OnabotulinumtoxinA Injection of the Sphenopalatine Ganglion for Treating Refractory Primary Headache Disorders and Neuropathic Facial Pain: Real World Data

Logghe Y.[1], Jerjir A.[1], D'hondt N.[1], Smet I.[1], Jerjir N.[2], Devos M.[1], Van Buyten J.-P.[1]

[1]Multidisciplinary Pain Center, VITAZ, Sint-Niklaas, Belgium; [2]Department of Radiology, VITAZ, Sint-Niklaas, Belgium.

Corresponding author: Yannick Logghe, MD, Multidisciplinary Pain Center VITAZ, Moerlandstraat 1, 9100 Sint-Niklaas, Belgium. Tel.: +32 478 479 443 - E-mail: logghe.yannick@hotmail.com

Abstract

Background: **OnabotulinumtoxinA (BTA) injections targeting the sphenopalatine ganglion (SPG) have been used in patients with refractory chronic cluster headache and idiopathic facial pain, causing a neuronal block. This study evaluated real world data on the effectiveness of BTA injections targeting the SPG in treating refractory primary headache disorders and neuropathic facial pain.**

Method: **We conducted a retrospective observational cohort study of patients who underwent treatment with a BTA injection of the SPG. Primary outcome focused on the impact on the number of headache attacks and pain intensity on an 11-point Numeric Rating Scale (NRS). As secondary outcomes, quality of life objectified by the Headache Impact Test-6 (HIT-6) questionnaire, patient satisfaction and Patient Global Impression of Change (PGIC) were analyzed.**

Results: **A total of 43 patients received treatment. In primary headache disorders, NRS declined from 7.7 points baseline to 5.0 (p = 0.017) and attack frequency from 64 attacks per month baseline to 24 based on 17 patients. Analgetic consumption declined in 50% of patients. For facial pain disorders, NRS improved from 6.5 baseline to 4.5 (p = 0.028) based on 10 patients. Better responses on NRS were seen when the needle tip was precisely positioned on the reflection of the lateral wall of the nasal cavity.**

Conclusion: **This real world study has shown that BTA injections have a favorable effect on pain sensation and quality of life in the treatment of primary headache disorders.**

Keywords: **Sphenopalatine ganglion, botulinum toxin, trigeminal autonomic cephalalgias, facial pain.**

Introduction

The sphenopalatine ganglion, also known as the pterygopalatine ganglion, nasal ganglion, or Meckel's ganglion, is located in the sphenopalatine fossa, posterior to the lateral insertion of the middle nasal concha and covered by a thin layer of mucosa. It is known as the largest parasympathetic ganglion. The ganglion includes parasympathetic, sympathetic, and somatosensory nerve fibers[1-5].

Role in primary headache disorders

The sphenopalatine ganglion (SPG) plays an important role in a group of primary headache disorders known as trigeminal autonomic cephalalgias (TAC). Primary headache is defined as a headache not secondary to another disorder[6]. TAC is subdivided into five primary headache syndromes, namely cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks, hemicrania continua and probable trigeminal autonomic cephalalgias. The SPG plays a role in the autonomic symptoms seen in TAC through activation of parasympathetic and sympathetic pathways. By targeting the SPG, blockage is thought to relieve TACs.

Interaction with facial pain

The direct connection of the maxillary nerve to the SPG explains why a blockage of the SPG might be helpful in treating pain attributed to a lesion or disease of the trigeminal nerve[2]. The role of the SPG in the pathogenesis of trigeminal neuralgia is not clear. Facial pain has been classified according to the International Classification of Headache Disorders (ICHD-3), based on their

distinct clinical characteristics and etiology[6]. The clinical manifestations of neuropathic facial pain are a tingling, burning, electricity-like pain with allodynia and/or hyperalgesia.

Interventional treatment

Because the SPG plays a central role in the transmission of signals, it is a therapeutic target of interest. There are three main types of interventions on the SPG commonly used: chemical nerve block or lysis, radiofrequency ablation and neurostimulation. Lidocaine application to the SPG had shown to be effective in the treatment of acute cluster headache, but the effect does not last long[7]. Irreversible chemical blockage is performed by alcohol injection, with good results in idiopathic facial pain and cluster headache. However, high recurrence rates are noted, and higher doses alcohol may diffuse, with possible severe side effects[8].

Radiofrequency ablation of the SPG may interrupt the parasympathetic pathway within the ganglion[9]. Radiofrequency ablation has been shown to be effective in episodic cluster headache that does not respond to pharmacological treatment. However, these interventional therapies are not yet recommended, since their safety and efficacy are still being investigated in randomized clinical trials[10]. The ablation of the SPG is thought to work by blocking the parasympathetic fibers, which leads to cerebral vasodilatation through the release of vasoactive intestinal peptide (VIP). The return to normal diameter of the vasculature should relieve the headache[11].

Because the parasympathetic synapse uses acetylcholine as a neurotransmitter, onabotulinumtoxinA (BTA), an inhibitor of acetylcholine release, can potentially cause a neural block. The use of BTA at the SPG causing a neural block has been shown to be safe in the study performed by Bratbak[12]. They treated ten patients with intractable chronic cluster headache with BTA injections at the SPG. A dose of 25IU or 50IU was safely used. No clear difference in adverse events was seen between both groups. As a secondary outcome, headache attack frequency and attack intensity were reduced. Average response lasted 4.6 months. In another study by Bratbak, the infrazygomatic (percutaneous) approach was performed on patients with intractable chronic migraine[13]. All patients were treated bilaterally. A significant reduction in headache days was seen. A recent retrospective analysis in safety and efficacy of BTA injections towards the sphenopalatine ganglion in 31 patients with refractory chronic cluster headache showed a 50% responder proportion of 69% after treatment[14]. Further evidence is limited, by the small size of studies and the lack of control groups for comparison, but it has been shown that off-label use of BTA should be considered in cluster headache. Further prospective randomized clinical trials are justifiable.

Objective

The primary outcome of this retrospective observational cohort study was to evaluate the effectiveness of a sphenopalatine ganglion onabotulinumtoxinA block in the treatment of refractory primary headache disorders and craniofacial pains. As secondary outcomes, safety profile, change in analgesic consumption, patients' satisfaction, patients' global impression of change (PGIC) and employment status have been analyzed in both patient groups. The impact of their headaches on daily life has been analyzed in patients with refractory primary headache disorders. Tertiary, we examined whether final needle tip position before BTA injection had an influence on outcome.

Methods

All patients with refractory primary headache and craniofacial pains who underwent a treatment with an onabotulinumtoxinA injection (Xeomeen® Merz Pharma) of the SPG in VITAZ between May 2020 and March 2023 were included in a retrospective observational cohort study. As part of the clinical practice, baseline data was noted before treatment. The following data has been gathered during follow-up consultations as part of normal clinical practice: number of headache attacks, pain intensity (11-point Numeric Rating Scale (NRS)), time before effect after treatment (in days), duration of pain-free interval asked in days before return of symptoms, autonomic symptoms, (acute) treatment if applicable, quality of life objectified by the Headache Impact Test-6 (HIT-6) questionnaire[15], patient satisfaction, Patient Global Impression of Change (7 point scale)[16], days of sick leave and possible side effects. All patients received a follow-up visit between 4 to 8 weeks post-procedure (clinical practice). Subsequent treatment(s) and visit(s) to the pain center were also added to the analysis.

All patients who received a onabotulinumtoxinA injection for the treatment of refractory primary headaches and neuropathic facial pain according to the ICHD-3 were included. The following exclusion criteria were applied: patients who received onabotulinumtoxinA injections of the SPG for causes other than refractory primary headaches and

neuropathic facial pain (spasticity e causa ignota).

An infrazygomatic approach under fluoroscopic guidance to reach the SPG was performed in all patients. The patient was placed in supine position. We rotated the C-arm until both rami of the mandible were superimposed on each other, to obtain accurate visualization of the pterygomaxillary fissure in lateral view. A line was drawn overlying the pterygomaxillary fissure, using a marker and metal ruler over the skin in this position. Then, we palpated along the line below the zygomatic arch and identified the mandibular notch, the entry point[17]. A 88mm, 22G Spinocan® (Braun®) needle was introduced and directed slightly cranially and ventrally. The tip was advanced through the pterygomaxillary fissure into the pterygopalatine fossa. Next, an antero-posterior (AP) view of the skull was obtained and the needle was advanced with its tip adjacent to the lateral wall of the nasal cavity (Figure 1). Patients received a dose of 25IU or 50IU BTA in 1ml of normal saline. Since this was a pilot study, initial patients were treated with a dose of 25IU BTA. As literature showed it was safe to use both doses, subsequent patients were treated with 50IU BTA[12]. All injections were unilateral. Patients with bilateral symptoms were treated on the most disabling side.

We analyzed whether variant needle tip positions in AP view and lateral view (LAT) had an impact on the change in the following scores: NRS, HIT-6, number of attacks per month and number of pain days. For this the sphenopalatine fossa was divided in five different zones according to AP as shown in Figure 1. In the lateral view, the sphenopalatine fossa was divided equally in a cranial, medial and caudal zone. The analysis was made for primary disorder headaches, as well as neuropathic facial pain.

All patients were informed and signed an informed consent form regarding the off-label use of botulinum toxin. The procedure and implications regarding off-label use were also discussed in clinic before the procedure was scheduled. The study protocol was approved on May 11, 2023 by the local ethics committee of VITAZ, Moerlandstraat 1, 9100 Sint-Niklaas, Belgium, EC 23018 and signed by chairman G. De la Meilleure, MD. After approval the data was extracted from the medical records, collected from routine clinical practice. Data was pseudonymized, with the use of a unique patient number for identification.

Statistical analysis was performed based on nonparametric statistics that are suitable for small sample analysis. The Wilcoxon matched-pairs signed ranks test (hereafter referred to as Wilcoxon test) and sign test were used for measuring the efficacy of the treatment. Correlation between satisfaction and PGIC was demonstrated with the Spearman Rank Correlation Coefficient. The Kolmogorov-Smirnov one-sample was used to find correlation between changes in NRS and medication use. The level of significance has been set at α=5% for all tests. The probability of occurrence under the null hypothesis H0 was one-tailed for all tests,

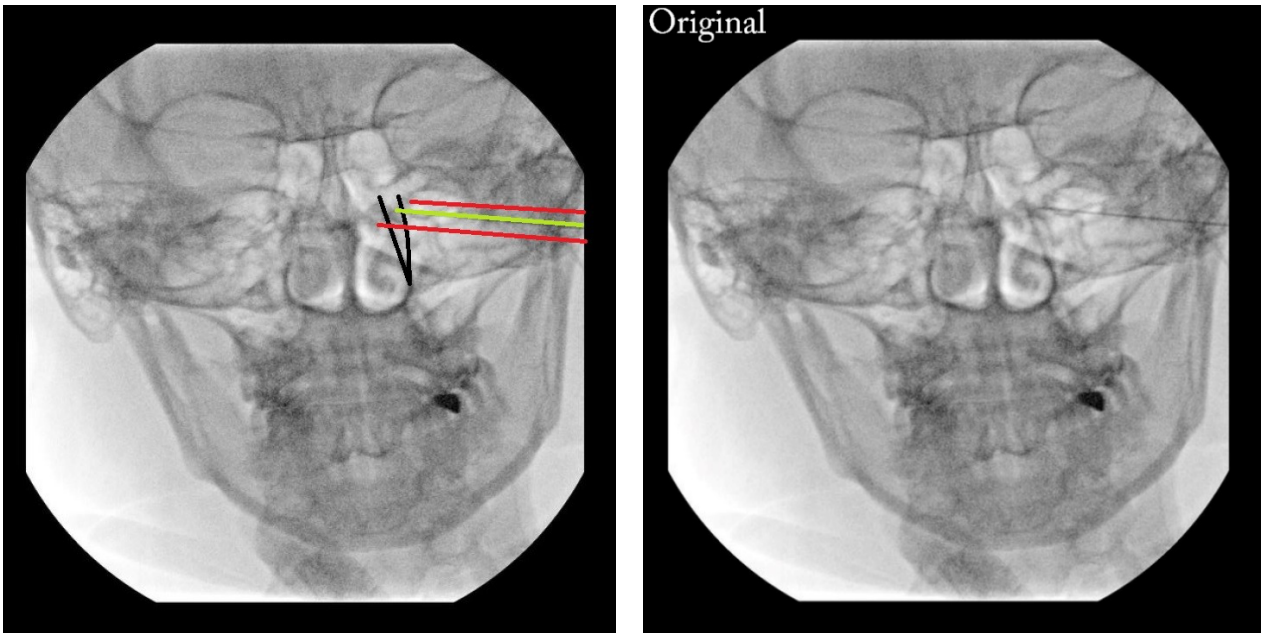

Fig. 1 — AP view with needle tip in sphenopalatine fossa. Green line: target needle position. Red lines: aberrant needle tip positions seen in some cases. The medial black line is a reflection of the lateral wall of the nasal cavity. The lateral black line is a second orientation marker in clinical practice and most likely corresponds to the reflection of the medial or lateral pterygoid plate, but is not identified in all cases. Both lines divide the sphenopalatine fossa in 5 zones: before the medial line, on the medial line, between the medial and lateral line on the lateral line and behind the lateral line.

except for the Kolmogorov-Smirnov one-sample test, where it was two-tailed. To limit interference of missing data, not all patients could be included for measuring the effectiveness of the treatment, due to the real-life character of the retrospective study. For each statistical test, we have excluded all patients for whom relevant data were missing or who did not show for follow-up. To strengthen the statistical results, the treatment effects were analyzed with regards to various variables as earlier defined. Statistical analysis of needle tip positioning was based on the linear regression technique, called 'ordinary least square' analysis (OLS).

Results

Between May 2020 and March 2023, 43 patients received a BTA treatment. 27 patients were treated for a refractory primary headache disorder and 16 patients for neuropathic facial pain (Table I). Demographic data is shown in Table II.

Primary headache disorders

After treatment, all patients with primary headache disorders were invited to a follow-up consultation 2 to 10 weeks (mean 5.7 weeks) after treatment.

The NRS before and after treatment was available for 17 out of the 27 patients. Both the Wilcoxon test and the less powerful sign tests (sample of 17 patients), showed a statistically significant positive impact of the treatment ($p = 0.017$), as measured by a change of NRS. The mean NRS improved from 7.7 to 5.0 after treatment. Four patients showed a reduction of NRS of more than 50% at follow-up. Analgesic consumption declined in 50% of patients. Based on statistical analysis, there were strong indications that a decrease in NRS correlated with a decrease in the use of prophylactic and rescue medication. In addition, results from the HIT-6 survey showed a statistically significant positive impact on daily life ($p = 0.010$) at first follow-up for 17 patients whose HIT-6 data was complete.

Finally, data on attack frequency was completed in 15 patients and showed a statistically significant positive impact of treatment at follow-up ($p = 0.007$). A similar trend was seen in number of monthly headache days completed in 16 patients, which showed a decrease or did not change. Effects of treatment on primary headache disorders are shown in Table III. A clear improvement in patient

Table I. — Indications for BTA.

Diagnosis	Number of patients
Refractory primary headache disorders	27
Chronic migraine	4
Episodic cluster headache	7
Chronic cluster headache	13
Atypical cluster headache	1
Hemicrania continua with dysautonomia	1
Short-lasting unilateral neuralgiform headache attacks	1
Neuropathic facial pain	16
Trigeminal neuropathy	6
Essential trigeminal neuralgia	1
Atypical trigeminal neuropathy	1
Atypical facial pain	4
Atypical facial pain (with dysautonomia)	3
Postherpetic neuralgia	1

Table II. — Demographic data and pain characteristics: primary headache disorders and neuropathic facial pain.

Primary headache disorders	All patients (n= 27)
Number of females / males	15 / 12
Median age, years (range)	47 (19 - 76)
Pain location bilateral / right / left	4 / 10 / 13
Mean years since onset of pain (range)	12 (0 - 47)
BTA dose 25IU / 50IU	6 / 21
Neuropathic facial pain	All patients (n= 16)
Number of females / males	8 / 8
Median age, years (range)	55 (23 - 85)
Pain location bilateral / right / left	2 / 7 / 7
Mean years since onset of neuropathic facial pain (range)	5 (1 – 13)
BTA dose 25IU / 50IU	4 / 12

Table III. — Effect of treatment on primary headache disorders.

Baseline	Mean (SD) Median (range)	Follow-up	Mean (SD) Median (range)	Difference	Wilcoxon test (T) (one-tailed α=5%)
NRS (n = 17)	7.7 (2.0) 8 (3-10)	NRS (n = 17)	5.0 (3.1) 6 (0-10)	-2.7 -2	T=12.5 < 26 (p = 0.017)
HIT-6 (n = 17)	69.7 (4.2) 69 (64-78)	HIT-6 (n = 17)	62.7 (11.1) 63 (36-78)	-7.0 -6	T=18.5 < 30 (p = 0.010)
Number of attacks per month (n=15)	64 (53) 45 (10-217)	Number of attacks per month (n=15)	24 (30) 10 (0-100)	-40 -35	T=11.5 < 21 (p = 0.007)
Number of headache days per month (n = 16)	30 (3) 31 (21-31)	Number of headache days per month (n = 16)	20 (13) 25 (0-31)	-10 -6	(*)
(*) As the number of headache days in each patient either decreased or remains unchanged, there was no purpose in performing the Wilcoxon test.					

satisfaction and PGIC was noted. 73% of patients were satisfied or very satisfied on follow-up and 63% of patients showed improvement. We also found a significant correlation between satisfaction and PGIC.

The subgroup with episodic cluster headache patients showed a significantly better response to treatment based on a mean change in NRS of -6,8 relative to the other categories mean change in NRS -0,6 (p = 0.001).

Table IV displays that the mean time before effect of BTA treatment was 11 days based on 9 patients, 2 patients showed immediate effect and 8 patients showed no effect at all. Unfortunately, data was missing in 10 patients. The mean time before recurrence of symptoms was 66 days based on 4 patients, although 6 patients showed ongoing effect at follow-up consultations. Again, data was missing in 9 patients.

Neuropathic Facial pain

Sixteen patients received BTA treatment of the SPG for neuropathic facial pain. Patients were invited to a follow-up consultation after 7.1 weeks on average (range 5-13 weeks) following treatment. Based on data of 10 patients with neuropathic facial pain, the NRS improved from 6.5 to 4.5 after treatment, a statistically significant impact of treatment (p = 0.028). Change in medication usage could not be analyzed due to missing data. PGIC score was available for 10 patients. We concluded that 7 patients reported no change, whereas the other 3 reported an improvement.

Side effects

Temporary facial paresis was seen in 3 patients, and diplopia was reported in 5 patients. All symptoms spontaneously resolved after 3 to 7 weeks.

Needle positioning during procedure

Although the lateral wall of the nasal cavity was the intended target during practice, minor variations in needle tip positioning were noted. We determined the correlation between anatomical needle positioning and effect of treatment.

We considered different linear regression models, in which the change in the relevant score between two measurement times appeared as the dependent variable and the position of the needle in AP and LAT as independent variables. Regression results suggested strong indications that better results were obtained when the final needle tip position was exactly on the medial line which serves as a reflection of the lateral wall of the nasal cavity. This result was independent according to the subgroups i.e. no subgroups were overrepresented in a specific area. According to T-student tests, the regression parameter corresponding to AP was significantly different from zero in NRS (p = 0.003 < 0.025 - two tailed). In lateral view, no superior position could be noted (p = 0.059 > 0.025 - two-tailed). Similar

Table IV. — Time-course effect of treatment and work situation during follow-up.

Time before effect (days)	11 days (n=9) No effect: n=8 Missing data: n=10
Mean time before return of symptoms (days)	66 days (n =4) Ongoing effect: n= 6 No effect: n=8 Missing data: n=9
Work situation	No change (n = 24) Missing data: n =3

conclusions concerning AP view could be taken for HIT-6 ($p = 0.005$), number of attacks per month ($p = 0.010$) and number of pain days ($p = 0.019$).

Discussion

Real world data is important to build evidence on the efficacy and safety of this novel treatment in highly refractory patients. Recent studies have primarily been conducted on refractory chronic cluster headache and refractory chronic migraine. The present study based on real world data showed the effect of BTA injections in patients with all kinds of refractory primary headache disorders and neuropathic facial pains. This explorative study shows the effectiveness of BTA as primary outcome. A significant reduction in NRS, number of attacks per month and number of headache days per month were observed, which correlated with a decrease in analgesic consumption. In addition, a significant reduction in HIT-6 scores along with an improvement in satisfaction and PGIC in patients with primary headache disorders were reported. Treatment in the group with refractory episodic cluster headache showed a much higher response on therapy, compared to other primary headache disorders, along with marked improvement in patient satisfaction and PGIC. This difference could be due to the fact that spontaneous remission in patients with episodic cluster headache occurred. Indeed, two patients with episodic cluster headache reported an NRS of 0 after treatment. Because no subsequent consultations followed, spontaneous remission in these patients cannot be excluded. A third patient also reported to be pain free (NRS 0) at follow-up, but consistently revisited for a new injection after 90-150 days because of recurrent symptoms with relief of symptoms after injection, suggesting a positive effect of treatment. Other patients with episodic cluster headache showed marked improvement of symptoms after treatment.

Post-hoc analysis in patients with BTA injections for persistent idiopathic facial pain, reported by Jamtøy, suggested that the effect of BTA may arise within the first 4 weeks post-injection[18]. In our study, the mean time before effect was 11 days. Average time before return of symptoms was 66 days, although effects up to more than a year were reported.

Since BTA is a substance with a low diffusion gradient, and as suggested by Rusu et al. that morphological variations may be the reason for failures of ablation of the sphenopalatine ganglion, needle orientation at the SPG could have an impact on the effect of therapy[19]. We concluded that a needle tip position adjacent to the medial line reflecting the lateral wall of the nasal cavity, seen on x-ray in AP view, showed better results in NRS, HIT-6, number of attacks per month and pain days compared to a less deep position.

Transient diplopia was the most common side effect, probably due to blockage of the inferior rectus muscle of the orbit. Ipsilateral facial paresis was also seen. All side effects spontaneously resolved within 7 weeks. No severe side effects have been reported. The infrazygomatic approach has been shown to be safe, as reported in previous studies[20].

The use of BTA in neuropathic facial pain has been reported in a randomized clinical trial[18]. No difference in pain severity was observed between placebo and BTA 5-8 weeks after treatment. However, during the first 4 weeks after treatment, pain intensity was significantly lower. BTA injections at the SPG for trigeminal neuralgia were studied by Crespi[21]. Secondary outcomes did not show a statistically significant reduction in the number of attacks. Although we had a small dataset, our study confirmed a limited effect on attack intensity in NRS. Injection with BTA on the SPG in an extraction of 3 patients with trigeminal neuropathy had only a marginal effect based on NRS compared to other facial pains.

BTA is not recommended for cluster headache by the American Headache Society guidelines because of a lack of randomized controlled trials[10]. BTA has been approved by the Food and Drug Administration (FDA) for chronic migraine with the PREEMPT protocol, but no treatment has been approved at the level of the SPG yet[22]. The present study indicates that BTA injection may be considered in primary headache disorders if medical therapies fail or are insufficient. Furthermore, it has been shown that BTA is safe and non-neurodestructive, compared to other invasive procedures or surgical treatments.

Limitations

This is a retrospective study reporting real life data. No-show at follow-up results in missing data probably assuming no effect or still effect after treatment which could lead to population bias. Different doses of BTA were used. The first 10 patients treated received only 25IU BTA instead of 50IU BTA. Clinical outcome could be influenced. The linear regression analysis only revealed strong indications that the needle position can have substantial outcome impact. For further refined statistical analysis providing conclusive results, more data is required.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of Conflicting Interests: The Authors declare that there is no conflict of interest.

Data availability statement: Data is available on request due to privacy/ethical restrictions.

Conclusion

BTA has shown to have a favorable effect on pain sensation and quality of life in the treatment of primary headache disorders. Off-label use of BTA should be considered in TAC when other drugs have failed[12]. There is a need for randomized controlled trials with larger patient population groups.

References

1. Netter FH. Atlas of human anatomy. 5th ed. Philadelphia, PA: Saunders/Elsevier, 2011.
2. Khonsary SA, Ma Q, Villablanca P, et al. Clinical functional anatomy of the pterygopalatine ganglion, cephalgia and related dysautonomias: A review. Surg Neurol Int 2013; 4: S422-428. DOI: 10.4103/2152-7806.121628.
3. Lundy JA and McNary T. Neuroanatomy, Pterygopalatine Ganglion. StatPearls. Treasure Island (FL), 2022.
4. Rusu MC and Pop F. The anatomy of the sympathetic pathway through the pterygopalatine fossa in humans. Ann Anat 2010; 192: 17-22. DOI: 10.1016/j.aanat.2009.10.003.
5. Robbins MS, Robertson CE, Kaplan E, et al. The Sphenopalatine Ganglion: Anatomy, Pathophysiology, and Therapeutic Targeting in Headache. Headache 2016; 56: 240-258. DOI: 10.1111/head.12729.
6. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018; 38: 1-211. DOI: 10.1177/0333102417738202.
7. Kittrelle JP, Grouse DS and Seybold ME. Cluster headache. Local anesthetic abortive agents. Arch Neurol 1985; 42: 496-498. DOI: 10.1001/archneur.1985.04060050098017.
8. Kastler A, Cadel G, Comte A, et al. Alcohol percutaneous neurolysis of the sphenopalatine ganglion in the management of refractory cranio-facial pain. Neuroradiology 2014; 56: 589-596. DOI: 10.1007/s00234-014-1354-y.
9. Sanders M and Zuurmond WW. Efficacy of sphenopalatine ganglion blockade in 66 patients suffering from cluster headache: a 12- to 70-month follow-up evaluation. J Neurosurg 1997; 87: 876-880. DOI: 10.3171/jns.1997.87.6.0876.
10. Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache 2016; 56: 1093-1106. DOI: 10.1111/head.12866.
11. Ho KWD, Przkora R and Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation - a systematic review. J Headache Pain 2017; 18: 118. DOI: 10.1186/s10194-017-0826-y.
12. Bratbak DF, Nordgard S, Stovner LJ, et al. Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic cluster headache. Cephalalgia 2016; 36: 503-509. DOI: 10.1177/0333102415597891.
13. Bratbak DF, Nordgard S, Stovner LJ, et al. Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic migraine. Cephalalgia 2017; 37: 356-364. DOI: 10.1177/0333102416648328.
14. Simmonds L, Jamtoy KA, Aschehoug I, et al. Open label experience of repeated OnabotulinumtoxinA injections towards the sphenopalatine ganglion in patients with chronic cluster headache and chronic migraine. Cephalalgia 2024; 44: 3331024241273967. DOI: 10.1177/03331024241273967.
15. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 2003; 12: 963-974. DOI: 10.1023/a:1026119331193.
16. Guy W. Clinical Global Impression Scale. The ECDEU Assessment Manual for Psychopharmacology-Revised 338. US Department of Health and Human Services, 1976.
17. Gauci DCA. Manual of RF Techniques - A practical manual of radiofrequency procedures in chronic pain management. CoMedical, 2011.
18. Jamtoy KA, Thorstensen WM, Stovner LJ, et al. Onabotulinum toxin A block of the sphenopalatine ganglion in patients with persistent idiopathic facial pain: a randomized, triple-blind, placebo-controlled, exploratory, cross-over study. Cephalalgia 2023; 43: 3331024231187132. DOI: 10.1177/03331024231187132.
19. Rusu MC, Pop F, Curca GC, et al. The pterygopalatine ganglion in humans: a morphological study. Ann Anat 2009; 191: 196-202. DOI: 10.1016/j.aanat.2008.09.008.
20. Aschehoug I, Bratbak DF and Tronvik EA. Long-Term Outcome of Patients With Intractable Chronic Cluster Headache Treated With Injection of Onabotulinum Toxin A Toward the Sphenopalatine Ganglion - An Observational Study. Headache 2018; 58: 1519-1529. DOI: 10.1111/head.13398.
21. Crespi J, Bratbak D, Dodick DW, et al. Pilot Study of Injection of OnabotulinumtoxinA Toward the Sphenopalatine Ganglion for the Treatment of Classical Trigeminal Neuralgia. Headache 2019; 59: 1229-1239. DOI: 10.1111/head.13608.
22. Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache 2011; 51: 1358-1373. DOI: 10.1111/j.1526-4610.2011.01990.x.

doi.org/10.56126/76.S.13