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BRIEF REPORT

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Efficacy and safety profile of Onabotulinum toxin-A injection at sphenopalatine ganglion in trigeminal neuralgia: a prospective observational study

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Abstract

Introduction The sphenopalatine ganglion (SPG) plays a role in orofacial pain and headaches and is a target for pain modulation. Onabotulinum toxin-A injections have been described as a treatment for several neuropathic pain conditions. However, there is limited evidence for using this medication at the sphenopalatine ganglion for orofacial pain. The goal of this study was to investigate the effectiveness, in terms of pain intensity and frequency of pain attacks, as well as the safety of fluoroscopy-guided Onabotulinum toxin-A injection administered directly to the sphenopalatine ganglion in patients with trigeminal neuralgia.

Method Fourteen patients diagnosed with trigeminal neuralgia who either could not tolerate the side effects of oral medication or did not respond to oral medication. Onabotulinum toxin-A 40 units was injected through the sphenopalatine ganglion under fluoroscopy guidance. The primary outcome was a reduction in pain intensity (using the Numerical Rating Scale). The secondary outcome was a reduction in the frequency of pain attack and safety profile of the procedure.

Results The average pain scores and frequency of pain decreased significantly (p-value < 0.001). The mean baseline pain score before the injection was 8.15 ± 1.91. The mean pain score reduction 60 days after the procedure was 4.15 (95% CI: 2.72, 5.59; $p < 0.001$). The frequency of pain attacks also decreased significantly from 12.15 ± 8.61 times per day to 3.38 ± 2.53 times per day at 60 days after the procedure ($p < 0.001$). Complications directly associated with the procedure included hemifacial palsy (76.9%) and diplopia (7.7%). These symptoms resolved within three months after the procedure.

Conclusion Onabotulinum toxin-A injection at the SPG is effective in reducing pain symptoms in trigeminal neuralgia patients who cannot tolerate the side effects of medication or are refractory to oral medication.

Trial registration This study was retrospectively registered in the Thai Clinical Trial Registry under registration number TCTR20240908004 on 3 September 2024.

Keywords Trigeminal neuralgia, Sphenopalatine ganglion, Onabotulinum toxin-A

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Background

Trigeminal neuralgia, as defined by the International Classification of Orofacial Pain, 1st edition (ICOP-1) is characterized by unilateral, paroxysmal, brief, electric shock-like facial pains [1]. The pain usually presents unilaterally along the distribution of one or more branches of the trigeminal nerve. Trigeminal neuralgia is categorized into two types: classical trigeminal neuralgia, where there is no ongoing background pain, and trigeminal neuralgia with concomitant continuous pain, which includes persistent background pain [1]. Trigeminal neuralgia can vastly affect patients' quality of life. It can be triggered by simple daily activities such as light touching, exposure to airflow, talking, brushing teeth, or eating [2]. Trigeminal neuralgia has a reported prevalence of 0.1–0.2 per thousand individuals, with an annual incidence of 4–27 cases per hundred thousand individuals, particularly among those over 60 years of age [3, 4].

Trigeminal neuralgia is typically attributed to vascular compression of the trigeminal nerve by an intracranial blood vessel. However, about 10% of patients did not demonstrate compressing blood vessels on imaging, a condition known as idiopathic trigeminal neuralgia [5]. This ambiguity in the pathophysiology of trigeminal neuralgia makes effective treatment challenging for this debilitating condition [6]. Treatment for trigeminal neuralgia ranges from pharmacotherapy, including medications like carbamazepine, gabapentin, lamotrigine, to invasive surgical interventions such as microvascular decompression for patients who do not respond to medication or could not tolerate the side effects. Several pain interventions, such as radiofrequency treatment of the Gasserian ganglion, stereotactic radiation therapy, and microvascular decompression, have been proposed. However, studies have shown that the success of these treatment remains variable [6]. Injection of Onabotulinum toxin A (BoNTA) at the trigger zone and along the trigeminal distribution is one option for trigeminal neuralgia treatment [7, 8]. The mechanism of BoNTA for trigeminal neuralgia is hypothesized to involve the inhibition of neurotransmitter exocytosis in the sensory pathway [9].

The sphenopalatine ganglion (SPG), located in pterygopalatine fossa, gives rise to multiple nerves, and is associated with the maxillary branch of the trigeminal nerve. It is a potential target for BoNTA treatment in patients with trigeminal neuralgia. Additionally, the SPG is the largest parasympathetic ganglion and is believed to play a role in the sensitization of intracranial nociceptors [10, 11]. Although the precise mechanisms linking the SPG to trigeminal neuralgia are not fully understood, its significant role in the transmission and modulation of pain signals in the trigeminal nerve highlights its potential as a therapeutic target for managing this condition [12]. BoNTA injection at SPG is a minimally invasive procedure associated with fewer complications compared to surgical interventions. This approach may serve as an alternative treatment for high-risk patients who are not suitable candidates for surgery or for those who are intolerant of or refractory to pharmacological treatments.

The aim of this study is to evaluate the efficacy, in terms of pain intensity and frequency of pain attacks, as well as the safety profile of BoNTA injections at the SPG in patients with trigeminal neuralgia who failed conventional medication therapy or could not tolerate systemic side effects. Our hypothesis is that BoNTA can significantly reduce both pain intensity and the frequency of attacks following the procedure.

Methods

Study designs and patient selection

This is an open-label prospective observational study recruited 15 patients diagnosed with trigeminal neuralgia according to ICOP-1 criteria between July 2023 and February 2024 at King Chulalongkorn Memorial Hospital in Bangkok, Thailand. All patients underwent magnetic resonance imaging (MRI) of the brain and cranial nerves to identify the etiology of trigeminal neuralgia. Patients were referred for neurosurgical consultation if the MRI showed neurovascular compression or secondary causes, such as tumors. Patients without pathological findings on MRI, those unsuitable for microvascular decompression (MVD), and those who did not benefit from medication or could not tolerate its side effects were enrolled in the study.

The inclusion criteria were as follows: age 18–85 years and a diagnosis of trigeminal neuralgia confirmed by both a neurologist and a pain specialist according to the ICOP-1 criteria; no benefits or cannot tolerate side effects from medications adjustment for at least 3 months.

The exclusion criteria included coagulopathy, infection in the facial area, pregnancy, allergy to contrast media or BoNTA, presence of head and neck cancer, and patients who are unable to communicate to complete the pain questionnaire assessment.

Ethical approval

This study was approved by the institutional review board of the Faculty of Medicine, Chulalongkorn University, Thailand (Certificate of Full Board Approval No. 1132/2023), and registered in the Thai Clinical Trial Registry (registration number TCTR20240908004). Written informed consent was obtained from all patients.

Procedure

Patients scheduled to receive BoNTA injections into the sphenopalatine ganglion under fluoroscopic guidance were treated in the supine position. Vital signs were

monitored according to American Society of Anesthesiologists (ASA) standards throughout the procedure. Local anesthetic, 2% lidocaine, was used to anesthetize the skin and subcutaneous tissue, with no sedation administered. The pterygopalatine fossa was identified on a lateral fluoroscopic image. A 22-gague spinal needle was then inserted and slowly advanced toward the SPG. The target location for the needle tip was the lateral fossa of the nasal cavity at the level of the middle turbinate, as seen in the anteroposterior fluoroscopic image where the SPG is located. The final, correct needle position was confirmed with a radiocontrast agent. Onabotulinum toxin type A (Allergan®) was prepared with 1 mL of normal saline, and 40 units (0.4 mL) of BoNTA were then injected into the SPG.

After the procedure, the patient was observed in the recovery room. The assigned nurse monitored and recorded the patient's vital signs and any potential complications for a period of two hours post-procedure. All analgesic medications were continued in the same regimen as before the procedure.

Outcomes measurement

The primary outcome is to assess the efficacy of BoNTA injection into the SPG by measuring post-procedure pain intensity using the numeric rating scale (NRS). Patient were asked to rate their pain intensity by selecting a single number on a scale from zero ("no pain") to ten ("worst pain") [13].

The secondary outcomes are to examine the frequency of pain episodes and safety profile of the procedure.

After the procedure, patients were instructed to record the frequency and pain scores for each instance of pain in a pain diary, as well as any complications that occurred after the procedure. The records were reviewed and verified at each follow-up visit. Follow-ups took place at the pain clinic or via telephone every 10 days for up to 60 days post-procedure.

Statistical analysis

In this study, we used G*power software, version 3.1.9.7, to calculate the required sample size using F-tests and ANOVA for repeated measures within factors. Based on an effect size of 0.399, a Type I error rate of 0.05, and a test power of 0.9, 13 patients was required [14].

Patient's demographics, pain characteristics, and medication use information were summarized as number (percentage) for categorical variables and median (interquartile range [IQR]) for continuous data.

Comparison of pain scores (NRS) and pain frequency per day before and after treatment procedure was tested using paired t-tests or Wilcoxon signed-rank tests, depending on the appropriateness of the data. Additionally, statistical analysis of variance (ANOVA), repeated measures ANOVA, repeated measures ANCOVA, generalized estimating equation (GEE), or generalized linear mixed model (GLMM) would be used to analyze changes in pain scores (NRS) and pain frequency per day throughout the study period, based on the appropriateness of the data.

Potential procedure-related complications, including facial blood vessel injury, postoperative infections, and neurological complications, were reported as frequencies and percentages. All data analyses were conducted using IBM SPSS Statistics for Windows, Version 28.0, with statistical significance set at $p<0.05$.

Results

We enrolled 14 patients in this study. One patient was excluded due to the inability to perform the procedure because of difficulty accessing the sphenopalatine fossa with the needle. Therefore, 13 patients were analyzed. The demographic data, characteristics of trigeminal neuralgia and analgesic medication are shown in Table 1. The median age was 60 [53, 62] and 76.9% were female. Among the patients, 61.5% had symptoms in the maxillary (V2) branch, while the others had symptoms in both the maxillary (V2) and the mandibular (V3) branches. Gabapentinoid and carbamazepine were the most prescribed medications, 84.6% and 76.9% respectively.

BoNTA injection into the sphenopalatine ganglion using fluoroscopy-guided techniques demonstrated significant pain relief in patients with trigeminal neuralgia. The baseline pain score before the procedure was 8.15 ± 1.91. Following the injection, average pain scores significantly decreased to 3.92 ± 2.50, 3.77 ± 2.89, and 4.00 ± 3.24 on days 10, 30, and 60, respectively. These reductions in pain scores were statistically significant ($p<0.001$) compared to baseline (Table 2; Fig. 1).

Additionally, the frequency of pain attack episodes decreased significantly after BoNTA injections compared to baseline ($p<0.001$). The baseline mean frequency of pain attacks before the procedure was 12.15 ± 8.61 times per day. Following the intervention, the mean frequency decreased to 4.31 ± 2.69, 3.54 ± 3.13, and 3.38 ± 2.53 episodes per day on days 10, 30, and 60, respectively (Table 3; Fig. 2).

Regarding the safety profile of the procedure, 10 patients (76.9%) reported hemifacial palsy on the side of the intervention, and 1 patient (7.7%) reported double vision at the first follow-up visit. All patients found these side effects tolerable. They were monitored closely and reported complete resolution of symptoms within three months post-procedure, while the analgesic effect persisted.

Table 1 Demographics data and clinical characteristics of the patients

Characteristic	Value, *n* (%) or median [IQR]
Gender	
Male	3 (23.1)
Female	10 (76.9)
Age (years)	60 [53,62]
Weight (kg)	56 [50,62]
Body mass index (kg/m^2)	22.2 [20.8, 24.5]
Duration of pain since diagnosis (months)	48 [36,60]
Affected side	
Left	4 (30.8)
Right	9 (69.2)
Affected trigeminal branch	
V2 branch	8 (61.5)
V2 + V3 branches	5 (38.5)
Trigger area	
Intra oral	9 (69.2)
Zygomatic area	3 (23.1)
Cheek	4 (30.8)
Analgesic use history	
Carbamazepine	10 (76.9)
Gabapentinoids	11 (84.6)
Lamotrigine	1 (7.7)
Nortriptyline	1 (7.7)
Side Effects from medication	
Nausea/vomiting	7 (53.8)
Drug allergy	2 (15.4)
Sleepiness	2 (15.4)
Dizziness	6 (46.2)

IQR = interquartile range, V2 = maxillary branch of trigeminal nerve, V3 = mandibular branch of trigeminal nerve

Table 2 Efficacy of Onabotulinum toxin-A injection into the sphenopalatine ganglion on pain intensity

Time (days)	Pain scores, mean ± SD	Change in pain scores from baseline (95% CI)	*p*-value
Pre-procedure	**8.15 ± 1.91**	**Reference**	
10	3.92 ± 2.50	−4.23 (-5.37, -3.10)	< 0.001
20	3.85 ± 2.27	−4.31 (-5.45, -3.17)	< 0.001
30	3.77 ± 2.89	−4.38 (-5.81, -2.95)	< 0.001
40	3.77 ± 2.62	−4.38 (-5.48, -3.29)	< 0.001
50	4.46 ± 2.88	−3.69 (-5.07, -2.32)	< 0.001
60	4.00 ± 3.24	−4.15 (-5.59, -2.72)	< 0.001

SD = standard deviation, 95% CI = 95% confidence interval

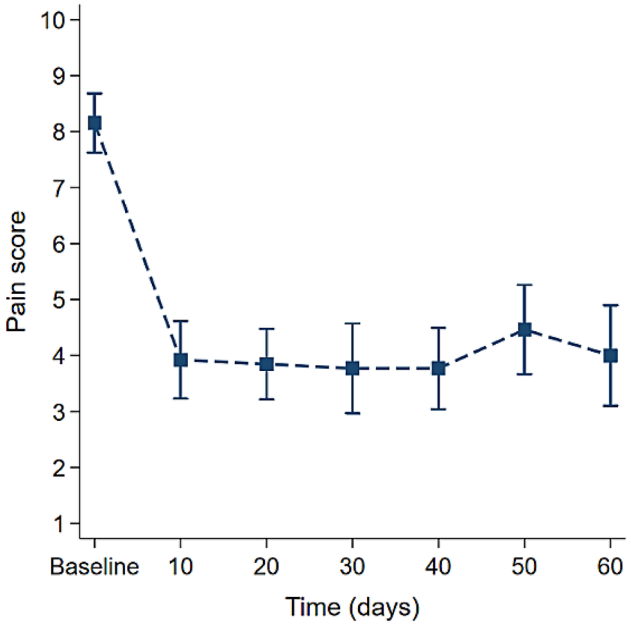

Fig. 1 This graph illustrates the reduction in pain intensity following Onabotulinum toxin-A injection into the sphenopalatine ganglion

Discussion

Our study demonstrates that fluoroscopic-guided BoNTA injections targeting the sphenopalatine ganglion can significantly reduce pain intensity and attack frequency in patients with trigeminal neuralgia. BoNTA injections are known to be effective in treating chronic migraine [15]; however, evidence supporting the efficacy of this treatment for trigeminal neuralgia remains limited. In 2016, Morra et al. conducted a systematic review and meta-analysis, concluding that BoNTA may be an effective treatment for trigeminal neuralgia. They found that the mean VAS score at two months post-BoNTA injection was significantly lower than the baseline (-2.47,

Table 3 Efficacy of Onabotulinum toxin-A injection into the sphenopalatine ganglion on pain frequency

Time (days)	Pain frequency episodes per day, mean ± SD	Change in pain frequency episodes per day from baseline (95% CI)	*p*-value
Pre-procedure	**12.15 ± 8.61**	**Reference**	
10	4.31 ± 2.69	-7.85 (-12.68, -3.01)	< 0.001
20	4.15 ± 3.89	-8.00 (-11.97, -4.03)	< 0.001
30	3.54 ± 3.13	-8.62 (-12.76, -4.47)	< 0.001
40	4.23 ± 4.04	-7.92 (-11.53, -4.32)	< 0.001
50	4.08 ± 3.73	-8.08 (-11.55, -4.60)	< 0.001
60	3.38 ± 2.53	-8.77 (-13.02, -4.52)	< 0.001

SD = standard deviation, 95% CI = 95% confidence interval

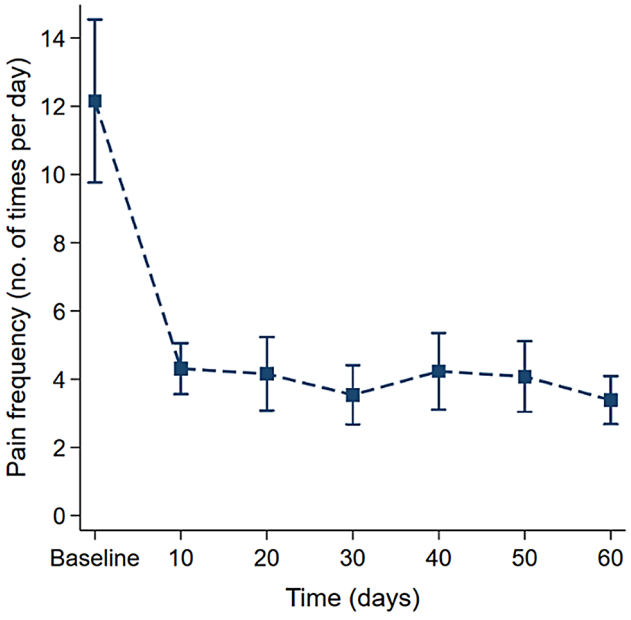

Fig. 2 This graph demonstrates the reduction in pain frequency per day after the intervention

95%CI [-3.96, -0.99], $p = 0.001$][16]. In contrast to our study, the studies included in this systematic review administered BoNTA either intradermally or subcutaneously, with none delivering the medication directly into the SPG, as in our approach, which demonstrated a greater reduction in pain intensity two months post-procedure.

Yoshida et al. described a technique using a customized computer-aided design/computer-assisted manufacturing (CAD/CAM) needle guide to administer botulinum toxin via intraoral routes directly to the SPG. Similar to our study, they found that both pain intensity and the frequency of pain attacks were significantly reduced compared to baseline [16]. Crespi et al. reported a pilot study on the percutaneous injection of BoNTA directly into the SPG using a specialized injection device, guided by surgical CT and/or MRI navigation in patients with trigeminal neuralgia. Although their study did not show a significant reduction in the number of daily pain attacks, it did demonstrate a significant decrease in pain attack intensity and in concomitant persistent pain 5–8 weeks post-procedure [17]. We believe that our study is the first to describe percutaneous fluoroscopic-guided BoNTA injection directly into the SPG. This technique is familiar to most pain interventionists, easy to perform, and does not require specialized equipment. It also allows for confirmation of correct needle placement within the SPG by injecting contrast media before delivering the medication, and our study demonstrate that this technique is well-tolerated and provided significant pain reduction in both intensity and frequency of attacks.

The pathophysiology of trigeminal neuralgia is thought to be multifactorial, involving central and peripheral sensitization, hyperexcitability neuronal state, and widespread neural plasticity change [18]. Although, the exact link between SPG and trigeminal neuralgia has not been establish, recent evidence supports that modulating pain signal at the SPG, which alters central and peripheral sensitization in the pain pathway, can be beneficial for many painful craniofacial conditions [11, 16]. Several pilot studies have explored the use of BoNTA injection directly into the SPG for various craniofacial pain conditions, including chronic cluster headache, persistent idiopathic facial pain, and intractable chronic migraine. However, the results have been inconsistent, likely due to small sample size and differences in the pathophysiology of these complex craniofacial pain conditions [19–22].

The pterygopalatine fossa houses the SPG, the largest peripheral parasympathetic ganglion, along with some sympathetic innervation [10]. The maxillary branch of the trigeminal nerve also travels through this fossa [10]. This multi-innervation, involving both the somatic and autonomic nervous systems, makes the SPG a compelling target for intervention in conditions with complex and unclear pathophysiology, such as trigeminal neuralgia [16].

While the exact mechanism of BoNTA in pain reduction is not yet fully understood, it is believed that the medication inhibits the release of neurotransmitters and algogenic neuropeptides, such as substance P, from primary sensory neurons and modulates pain signals [9, 22]. Moreover, studies have shown that BoNTA can undergo intracellular trafficking either retrograde or anterograde along the nerve through the microtubule [23, 24]. This phenomenon may explain the observation in our study that the patient who had symptoms in the maxillary branch (V2) also benefited from this intervention.

There is no consensus on the recommended dose of BoNTA for trigeminal neuralgia, with dose reported in the existing literature ranging from 25 to 200 units [22]. Zhang et al. reported similar short-term efficacy between low-dose (25 units) and high-dose (75 units) BoNTA

injections administered intradermally and/or via the oral submucosa for trigeminal neuralgia [8]. Previous pilot studies that directly injected BoNTA into the SPG for craniofacial pain conditions reported doses ranging from 25 to 50 units. While the results remain inconsistent, studies using 50 units of BoNTA tended to show more positive outcomes [17, 19–21].

In terms of safety profile, transient facial palsy and diplopia were observed in our study. Hemifacial palsy was also observed in the previous studies, particularly in those where BoNTA was injected submucosally or transdermally [25]. We suspect that these adverse effects arise from the backflow of the medication through the needle, leading to its spread to the facial muscles and resulting in facial muscle weakness. Diplopia may occur due to the medication spreading to the orbit through connections from the pterygopalatine fossa. We speculate that adjusting the dose and volume of the BoNTA injectate might reduce the prevalence of these adverse effects. Unlike traditional SPG radiofrequency treatment, we did not observe facial paresthesia, facial swelling, hematoma, or epistaxis in our study [12]. This is likely because this technique requires less needle manipulation and utilizes a smaller needle to navigate through such a small and dense space.

This study has several limitations. First, it is an observational study with a small sample size. Although the reductions in pain intensity and attack frequency were statistically significant, the effect size used to calculate our sample size was only weak to moderate (Cohen's effect size=0.399). Second, our primary objective was to demonstrate the efficacy of direct BoNTA injection into the SPG for reducing pain intensity. We did not assess improvements in other aspects of pain-related burden or quality of life following the procedure. Lastly, our follow-up period was limited to 60 days, so long-term outcomes were not explored.

Further research, including larger-scale, long-term follow-up randomized controlled trials, is needed to confirm the efficacy of this potentially beneficial intervention. Additionally, studies to determine the optimal dose and concentration of BoNTA to maximize benefits while minimizing potential complications would be valuable.

Conclusion

Botulinum toxin type A injections directly into the sphenopalatine ganglion by fluoroscopic technique can significantly reduce pain intensity and frequency of attack in patients with trigeminal neuralgia who cannot tolerate or do not benefit from medications. However, common side effects, such as transient facial palsy, should be discussed with patients before the procedure.

Abbreviations

SPG	Sphenopalatine ganglion
BoNTA	Onabotulinum toxin A
MRI	Magnetic resonance imaging
NRS	Numeric rating scale
SD	Standard deviation
IQR	Interquartile range

Acknowledgements

Not applicable.

Author contributions

All authors conceptualized the study. MT, PA, PT designed the study protocol and recruited the patients. MT and PT performed the procedure and acquired the data. MT, PT and CT analyzed the data, interpreted the result, created the intellectual content, figures, and tables. All authors draft the manuscript. CT, PA, and MT revised the manuscript for the intellectual content. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Approval was obtained from the ethics committee of Chulalongkorn University (IRB no 0270/66, Certificate of full board approval no. 1132/2023). The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all the patients before participating in the study.

Competing interests

The authors declare no competing interests.

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