX-A solution in the trigger zones. Patients generally improve with regard to frequency and severity of pain attacks and in many, the pain is completely eradicated and there is no need for further medication. In some patients, nonsteroidal anti-inflammatory drugs (NSAIDs) may be needed to alleviate pain attacks. All patients develop higher pain thresholds after injections. Complications of BTX therapy include transient paresis of the facial nerve. BTX-A therapy is a minimally invasive method that can play a role in treating TN before other more invasive therapies, i.e., radiofrequency and surgery, are sought. In this chapter, we discuss the indication and method to treat TN via BTX-A in patients refractory to medical treatment.

Keywords: trigeminal neuralgia, botulinum toxin type A, treatment, drug-refractory, method

1. Introduction

The prevalence of trigeminal neuralgia (TN) in the population is about 1 in 25,000 people, and is slightly more in women. Patients are usually in midlife or older [1]. Numerous modals have been used to reduce or alleviate pain intensity and frequency. Drug therapy using anticonvulsive drugs is usually the first choice. Surgery (i.e., microvascular decompression [MVD], stereotactic rhizotomy, percutaneous balloon compression, and other methods) may be indicated [2]. Some of these treatment modalities may have severe complications. Confrontation of patients presenting with refractory cases also known as drug-refractory trigeminal neuralgia (DR-TN) show that further research is still warranted [3]. Botulinum toxin type A (BTX-A) is used to treat pains such as occipital neuralgia and migraine [4]. We have used BTX-A to treat DR-TN with good results.

1.1. Diagnosis

Patients were treated for DR-TN clinically documented according to the criteria defined for TN by the International Headache Society [5] and Winn's criteria (presence of paroxysmal unilateral sharp stabbing pain limited to a branch or branches of the trigeminal nerve, painful trigger zones (TZs), frequent pain-free intervals between paroxysms, unresponsive to anticonvulsants, and no neurologic deficit). Patients with a musculoskeletal disorder (considered to be a relative contraindication for BTX-A injection) or with a history of a surgical procedure on the cranial base for TN or pathologies (e.g., tumors) were not treated.

1.2. Trigger zones

TZs were identified by the patients and by clinical examination. Injection of lidocaine into TZs can both confirm the diagnosis (when the pain stops) and guide us to where we can inject the BTX (ensuring that we do not inject in the area of the branches of the facial nerve).

2. Treatment

Patients who have undergone medical treatment protocols (carbamazepine, antiepileptic drugs like gabapentin, cannabinoids, etc., for months to a year) can be treated with BTX-A. If they are or become ineffective then the patient is first injected with 1.8 ml lidocaine at the TZ. Injection of lidocaine into TZs alleviates the pain until the anesthetic wears off [6]. Pain recurs after the duration of the local anesthetic. This also ensures that the injection site (the TZ) is not on the facial nerve. The possibility of transient paresis is explained to the patients. Patient demographics, age, gender, presence of TZ, involvement site, involved nerve branch, total/partial success (after injection), and complications are documented. Pain symptoms, duration, provoking factors, nerve branch involved, frequency of attacks (per day), and pain severity (via visual analog scale) are documented just before injections and after 1 week, 1 month, and 6 months. The overall response to treatment is assessed and compared with that at baseline (before injection) [6].

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2.1. Technique

2.1.1. Preparation of the injection

Hundred patients between 22 and 70 years of age suffering from TN were treated at our center. The patients were first injected with 1.8 ml lidocaine at the TZ. This alleviates the pain until the anesthetic wears off [6]. This also ensures that the trigger point is not on the facial nerve. Three milliliters of normal saline solution is mixed in a vial of BTX-A; a fresh solution is prepared; 50 U of reconstituted BTX-A is injected at the TZs.

3. Outcomes

Data and pain characteristics of 100 patients between 22 and 70 years (mean 47 years) of age who were suffering from TN for 3 months to 24 years are presented in **Table 1**. In 35 patients, the mandibular nerve alone was the origin of pain and in 38 patients, it was the maxilla nerve. More than 1 branch of the trigeminal nerve was involved in 28 patients (both maxilla and mandible nerves in 4 patients, both maxilla and ophthalmic nerves in 1 patient). The ophthalmic nerve alone was involved in 5 patients. All of the patients improved regarding frequency and severity of pain attacks up to 6 months after injection (**Table 2**). In 35 patients, pain was completely eradicated; there was no need for further medication. In 34 patients, nonsteroidal anti-inflammatory drugs (NSAIDs) were enough to alleviate pain attacks, and 25 patients became responsive to anticonvulsive drugs after injection. Six months after the injection, a significant improvement in all the patients in the patient global assessment scale was seen. Complications included transient paresis of the buccal branch of the facial nerve in 3 patients; in 7 of them, it was not significant and resolved in 2 weeks; in the third patient, the paresis was severe, requiring physiotherapy for 3 months.

Patient	Gender	Age (y)	Provoking factors	Duration (mo)	Affected branch			Complications
					Mandible	Maxilla	Ophtalmic	
1	M	67	Spontaneous	36			x	Transient partial paralysis
2	M	28	Spontaneous	6	X	x		----
3	F	55	Spontaneous	24	×			Transient partial paralysis
4	M	62	Spontaneous	60		x		----
5	M	32	Spontaneous	12	×			----
6	M	48	Cold-Spontaneous	288		x	×	----
7	F	45	Touch-cold-stress	24	×	×		----
8	M	53	Speaking	48	×			----
9	M	65	Spontaneous	8		x		----
10	F	60	Spontaneous	60		x		----

Patient	Gender	Age (y)	Provoking factors	Duration (mo)	Affected branch			Complications
					Mandible	Maxilla	Ophtalmic	
11	F	29	Spontaneous-stress	18	x	x		----
12	M	34	Spontaneous	24	x			----
13	F	46	Spontaneous	6	x			----
14	F	51	Spontaneous	96		x		----
15	F	58	Spontaneous	24	x	x		Transient partial paralysis
16	F	**45**	Spontaneous-stress	**36**		X	X	----
17	M	**65**	Spontaneous	**12**	x			----
18	F	**22**	Spontaneous	**6**		x		----
19	M	**70**	Stress-touch	48	x			----
20	M	**34**	Spontaneous-touch	12	x			----
21	F	48	Spontaneous	6	x			----
22	M	61	Speaking-touch	48	x			----
23	M	66	Spontaneous	240		x		----
24	F	71	Spontaneous	8			X	----
25	F	65	Spontaneous	48		x		----
26	F	35	Speaking	48	x			----
27	M	46	Spontaneous	36	x	x		----
28	M	73	Spontaneous	240		x		----
29	F	51	Spontaneous	12		x		----
30	F	65	Spontaneous-touch-Speaking	120		x		----
31	M	74	Spontaneous	60	x			----
32	F	35	Spontaneous	6		X		----
33	F	55	Spontaneous	18	X			----
34	M	31	Spontaneous	12	X			----
35	M	59	Spontaneous	60	x			----
36	M	42	Spontaneous-touch	9		x		----
37	F	46	Spontaneous	12				----
38	F	32	Spontaneous	18	x	X		----
39	F	64	Spontaneous-touch	12		x		----
40	M	66	Spontaneous	180	x	X		----
41	M	44	Spontaneous	24		X		----

Patient	Gender	Age (y)	Provoking factors	Duration (mo)	Affected branch			Complications
					Mandible	Maxilla	Ophtalmic	
42	M	71	Spontaneous-stress	240			X	Transient partial paralysis
43	F	65	Spontaneous	9		x		----
44	F	42	Spontaneous	120	x	x		----
45	M	44	Spontaneous	24	X	X		----
46	F	53	Spontaneous	48		X		----
47	F	32	Spontaneous	12			X	----
48	M	32	Spontaneous	12	x			----
49	M	65	Spontaneous	12		x	X	----
50	F	46	Cold-Touch	6	×			----

Table 1. Demographic data and pain characteristic of TN patients.

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
16	7	1	1	22	3	3	RECENT CASE< 6 MO
17	5	2	1	12	1	2	RECENT CASE< 6 MO
18	8	0	0	16	0	0	RECENT CASE< 6 MO
19	10	3	3	34	2	2	RECENT CASE< 6 MO

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	
20	4	0	0	10	0	0	RECENT CASE< 6 MO
21	8	1	1	35	4	4	RECENT CASE< 6 MO
22	9	0	0	50	0	0	RECENT CASE< 6 MO
23	10	3	3	30	1	3	RECENT CASE< 6 MO
24	6	0	0	50	0	0	RECENT CASE< 6 MO
25	4	1	1	25	1	3	RECENT CASE< 6 MO
26	8	2	2	20	5	5	RECENT CASE< 6 MO
27	10	3	1	35	5	5	RECENT CASE< 6 MO
28	7	0	0	10	0	0	RECENT CASE< 6 MO
29	6	3	4	15	10	10	RECENT CASE< 6 MO
30	8	2	2	10	3	2	RECENT CASE< 6 MO
31	5	1	1	40	15	20	RECENT CASE< 6 MO
32	10	3	4	15	3	3	RECENT CASE< 6 MO
33	7	0	0	35	10	10	RECENT CASE< 6 MO
34	3	0	0	20	5	8	RECENT CASE< 6 MO
35	6	0	0	25	0	0	RECENT CASE< 6 MO
36	10	3	3	60	10	10	RECENT CASE< 6 MO
37	8	0	0	20	0	0	RECENT CASE< 6 MO
38	6	3	3	40	5	5	RECENT CASE< 6 MO
39	10	0	0	50	0	0	RECENT CASE< 6 MO
40	7	0	0	30	0	0	RECENT CASE< 6 MO
41	**6**	**4**	**4**	**30**	**10**	**15**	RECENT CASE< 6 MO
42	9	1	1	20	5	5	RECENT CASE< 6 MO
43	10	5	5	30	10	10	RECENT CASE< 6 MO
44	5	0	0	50	0	0	RECENT CASE< 6 MO
45	8	3	3	60	30	30	RECENT CASE< 6 MO
46	10	0	0	30	0	0	RECENT CASE< 6 MO
47	4	0	0	15	0	o	RECENT CASE< 6 MO
48	7	5	6	25	20	20	RECENT CASE< 6 MO
49	9	1	1	30	2	3	RECENT CASE< 6 MO
50	8	0	0	60	0	0	RECENT CASE< 6 MO

Table 2. Pain severity and frequency during the course of treatment.

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Because TN is a painful neuropathic disorder, it typically presents as paroxysmal or abrupt facial pain lasting from seconds to several minutes and rarely up to hours. The pain is described as stabbing electric shocks occurring spontaneously or after stimulation of a TZ. Idiopathic TN is seen in 1 in 100,000 people and more frequently in those aged more than 50 years. It may be typical (paroxysmal pain only) or atypical (association of a permanent background of pain). The facial skin is painful upon attacks in the area innervated by V1, V2, or V3 of the trigeminal nerve. An etiology often cannot be found. Pain is severe and may begin while talking or swallowing. Analgesics are usually ineffective. There may be a trigger point in the oral cavity that sparks the attack [7]. Treatment of TN is possible via medication or surgery.

4. Differentiation of dental pain and trigeminal neuralgia

4.1. Dental pain

Pulpitis or periapical infection can result in severe dental pain. In pulpitis, the patient often has nocturnal pain exacerbated by heat; radiographic findings may present caries or deep restorations. In a patient with the mentioned radiographic findings or endodontic treatment, there may be pain from a periapical infection not yet apparent on radiographs. In this case, the tooth may be felt to be extruded and painful upon percussion and to palpation over the apex of the tooth root in the vestibule; however, pain does not involve the facial skin. In dental pain, the cause is often apparent and the pain usually responds to analgesics. Radiographic findings are usually diagnostic and the origin of pain to the oral cavity, tooth or gum can be traced.

4.2. Trigeminal neuralgia pain

The pain from TN is said to feel like stabbing, electric shocks occurring spontaneously or following a TZ stimulation. TN pain is excruciating; this neuropathic disorder presents typically as paroxysmal or abrupt attacks lasting from seconds to one or more minutes and rarely up to several hours [7]. Idiopathic TN occurs in 1 in 100,000 people and is more frequently found in patients aged more than 50 years. It may be typical (i.e., with only paroxysmal pain) or atypical (i.e., association with 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; radiographic findings are often lacking and pain is not necessarily nocturnal. Often an etiology is not found. Pain is severe and may ensue when talking or swallowing. Analgesics are usually ineffective. Radiographs are not diagnostic and the origin of pain cannot be traced to the oral cavity upon examination. However, a trigger point in the oral cavity may be found that sparks the attack.

5. Other treatment approaches

5.1. Medical treatment approach

A medical approach is often used primarily in an attempt to treat TN noninvasively. This is usually accomplished using anticonvulsants. Carbamazepine is the classic medication chosen for this purpose. However, long-term studies have shown a gradual decrease in efficacy. Initial response is 80%. After 10 years, its effectiveness decreases by 50% [7]. Other antiepileptic drugs, such as gabapentin and cannabinoids, have also been used.

5.2. Neurectomy

Another method to treat TN is neurectomy. It has been reported to be successful in 88.2% patients. Balloon compression is another method used to treat TN, for which initial pain relief has been reported in 93% patients. Unilateral facial sensory loss has been reported in 61% of these patients [7].

5.3. Microvascular decompression

Use of MVD for TN which is caused by venous pressure is another effective method of treatment; pain recurrence ranges from 31.0% to 75%, within 1 to 3 years after operation, owing to development of new veins around the nerve root in 87.5% patients. Lee [8] did an electronic search of patient records from 1988 to 1998 and found that in 393 patients 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 [7].

5.4. Radiofrequency

Percutaneous radiofrequency thermocoagulation of the trigeminal ganglion (PRTTG) is an interventional treatment that is relatively safe and patients are treated as outpatients. It is less invasive in comparison to other invasive modes of treatment, is not very time consuming (30–60 minutes), and has a low complication rate. Motamedi and colleagues [7] did a study from 2000 to 2006, in which data from 65 patients treated for clinically documented TN (according to Winn's criteria) were assessed. Out of 65 patients, 36 (55.4%) females and 29 (44.6%) males with a mean age of 52.4 years (ranging from 21–75 years), a total of 51 (78.5%) patients were successfully treated; 14 (21.5%) were unsuccessful. The success rate was significantly higher for patients with defined TZs (74.5%) in comparison with those without defined TZs (25.5%). There was no need to repeat RF for the majority (72.3%) of the patients.

5.5. Botulinum toxin injection

Several studies have documented the beneficial effects of BTX-A on reducing the frequency and severity of TN. The actual mechanism is not well understood. Some believe that botulinum toxin injection inhibits secretion of acetylcholine in nerve endings, leading to relaxation of

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muscles and relief of pain; others think that the injection stops secretion of nociceptive neuropeptides in addition to acetylcholine, which helps prevent pain [9–11].

6. Conclusion

All our patients with DR-TN received 50–100 U BTX-A at each TZ. All experienced considerable pain relief and some were completely cured up to the time of writing. These findings were in accordance with the studies by Türk et al. [12] and Zúñiga et al. [13]. In both studies, the pain attacks were considerably alleviated. Türk et al. conducted a relatively similar study, in patients who were suffering from TN and injected with 100 U of botulinum solution below the zygomatic arch at the involved site [12]. Zúñiga et al. injected BTX into the subcutaneous tissue in patients suffering from TN and got good results [13]. In our study, partial paresis occurred in 3 patients, which resolved spontaneously in 2 cases and disappeared in the third patient after physiotherapy for 3 months. Injection of local anesthetic at the site before BTX injection may have prevented this. In series by Türk et al., no paresis was reported and complications were dysesthesia in one patient and difficulty in chewing in another [12]. In study by Zúñiga et al., paresis was reported in 1 patient who recovered spontaneously. In our study, complete cure was seen in 7 patients (1 had a 24-year history of severe pain).

In the other 8 patients, the severity and frequency of pain were reduced considerably. In all of these patients, pain threshold improved and a stronger stimulus was necessary to provoke TN pain, and pain attacks got weakened and duration got decreased. 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 are sought. However, long-term assessment is still under study.

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