Sphenopalatine Ganglion Block with Botulinum Neurotoxin for Treating Trigeminal Neuralgia Using CAD/CAM–Derived Injection Guide

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Aims: To examine the effectiveness and safety of using a CAD/CAM–derived injection guide for botulinum neurotoxin block of the sphenopalatine ganglion for trigeminal neuralgia treatment. **Methods:** Ten patients with second-division trigeminal neuralgia who did not respond to submucosal administration of botulinum neurotoxin were enrolled in this study. The target point around the sphenopalatine fossa was determined after fusion of computed tomography data with a scan of a maxillary model using a software program for dental implant surgery. A CAD/CAM–derived injection guide was fabricated. The guide was affixed to the patient's maxilla, and a needle was inserted to an exactly analyzed depth. Subsequently, 50 units of botulinum neurotoxin were injected. Pain intensity evaluated using a visual analog scale and pain frequency were measured. **Results:** By using the guides, sphenopalatine ganglion block with botulinum toxin was performed 18 times without any complications. The visual analog scale score (8.1 ± 1.0) and pain frequency (19.4 ± 8.8 times/day) decreased (to 1.9 ± 1.4 and 4.9 ± 5.4 times/day, respectively) significantly ($P < .001$). After 4 weeks, the mean subjective improvement achieved was 77.5% ± 13.8%, and all patients responded to treatment. **Conclusion:** Even without prior experience of sphenopalatine ganglion block, the CAD/CAM–derived guide enabled the accurate and safe administration of botulinum neurotoxin to the sphenopalatine ganglion for the treatment of trigeminal neuralgia. *J Oral Facial Pain Headache 2020;34:135–140. doi: 10.11607/ofph.2510*

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Trigeminal neuralgia is characterized by recurrent, brief, unilateral, electric shock–like pains that are abrupt in onset and termination and limited to the distribution of one or more divisions of the trigeminal nerve.[1] The age of onset is usually between 40 and 60 years. The pain may occur spontaneously or after stimulation of a trigger zone. Although trigeminal neuralgia is most commonly related to microvascular compression, the pathophysiologic mechanisms underlying its development are not fully understood. Pharmacologic therapy using oral antiepileptic drugs such as carbamazepine remains the first line of treatment. Most patients respond to these medications; however, some cases may require surgical interventions, including microvascular decompression, gamma knife stereotactic radiosurgery, and percutaneous radiofrequency thermocoagulation. However, surgical interventions are not always effective and occasionally result in severe complications or recurrence of symptoms.

Botulinum neurotoxin is produced by the bacterium *Clostridium botulinum*, which is one of the most lethal biologic toxins known to man. It exerts a paralytic action by rapidly and strongly binding to presynaptic cholinergic nerve terminals.[2] Then, it internalizes and ultimately inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. Consequently, the toxin has been mainly applied for treating diseases accompanied by hyperactive muscle tonus like involuntary movements. The author has also used these medications

Table 1 Patient Characteristics

Patient no.	Age (y)	Sex	Disease duration (mo)	Submucosal botulinum neurotoxin injection (no. of times)	VAS (0–10)	Pain frequency (no. of times/d)
1	69	F	12	1	6.2	10.2
2	40	F	19	2	8.2	12.3
3	80	F	144	1	7.5	15.7
4	69	M	24	1	9.4	38
5	57	F	62	1	9.2	27.5
6	45	F	15	1	8.3	18.2
7	80	F	120	1	8.1	21
8	62	F	60	1	7.8	11.5
9	59	M	72	1	8.8	25.4
10	75	F	36	1	7.3	14.2
Mean (SD)	63.6 (13.7)	–	56.4 (45.4)	1.1 (0.3)	8.1 (1.0)	19.4 (8.8)

VAS = visual analog scale; SD = standard deviation.

for oromandibular dystonia.[3–6] Furthermore, botulinum neurotoxin has been investigated as a promising option for pain relief. However, the mechanism of its analgesic effect remains uncertain. Several authors have suggested that the subcutaneous or submucosal injection of botulinum neurotoxin type A to the trigger zone may be an effective and safe treatment option for patients with trigeminal neuralgia.[7–14] However, not all patients respond to this treatment.

The sphenopalatine ganglion is situated below the maxillary branch of the trigeminal nerve in the pterygopalatine fossa. Sphenopalatine ganglion block has been used by clinicians in the treatment of various headache disorders, including cluster headaches, migraines, and trigeminal neuralgia. Although administering the sphenopalatine ganglion block requires adequate experience, the procedure is not frequently performed in clinical practice; thus, it is difficult to become skilled in the procedure. A novel injection device that could perform a surgical navigation-assisted administration of botulinum neurotoxin was developed, but all participants experienced adverse events such as pain, swelling, numbness, and jaw problems.[15] Therefore, it became necessary to establish a method that enables inexperienced physicians to inject botulinum neurotoxin for sphenopalatine ganglion block correctly and safely.

During dental implant surgery, computed tomography (CT)–based templates are typically used to ensure precise implant placement and to reduce the risk of damage to adjacent structures. The author modified the surgical template to enable the injection of botulinum neurotoxin into the lateral pterygoid muscles.[4,5] In this report, the author describes a customized computer-aided design/computer-assisted manufacturing (CAD/CAM)–derived needle guide used during the injection of botulinum neurotoxin into the sphenopalatine ganglion for the treatment of second-division trigeminal neuralgia.

Materials and Methods

Patients

Ten patients (8 women and 2 men, mean age: 63.6 ± 13.7 years) with second-division trigeminal neuralgia were diagnosed with classical trigeminal neuralgia according to the beta version of the 3rd edition of the International Classification of Headache Disorders.[1] The patients had a consultation in the neurosurgery department and underwent magnetic resonance imaging, which did not reveal any apparent structural pathology. The author administered 50 units of botulinum neurotoxin type A (Botox, Allergan) into the submucosal trigger zone of all patients. Nonresponders were defined as patients with < 30% fall in visual analog scale (VAS) pain scores (0–10) and pain frequency from baseline to 4 weeks. The 10 patients were refractory to submucosal administration of botulinum neurotoxin trigger zone (Table 1). One patient preferred a second submucosal injection despite limited improvement from the first injection. Their demographic characteristics are shown in Table 1.

CAD/CAM–Derived Injection Guide

Computed tomography (CT) scans were performed on the patients while occluding their incisors on an elastic bite block to avoid overlapping of the opposing arches in the dental images. The CT data (slice width, 0.5 mm) were stored in the digital imaging and communications in medicine (DICOM) format. After the direct importation and fusion of the patients' CT scans and images of their maxillary plaster models using NobelProcera 2G (Nobel Biocare),[4] the target point of needle insertion near the sphenopalatine fossa was determined using NobelClinician version 2.4 (Nobel Biocare) (Fig 1a). The insertion point was the mucobuccal fold of the distal root of the maxillary second molar. To avoid contact with the adjacent bony structures during insertion, the orientation

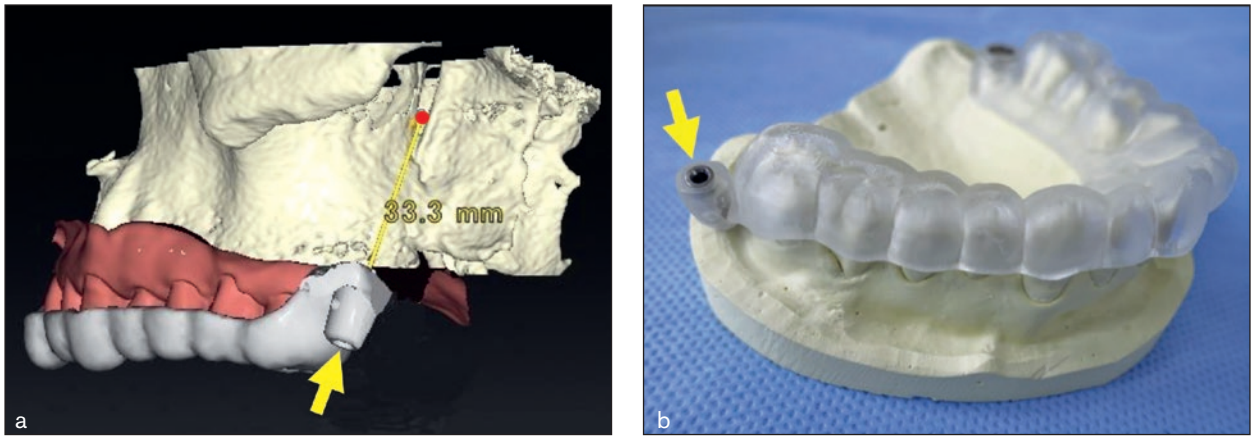

Fig 1 CAD/CAM injection guide based on the data obtained from CT and a plaster model. **(a)** After checking the sphenopalatine fossa with CT images, a point near the sphenopalatine fossa was determined as the target point (red circle) of botulinum neurotoxin injection. **(b)** A completed injection guide on the maxillary model. Arrows indicate the direction of needle insertion.

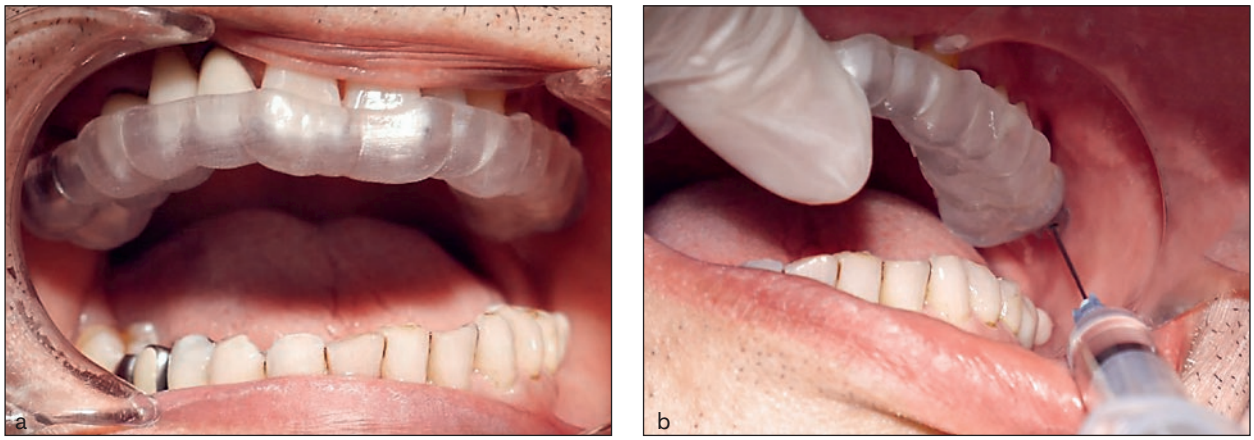

Fig 2 Sphenopalatine ganglion block with botulinum neurotoxin using the CAD/CAM injection guide. **(a)** The guide is stabilized with the help of the teeth. **(b)** The needle is inserted through the metal sleeve to the planned depth.

of the needle was adjusted from the insertion point to the target point around the sphenopalatine ganglion (Fig 1a). The distance from the metal sleeve penetration point to the target point was recorded. Furthermore, a CAD/CAM–derived injection guide was fabricated using a rapid prototyping machine (NobelGuide, Nobel Biocare) (Fig 1b).

Sphenopalatine Ganglion Block with Botulinum Neurotoxin

Botulinum neurotoxin type A (50 units; Botox, Allergan) was reconstituted with 1 mL of normal saline. After gargling with a solution of Neostelin Green 0.2% mouthwash solution (Nippon Shika Yakuhin), the guide was affixed to the patient's maxilla (Fig 2a), and a disposable needle (60 mm × 23 G, Terumo) was inserted through a metal sleeve to the analyzed depth (Figs 1a and 2b). Subsequently, the botulinum neurotoxin was slowly injected. Since the procedure was well-tolerated by the patients, local anesthesia was not necessary. The guides were cleaned with an ultrasonic cleaner before being stored to allow for re-sterilization and use for subsequent injections.

The patients received a detailed explanation of the planned treatment and publication of results and provided written informed consent. This study was carried out in accordance with the Declaration of Helsinki after obtaining the approval of the institutional review board and ethics committee of the Kyoto Medical Center (15-031).

Analysis

The severity of pain was evaluated using the VAS for pain and pain frequency. The patients were requested to keep a pain diary during the treatment, and subjective improvement was assessed using a linear self-rating scale ranging from 0% (no improvement) to 100% (complete recovery). After the treatment, the patients were asked to rate their improvement from 0% to 100%.

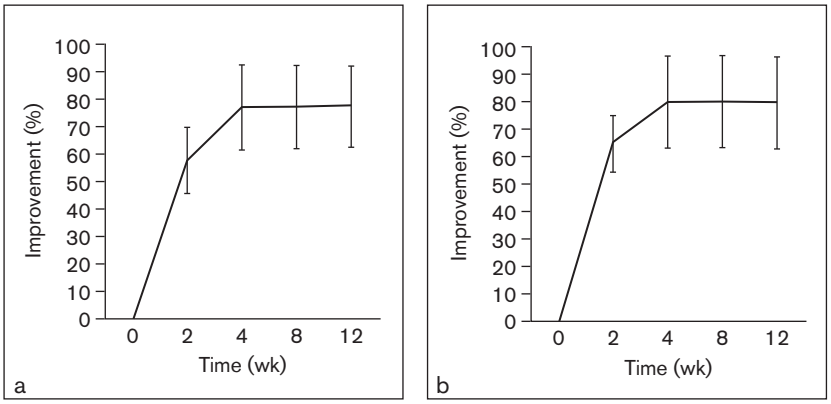

Fig 3 Changes in degree of improvement (± standard deviation) in **(a)** visual analog scale for pain intensity and **(b)** pain frequency measures 2, 4, 8, and 12 weeks after sphenopalatine ganglion block.

Table 2 Results Obtained Using the CAD/CAM Guides

Patient no.	SPG block (no. of times)	VAS (0–10)					Pain frequency (no. of times/d)					Subjective improvement (%)
		Baseline	2 wk	4 wk	8 wk	12 wk	Baseline	2 wk	4 wk	8 wk	12 wk	
1	1	6.2	2.9	1.2	1.2	1.2	10.2	4	1	1	1.1	80
2	3	8.2	4.1	3.1	3.1	2.9	12.3	3.4	2.1	2	2.1	75
3	3	7.5	2.1	0	0	0	15.7	3	0	0	0	100
4	1	9.4	6.2	4.1	3.9	3.9	38	19.4	15	15	15	60
5	2	9.2	4.5	3.3	3.2	3.3	27.5	13.3	12	12	12.1	60
6	1	8.3	3.2	2.5	2.3	2.5	18.2	6.7	5.4	5.3	5.3	70
7	2	8.1	2.6	0.8	0.9	0.9	21	5.4	0.5	0.4	0.4	90
8	1	7.8	2.9	1.5	1.5	1.5	11.5	3.6	2.8	2.7	2.7	75
9	2	8.8	4.3	2.9	2.9	3	25.4	11.6	9.3	9.1	9.1	70
10	2	7.3	1.9	0	0	0	14.2	3.5	0	0	0	95
Mean (SD)	1.8 (0.79)	8.1 (1)	3.5 (1.3)	1.9 (1.4)	1.9 (1.4)	1.9 (1.4)	19.4 (8.8)	7.5 (5.5)	4.8 (5.4)	4.8 (5.4)	4.8 (5.5)	77.5 (13.8)

After sphenopalatine ganglion (SPG) block, visual analog scale (VAS) scores and pain frequency were reduced significantly ($P < .001$) at 2, 4, 8, and 12 weeks from baseline. SD = standard deviation.

VAS and pain frequency were evaluated at baseline and at 2 weeks, 4 weeks, 8 weeks, and 12 weeks after the last botulinum neurotoxin injection. The results obtained before and after the botulinum neurotoxin therapy were compared. The degree of improvement (%) was calculated using the following formula:

$$\frac{\text{pretreatment score} - \text{posttreatment score}}{\text{pretreatment score}}$$

where 0% represents no improvement and 100% indicates complete recovery. Responders to treatment were defined as patients with ≥ 50% reduction in the mean VAS score and pain frequency from baseline to endpoint. If pain reappeared, the same treatment was repeated within at least a 12-week interval, and then the VAS score and pain frequency were recorded again. The adverse events were recorded at each visit.

Two-tailed paired *t* test was performed using SPSS version 14.0 (SPSS Japan). A value of $P < .05$ was considered statistically significant.

Results

Sphenopalatine ganglion injection of botulinum neurotoxin was performed 18 times for 10 patients. In each case, the needle was easily inserted on the first attempt, and no complications occurred.

The results of the sphenopalatine ganglion block using the guides after 2, 4, 8, and 12 weeks are summarized in Table 2. The VAS at baseline (8.1 ± 1.0) was reduced significantly (2 weeks: 3.5 ± 1.3; 4 weeks: 1.9 ± 1.4; 8 weeks: 1.9 ± 1.4; 12 weeks: 1.9 ± 1.4) ($P < .001$). Pain frequency also decreased significantly ($P < .001$) from baseline (19.4 ± 8.8 times/day) after the sphenopalatine ganglion block (2 weeks: 7.5 ± 5.5; 4 weeks: 4.8 ± 5.4; 8 weeks: 4.8 ± 5.5; 12 weeks: 4.8 ± 5.4 times/day) (Table 2). Changes in the degree of improvement of VAS scores and pain frequency are shown in Fig 3. Mean response according to VAS was 57.9% ± 12.2% at 2 weeks, 77.2% ± 15.6% at 4 weeks, 77.4% ± 15.1% at 8 weeks, and 77.5% ± 15% at 12 weeks. Mean response according to pain frequency was 64.6% ± 10.3% at 2 weeks, 79.7% ± 16.9% at 4 weeks, 80% ± 16.8% at 8 weeks, and 79.5% ± 16.8% at 12 weeks. The

mean subjective improvement was 77.5% ± 13.8% at the endpoint, and all patients responded to treatment (Table 2). Mean follow-up was 24.5 ± 8.9 months.

Discussion

The present study is the first to report on the clinical use of CAD/CAM–derived needle guides during botulinum neurotoxin block of the sphenopalatine ganglion for nonresponders to submucosal administration. The guide was very helpful for facilitating easy, precise, and safe botulinum neurotoxin injection, even for less experienced physicians.

Some authors have reported on freehand insertion of the needle into the sphenopalatine ganglion region[16,17]; but this procedure may be easy for experienced practitioners but risky when performed by inexperienced physicians. Some researchers also reported adverse effects such as bleeding, swelling, and epistaxis accompanying the procedure.[15–17] The more times the needle is inserted, the greater the risk of adverse effects.[4,18] Since botulinum neurotoxin tends to have a low diffusion gradient, it is crucial to administer a sufficient dosage to reach the desired target. By using the CAD/CAM–derived guide, the needle was easily inserted without any complications in all of the procedures performed in this study; thus, this result may be related to the single insertion using the injection guide. The injection should be minimally invasive. Although the author has not applied this guide for cluster headaches or migraines, the method could be effective for these conditions. The dental technique can also play a role in the treatment of headaches.

Botulinum neurotoxin has been investigated as a promising option in the treatment of headache syndromes. The mechanism of its analgesic effect is not entirely clear; however, it is believed to inhibit neurotransmitter release from primary sensory neurons, thereby inhibiting peripheral and possibly central sensitization.[2] Botox (Allergan) has been approved by the regulatory agency of medicines and health care products in the UK and by the US Food and Drugs Administration for prophylaxis of headaches in adults with chronic migraine. In a meta-analysis,[19] four double-blind randomized controlled trials were identified.[11–14] The studies reported that subcutaneous or submucosal injection of botulinum neurotoxin was effective for adult trigeminal neuralgia patients, and the results showed a significant benefit over placebo.[11–14] In most studies, a response was achieved in approximately 70% to 90% of patients, and mean pain intensity and frequency were reduced by approximately 50% to 90% at 4 weeks after the injection. The dose of botulinum neurotoxin used was 25 to 100 U. In the four studies, botulinum neurotoxin was administered subcutaneously, intradermally, or submucosally. Adverse effects included edema, hematoma, pain, facial asymmetry, and masticatory disturbance.[11–14] The last two complications can be related to the effects of botulinum toxin on the masseter muscle. Conversely, about 90% of patients responded by 6 months in two open-label studies on botulinum neurotoxin therapy via sphenopalatine ganglion injection.[16,17] Adverse effects included bleeding, swelling, epistaxis, and masticatory disturbance. In the present report, the author performed botulinum neurotoxin injections using the CAD/CAM guides for nonresponders to submucosal injection. All patients responded without any complications. The reasons for these results are not clearly understood; however, it has been suggested that due to the low diffusion gradient of the botulinum toxin, it might be necessary to administer adequate doses closer to the sphenopalatine ganglion. Further long-term studies are required to confirm this hypothesis.

There were limitations to this preliminary, open-label, uncontrolled study. Since the pain parameters used in this study (VAS, pain frequency, and subjective improvement) can be influenced considerably by a placebo effect, the results must be interpreted cautiously. Therefore, the placebo effect associated with the use of a novel method cannot be excluded in this study. Furthermore, as only nonresponders for trigger zone injection were enrolled in this study, the sample size was too small for a reliable statistical analysis. In the future, well-designed randomized controlled trials with larger sample sizes and longer follow-ups are required to determine the therapeutic efficacy, optimal dose, duration of effect, and indications for botulinum neurotoxin therapy.

The author has published a website concerning involuntary movements of the orofacial region.[20] Many patients, including those with trigeminal neuralgia, were referred to the author from long distances.[21] If local physicians could perform such injections using the needle guide, it would reduce the economic burden and time constraints associated with repeated long-distance health tourism. If a physician could send the patient's CT and digital surface data generated by intraoral scans, the author could prepare the guide at the patient's first visit. Subsequently, the follow-up examinations and injections could be performed by the attending physicians.

Conclusions

Even without experience, the injection guides produced using CAD/CAM are very useful for ensuring the accurate and safe administration of botulinum neurotoxin around the sphenopalatine ganglion in patients with trigeminal neuralgia.

Acknowledgments

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